Original Article

J Chin Med Assoc
2004;67:442-446

Serum Interleukin-6, Tumor Necrosis Factor α and C-reactive Protein in Early Prediction of Severity of Acute Pancreatitis

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Key Words
acute pancreatitis;
C-reactive protein;
interleukin-6;
tumor necrosis factor α

Background. It has been discussed that cytokine determination is a simple, cheap and accurate way to predict the severity of the acute pancreatitis. In this study, the usefulness of interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and C-reactive protein (CRP) to assess the prognosis of acute pancreatitis was evaluated.

Methods. Blood tests for the IL-6, TNF-α and CRP in patients with acute pancreatitis on the 1st, 2nd, 3rd, and 7th hospital days were performed. Patients were divided into severe and mild disease groups according to the Atlanta criteria, and the sensitivity, specificity and diagnostic accuracy of the serum concentrations of these 3 markers were compared.

Results. Thirty-three patients with acute pancreatitis admitted to our hospital between January 2002 to March 2003 were studied, 19 mild-group patients and 14 severe-group. Serum concentrations of IL-6 and CRP were highly significantly different ($p < 0.005$) between the severe group and the mild group on the day of admission and on the 2nd, 3rd and 7th days. TNF-α only had a significant difference ($p < 0.05$) in these 2 groups on the first 2 days. IL-6 and TNF-α had a peak value on the 1st day of admission, while CRP reached peak value on the 2nd hospital day. On day 1, IL-6 had a highest sensitivity (100%) specificity (89.7%) and accuracy (91%) among these 3 markers. On day 2, CRP had a relatively higher value in sensitivity (83.3%) and accuracy (80.0%).

Conclusions. The serum concentration of IL-6 on the first day and/or the serum concentration of CRP on the 2nd day of admission are useful for early prediction of the severity of acute pancreatitis.

Acute pancreatitis is a protean disease of wide clinical variation ranging from mild abdominal discomfort to a severe hemorrhagic necrotizing attack or even mortality. Early assessment of the severity and prediction the prognosis of acute pancreatitis is an important issue for managing the patients.

There are a number of well-known measurements for evaluating the prognosis of acute pancreatitis, such as the Ranson and Glasgow and Acute Physiology and Chronic Health Evaluation (APACHE II) evaluating scoring systems. All of these require measurement of many clinically-based parameters and are very complicated and time-consuming. Optimally, a single, simple and reliable marker would be available to assess the severity of acute pancreatitis. The usefulness of cytokine detection for early assessment of the severity of acute pancreatitis has been reported in the literature,[1-8] and its sensitivity, specificity and diagnostic accuracy have been discussed also.[8,9]

The aim of this study was to evaluate the capability of serum concentrations of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) for early assessment of the severity of acute pancreatitis and compare their sensitivity, specificity and diagnostic accuracy.

METHODS

Thirty-three patients with acute pancreatitis admitted to the Far Eastern Memorial Hospital from Jan. 2002 to

Received: July 3, 2003.
Accepted: April 28, 2004.

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March 2003 were enrolled. All the patients were admitted via Emergency unit. Diagnosis of acute pancreatitis was based on the chief complaints of typically persistent upper abdominal pain for a few hours before consulting our emergency unit associated with 3-fold increase of serum amylase and lipase. The diagnosis was confirmed by abdominal ultrasonography or abdominal computed tomography (CT) scan examination. Those patients with high amylase or lipase levels in case of trauma, surgery, post-endoscopic retrograde cholangiopancreatography (ERCP), pancreatic tumor, diabetic ketoacidosis (DKA), and uremia were excluded.

These 33 patients were divided into 2 groups according to the Atlanta criteria[10] – the definition of severe acute pancreatitis is associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst. Severe pancreatitis is further characterized by 3 or more Ranson criteria or 8 or more APACHE (Acute Physiology And Chronic Health Evaluation) points. Organ failure is defined as shock, pulmonary insufficiency, renal failure or gastrointestinal bleeding more than 500 mL/24 hours. Systemic complications, such as disseminated intravascular coagulation or severe metabolic disturbance may also be seen. Mild acute pancreatitis is associated with minimal organ dysfunction and an uneventful recovery, and it lacks the described features of severe acute pancreatitis and lacks the local complications. Patients with mild acute pancreatitis respond to appropriate fluid administration with prompt normalization of physical signs and laboratory values. Group A was a mild disease group and Group B was a severe disease group.

