Early prediction of infected pancreatic necrosis secondary to necrotizing pancreatitis

Hong-Ze Chen, MM, Liang Ji, MD, Le Li, MD, Gang Wang, MD, Xue-Wei Bai, MD, Chun-Dong Cheng, MM, Bei Sun, MD, PhD

Abstract

To assess the association between the clinical parameters within 48 hours of admission and the occurrence of infected pancreatic necrosis (IPN) during the late phase of necrotizing pancreatitis (NP).

All patients were divided into 2 groups, the IPN and non-IPN groups. The clinical data were retrospectively analyzed. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship between clinical parameters and IPN secondary to NP. The performance of each independent variable was plotted by the receiver-operating characteristic (ROC) curve. Consequently, the cut-off level of each independent variable with its sensitivity and specificity was calculated.

A total of 215 patients were enrolled in our study. Among them, 87 (40.5%) patients developed IPNs after a median of 13.5 (9.5–23.0) days from admission. Multivariate analysis indicated that the level of hematocrit (HCT) from 40% to 50% (OR = 2.407), HCT over 50% (P < .009, OR = 6.794), blood urea nitrogen (BUN) (P = .040, OR = 1.894), C-reactive protein (CRP) (P = .043, OR = 1.837), and procalcitonin (PCT) (P = .002, OR = 2.559) were independent risk factors of IPN secondary to NP. The ROC curves revealed that the area under the ROC (AUC) of the maximum level of HCT, BUN, CRP, and PCT within 48 hours of admission was 0.687, 0.620, 0.630, and 0.674, respectively. Furthermore, the combination of these 4 individual parameters contributes to a more preferable AUC of 0.789 with a sensitivity of 67.8% and specificity of 77.3%.

The maximum levels of PCT, CRP, HCT, and BUN within 48 hours of admission are independent factors of IPN and their combination might accurately predict the occurrence of IPN secondary to NP.

Abbreviations: APACHE = acute physiology and chronic health evaluation, AUC = area under the ROC, BMI = body mass index, BUN = blood urea nitrogen, Cr = creatinine, CRP = C-reactive protein, CT = computed tomography, CTSI = computed tomography severity index, HCT = hematocrit, ICU = intensive care unit, IPN = infected pancreatic necrosis, MSAP = moderate severe acute pancreatitis, OR = odds ratio, PCD = percutaneous catheter drainage, PCT = procalcitonin, PLT = platelet, ROC = receiver-operating characteristic curve, SAP = severe acute pancreatitis, SOFA = sequential organ failure assessment, WBC = white blood cell.

Keywords: combined diagnosis, hematocrit, infected pancreatic necrosis, necrotizing pancreatitis, procalcitonin

1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder in pancreas. It leads the most common gastrointestinal problem of hospital admissions with increasing incidence in the United State and other countries.[1] Although it presents a mild and limited course in most of the cases, the manifestation and the etiology is multifactorial and complex. Approximately 15% to 20% of patients develop necrotizing pancreatitis (NP), which is a severe disease accompanied by eventful outcomes during the natural course of AP.[2] NP most commonly manifests as necrosis involving the pancreas and peripancreatic tissues, which can remain sterile or become infected. The development of secondary infection in pancreatic necrosis is associated with an increased morbidity and mortality.[3,4]

The 2012 revised Atlanta Classification represents a global consensus that infected pancreatic necrosis (IPN) serves as a key determinant of the severity in the late phase of AP.[5] As IPN is the major determinants of mortality in AP, determining the best available predictors of this determinant of severity is urgent. An accurate indicator of IPN allows early triage of those patients who require transfer to a referral center, treatment in an intensive care unit (ICU), and/or specific interventions. The Ranson score was the first prognostic clinical score that represents a major advance in evaluating the severity of AP. Other scoring systems, including the acute physiology and chronic health evaluation-II (APACHE-II) score, computed tomography severity index (CTSI) have been explored for predicting the severity of AP. However, none of them could balance the accuracy with simplicity in clinical practice. The major drawback of these systems is the
complexity and cumbersome to calculate. Meanwhile, several scoring systems require a relatively extended period (more than 48 hours) and this may miss a potentially therapeutic window. Besides, these systems could not predict the sterile or infected pancreatic necrosis specially.\[^6\]

Several serum laboratory indicators are served as predictors for the disease severity, including C-reactive protein (CRP), procalcitonin (PCT), and others. Although CRP increases slowly and peaks up later than 72 hours after the onset of symptoms, the higher accuracy makes it the most valuable among them.\[^7\] PCT is also an effective predictor for the severity of AP and the risk of developing IPN. Many studies suggest the value of PCT as a predictor for the diagnosis of severity of AP and IPN if following repeated measurements over a 2-week period.\[^8\]

