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Prognostic factors of critical acute pancreatitis: A prospective cohort study

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ABSTRACT

Background: Patients with critical acute pancreatitis (CAP) have the highest risk of mortality. However, there have been no studies specifically designed to evaluate the prognostic factors of CAP.
Aims & methods: This was a prospective observational cohort study involving patients with CAP. Three aspects including organ failure, (peri)pancreatic necrotic fluid cultures and surgical interventions were analyzed specifically to identify prognostic factors.
Results: Of the 102 consecutive patients with CAP, 83 patients (81.4%) received step-up surgical treatment, the mortality of the step-up group was 25.3% (21/83). 19 patients (18.6%) underwent step-down surgical treatment, the mortality of the step-down group was 57.9% (11/19). Overall mortality in the whole cohort was 31.4% (32/102). Multivariate analysis of death predictors indicated that multiple organ failure (MOF) (OR = 5.3; 95% CI, 1.5–18.2; $p = 0.008$), long duration (≥5 days) of organ failure (OR = 6.4; 95% CI, 1.2–54.3; $p = 0.029$), multidrug-resistant organisms (MDROs) infection (OR = 4.6; 95% CI, 1.3–15.8; $p = 0.013$), OPN (OR = 3.7; 95% CI, 1.5–8.8; $p = 0.004$) and step-down surgical treatment (OR = 3.5; 95% CI, 1.2–10.1; $p = 0.019$) were significant factors.
Conclusion: Among patients with CAP, MOF, long duration (≥5 days) of organ failure, MDROs infection, OPN and step-down surgical treatment were identified as the predictors of mortality.

1. Introduction

Acute pancreatitis (AP) is a common disease with the potential to cause significant morbidity and mortality [1]. The clinical course of AP greatly varies among patients, which makes the accurate classification very crucial for the clinical decision-making [2–4]. Consequently, the determinant-based classification (DBC) has been developed and validated in 2012 [5]. The new DBC of AP severity was systematically introduced to classify AP severity into 4 categories (mild, moderate, severe, and critical) based on the presence or absence of local and systemic determinants as well as their combinations. One of the highlights of the DBC classification is a newly-defined category called critical acute pancreatitis (CAP). This category incorporates patients characterized by the presence of both persistent organ failure (POF) and infected pancreatic necrosis (IPN).

Several cohort studies indicated that CAP was strongly associated with the highest risk of adverse outcome [6–8]. It was reported that CAP accounts for only 2%–7% of AP, while the mortality is as high as 18%–88% [6,7]. Considering the high morbidity and mortality, CAP patients need to be identified early, be monitored closely and be concentrated more resources on. To the best of our knowledge, the optimal management for these patients remains unclear [9] and there have been no studies evaluating the prognostic factors related with CAP. The aim of this study was to investigate the risk factors correlated with poor outcomes of CAP and to determine an optimal surgical treatment strategy for such highly-lethal subgroup of AP patients.

2. Patients and methods

2.1. Patient identification and definitions

Patients with CAP were prospectively and consecutively enrolled at the Xiangya Hospital of Central South University (a ter-

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Table 1
Definitions.

Organ failure
It is defined for 3 organ systems (pulmonary, circulatory and renal) on the basis of the worst measurement over a 24-h period.
- Pulmonary failure: $PaO_2/FiO_2 \leq 300$ mmHg ($\leq$40 kPa) or a need for mechanical ventilation.
- Circulatory failure: need for inotropic agent.
- Renal failure: creatinine $\geq$171 μmol/L ($\geq$2.0 mg/dL) or a need for hemofiltration or hemodialysis.
Multiple organ failure
Failure of at least 2 organ systems on the same day.
Persistent organ failure
Organ failure in the same organ system for 48 h or more.
Infected (peri)pancreatic necrosis
It is defined as a positive culture of (peri)pancreatic necrotic fluid obtained during the first drainage or necrosectomy.

tiary referral center with an average of 600 admissions with AP annually) from January 2011 to August 2018. CAP was defined as the presence of both POF and IPN [5]. Multi-drug resistant organisms (MDROs) were defined as microorganisms that are resistant to two or more classes of antimicrobial agents [10]. The definitions of OF and IPN are listed in Table 1.

