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ORIGINAL ARTICLE

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급성췌장염의 중증도 예측에 대한 혈청 Procalcitonin의 효용성 및 절단값

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Comparison of Serum Procalcitonin with Ranson, APACHE-II, Glasgow and Balthazar CT Severity Index Scores in Predicting Severity of Acute Pancreatitis

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Background/Aims: The aim of this study is to assess serum procalcitonin (PCT) for early prediction of severe acute pancreatitis compared with multiple scoring systems and biomarkers.
Methods: Forty-four patients with acute pancreatitis confirmed by radiological evidences, laboratory assessments, and clinical manifestation were prospectively enrolled. All blood samples and image studies were obtained within 24 hours of admission.
Results: Acute pancreatitis was graded as severe in 19 patients and mild in 25 patients according to the Atlanta criteria. Levels of serum PCT were significantly higher in severe acute pancreatitis (p=0.001). The accuracy of serum PCT as a predicting marker was 77.3%, which was similar to the acute physiology and chronic health examination (APACHE)-II score, worse than the Ranson score (93.2%) and better than the Balthazar CT index (65.9%). The most effective cut-off level of serum PCT was estimated at 1.77 ng/mL (AUC=0.797, 95% CI=0.658-0.935). In comparision to other simple biomarkers, serum PCT had more accurate value (77.3%) than C-reactive protein (68.2%), urea (75.0%) and lactic dehydrogenase (72.7%). Logistic regression analysis revealed that serum PCT has statistical significance in acute severe pancreatitis. Assessment of serum PCT levels and length of hospital stay by simple linear regression analysis revealed effective p-value with low R square level, which could make only possibilty for affection of serum PCT to admission duration (r2=0.127, p=0.021).
Conclusions: Serum PCT was a promising simple biomarker and had similar accuracy of APACHE-II scores as predicting severity of acute pancreatitis. **(Korean J Gastroenterol 2011;58:31-37)**

Key Words: Serum procalcitonin; Acute necrotizing pancreatitis; Multiple scoring systems

INTRODUCTION

Acute pancreatitis has an acute inflammatory process ranging from mild discomfort with localized inflammation to severe disease with multiple organ failure.[1] Multiple scoring systems, including the Ranson, Glasgow and acute physiology and chronic health examination (APACHE)-II scores, and several biochemical markers have been developed for the early prediction of severity of acute pancreatitis which facilitate early treatment in an intensive care unit.[2-4] Serum procalcitonin (PCT) is an early marker of systemic bacterial infection, sepsis, and multi-organ failure.[5] The major complica-

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tions of acute pancreatitis are infected pancreatic necrosis, sepsis, and multi-organ failure. We therefore hypothesized that increased serum levels of PCT could predict a severe acute pancreatitis and poor outcome of treatment.[6] Serum PCT has been previously analyzed with certain acute-phase proteins and mediators and APACHE-II scoring system[7-10] but not compared to CT severity index and Glasgow system. The correlation between levels of serum PCT and length of hospital stay has not been reported yet.

Thus, we designed the aim of this prospective study with two-fold. First was to assess the clinical usefulness of serum PCT as a predictive marker for severity in early course of acute pancreatitis, in comparison to established indices including C-reactive protein (CRP), Ranson score, Glasgow score, APACHE-II score, Balthazar CT severity index and, other routinely measured biochemical parameters. Second was to evaluate the correlation of serum PCT with length of hospital stay.

SUBJECTS AND METHODS

1. Subjects

This prospective study included forty-four consecutive patients with acute pancreatitis over a 10-month period. The diagnosis of acute pancreatitis was based on the clinical manifestation of acute upper abdominal pain associated with a raised serum amylase level greater than three times of normal value or elevated serum lipase levels and radiological evidences compatible with acute pancreatitis.[9,11] CT was performed in all patients. 32 patients were performed with contrast CT and 12 patients were performed with non-contrast CT owing to elevated serum creatinine levels. We classified patient as mild and severe pancreatitis by Atlanta classification[8,12] and analysed with variable data obtained within 24 hours on admission. We treated patients according to the accepted standard management of acute pancreatitis.[11,12] All patients were fasted soon after admission and administered fluids, ions, and analgesics parenterally. If necessary, systemic antibiotics were applied.[13] Patients with a suspected biliary cause of acute pancreatitis underwent endoscopic retrograde endoscopic retrograde cholangiopancreatography within the first 24 hours.

2. Methods

Blood samples for PCT, CRP and routine biochemical tests were collected on admission. The blood samples were centrifuged for 10 mins at 3,000 rotation/min at -4°C. The serum was subsequently removed and stored at -80°C until biochemical analysis. PCT concentration was measured with a chemo luminescent immunoassay (LUMItest® PCT). The reference value range established for this method was less than 0.05 ng/mL. Serum CRP levels were measured via immunoturbidimetry (Denka Seiken Co. Ltd., Japan). The reference value range established for this method was 0 to 0.5 mg/dL. Appropriate laboratory and physiological data were recorded concurrently together with weightings for age and chronic health state to permit calculation of Ranson score, Glasgow score and APACHE-II score. This study was approved by the Institutional Review Board of Dong-A University Hospital, Busan, South Korea.