Serum samples for IL-6, TNF-α and CRP were collected on admission (day 1) and on the mornings of days 2, 3 and 7 after admission. All the blood serum samples were frozen immediately after collection and stored at -70 °C until analysis. Serum levels of IL-6 and TNF-α were determined with chemiluminescence immunoassay (LIA) using immulite kit (Diagnostic Products Corporation, Los Angles, CA, USA) (The cost of 1 kit -50 tests of IL-6, also for TNF-α is about NT 18000). The minimum detectable values of IL-6 and TNF-α were 5 pg/mL and 1 pg/mL, respectively. The CRP was determined with nepherometric technique (Beckman Coulter, Image Immunochemistry System, USA) with normal range 0~0.8 mg/dL.

Statistical analysis was performed with Mann-Whitney rank sum test. Data were expressed as mean ± SD. The correlations between serum markers were analysed by Pearson and Spearman's correlation. A p value < 0.05 was defined as statistically significant. Receiver operating characteristic (ROC) curves and the respective area under the curves (Table 1) were calculated to provide information about the capacity of the 3 markers to distinguish severe acute pancreatitis from mild disease. The best cutoff values were chosen as the values that maximized the likelihood ratio obtained.[11] Sensitivity was defined as the proportion of patients with severe attacks correctly predicted. Specificity was the proportion of mild disease correctly predicted, and accuracy was defined as the proportion of patients correctly classified.[12]

RESULTS

A total number of 33 patients (26 male, 7 female) with a mean age of 48.0 (range 24 to 90 yrs) were studied. According to the Atlanta criteria,[10] 19 patients were classified as mild pancreatitis (group A) and 14 patients were the severe cases (group B). The etiologies were alcoholic, biliary and idiopathic. The clinical characteristics of these patients are shown in Table 2.

Table 1. Value of areas under ROC curves of serum interleukin-6, tumor necrosis factor-α and C-reactive protein at each evaluation day

	Day 1	Day 2	Day 3	Day 7
IL-6	0.9090	0.9460	0.8970	0.7359
TNF-α	0.7688	0.7237	0.7037	0.6892
CRP	0.8308	0.8459	0.8727	0.8654

ROC = receiver operating characteristic; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α; CRP = C-reactive protein.

Table 2. Characteristics of patients with acute pancreatitis

	Gr. A (n = 19)	Gr. B (n = 14)	Total (n = 33)
Male:female	15:4	11:3	26:7
Age (yr.)	46.9 (27-82)	49.5 (24-90)	48.0 (24-90)
Etiology			
Alcoholic	10	9	19
Biliary	3	4	7
Idiopathic	6	1	7

Gr. A = mild group; Gr. B = severe group.

On the first day of admission and on the 2nd, 3rd and 7th days, the IL-6 and CRP were highly significantly different ($p < 0.005$) between the severe group and the mild group. TNF-α was also higher ($p < 0.05$) in the severe group than in mild cases on days 1 and 2 (Figs. 1-3).

Among the 14 patients with severe acute pancreatitis, there were 2 mortality cases. The serum concentration of IL-6, TNF-α and CRP of the 2 mortality cases were similar to those of others and showed no significant difference.

Values of 50 pg/mL for IL-6, 2 pg/mL for TNF-α, 16 mg/dL for CRP were the best cutoff values to differentiate severe from mild acute pancreatitis. Using these limits, the sensitivity, specificity and diagnostic accuracy of IL-6, TNF-α, and CRP in predicting the severity of pancreatitis on days 1, 2, 3 and 7 are shown in Table 3. On day 1, IL-6 had a higher sensitivity (100%), specificity (89.7%) and accuracy (91%) compared with TNF-α and CRP. Whereas on day 2 the CRP also had good values in sensitivity (83.3%) and accuracy (80.0%). The TNF-α had lowest sensitivity and diagnostic accuracy among these 3 markers on the first 3 days.