Reproducible developing IPN. Many studies suggest the value of PCT as a predictor for the severity of AP and the risk of developing IPN. Many studies suggest the value of PCT as a predictor for the diagnosis of severity of AP and IPN if following repeated measurements over a 2-week period.\[^8\] Reproducible and routine laboratory parameters including blood urea nitrogen (BUN), hematocrit (HCT), and creatinine (Cr) have been explored as the great potential and having standardized reference ranges for evaluating the severity. Several studies have shown that dynamic increase in these simple and inexpensive biochemical parameters would be of significant association with severe disease.\[^9,10\]

Patients with NP have a higher risk for developing IPN compared with AP. Thus, the best prediction strategy is to find valuable parameters in patients with confirmed pancreatic necrosis rather than in AP patients.\[^11\] Few studies provide simple and practical predictions for the development of IPN.\[^6,12\]

The present study aimed to explore the early clinical parameters that were independently associated with IPN secondary to NP.

### 2. Materials and methods

#### 2.1. Patient identification and definition

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Harbin Medical University. Consecutive adult patients (≥18 years) with a first episode of AP who were admitted to the Department of Pancreatic and Biliary Surgery, First Affiliated Hospital of Harbin Medical University from January 2012 to August 2016 were enrolled. Transferred patients were excluded from this study. The detailed exclusion criteria for patients are shown in a flow chart (Fig. 1). All data were collected from the database, which was established in 2010 and modified according to the revised Atlanta classification, if necessary. The diagnosis of AP followed at least 2 of the following 3 criteria: abdominal pain consistent with AP, serum lipase level (or amylase level) at least 3 times greater than the upper limit of normality, and abdominal imaging findings in accordance with AP. Pancreatic necrosis was diagnosed by lack of pancreatic gland enhancement in patients with available contrast-enhanced computed tomography (CT) of the abdomen. All enrolled patients were followed up for 3 months after discharge. The presence of IPN was suspected by the patients’ clinical courses, including continuous fever and general deterioration, and it was confirmed by the CT evidence of free air within the necrotic tissue or peripancreatic collections. Microbiological confirmations were established with positive cultures of samples obtained by fine needle aspirations under CT/ultrasound guidance and/or samples obtained during invasive therapeutic procedures. We defined IPN as any infection of the necrotic pancreatic parenchyma or peripancreatic collections that developed prior to any invasive interventions. Respiratory, cardiovascular, and renal systems were assessed to define the organ failure. Organ failure was defined as a score of 2 or more for 1 of these 3 organ systems using the modified Marshall scoring system.\[^5\]

#### 2.2. Clinical management protocols

All patients received individualized conservative therapy immediately after admission, including intensive resuscitation, fluid and electrolyte monitoring, nutritional support (nasojejunal feeding or total parenteral nutrition), and supportive care.\[^13\]

Antibiotics were not administered prophylactically unless indicated by infections in other systems (e.g., biliary tract, urinary, and tract).\[^14,15\] Contrast-enhanced CT was performed on the third day after admission, the modified CTSI and percentage of pancreatic necrosis was calculated. When the temperature was over 38.0°C, a blood culture was drawn. A sequential culture result is important for patients with fever and clinical deterioration. We tried to perform percutaneous catheter drainage (PCD) with a pigtail catheter if patients had persistent fever and/or progressive clinical deterioration in the presence of fluid collection on CT scanning. Retroperitoneal pancreatic necrosectomy and open pancreatic necrosectomy ensued for patients if the infection was not controlled due to inadequate drainage.\[^16–18\] Cultures were collected during all the procedures to confirm the diagnosis of IPN and to guide antibiotic therapies.

#### 2.3. Data collection

The baseline variables were recorded within 48 hours of admission, including demographic data, such as the age, gender, etiology, and body mass index (BMI), and the maximum value of the following clinical data within 48 hours: white blood cell (WBC) count, HCT, platelet (PLT) count, BUN, Cr, D-dimer, CRP, PCT, and heart rate. APACHE-II and Imrie scores were evaluated on the second day after admission. Additionally, the modified Marshall scoring system, sequential organ failure assessment (SOFA) score, and modified CTSI at the end of third day were also documented.