2.2. Management protocol and data collection

All patients received standard conservative treatment according to the latest international guidelines [9,11,12]. Patients with OF were treated with organ-specific support as needed, including mechanical ventilation, continuous renal replacement therapy, vasoactive agents, and others. Surgical interventions were generally performed in case of suspected IPN and, if possible, postponed at least 3–4 weeks since disease onset. A step-up approach consisting of percutaneous catheter drainage (PCD) [13,14] and subsequent minimally invasive or open pancreatic necrosectomy (OPN), was a preferred strategy for managing IPN [15,16]. Minimally invasive technique adopted in this cohort was minimal access retroperitoneal pancreatic necrosectomy (MARPN) [17,18]. When sepsis could not be controlled despite active minimally invasive techniques was used or severe complications (massive bleeding, intestinal leakage) occurred, OPN would be the final resort of step-up approach. As contrasted, OPN could also be adopted as the initial surgical procedure to remove the infected necrosis when there was no route for PCD or transluminal drainage. In addition, we realized that one of the main drawbacks of the step-up approach was prolonged treatment duration and potential requirement for multiple operations. To expedite the recovery of the patients and shorten the in-hospital stay, we adopted OPN as the first choice of treatment for a well-defined collection localized in the lesser sac, even when the route for percutaneous or endoscopic drainage was available. If indicated, PCD or MARPN could act as subsequent adjuvant procedures to control the infection, which is also known as step-down approach [15]. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was waived in our institute based on the observational nature of this study and written informed consent was obtained from all patients or their representative for publication of data. We followed the STROBE statement for the reporting of data [19].

2.3. Statistical analysis

Death was the primary endpoint. Continuous variables were expressed using medians with standard deviations (SD), and categorical variables were described in absolute numbers and in percentages. In the univariate analysis, the Fisher exact test, the χ^2 test, and binary logistic regression analysis were used for bivariate comparisons. Significant variables were included in the multivariable analysis, which were performed using logistic regression analysis. *P*-values <0.05 was considered to be statistically significant. All the statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) 22.0 statistical software package (IBM Analytics, Armonk, NY) in this study.

Table 2
Mortality in the patients with organ failure.

	Mortality Rate (%)	*P* value
Organ failure		0.002
Persistent single organ failure	5/38 (13.2)	
Persistent multiple organ failure	27/64 (42.2)	
Duration of organ failure		<0.001
Any organ failure lasts for 48h~5 days	12/68 (17.6)	
Any organ failure lasts for $\geq$ 5 days	20/34 (58.8)	
Different types of organ failure		–
Pulmonary failure	23/87 (26.4)	
Renal failure	27/61 (44.3)	
Circulatory failure	29/37 (78.4)	

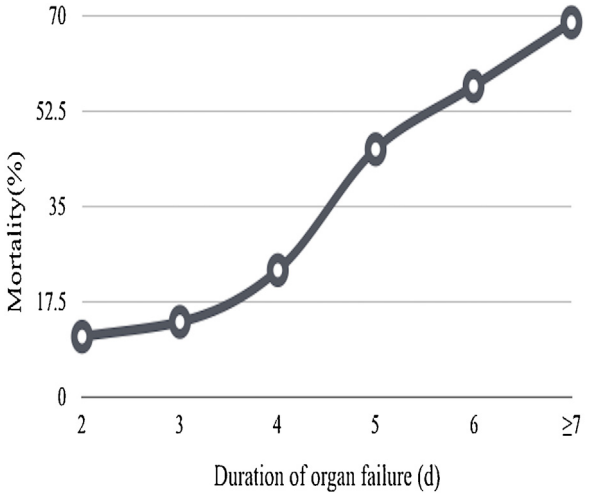

Fig. 1. The relationship between duration of OF and mortality in CAP patients.

3. Results

3.1. Patient characteristics

During the study period from January 2011 to August 2018, a total of 4910 cases of AP were admitted: 61.1% of them had mild AP, 29.7% had moderate AP, 7.1% had severe AP, and 2.1% had CAP. The proportion of etiology were 51.3% of biliary, 26.8% of hyperlipidemia, 5.9% of alcoholic and 16.0% of other causes.