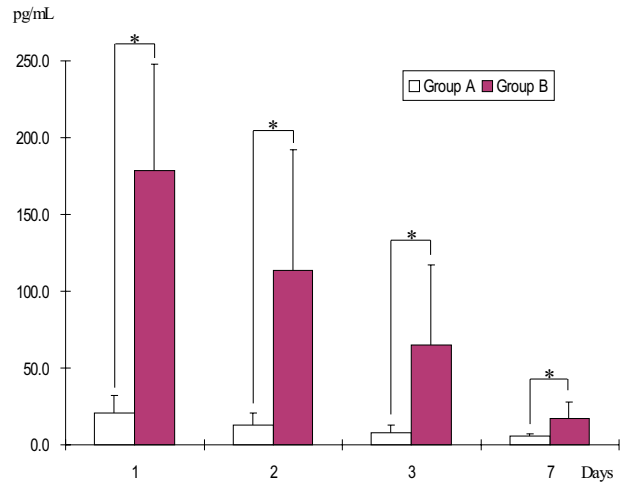

Fig. 1. Serum concentrations of IL-6 in patients with mild (□) and severe (■) pancreatitis on hospital days 1, 2, 3 and 7. Data are expressed as mean ± SD. * $p < 0.001$.

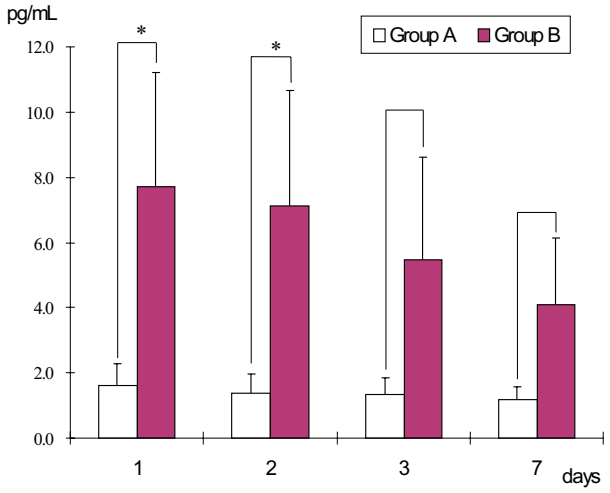

Fig. 2. Serum concentrations of TNF-α in patients with mild (□) and severe (■) pancreatitis on hospital days 1, 2, 3 and 7. Data are expressed as mean ± SD. * $p < 0.05$.

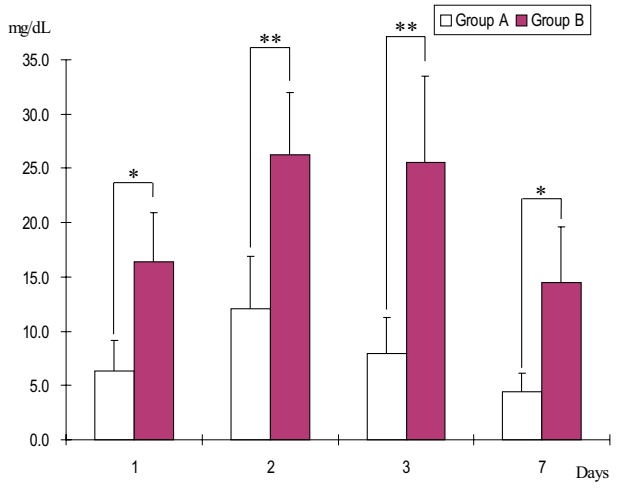

Fig. 3. Serum concentrations of CRP in patients with mild (□) and severe (■) pancreatitis on hospital days 1, 2, 3 and 7. Data are expressed as mean ± SD. * $p < 0.005$; ** $p < 0.001$.

Table 3. Sensitivity, specificity, and accuracy of interleukin-6, tumor necrosis factor α, C-reactive protein in predicting severity of acute pancreatitis

	Day 1	Day 2	Day 3	Day 7
Sensitivity (%)				
IL-6	100	92.0	80.0	41.3
TNF-α	62.3	57.1	50.0	58.3
CRP	42.9	83.3	78.6	41.7
Specificity (%)				
IL-6	89.7	86.7	96.0	94.0
TNF-α	78.9	89.5	88.9	92.0
CRP	89.5	73.7	77.7	79.0
Accuracy (%)				
IL-6	91.0	88.0	80.0	66.0
TNF-α	72.7	75.8	73.3	80.0
CRP	69.7	80.0	75.8	72.0

Cutoff values: IL-6 = 50 pg/mL; TNF-α = 2 pg/mL; CRP = 16 mg/dL.

