ORIGINAL RESEARCH

Predictors of Mortality and Drug Resistance Among Carbapenem-Resistant *Enterobacteriaceae*-Infected Pancreatic Necrosis Patients

Di Wu · Jie Xiao · Junjie Ding · Yan Jia · Zimeng Guo · Huanmiao Liu · Jie Peng

ABSTRACT

Introduction: Carbapenem-resistant *Enterobacteriaceae* (CRE) has emerged as a global threat to hospitalization patients. Infected pancreatic necrosis (IPN) leads to high risks of CRE infections with increasing mortality. Our study aims to determine the predictors related to 90-day overall mortality of CRE IPN.

Methods: We retrospectively reviewed the drug resistance rates and clinical characteristics of CRE IPN patients from January 1, 2016, to January 1, 2021. Independent predictors of mortality were identified via univariate and multivariate analyses.

Results: During the 5-year period, 75 IPN patients suffered from 135 episodes of CRE infections with mortality up to 50.7%. CRE strains were highly resistant (> 50%) to nine of ten common antibiotics, except tigecycline (18%). The most common pathogen was carbapenem-resistant *Klebsiella pneumoniae* (84 of 135). Lung was the main site of extrapancreatic infections, followed by bloodstream and biliary tract. The independent predictors of mortality were Sequential Organ Failure Assessment (SOFA) score > 2 (hazard ratio 3.746, 95% confidence interval 1.209–11.609, $P = 0.022$) and procalcitonin > 6 ng/l (hazard ratio 2.428, 95% confidence interval 1.204–4.895, $P = 0.013$).

Conclusion: CRE is widespread as a global challenge with a high mortality rate among IPN patients due to limited therapeutic options. Carbapenem-resistant *K. pneumoniae* is the leading category of CRE which requires more attention in clinical practice. High SOFA score and procalcitonin level represent two independent predictors of mortality in CRE IPN patients. Greater efforts are needed toward timely therapeutic intervention for CRE IPN.

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Key Summary Points

Why carry out this study?

Carbapenem-resistant Enterobacteriaceae-infected pancreatic necrosis is a life-threatening complication of acute pancreatitis.

This study aimed to investigate the predictors of mortality among this population to improve the clinical outcomes.

What was learned from the study?

Carbapenem-resistant Enterobacteriaceae is widespread as a global challenge with a high mortality rate among infected pancreatic necrosis patients due to limited therapeutic options.

Carbapenem-resistant *Klebsiella pneumoniae* is the leading category of carbapenem-resistant Enterobacteriaceae which requires more attention in clinical practice.

High Sequential Organ Failure Assessment score and procalcitonin level represent two independent predictors of mortality.

INTRODUCTION

Acute pancreatitis (AP), one of the most common gastrointestinal diseases, has a varying clinical course with mortality up to 40% [1]. In the past decade, considerable changes in therapy for AP resulted in the reduction of mortality rate [2]. Complicated infections, including pancreatic and extrapancreatic infections, have gradually replaced systemic inflammatory reaction syndromes as the predominant cause of mortality [3]. AP patients have become a particularly vulnerable population and are at high risk of multidrug-resistant (MDR) bacterial infections due to early anti-inflammatory drugs and antimicrobial overuse.

The crisis of MDR bacterial infection is more frequently occurring in developing countries including China where more than half of strains are MDR [4, 5]. Most publications have shown that MDR bacterial infections are significantly associated with increased mortality among AP patients, and gram-negative bacteria have replaced the gram-positive isolates as the dominating bacteria in AP patients [3, 6–9]. Carbapenems are considered as last option for MDR gram-negative bacterial infections including *Enterobacteriaceae*. The Guideline of the American College of Gastroenterology supports the use of carbapenems in AP patients for infected pancreatic necrosis (IPN) based on the microbiologic profile and necrotic tissue penetration ability [10]. However, with the indiscriminate use of carbapenems, carbapenem-resistant *Enterobacteriaceae* (CRE), one of the most dangerous pathogens, has emerged as a serious global threat to hospitalization patients with limited therapeutic options and a high mortality rate [11]. Overused prophylactic antibiotic treatments for 'suspected' IPN could result in the acquisition of MDR or carbapenem resistance [1]. Precious studies reported that CRE, as a mainly infectious MDR pathogen, has spread worldwide and influenced the outcome of IPN patients especially in India and China [7, 12–16].

