Editorial

J Chin Med Assoc
2004;67:439-441

Serum Markers in the Early Assessment of Severity of Acute Pancreatitis: Which is the Most Useful?

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Acute pancreatitis is a common and significant disorder. Most of the cases (around 75%) are caused by biliary stones or heavy alcohol drinking. It affects approximately 200,000 individuals annually in the U.S.[1] The spectrum of acute pancreatitis ranges from mild edematous disease to severe necrotizing process that is usually complicated with local or systemic complications or even mortality. The mortality of severe attacks (about 25% of acute pancreatitis) has been reported between 10% and 30%.[2] Early deaths (within the first week) due to severe acute pancreatitis are generally caused by massive inflammatory responses that result in multiple organ failure. Late deaths are primarily related to septic complications, especially infected pancreatic necrosis.

Although the exact mechanisms that trigger the inflammatory and necrotizing processes are not completely understood, it is generally accepted that activated leukocytes play an important role in the pathogenesis of acute pancreatitis.[3] The serum levels of proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin(IL)-1 beta (IL-1β), IL-6, and IL-8, have been reported to be significantly higher in severe acute pancreatitis compared with mild pancreatitis.[3-5] Proinflammatory cytokines are associated with systemic inflammatory response syndrome (SIRS) and multiple organ failure syndrome in acute pancreatitis. A compensatory anti-inflammatory response occurs in parallel with SIRS. Anti-inflammatory cytokines including IL-10, IL-1β receptor antagonist, and soluble IL-2 receptor were also significantly higher in patients with severe acute pancreatitis.[5-7] Using endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis as a model, significant increase of proinflammatory and anti-inflammatory cytokines was confirmed in the early stage of post-ERCP pancreatitis.[8]

Early prediction of the severity of acute pancreatitis is important for early institution of therapeutic interventions, such as enteral feeding, ERCP with sphincterotomy, prophylactic antibiotics, and intensive care monitoring, that have been shown to decrease the morbidity associated with severe acute pancreatitis.[1] The inability to correctly identify severe acute pancreatitis on admission using clinical information alone has led to the development of a number of more objective means of severity assessment, including the Ranson, Glasgow and Acute Physiology and Chronic Health Evaluation (APACHE II) scoring systems. The application of these scoring systems in clinical practice has been limited by a time delay of at least 48 hours in the former 2 and by being cumbersome in the latter.

A variety of single serum parameters, such as C-reactive protein (CRP), polymorphonuclear (PMN) elastase, phospholipase A_2, α_1-antitrypsin, α_2-macroglobulin, trypsinogen activation peptide, and procalcitonin, have been reported to be useful indicators of the severity of acute pancreatitis.[1,9] Among these biochemical markers, the simplest and most widely available test is CRP. Serum CRP levels above 12~15 mg/dL correlate with severe disease.[1,4,9] However, CRP measurements involve a delay of 48 hours or longer before prediction. The sensitivity of CRP on day 1 after admission is not as good as it is on day 2 (56% *vs*. 83%).[4]

The recognition of early involvement of inflammatory cytokines in acute pancreatitis as mentioned above and cytokines as the mediators of the acute phase protein response has generated significant research interest in the utility of cytokine levels to serve as early prognostic indicators. Cytokines studied have included TNF-α, IL-1, IL-6, IL-8, IL-10, IL-11, IL-12, IL-18, IL-1 receptor antagonist, and soluble TNF-α receptors. Are all of these inflammatory cytokines good enough to predict the disease severity? Which of them is the most useful? In

literature review, serum IL-6 level has the best sensitivity and specificity for early assessment of severity of acute pancreatitis among the proinflammatory and anti-inflammatory cytokines.[1] In our previous study, the IL-6 values at admission were more accurate (88%) than those of TNF-α (72%), IL-1β (82%), IL-8 (74%) and CRP (80%).[4]

In this issue of *Journal of the Chinese Medical Association*, Jiang *et al*.[10] examine the usefulness of IL-6, TNF-α, and CRP to assess the prognosis of acute pancreatitis. The sensitivity, specificity and accuracy of IL-6, TNF-α, and CRP on day 1 of admission are similar to those in our previous report.[4,10] The authors confirmed that serum IL-6 levels on the first day and CRP on the second day of admission were useful for early prediction of the severity of acute pancreatitis. The sensitivity and specificity of IL-6 were 100% and 89.7%, respectively, although the cut-off value of IL-6 in this study (50 pg/mL) was lower than in our study (400 pg/mL).[4]

The serum concentrations of the mediators of the acute phase protein response, cytokines, have been considered to be more rapid possible predictors of prognosis. IL-6 induces the production of acute phase proteins, such as CRP. Thus, elevated IL-6 levels may precede elevated CRP levels in cases of severe acute pancreatitis. Jiang *et al.*[10] confirmed that serum IL-6 levels on days 1 and 2 significantly correlated with CRP levels, with the peak of IL-6 on day 1 and the peak of CRP on day 2.

Can plasma cytokine levels predict mortality in patients with severe acute pancreatitis? Although hospital mortality was linked to 6 factors in univariate analysis (age, cirrhosis, delay between hospitalization and intensive care unit admission, severity of illness, and IL-10 and IL-6 plasma levels), cytokine plasma concentrations were unable to predict death accurately in individual patients.[7] In Gross *et al.* and our reports, the serum levels of IL-6 and IL-10 in mortality cases were markedly high on days 1 and 2 compared with those of other patients with severe pancreatitis.[3,4,6] No mortality data are available in the report of Jiang *et al.*[10]

Although no single serum test is optimal to distinguish mild and severe acute pancreatitis, current evidence concluded that serum IL-6 level at admission has the best value among cytokines for early assessment of severity of acute pancreatitis. CRP at 48 hours of hospitalization appears as useful as Ranson or Glasgow scoring system. Some useful tools for the assessment of severity of acute pancreatitis are listed in Table 1. We recommend that measurement of serum IL-6 levels should be performed on the day of admission in all patients with acute pancreatitis when a rapid and cheap IL-6 assay is available.

Table 1. Useful tools for the assessment of severity in acute pancreatitis

Widely used in clinical practice
Ranson criteria, Glasgow criteria, APACHE II
C-reactive protein
Balthazar computed tomography criteria
Promising tests in clinical practice
Interleukin-6
Polymorphonuclear elastase
Trypsinogen activation peptide

APACHE = Acute Physiology and Chronic Health Evaluation.

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