Over the same period, a total of 102 patients with CAP were enrolled. Of these, 77 patients were male and 25 were female, and the average age was 46.2 ± 15.7 years old. Hyperlipidemia was the most common cause (n = 44, 43.1%), followed by biliary (n = 42, 41.2%), idiopathic (n = 11, 10.8%), and alcoholic (n = 5, 4.9%).

3.2. Organ failure

Persistent single and multiple organ failure occurred in 38 (37.3%) and 64 (62.7%) of the 102 patients, respectively (Table 2). Mortality in the persistent MOF group was significantly higher than that in the persistent single OF group (42.2% *vs.* 13.2%, $p = 0.002$). Higher mortality occurred among patients with OF lasting for 5 or more days compared with that with OF less than 5 days (58.8% *vs.* 17.6%, $p < 0.001$). The longer the organ failure lasted, the higher mortality the patients would have (Fig. 1).

Table 3
Mortality and morbidity in different subgroups of patients based on intervention strategy.

Treatment	Total (n = 102)	Died (n = 32)	Survived (n = 70)	Morbidity
Step-up	83 (81.4%)	21 (65.6%)	62 (88.6%)	36 (43.6%)
PCD alone	29 (28.4%)	10 (31.3%)	19 (27.1%)	9 (18.8%)
PCD-MARPN	35 (34.3%)	4 (12.5%)	31 (44.3%)	12 (25.0%)
PCD-OPN	10 (9.8%)	5 (15.5%)	5 (7.1%)	10 (20.8%)
PCD-MARPN-OPN	5 (4.8%)	2 (6.3%)	3 (4.4%)	2 (4.2%)
PCD-OPN-MARPN	4 (3.9%)	0 (0)	4 (5.7%)	3 (6.3%)
Step-down	19 (18.6%)	11 (34.3%)	8 (11.4%)	12 (63.2%)
OPN	13 (12.7%)	8 (25.0%)	5 (7.1%)	8 (16.7%)
OPN-MARPN	6 (5.9%)	3 (9.3%)	3 (4.3%)	4 (8.3%)

Morbidity includes pancreatic fistula, biliary fistula and intestinal fistula.

Table 4
Predictors of mortality in CAP patients.

Variable	n (%)		Univariable			Multivariable		
	Died [n = 32 (31.4%)]	Survived [n = 70 (68.6%)]	OR	95%CI	*P*	OR	95%CI	*p*
Male (vs. female)	25	52	1.2	0.8–1.3	0.62	1.03	0.97–1.08	0.386
Duration of organ failure (≥5 days vs. 48 h~5 days)	20 (62.5)	14 (20.0)	6.7	1.6–42.3	0.013	6.4	1.2–54.3	0.029
Multiple organ failure (vs. single)	27 (84.4)	37 (52.9)	4.8	2.0–19.7	0.002	5.3	1.5–18.2	0.008
MDROs infection (vs. no)	26 (81.3)	35 (50.0)	4.3	1.9–16.7	0.021	4.6	1.3–15.8	0.013
CRE infection (vs. no)	12 (37.5)	27 (38.6)	1.0	0.3–2.1	0.76	0.9	0.4–2.9	0.92
Fungal infection (vs. no)	7 (21.9)	21 (30.0)	1.5	0.7–7.9	0.19	1.8	0.5–4.5	0.36
Multiple organisms infected (vs. Single)	21 (65.6)	53 (75.7)	1.6	0.5–2.1	0.68	1.3	0.3–2.5	0.71
OPN (vs. no)	19 (59.4)	19 (27.1)	3.9	1.2–12.3	0.002	3.7	1.5–8.8	0.004
Step-down surgical approach (vs. step-up)	11 (34.4)	8 (14.4)	4.1	1.5–16.4	0.007	3.5	1.2–10.1	0.019

MDROs indicates multidrug-resistant organisms; CRE indicates Carbapenem-resistant Enterobacteriaceae.
OPN indicates open pancreatic necrosectomy; CI, confidence interval; OR, odds ratio.

Organ distribution of POF in this study was varied. The most prevalent POF was pulmonary failure which occurred in 87 of the 102 patients (85.3%) with a median duration of 3 days. Renal failure was the second common organ failure with the incidence of 59.8% (n = 61) and the median duration of renal failure was 4 days. After that, circulatory failure occurred in 37 of the 102 patients (36.3%), and the median duration of circulatory failure was 2 days. The mortality of the patients with pulmonary failure, renal failure, and circulatory failure were 26.4%, 44.3%, 78.4%, respectively.