#### 2.4. Statistical analyses

The data were analyzed using SPSS version 22.0 (IBM Corp, Armonk, NY). Quantitative variables are presented as the mean ± standard deviation for normal distributions or as the median (inter quartile range, IQR) in case of non-normal distributions.
Categorical variables are presented as absolute numbers and proportions. The variables found to be statistically significant in the univariate logistic regression analysis were introduced into a multivariate logistic analytic model to identify the independent risk factors with odds ratios (ORs) and 95% confidence intervals. Furthermore, utilizing receiver operating characteristic (ROC) curves, the areas under the curves (AUCs) and cut-off values with the associated sensitivities and specificities of the qualified independent risk factors were calculated. A P value less than .05 was considered to indicate statistical significance (http://links.lww.com/MD/B808).

3. Result
A total of 215 patients with moderate severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) were enrolled in our study. The average age was 42.2 ± 11.6 years. Among all patients, there were 141 (65.6%) males, 79 (36.7%) patients had a biliary etiology, 59 (27.4%) patients had hyperlipidemia, 44 (20.5%) patients had an alcoholic etiology, and 33 (15.4%) patients had other etiology, such as post-ERCP, pancreatic cancer, anatomical abnormalities, and idiopathic. Eighty-seven (40.5%) patients developed into IPN with a median 13.5 (9.5–23.0) days after admission. The overall in-hospital mortality was 8.4% (18/215). The demographic characteristics of both IPN and non-IPN groups are shown in Table 1.

Among the IPN patients, mixed infections (53, 61.3%) were dominant, which was followed by infections with gram-positive bacteria alone (28, 32.2%) and gram-negative bacteria alone (8, 9.2%). In addition, concomitant fungal infection was found in 17 (19.5%) patients. Among the infectious microbes, *Escherichia coli* (26, 29.9%) and *Staphylococcus* (21, 24.1%) were the most commonly isolated. The results of univariate logistic regression analysis showed that the maximum levels of WBC (P = .005), D-dimer (P < .001), HCT (P < .001), BUN (P = .003), CRP (P = .001), and PCT (P < .001) within 48 hours of admission were statistically significant between the IPN and non-IPN groups (Table 2). Furthermore, multivariate logistic regression analysis was performed, and the results indicated that the maximum levels of HCT within 48 hours after admission between 40% and 50% (P = .012, OR = 2.407, 95% CI = 1.214–4.772) as well as more than 50% (P < .009, OR = 6.794, 95% CI = 1.618–28.520) were both the independent risk factors of IPN. Furthermore, the maximum levels of BUN (P = .040, OR = 1.894, 95% CI = 1.03–3.482), CRP (P = .043, OR = 1.837, 95% CI = 1.018–3.314), and PCT (P = .002, OR = 2.559, 95% CI = 1.409–4.649) were also the independent risk factors of IPN (Table 3). We then plotted ROC curves to explore the performance of these predictors and the results indicated that the AUC of the maximum level of HCT within 48 hours of admission was 0.687. The cut-off value of the HCT was 42.86% with sensitivity of 56.3% and specificity of 73.4%. The AUC of the maximum BUN level within 48 hours of admission was 0.620 and the cut-off level was 8.42 mmol/L with a sensitivity of 69.0% and specificity of 54.7%. The AUC of the maximum level of CRP within 48 hours of admission was 0.630, and the cut-off value of CRP was 257.50 mg/L with a sensitivity of 44.8% and specificity of 89.1%. The AUC of the maximum level of PCT within 48 hours of admission was 0.674 and the cut-off value of PCT was 1.39 mg/mL with a sensitivity of 60.9% and specificity of 75.0%. Furthermore, the AUC of combined diagnosis, which consisted of the aforementioned parameters, was 0.789 with a sensitivity of 67.8% and specificity of 77.3%. All the results are shown in Table 4 and Fig. 2.

4. Discussion
Although IPN typically occurs in the late phase of AP, it accounts for up to 50% to 80% of mortalities.[11,20] Identifying the subgroups of patients who are prone to IPN facilitates patients’ timely transfer to disease-specific diagnosis, allowing for improvements in individualized treatment.[21,22]

An early and late peak of mortality followed in the dynamic disease process of AP. The late phase is characterized by persistence of systemic and local signs of inflammation which merely occurs in patients with MASP or SAP. Infection is the major cause of death in the late phase of disease.[23] Secondary infection of pancreatic or periapical necrotic tissue, accompanied with gut barrier dysfunction and a series of bacterial translocation are correlated with the development of sepsis.[24] In addition, abdominal infection and sepsis will accordingly aggravate the state of IPN and lead to a higher mortality of 80% to 85% in the late phase.[25] In our study, the mortality of patients with IPN is 13.8% (12/87), which is significantly higher than the mortality of patients with sterile necrosis (4.7%, 6/128). Tenner et al.[26] reported that patients with IPN suffered an essential increase in mortality ranging from 14% to 69% due to sepsis and multiple organ failure, compared with patients with sterile necrosis. The improvement of intensive care and supportive treatment of organ function, as well as increased emphasis on early fluid resuscitation result in a lower mortality in the early phase of disease. However, the overall mortality of SAP is still higher. The main reason is that IPN and sepsis contribute to the high mortality and morbidity in the late phase of course.[27]