In recent years, although a step-up approach has been rapidly accepted and recognized as the preferred method for IPN treatments, both the step-up approach and open necrosectomy have been widely adopted regimens, being chosen based on the disease progress [17]. Shenvi et al. found that markers of inflammation may be helpful to determine the timing and choice of IPN therapeutic intervention [18]. Despite recent clinical research focused on MDR IPN among AP patients, there are still important knowledge gaps and a lack of accurate clinical data among the CRE IPN population [7, 8, 12].

To our knowledge, no literature has been published in this area, and our retrospective cohort study was the first to focus on the clinical manifestations and microbiologic profile among IPN patients complicated with CRE

infections. Herein, as the first cohort study investigating CRE IPN among AP patients, our objectives were to: (1) identify the predictor of poor outcomes to improve the survival and prognosis and (2) summarize drug resistance to shed light on the antibiotic therapy.

METHODS

Study Design and Setting

A retrospective cohort study enrolled 75 IPN patients who were confirmed to have CRE infections from January 1, 2016, to January 1, 2021, in two tertiary teaching hospitals, Xiangya Hospital, Central South University, a 3500-bed tertiary-care teaching hospital, and Third Xiangya Hospital, Central South University, an 1800-bed tertiary-care teaching hospital, both in Hunan, China. Clinical characteristics included etiology and classification of AP, age, site of infections, sex, length of hospitalization, referral, antibiotic therapy and therapeutic intervention for IPN. Sequential Organ Failure Assessment (SOFA) score and laboratory records were collected and analyzed within the first 24 h after the therapeutic interventions for CRE IPN. The follow-up period for all patients was 90 days after the therapeutic intervention. As Fig. S1 shows, the outcomes were divided into alive and death groups for risk analysis.

Ethics

Informed consents were waived for all the patients because of the retrospective nature. Ethical approvals of this retrospective cohort study were granted by the Institutional Review Board of Xiangya Hospital (no. 202105092) and Third Xiangya Hospital (no. 21048).

Patients and Management Protocol

Patients between 18 and 80 years old were enrolled. Patients without therapeutic intervention of IPN or only positive result of extra-pancreatic infections were excluded. At the initial admission, all patients were assessed and managed via the multi-disciplinary team, including gastroenterology physicians, intensive care unit physicians and pancreatic surgeons, according to the latest international guidelines [19]. Fine-needle aspiration was never used for diagnosis of IPN in either medical center. For the treatment of IPN, the step-up approach, including surgical and endoscopic techniques, was the preferred strategy, but open necrosectomy was also adopted in our cohort based on the patients' conditions, such as no opportunity for the step-up approach [20]. The antibiotic therapy we recorded in this cohort was the initial regimen after obtaining the microbiology profile of IPN. Carbapenem (high-dose, extended infusion) was considered an effective anti-infective choice for initial therapy. Tigecycline was prescribed as 50 mg every 12 h (100 mg the first time).

Definitions

Diagnosis and classification of AP were done according to the Revised Atlanta Classification [21]. Criteria of etiology were as follows: (1) hypertriglyceridemia: triglycerides > 5.6 mmol/l without other known cause; (2) gallstone: cholelithiasis or choledocholithiasis via contrast-enhanced computerized tomography; (3) alcoholism: regular consumption of alcohol (at least 50 g/day) [22]. The diagnoses of CRE IPN were based on: (1) contrast enhanced computed tomography; (2) positive microbiologic profiles from (peri)pancreatic necrosis obtained by the first therapeutic interventions [6]. Referrals were defined as patients transferred from lower-level hospitals 48 h after the AP occurred. Isolations of CRE were defined as positive specimens obtained from blood, bronchoalveolar fluid, bile and the first drainage of the IPN [11]. For anti-infective therapy, we recorded the antibiotic treatment at the initial choice (3–5 days). If the patient conditions worsened, we changed or combined new antibiotics as soon as possible. Sites of infection were diagnosed according to clinical manifestations and positive microbiologic profiles based the criteria of the Centers for Disease Control [23]. SOFA score was calculated based on the latest recommended

guideline to assess the hazard of mortality in the first 24 h after the therapeutic intervention [24].