3.3. Microbiological data

There were 208 microbiological samples obtained from the necrotic tissue or drainage fluid. The predominant pathogens cultured from drainage were *Acinetobacter baumannii* (25.5%, 53/208), followed by *Klebsiella pneumoniae* (19.7%, 41/208), *Enterobacterium faecalis* (13.0%, 27/208), and *Escherichia coli* (11.1%, 23/208). MDROs infections occurred in 109 of 208 microbiological samples (52.4%), and the most common MDROs isolated from (peri)pancreatic drainage were multidrug-resistant *Acinetobacter baumannii* (MDRO-AB) (29.4%, 32/109). The mortality of MDROs infection group was higher than the common bacterial infection group [42.6% (26/61) vs. 14.6% (6/41), OR = 4.6; 95% CI, 1.3–15.8; $p = 0.013$]. Carbapenem-resistant Enterobacteriaceae (CRE) infections occurred in 39 of 208 microbiological samples (18.7%), and *Klebsiella Pneumoniae Carbapenemase* (KPC) was the predominant CRE pathogen (64.1%, 25/39). Fungal isolates were identified in 28 patients. However, stratified analysis revealed that there were no statistical differences in mortality between the CRE infection group and the non-CRE infection group [30.7% (12/39) vs. 31.7% (20/63), $p = 0.92$] and between the fungal infection group and non-fungal infection group [25.0% (7/28) vs. 33.8% (25/74), $p = 0.36$].

3.4. Surgical interventions

Surgical interventions were outlined in Table 3. Morbidity of step-up and step-down treatment was 43.6% (36/83) and 63.2% (12/19), while mortality was 25.3% (21/83) and 57.9% (11/19), respectively. CAP patients who underwent step-up strategy had a lower mortality [25.3% (21/83) vs. 57.9% (11/19)], as showed in Table 3.

3.5. Predictors of mortality

Overall mortality in the whole cohort was 31.4% (32/102). Baseline characteristics were equally distributed between groups. Table 4 lists the potential parameters which might be used to predict death in the patients with CAP. In the multivariate logistic regression analysis, persistent MOF ($p = 0.008$), long duration (≥5 day) of organ failure ($p = 0.029$), and MDROs infection ($p = 0.013$) were identified as significant factors leading to higher mortality in CAP patients. Furthermore, step-up approach presented significantly lower mortality rate than step-down approach [25.3% (21/83) vs. 57.9% (11/19), $p = 0.019$], and the mortality rate of CAP patients whoever underwent OPN was significantly higher compared with those who never underwent OPN [50.0% (19/38) vs. 20.3% (13/64), OR = 3.7; 95% CI, 1.5–8.8; $p = 0.004$].

4. Discussion

This is, to our knowledge, the largest study to specifically evaluate the prognostic factors associated with the most severe category of AP (CAP). We found that MOF, long duration (≥5 day) of organ failure, MDROs infection, OPN and step-down surgical treatment were associated with higher mortality in patients with CAP. Also, step-up minimal invasive techniques such as PCD and MARPN were associated with better outcomes and therefore should be favored over traditional pancreatic necrosectomy. These results gave an update to our current knowledge on CAP.

Systemic and local complications determine the outcomes of patients with AP and this has been highlighted in DBC. It appears that both Atlanta 2012 and DBC outperform Atlanta 1992 [20–23]. The newly introduced critical category in DBC includes patients with POF and IPN at the highest risk of adverse outcomes. A meta-