Therefore, accurately predicting the occurrence of IPN in the early course plays a critical role in improving patients’ outcomes. The HCT is routinely measured at a low cost in every AP case starting at admission. An elevated admission HCT ≥ 44% or failure to decrease the HCT within the first 24 hours of admission is a significant risk factor for developing pancreatic necrosis and organ failure according to a prospective study.[28] However, our data suggested that the increased maximum level of HCT in
Organ failure\(^*\) (n, %)
- Yes 66 (75.86) 93 (72.66) .599
- No 21 (24.14) 35 (27.34) –

Evaluated on the third day after admission.

\(^{\ast}\)The maximum level in the first 48 hours after admission.

\(^{\dagger}\)Evaluated at the end of the second day from admission.

\(^{\ddagger}\)Evaluated on the third day after admission.

### Table 3

| Variables                  | IPN (n=87) | Non-IPN (n=128) | P value |
|----------------------------|------------|-----------------|---------|
| Age, y                     |            |                 |         |
| 18–25                      | 5 (6.75)   | 8 (6.25)        | –       |
| 25–34                      | 14 (16.09) | 32 (25.00)      | –       |
| 35–44                      | 26 (29.89) | 38 (29.69)      | .454    |
| 45–54                      | 26 (29.89) | 35 (27.34)      | –       |
| 55+                        | 16 (18.39) | 15 (11.72)      | –       |
| Gender n, %                |            |                 |         |
| Male                       | 60 (68.97) | 81 (63.28)      | .389    |
| Female                     | 27 (31.03) | 47 (36.72)      | –       |
| Etiology, n, %             |            |                 |         |
| Alcohol                    | 11 (12.64) | 33 (25.78)      | –       |
| Gallstone                  | 33 (37.93) | 46 (35.94)      | .069    |
| Hyperlipidemia             | 30 (34.48) | 29 (22.66)      | –       |
| Others                     | 13 (14.94) | 20 (15.63)      | –       |
| BMI, n, %                  |            |                 |         |
| BMI<18.5                   | 1 (1.15)   | 3 (2.34)        | –       |
| 18.5<BMIC<24               | 33 (37.93) | 53 (41.41)      | .769    |
| BMI≥28                     | 21 (24.14) | 33 (25.78)      | –       |
| Percentage of pancreatic necrosis\(^*\) (n, %) | | | |
| <30%                       | 50 (57.47) | 73 (57.03)      | .990    |
| 30%–50%                    | 30 (34.48) | 44 (34.38)      | –       |
| >50%                       | 7 (8.05)   | 11 (8.50)       | –       |

### Table 4

| Variables                  | IPN 95% CI | Non-IPN 95% CI |
|----------------------------|------------|---------------|
| HCT\(^*\)                  | 0.512–2.407 | 1.214–4.772   |
| ≥50                        | 0.009–6.794 | 1.618–28.520  |
| BUN\(^*\)                  | 0.040–1.894 | 1.030–3.482   |
| CRP\(^*\)                  | 0.043–1.837 | 1.018–3.314   |
| PCT\(^*\)                  | 0.002–2.559 | 1.409–4.649   |

IPN: Yes = 1, and No = 0.

NP = necrotizing pancreatitis, variable assignment, HCT = hematocrit, BUN = blood urea nitrogen, CRP = C-reactive protein, PCT = procalcitonin.

\(^{\ast}\)The maximum level in the first 48 hours after admission.

\(^{\dagger}\)Evaluated on the third day after admission.

\(^{\ddagger}\)Evaluated on the second day after admission.