Microbiology

Identification of CRE was performed via the Vitek-2 system (bioMérieux, Marcy L'etoile, France). Drug susceptibility and minimum inhibitory concentration were determined and measured by Kerby-Bauer disk diffusion and agar dilution, respectively. All the antimicrobial reagents were products of Oxoid Ltd. Carbapenem-resistance was defined as acquired nonsusceptibility to meropenem or imipenem (minimal inhibitory concentration $\geq$ 2 mg/l) [11]. Drug resistances of polymyxin and ceftazidime-avibactam were not described, because our hospitals did not perform the drug resistance tests of these two antibiotics until 2020 and most patients in our cohort did not take this test. Intermediate susceptibility in vitro was considered resistance to the antibiotic.

Statistical Analysis

Continuous variables, compared with Student's t-test or Mann–Whitney U-test, were expressed as mean $\pm$ standard deviation, and categorical variables were compared with the χ^2 test or Fisher exact tests in the univariate analysis. All the variables with $P < 0.05$ in the univariate analysis were entered into the multivariate Cox regression analysis to determine independent predictors of mortality. Hazard ratio (HR) and 95% confidence interval (CI) were performed to assess the power of predictors. We described the survival distribution among all the independent predictors via Kaplan-Meier curve. P-value < 0.05 (two-tailed) was considered statistically significant, and all the statistical analyses were performed via SPSS 24.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, US).

RESULTS

Over the 5-year period, 3960 AP patients were admitted: 2693 mild AP, 1069 moderately severe AP and 198 severe AP patients; There were 1.9% AP patients (75 of 3960), in 472 because of pancreatic necrosis, who suffered from CRE IPN with a mortality rate up to 50.7% (38 of 75). Fifty-two patients (69.3%) were male with a mean age of 49.1 $\pm$ 12.7 years. Hypertriglyceridemia ($n = 27$, 36.0%) was the main etiology in this AP cohort, followed by gallstone ($n = 25$, 33.3%), alcoholism ($n = 5$, 6.7%) and others ($n = 18$, 24.0%). Sixty-five patients (86.7%) were referred from other hospitals after 48 h from the onset of AP. Thirty-eight patients (50.7%) received therapeutic interventions with positive specimens of CRE within 30 days from the onset of AP. Sixty patients first had positive results from IPN, and the remaining patients ($n = 15$) suffered from antecedent extrapancreatic infections before developing IPN. For antibiotic therapy, carbapenem (high dose, extended infusion) or carbapenem combined with tigecycline were the main choices in 28 and 26 patients, respectively. Step-up approach (percutaneous catheter drainage to minimal access retroperitoneal necrosectomy) was the most common therapeutic intervention for IPN. These data were not significantly different between the survival and mortality group.

In the univariate analysis, 54 patients, including 35 deaths, were classified into severe AP, and the remaining 21 patients had moderately severe AP ($P < 0.001$). According to the microbiologic profile, 33 patients had multisite infections ($P = 0.024$). SOFA score > 2 ($P < 0.001$), procalcitonin > 6 ng/l ($P < 0.001$), bacteremia ($P = 0.001$) and hemorrhage ($P < 0.001$) were also significantly associated with mortality (Table 1).

In the multivariate analysis, only SOFA score > 2 (HR 3.746, 95% CI 1.209–11.609, $P = 0.022$) and procalcitonin > 6 ng/l (HR 2.428, 95% CI 1.204–4.895, $P = 0.013$) were independent predictors of overall mortality (Table 2). The survival time and Kaplan-Meier curve of patients with independent predictors are described in Fig. 1. For the outcome of patients with SOFA score > 2 versus $\leq$ 2, the survival rate in the SOFA score > 2 group was significantly lower (29.2% vs. 85.2%, $P < 0.001$). Compared with the procalcitonin $\leq$ 6 ng/l group, the survival rate was

Table 1 Clinical characteristics and comparison of outcomes among 75 AP patients with CRE