Table 4. Correlation between serum TNF-α, IL-6 and CRP on days 1, 2, 3, 7

	Day 1	Day 2	Day 3	Day 7
IL-6/ TNF-α	0.847	0.652	0.741	0.571
	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p = 0.003$)
IL-6/CRP	0.506	0.568	0.546	0.765
	($p = 0.003$)	($p < 0.001$)	($p = 0.002$)	($p < 0.001$)
TNF-α/CRP	0.462	0.373	0.331	0.398
	($p = 0.007$)	($p = 0.033$)	($p = 0.074$)	($p = 0.049$)

IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α; CRP = C-reactive protein.

The correlation between these 3 markers are shown on (Table 4). There were good correlation between IL-6 and TNF-α, IL-6 and CRP from days 1~7 but not between TNF-α and CRP.

DISCUSSION

Acute pancreatisis is a protean disease with wide clinical variation. Thus, earlier prediction and assessment of the disease is an important determinant in the management of the patients.[10,13] The clinically-based data of prognostic criteria of Ranson and Glasgow require a 2-day delay after the onset of the disease and are so cumbersome to memorize, and even more cumbersome is the APHCHE II scoring system.[14] Hopefully, it has been reported that many single markers[1-6,14] are applicable to assess the severity of acute pancreatitis. The mediators of acute phase protein response-cytokines were considered as an earlier predictors.[8-10,12-14] However, there is no single method is ideal in assessing the severity of the disease. Individual preference and available institutional facilities influence the method chosen for prognostic assessment of acute pancreatitis.[13] We compared the 3 markers for their sensitivity, specificity and diagnostic accuracy in assessment of the severity of acute pancreatitis.

Our data confirmed the findings that IL-6, TNF-α and CRP are significantly higher in severe acute pancreatitis than in the mild disease, from day 1 to day 7, especially in the first and 2nd days. The results suggest that in the early stage of acute attack, the inflammatory cytokines may play an important role in the pathogenesis of acute pancreatitis.[6,15,16]

Earlier prediction and assessment of the severity of the acute pancreatitis is an important issue in the management of patients.[10,13] Our data showed in the days 1 and 2, IL-6 had the highest sensitivity and diagnostic accuracy, whereas the CRP had a relatively higher sensitivity and diagnostic accuracy on day 2. For TNF-α, our data showed that it had highly significant difference between severe and mild groups in the first 2 days. In predicting the severity of acute pancreatitis, TNF-α was not as good as IL-6 and CRP in the early stage (days 1 and 2) of the acute pancreatitis. It was only 57.1~62.3% and 72.7~75.8% in sensitivity and diagnostic accuracy, respectively.

Banks *et al.*[16] reported the TNF-α was higher in the severe pancreatitis group but no significantly different from the mild disease group. Exley *et al.* [17] showed the association between TNF-α and biliary pancreatitis was stronger. In our series, gallstone pancreatitis was the minority, only 7 in total of 33 cases.

Our data also showed the serum concentration of IL-6 was correlated both with TNF-α and CRP. Significantly higher serum level of IL-6 in the severe group and the correlations between plasma concentration of IL-6, TNF-α and CRP may suggest a causal role for IL-6 in the acute phase response.[18] IL-6 is the mediator of acute phase protein synthesis, in which CRP is an important component.[4,19] The addition of human recombinant IL-6 to hepatoma cell lines has been shown to produce maximal acute phase protein response between 20 to 36 hours.[19] Our data showed results similar to those of other workers, that the IL-6 reached the peak on the first day of disease onset and CRP reached its peak on the 2nd day.

In conclusion, determining the serum concentration of IL-6 on the first day and/or together with serum CRP concentration on the 2nd day of admission are helpful in earlier prediction and assessment of the severity of acute pancreatitis.

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