\(^{\ddagger\ddagger}\)Evaluated on the third day after admission.
48 hours of admission from 40% to 50% to over 50% increases the odds ratio of IPN from 2.407 to 6.794. These findings indicated that the maximum level of the HCT within the first 48 hours of admission could be reliably used to identify the patients who might eventually develop IPN. Previous studies showed hemoconcentration can be used to predict necrosis and mortality rates in AP, which supported our hypothesis that an increase in the HCT could predict the development of IPN. Hemoconcentration and disrupted microcirculation are commonly detected during the course of AP and they are associated with pancreatic tissue perfusion and pancreatic necrosis, which are susceptible to secondary infections. The sensitivity (56%) of the HCT level was relatively lower, while we achieved a relatively higher specificity of 73.4%. Along with the HCT, the BUN is also a convenient, inexpensive, and baseline clinical parameter for predicting IPN secondary to NP. Koutroumpakis et al reported that the elevation of BUN at 48 hours may be the optimal predictor in pancreatic necrosis. Meanwhile, changes in its value at 48 hours from admission may reflect responses to the initial treatment and tailor further management decisions. Additionally, elevation of BUN by 5 mg/dL within 48 hours of admission was associated with developing primary IPN. Our data indicated that the maximum BUN level in the first 48 hours after admission was correlated with the presence or absence of IPN. The maximum BUN level was an independent risk factor of IPN secondary to NP. PCT is the inactive 116 amino acid propeptide of the biologically active hormone calcitonin, which was first described to have significantly increased concentrations in patients with bacterial and fungal infections. The PCT level is considered a valuable predictive factor for severity of AP and the risk of developing IPN. In a previous study, a cut-off PCT level >0.5 ng/mL seems to be an accurate predictor of severity. However, our data suggested that a maximum level of PCT within 48 hours after admission was an independent risk factor of IPN. The heterogeneity among patients likely contributes to the discrepancy in cut-off levels of PCT among these studies. As one of the biggest tertiary pancreatic centers in the northeast of China, our department recruits a larger number of patients in critical condition than primary care centers, which may contribute to a relatively higher average PCT. Although the greatest PCT value from serial daily measurements over a long period outperformed the identification of IPN compared with intermittent measurement, a modest timeframe (the first 48 hours after admission) was proposed in our study for the diagnostic timeliness and financial cost. CRP has recently been shown to be a predictor of the development of infected necrosis in AP. Our data revealed that the maximum CRP levels within the first 48 hours were associated with the presence or absence of IPN (P = 0.012), and these levels are significantly associated with the development of IPN (P = 0.043, OR = 1.837, 95% CI 1.018–3.314). Although the specificity (89.1%) of the maximum level of CRP within the 48 hours of admission was high, the sensitivity (44.8%) was not preferable. This appears to be a common problem with most of the potential predictors. In this context, a high specificity seems to be more meaningful, which indicates that in the absence of an increased level of CRP within 48 hours of admission, the likelihood to develop IPN is low.

Furthermore, these 4 independent risk factors were incorporated into a combined diagnostic manner. Our results revealed that the AUC of combined diagnosis increased to 0.789 with the highest sensitivity (67.8%) compared with all the other single parameters, and the specificity was relatively high (77.3%), which performed better than the PCT (75%), HCT (73.4%), and BUN (54.7%), respectively. The highest Youden index (0.451) of combined diagnosis supported that a notable effect of predicting the development of IPN benefits from the combination of the maximum level of the HCT, BUN, PCT, and CRP within 48 hours of admission. To the best of our knowledge, this study is among the very few that had used all these 4 common parameters to indicate the disease dynamics for predicting the subsequent development of IPN within 48 hours of admission. The predictive value of each single parameter was relatively confined. We attribute this to the timing and method of parameters measurement. First, the observation was set to the first 48 hours of admission because we preferred to timely and effectively react to a relatively higher average PCT. Although the greatest PCT value from serial daily measurements over a long period better identifies IPN compared with intermittent measurements. Second, the highest PCT value from serial daily measurements over a long time period better identifies IPN than intermittent measurements. However, measurements of full serial serum parameters can pose financial and logistical challenges, especially for PCT. Therefore, we proposed the use of the maximum level in the first 48 hours after admission to predict the development of IPN. The combined diagnosis of the maximum level of the PCT, CRP, HCT, and BUN in the first 48 hours after admission performed satisfactorily with a high sensitivity and specificity, which may offset the diagnostic deficiency. Our previous study suggested that the maximum D-dimer level was an independent risk factor of IPN secondary to SAP. However, we found that D-dimer was not independent risk factor in this study. We attribute this discrepancy to the
increased number of patients and the change of the predictive timeliness.

There are some limitations of this study. First, the limited numbers of patient involved and retrospective nature of the study result in a lower sensitivity and specificity of each individual parameter. Second, the definition of IPN was based on the microbiologically proven infection. We may miss a small proportion of cases that responded to the conservative management. Finally, our database was established in 2010 and modified by the revised Atlanta classification. Other vital parameters relevant to the development of IPN may be missed.

5. Conclusion

In this study, we have shown that the maximum level of the HCT, BUN, PCT, and CRP within 48 hours of admission is an independent factor for IPN. Furthermore, the combined diagnosis with these 4 parameters might accurately predict the occurrence of IPN secondary to NP within the time frame of 48 hours since admission.

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