Characteristics	Total	Survival (*n* = 37)	Mortality (*n* = 38)	*P*
Age, years (mean ± SD)	49.1 ± 12.7	46.8 ± 12.9	51.4 ± 12.2	0.116
Sex, *n* (%)				0.743
Male	52 (69.3)	25 (67.6)	27 (71.1)	
Female	23 (30.7)	12 (32.4)	11 (28.9)	
Etiology, *n* (%)				0.628
Hypertriglyceridemia	27 (36.0)	15 (40.5)	12 (31.6)	
Gallstone	25 (33.3)	10 (27.0)	15 (39.5)	
Alcoholism	5 (6.7)	2 (5.4)	3 (7.9)	
Others	18 (24.0)	10 (27.0)	8 (21.1)	
Classification of AP, *n* (%)				< 0.001*
Moderately severe AP	21 (28.0)	18 (48.6)	3 (7.9)	
Severe AP	54 (72.0)	19 (51.4)	35 (92.1)	
Initiation site of infections, *n* (%)				0.065
Pancreas (peri)	60 (80)	33 (89.2)	27 (71.1)	
Lung	9 (12.0)	1 (2.7)	8 (21.1)	
Bloodstream	5 (6.7)	2 (5.4)	3 (7.9)	
Biliary tract	1 (1.3)	1 (2.7)	0 (0)	
Bacteremia, *n* (%)	23 (30.7)	5 (13.5)	18 (47.4)	0.001*
Multisite infections, *n* (%)	30 (42.0)	10 (27.0)	20 (52.6)	0.024*
Polymicrobial infections, *n* (%)	17 (22.7)	6 (16.2)	11 (28.9)	0.188
Referred patient, *n* (%)	65 (86.7)	33 (89.2)	32 (84.2)	0.526
Onset of enteral nutrition after hospital admission > 3 days	27 (36.0)	17 (43.2)	11 (28.9)	0.197
Timing of intervention for IPN from onset of AP, *n* (%)				0.133
15–30 days	37 (49.3)	15 (40.5)	22 (57.9)	
> 30 days	38 (50.7)	22 (59.5)	16 (42.1)	
SOFA score at the intervention of IPN, *n* (%)				< 0.001*
≤ 2	27 (36.0)	23 (62.2)	4 (10.5)	
> 2	48 (64.0)	14 (37.8)	34 (89.5)	
Laboratory variables at the intervention for IPN, *n* (%)				
Albumin < 25 g/l	19 (25.3)	7 (18.9)	12 (31.6)	0.208
Neutrophil count > 15,000/mm^3	18 (24.0)	9 (24.3)	9 (23.7)	0.948

Table 1 continued

Characteristics	Total	Survival (*n* = 37)	Mortality (*n* = 38)	*P*
Lymphocyte count < 300/mm^3	6 (8.0)	2 (5.4)	4 (10.5)	0.695
Procalcitonin > 6 ng/l	24 (32.0)	4 (10.8)	20 (52.6)	< 0.001[*]
Antibiotic therapy, *n* (%)				0.264
Carbapenem (high dose, extended infusion)	28 (37.3)	11 (29.7)	17 (44.7)	
Penicillins/β-lactamase inhibitors	6 (4.0)	1 (2.7)	5 (13.2)	
Tigecycline	5 (6.7)	2 (5.4)	3 (7.9)	
Quinolone	3 (4.0)	2 (5.4)	1 (2.6)	
Carbapenem and tigecycline	26 (34.7)	16 (43.2)	10 (26.3)	
Polymyxins and fosfomycin	5 (6.7)	4 (10.8)	1 (2.6)	
Carbapenem and sulfonamides	2 (2.7)	1 (2.7)	1 (2.6)	
Intervention for IPN, *n*				0.449
Only PCD	9 (12.0)	3 (8.1)	6 (15.8)	
Only ETD	10 (13.3)	5 (13.5)	5 (13.2)	
PCD to minimal access retroperitoneal necrosectomy	30 (40.0)	19 (51.4)	11 (28.9)	
PCD to video-assisted retroperitoneal debridement	5 (6.7)	3 (8.1)	2 (5.3)	
ETD to endoscopic transluminal necrosectomy	7 (9.3)	2 (5.4)	5 (13.2)	
Step-up to OPN	8 (10.7)	3 (8.1)	5 (13.2)	
OPN	6 (8.0)	2 (5.4)	4 (10.5)	
Hospitalization, days (mean ± SD)	44.9 ± 29.1	25.8 ± 4.2	31.4 ± 5.1	0.090
Major complications, *n* (%)				
Hemorrhage	23 (30.7)	2 (5.4)	21 (55.3)	< 0.001[*]
Intestinal leakage	17 (22.7)	6 (16.2)	11 (28.9)	0.188
Pancreatic fistula	9 (12.0)	5 (13.5)	4 (10.5)	0.966