3. Statistical analysis

We expressed the results as median followed by range or 95% confidence interval. Statistical analysis between the groups was calculated by Mann-Whitney U test for non-categorical data. Fisher's exact test was used to examine differences in sex ratio, etiology, and death ratio. The mean values of serum PCT were compared by Mann-Whitney U test according to the severity of acute pancreatitis. The cut-off values of serum PCT and other parameters were determined by the Receiver operating characteristic (ROC) curves. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and likelihood ratios were also calculated. Logistic regression analysis was used to establish the influence of the chosen parameters on the prognosis of acute pancreatitis. Linear regression analysis was conducted to estimate the relationship between the serum values of PCT and length of hospital stay. A p value of <0.05 was considered to be statistically significant. The SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows was used to perform all statistical analyses.

RESULTS

Of the 44 patients, 28 patients were men, and 16 patients were women. The median age of the patients was 61.5 years. According to the Atlanta criteria, 25 patients were classified as mild acute pancreatitis and 19 patients were classified as severe acute pancreatitis. There was no statistical sig-

Table 1. Characteristics of Patients with Acute Pancreatitis

	Mild pancreatitis (n=25)	Severe pancreatitis (n=19)	Total (n=44)	p-value
Men/Women	17/8	11/8	28/16	0.490
Age (yr); median (range)	55 (22-89)	66 (39-79)	61.5 (22-89)	0.061
Death	0	4	4	0.029
Duration of admission (days); median (range)	11.5 (6-35)	20 (2-40)	14.5 (2-40)	0.147
Etiology				0.465
Alcoholic	10	9	19	
Biliary	8	3	11	
Idiopathic and miscellaneous	7	7	14	
Scoring system and biochemical markers: median (range)				
APACHE II score	4 (0-8)	11 (2-19)	6 (0-19)	<0.001
Ranson score	2 (0-5)	4 (2-9)	2 (0-9)	<0.001
Glasgow score	1 (0-4)	3 (1-7)	2 (0-7)	<0.001
BCTSI	2 (0-4)	3 (1-10)	2 (0-10)	0.024
PCT (ng/mL)	0.43 (0.01-18.82)	4.28 (0.01-166.69)	1.66 (0.01-166.69)	0.001
CRP (mg/dL)	3.69 (0.03-42.91)	11.73 (0.79-44.08)	7.9 (0.03-44.08)	0.015
Total calcium (mg/dL)	8.6 (4.1-11)	8.2 (3.9-11.1)	8.6 (3.9-11.1)	0.380
LDH (IU/L)	432 (155-2047)	645 (279-3321)	550 (155-3321)	0.014
Glucose (mg/dL)	128 (89-316)	157 (89-567)	138.5 (89-567)	0.112
Urea (mg/dL)	16 (5-75)	28 (6-220)	19 (5-220)	0.011

APACHE, acute physiology and chronic health examination; BCTSI, balthazar CT severity index; PCT, procalcitonin.

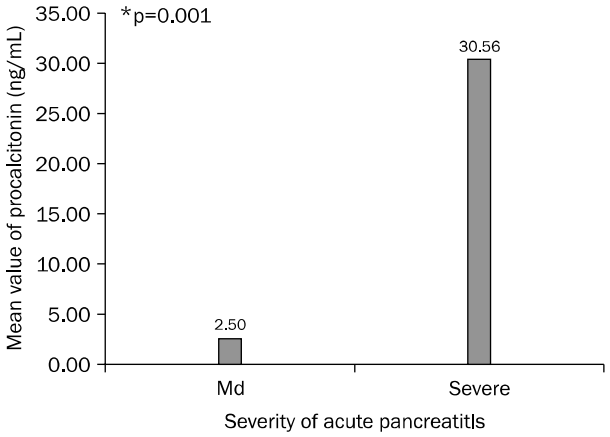

Fig. 1. Mean value of serum levels of procalcitonin in mild and severe acute pancreatitis clossified by Atlanta criteria. Levels of serum procalcitonin were significantly higher in severe acute pancreatitis. Md, mild acute pancreatitis (n=25, SD=4.614); Severe, severe acute pancreatitis (n=24, SD= 53.433). *Mann-Whitney U test, p=0.001.

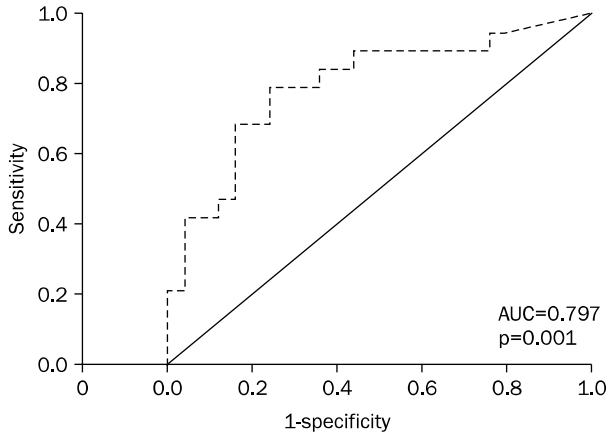

Fig. 2. Receiver operation characteristic curve of serum levels of procalcitonin in prediction of severity of acute pancreatitis. Numbers of observation=44. AUC, area under curve.

nificance of age (p=0.061) and sex (p=0.490) (Table 1). The causes of acute pancreatitis were alcoholic, biliary, and idiopathic or miscellaneous conditions and it had no significance (p=0.465).