analysis of 14 studies comprising 1478 patients showed that the effects of OF and IPN on mortality were comparable and had concluded that the presence of both OF and IPN doubled the risk of mortality as compared to the occurrence of either of them alone [24]. In a British cohort, seven of eight patients in this critical category died in the hospital, compared with 15 of 34 with severe pancreatitis based on Atlanta 2012. Among patients with CAP, the in-hospital mortality rate was doubled, ICU stay was more than twice as long, and the need for surgical intervention was greater than that for patients with severe pancreatitis according to the Atlanta 2012 system [23]. A nation-wide multicenter prospective cohort study from the Spain group comprising 1655 AP patients showed that mortality of CAP patients reached as high as 54.1% [25]. Therefore, identification of patients classified as "critical" has definite implications for prognosis and for the management choices. The four categories of DBC will better accomplish the main objectives of the revision of the Atlanta classification, which are to improve clinical assessment, facilitate communication between physicians and promote standardization for reporting clinical studies. However, most of the published data showed that the percentage of the critical type was quite low, ranging from 0.6% to 7% [20–23,25]. Due to the small numbers of patients in the critical category, it was not easy to analyze the prognostic factors of CAP patients. In addition, the management of patients with CAP remains unclear. There is still great controversy regarding the optimal interventions and the optimal timing. Herein, we attempted to investigate the prognostic factors of CAP, especially from 3 aspects including organ failure, infection as well as surgical interventions, with the aim of shedding some lights on the optimal surgical strategy.

OF was identified as the most important risk factors for outcome in acute pancreatitis. Many previous studies have shown that POF or MOF was associated with increased morbidity and mortality compared with transient OF or single OF [25–27]. However, whether the same conclusions could be drawn in CAP patients has never been answered yet. In this study, significantly more deaths occurred among CAP patients with OF lasting for 5 or more days, compared with that lasting between 48 h to 5 days. Furthermore, MOF was also associated with higher mortality than single OF in CAP patients. Thus, in future risk stratification of CAP, these 2 factors should be considered. It sounds rational that in the critical group, the longer the organ failure lasts or the more numbers of organs are involved, the higher mortality the patients will have. However, this was not the case in a recent multicenter study, which found no association between duration of organ failure and mortality [28]. In that study, even the mortality in patients with transient organ failure was not significantly different from that in POF. The major difference between our investigation and Schepers's study was the background of the patients. All the patients in our study were CAP patients with both persistent OF and IPN, whereas in Scheper's study, all the patients had acute necrotizing pancreatitis, either sterile or infected. In other words, if the results in both studies held true, we might conclude that the clinical impact of the duration of OF would at least partially be associated with infection.

Antibiotics resistance has received global attention as a leading public threat [10,29]. The underlying reason was thought to be the selection pressure from antimicrobial overuse. Even though most meta-analysis including the newer double-blind, placebo-controlled trials on prophylactic antibiotics in AP since 2012 showed no beneficial effect on the outcome [30], this strategy is still widely used in clinical settings worldwide. As a result, more and more samples of pancreatic necrotic collection were found to have MDROs. Recent investigations suggested that the incidence of infections caused by MDROs was increasing in AP [31]. Critically ill patients are more likely to be exposed in long-term broad-spectrum antibiotics. Thus, theoretically CAP patients are more likely to be infected by MDROs. However, it has never been proven before. In this cohort, 52.4% of the isolated microorganisms from the peripancreatic collection were found to be MDROs. MDROs has become a major concern for physicians involved in the care of CAP patients. In post-transplant patients [32], hematologic patients [33] and other critical ill patients, MDROs infection was found to be associated with poor outcomes and high medical costs. However, its roles in AP are still lack of data and are controversial. Lee et al. [31] reported that MDROs were found in 29 (63.0%) of 46 patients with IPN. They demonstrated that MDROs infection was associated with longer ICU stay, but not associated with increased mortality. In contrast, Jain et al. [34] found that complicated IPN with MDROs infection was one of the independent predictors of mortality in patients with AP. In the present study, MDROs infection resulted in a mortality of 42.6%, significantly higher than patients with non-MDROs infection (14.6%) ($p = 0.013$). These findings have important implications for the management of patients with CAP. In patients with POF, if IPN is suspected, empirical antibiotic administration will always be the first step. A minority of patients with IPN could be successfully managed with supportive care and antibiotic therapy, without additional intervention. Broad spectrum antibiotics were basically the first choice to be given to cover both gram-positive and gram-negative bacteria. Nearly all patients with CAP in our center received antibiotics before sampling. Once patients with persistent organ failure manifested with signs of sepsis, empirical antibiotics was administered before microbiological evidence was obtained. However, over half of the isolated microorganisms in CAP patients were MDROs, which means that the antibiotics decision-making is challenging. Teamwork among surgeons, intensivist and infection control physicians in the hospital might provide a wise decision [35]. Of course, new antibiotics are eagerly called for [36]. Unlike other technical counterparts, antibiotics represent a limited healthcare resource. Thus, to be realistic, more efforts should be put on how to control the infection sources in a more minimally invasive and a more effective way [37,38].