SD standard deviation, *AP* acute pancreatitis, *ARDS* acute respiratory distress syndrome, *SOFA* Sequential Organ Failure Assessment, *IPN* infected pancreatic necrosis, *PCD* percutaneous catheter drainage, *ETD* endoscopic transluminal drainage, *OPN* open necrosectomy

[*] *P* values are statistically significant between survival and mortality groups

significantly lower in the procalcitonin > 6 ng/l group (16.7% vs. 64.7%, *P* < 0.001).

In total, 135 CRE strains were detected among all 75 AP patients in our cohort (Table 3). *Klebsiella pneumoniae* (*n* = 84), *Escherichia coli* (*n* = 21) and *Klebsiella ozaenae* (*n* = 17) were the main CRE strains. Lung was the main site of extrapancreatic infections, followed by bloodstream and biliary tract. Drug resistance rates of each category and total are shown in Table 4. CRE strains were highly resistant (> 50%) to nine of ten common antibiotic categories, except tigecycline (18%). As the secondary common pathogen, *E. coli* was less

Table 2 Multivariate analysis of predictors for mortality in carbapenem-resistant *Enterobacteriaceae*-infected pancreatic necrosis patients

Variable	HR (95% CI)	P
Procalcitonin > 6 ng/l	2.428 (1.204–4.895)	0.013[*]
SOFA score > 2	3.746 (1.209–11.609)	0.022[*]
Severe acute pancreatitis	2.908 (0.798–10.595)	0.106
Multisite infections	1.229 (0.579–2.605)	0.591
Bacteremia	2.039 (0.946–4.238)	0.058
Hemorrhage	1.099 (0.512–2.359)	0.809

HR hazard ratio, *CI* confidence interval, *SOFA* Sequential Organ Failure Assessment
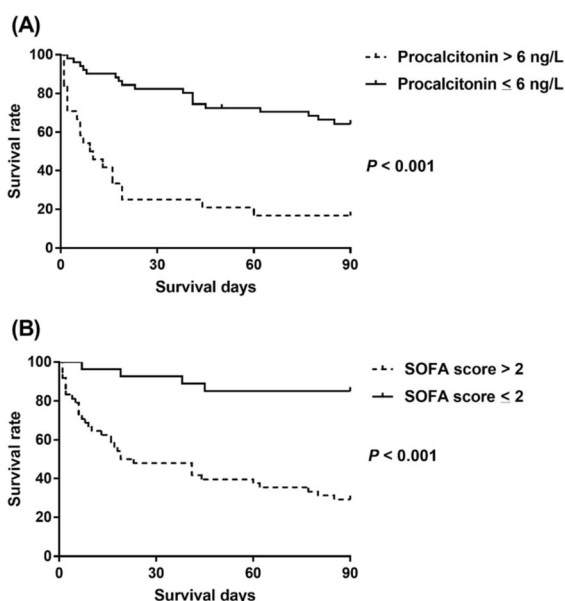
Fig. 1 A Survival rate was significantly lower in the procalcitonin > 6 ng/l group (16.7% vs. 64.7%, $P < 0.001$); **B** SOFA score > 2 group vs. ≤ 2 group (29.2% vs. 85.2%, $P < 0.001$)

resistant than the total. On the other hand, resistance rates of *K. pneumoniae* were higher than the total.

DISCUSSION

Over the past decade, CRE has caused life-threatening infections with high mortality and economic burden in the global healthcare systems [11, 25]. AP patients, especially those complicated with IPN, are vulnerable to many potential risk factors associated with acquisition of MDR bacterial or CRE infections, such as overuse of prophylactic antibiotics, longer length of hospitalizations and anti-inflammatory conditions [3, 9, 14]. To date, this is the first cohort study focusing on the predictor of mortality and drug resistance rate among CRE IPN patients.

Mortality of IPN patients with CRE infections (50.7%) in our cohort was much higher than in those with MDR bacterial infections as Ning et al. reported (35.2%), indicating that CRE infections had greater hazards [3]. In line with Li et al., hyperlipidemia ($n = 27$, 36.0%) was the most common primary etiology among Chinese AP patients complicated with CRE infections in our cohort [9]. Unhealthy lifestyles, such as eating spicy foods and high-fat diets, may be a possible reason contributing to the high proportion of hyperlipidemia in China. However, the difference in the etiologic factors was not statistically significant in our study ($P = 0.628$).

Antibiotic therapy was used before having a clear microbiologic profile, but duration of antibiotic treatment was often dependent on the potency of infectious source control in the process of IPN treatment [13]. Recent guidelines recommended performing first procedures once walled-off necrosis occurs instead of 4 weeks later, because long-term conservative treatment can increase the risk of MDR bacterial and invasive fungal infections [26]. Furthermore, some IPN patients could die because of severe infections within 4 weeks. In line with Shenvi et al., the timing of the first intervention, whether > or < 30 days, was not associated with mortality in our cohort, and it may be more appropriate to choose the timing based on the respective clinical situations rather than general criteria [18].

Main findings of our study were: SOFA score > 2 and procalcitonin > 6 ng/l at the therapeutic intervention of IPN are first reported as independent predictors of mortality among IPN patients with CRE infections. SOFA score that assesses organ failure can be an

Table 3 Composition of pathogens causing carbapenem-resistant *Enterobacteriaceae* secondary infections in 75 AP patients

Pathogens	Strains, *n*	Infection sites, *n*				Constituent ratio, %
		Pancreas (peri)	Bloodstream	Lung	Biliary tract	
Klebsiella pneumoniae	84	44	15	24	1	62
Escherichia coli	21	17	2	1	1	16
Klebsiella ozaenae	17	9	5	3	–	13
Enterobacter cloacae	5	2	1	1	1	4
Proteus mirabilis	4	2	-	1	–	3
Enterobacter aerogenes	2	2	–	–	–	1
Klebsiella oxytoca	2	2	–	–	–	1
Total	135	79	23	30	3	100

Table 4 Drug resistance rates of 135 CRE isolates to 10 antibiotics according to category in 75 carbapenem-resistant Enterobacteriaceae-infected pancreatic necrosis patients (%)

ATB	*K. pneumoniae*, %	*E. coli*, %	*K. ozaenae*, %	*E. cloacae*, %	*P. mirabilis*, %	Others, %	Total, %
AN	64	29	60	20	0	0	54
AZT	99	82	100	100	33	100	95
CPFX	95	88	100	80	100	75	94
GEN	90	76	73	20	100	50	83
LVF	96	88	100	20	33	50	90
SMX	61	76	47	20	100	0	52
TOB	80	94	67	40	100	100	77
TZP	96	53	100	100	67	75	89
MAC	100	94	100	100	NS	100	99
TGC	19	0	7	60	NS	50	18

ATB antibiotic, *AN* amikacin, *AZT* aztreonam, *CPFX* ciprofloxacin, *GEN* gentamicin, *LVF* levofloxacin, *SMX* sulfamethoxazole, *TOB* tobramycin, *TZP* piperacillin-tazobactam, *MAC* macrodantin, *TGC* tigecycline, *NS* no significance

indicator of septic shock in critical illness, which has already been validated in AP patients with infections [27, 28]. Higher SOFA score not only represents multi-organ dysfunction, but also objectively indicates the severity of sepsis. However, there is still no report on the relationship between a high SOFA score and outcomes in CRE IPN patients. Our study first provided this important evidence suggesting

clinicians should observe the SOFA score at the pre-intervention phase. Yunus et al. proved that procalcitonin is a valuable marker of infection and is positively associated with the degree of infection [29]. Our result also revealed the key role of procalcitonin in the clinical evaluation, which alerts us to monitor procalcitonin and carry out anti-infective therapy in a timely manner. These two independent predictors may

be potential clinical markers of IPN, which needs to be verified in a further randomized trial such as the POINTER trial [30].