Traditionally, OPN was regarded as the gold standard in the treatment of IPN, but this invasive approach was always associated with high rates of complications (30–98%) and death (20%–40%) as well as a higher risk of long-term exocrine and endocrine pancreatic insufficiency [15]. As an alternative to OPN, minimal invasive techniques, including percutaneous catheter drainage (PCD) [13,39], endoscopic drainage [40], minimal access retroperitoneal pancreatic necrosectomy (MARPN) drainage [17,18] and video-assisted retroperitoneal debridement (VARD) [41], are increasingly being performed. Particularly, considerable interests have been generated on the step-up approach, which consists of drainage, either percutaneous or transluminal, followed by surgical or endoscopic transluminal debridement only if needed [15,16]. Step-up approach, as compared with OPN, was associated with less new-onset MOF, lower rate of incisional hernia and new-onset diabetes. However, the death rate did not differ significantly between the two groups [15]. In a large international collaborative study involving 1980 patients with necrotizing pancreatitis, minimally invasive surgical necrosectomy or endoscopic necrosectomy significantly reduced the mortality among high-risk and very high-risk patients compared with OPN [42]. These findings suggested that treatment guidelines should discourage the open approach as initial treatment in high-risk or very high-risk patients with IPN. Using propensity score matching with risk stratification, four categories of predicted risk of death were grouped: low, intermediate, high and very high risk. However, these four categories are not fully in line with DBC classification. Therefore, these results could not be applied to CAP patients indiscriminately. The present study showed that the minimally invasive step-up approach, as compared with step-down approach, reduced the rate of death. With the step-up approach, about 27% of CAP patients were treated successfully

with PCD alone and did not require further necrosectomy, which is consistent with a previous small randomized controlled trial and a systematic review, reporting that catheter drainage as a first step obviated the need for necrosectomy in 25–50% of patients [13]. Additionally, it is worth mentioning that more deaths occurred among CAP patients whoever underwent OPN during admission compared with those who never underwent OPN (50.0% *vs.* 20.3%, $p < 0.05$). Therefore, we might conclude that OPN should be avoided in the treatment options for CAP patients as far as possible. However, in this cohort, 37% of patients underwent OPN, either as the first choice (18.6%) or as the last resort (14.7%). In the era of minimally invasive techniques, OPN still plays an important role in the management of IPN. OPN might be the only and life-saving alternative when there was no route for PCD or transluminal drainage, when persistent sepsis still could not be controlled through minimally invasive techniques or when severe complications (such as massive bleeding or intestinal leakage) occurred. In addition, we realized that one of the main drawbacks of the step-up approach was prolonged treatment duration and potential requirement for multiple operations. To expedite the recovery of the patients and shorten the in-hospital stay, we adopted OPN as the first choice of treatment for a well-defined collection localized in the lesser sac, even when the route for percutaneous or endoscopic drainage was available.

This study has several limitations. One of the limitations is that our cohort was conducted at a tertiary care center. Most of the enrolled patients were referred from other institutions during the varying course of AP. Details before referral could not be ascertained, resulting in selection bias and potential confounding effects. Another limitation is that in our institution, PCD and MARPN are the main options of minimally invasive techniques, whereas endoscopic drainage and debridement are seldomly practiced. In a recent multicenter randomized trial [43], endoscopic step-up approach was superior to the surgical step-up approach in reducing the rate of pancreatic fistula and length of hospital stay. A combined approach including both the endoscopic and surgical step-up approach might be required in some CAP patients. The results of the current study, which derive from a single-center experience could not be generalized to other hospitals. Therefore, a multicenter, prospective study would provide more patients for review and reduce potential confounding of results.

This study has demonstrated for the first time that MOF, long duration ($\geq$ 5 day) of organ failure, MDROs infection, OPN and step-down surgical treatment are associated with higher mortality in patients with CAP. In addition, step-up minimal invasive techniques such as PCD and MARPN are confirmed to provide better outcomes and therefore should be favored over traditional pancreatic necrosectomy in cases of CAP.

Conflict of interest

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