Consistent with recent guidelines emphasizing early treatment within the first 72 h from onset of AP, Muktesh et al. found that delayed referral (> 7 days) resulted in poor outcomes [1, 31]. The high referral rate (n = 65, 86.7%) in our cohort was not surprising, as our centers are the most famous hospitals in Hunan Province and are preferred by critically ill patients from the surrounding area. Referral, after 48 h of onset, was not associated with the mortality (P = 0.526), which may suggest a 48-h delay could be an acceptable time because of increasing quality of therapy in lower-level hospitals. Most Chinese doctors, including those in our two centers, indiscriminately used antibiotic prophylaxis in the AP patients with 'suspect' infections, which may do harm in natural courses and lead to the occurrence of MDR bacterial IPN [13, 32]. Recent guidelines also recommended not preventing IPN with antibiotic prophylaxis, but we could not analyze the impact of antibiotic prophylaxis on IPN because of the high referral rate and lack of important data before admission, which needs to be verified in the future [19].

In our study, carbapenem-resistant *K. pneumoniae* (CRKP) was the leading pathogen of CRE strains in line with a previous study focused on the bacterial category [8]. Bacterial colonization and translocation may be the main reasons for attribution of CRKP. In line with a previous study, drug resistance rates of CRKP were more serious than total CRE strains with limited antibiotic choices, which may alert physicians to pay more attention to the emergency hazard of CRKP [4]. Although only tigecycline kept a low resistance rate, we should also use these antibiotics with a microbiologic profile cautiously to preclude the occurrence of drug resistance according to our previous study [11]. Similar to Montravers et al., there was no significant difference between different antibiotic therapies in our cohort, indicating that anti-infective therapy was not related to mortality with a high risk of drug resistance [32]. In line with a previous study, carbapenem (high dose, extended infusion), piperacillin and quinolone may be recommended as anti-infective therapies for CRE IPN according to microbiology results because of effective penetration [13]. Recent guidelines recommended combination therapy as an effective choice for CRE intra-abdominal infection, but there is still no evidence for combination therapy focusing on efficacy and safety in CRE IPN, which was also not fully confirmed in our retrospective cohort [33]. Data on polymyxin, as the most effective antibiotic for CRE infections, was not available because only six patients in our cohort underwent the polymyxin-resistance test. This needs to be verified in the future. In the era of increasing drug resistance, the next step should be not only creating novel antibiotics, but also defining the resistance mechanisms and preventing infections.

There were several limitations in our study. First, the power of risk analysis for the influence of both antibiotic therapy and therapeutic intervention for IPN on outcomes (no statistical significance) was limited because of the small sample size. In addition, most patients suffered from co-infections and major complications, and we could only analyze the overall mortality but not exclude these patients from CRE-infection-related mortality because of the limited sample size. Second, our findings were derived from two large tertiary hospitals in China which may not be generalized to areas with lower prevalence of CRE infections. Third, we decided to exclude the 'suspect' IPN patients with positive extrapancreatic results instead of therapeutic intervention to obtain the positive (peri)pancreatic result, which may lead to a bias in the evaluation of extrapancreatic infections. Fourth, novel molecular technology or diagnostic method need to be used for underlying mechanisms and rapid diagnosis of infections in the future. Finally, some important variables, such as specific radiologic signs, persistent bacteremia and septic shock, were lacking because of the retrospective nature. According to the above limitations, our findings should be interpreted cautiously. This 5-year Chinese bicentric cohort study may be beneficial because of its universally adopted findings but requires more validation in the future.

CONCLUSION

CRE is widespread as a global challenge with a high mortality rate among IPN patients due to limited antimicrobial therapy. CRKP is the leading category of CRE with a high drug resistance rate which requires more attention in clinical practice. High SOFA score and procalcitonin level represent two independent predictors of mortality in CRE IPN patients.

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Compliance with Ethics Guidelines. Informed consents were waived for all patients because of the retrospective nature. Ethical approval of this retrospective cohort study was granted by the Institutional Review Board of Xiangya Hospital (no. 202105092) and Third Xiangya Hospital (no. 21048).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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