Total 4 patients died, 3 patients had multiple organ failure, and 1 patient had extensive necrotizing pancreatitis. The APACHE-II scores, Ranson scores and Glasgow scores in severe acute pancreatitis were significantly higher than those in the mild attacks on admission ($p < 0.001$). The Balthazar CT severity index was also significantly higher in patients with severe acute pancreatitis than mild acute pancreatitis (p=0.024). Both serum CRP and lactic dehydrogenase (LDH) were significantly higher in severe acute pancreatitis, but the levels of total serum calcium and glucose were not different between mild and severe acute pancreatitis. The levels of serum PCT were in severe acute pancreatitis were significantly higher than those in mild pancreatitis ($p < 0.001$, Table 1, Fig. 1). The accuracy of serum PCT as a biochemical marker was 77.3%, which was same as APACHE-II score, worse than the Ranson score (93.2%) and better than the Balthazar CT se-

verity index (65.9%). We analysed 4 cut-off values for serum PCT levels (0.50, 1.00, 1.77, and 2.65 ng/mL), among them, level of 1.77 ng/mL (area under the curve, AUC=0.797; 95% confidence interval, CI=0.658-0.935, Fig. 2))had the best accuracy and best positive predictive value and likelihood ratio (77.3%, 71.4%, 13.797, respectively). It could be estimated that the efficacy of serum PCT was similar to APACHE-II scores (Table 2) and its' best cut-off level is 1.77 ng/mL (Table 3).

We evaluated serum PCT and other parameters according to severity of pancreatitis by logistic regression analysis and found that serum levels of PCT, CRP, LDH and urea were significantly correlated with severity of pancreatitis. The odds ratio of serum PCT was 11.875 (p=0.001) (Table 4). The serum levels of total calcium and glucose were not correlated with the severity of pancreatitis (p=0.577, p=0.132, respec-

Table 2. Analysis of Acute Pancreatitis Parameters

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Likelihood ratio
APACHE II score ≥7	78.9	76	71.4	82.6	77.3	13.795
Ranson score ≥3	89.5	96	94.4	92.3	93.2	38.35
Glasgow score ≥3	63.2	92	85.7	76.7	79.6	16.097
BCTSI ≥4	42.1	84	66.7	65.6	65.9	3.716
PCT (ng/mL) ≥1.77	78.9	76	71.4	82.6	77.3	13.795
CRP (mg/dL) ≥8.2	68.4	68	61.9	73.9	68.2	5.864
Total-calcium (mg/dL) ≥9.04	31.6	76	50	59.4	56.8	0.311
LDH (IU/L) ≥453	94.7	56	62	93.3	72.7	14.332
Glucose (mg/dL) ≥140	63.2	60	54.6	68.2	61.4	2.338
Urea (mg/dL) ≥20	73.7	76	70	79.2	75	9.358

APACHE, acute physiology and chronic health examination; BCTSI, balthazar CT severity index; PCT, procalcitonin; PPV, positive predictive value; NPV, negative predictive value.

Table 3. Serum Procalcitonin in Prediction of Severe Acute Pancreatitis

Cutoff value (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Likelihood ratio
0.50	89.5	56	60.71	87.5	70.5	10.599
1.00	84.2	64	64	84.2	72.7	10.931
1.77	78.9	76	71.4	82.6	77.3	13.795
2.65	68.4	76	68.4	76	72.7	8.923

PPV, positive predictive value; NPV, negative predictive value.

Table 4. Logistic Regression Analysis of Risk Factors for Severe Acute Pancreatitis

	B	Odds ratio	p-value	95% confidence Interval	
				Upper	Lower
Sex	0.435	1.545	0.491	0.448	5.336
APACHE II score ≥7	2.474	11.875	0.001	2.828	49.865
Ranson score ≥3	5.318	204	<0.001	17.091	2434.945
Glasgow score ≥3	2.981	19.714	<0.001	3.532	110.039
BCTSI ≥4	1.340	3.818	0.062	0.937	15.554
PCT ≥1.77	2.474	11.875	0.001	2.828	49.865
CRP (mg/dL) ≥8.2	1.527	4.604	0.02	1.278	16.582
Total calcium (mg/dL) ≥9.04	0.379	1.462	0.577	0.385	5.545
LDH (IU/L) ≥453	3.132	22.909	0.005	2.634	199.241
Glucose (mg/dL) ≥140	0.994	2.571	0.132	0.753	8.784
Urea (mg/dL) ≥20	2.182	8.867	0.002	2.246	34.998

APACHE, acute physiology and chronic health examination; BCTSI, balthazar CT severity index; PCT, procalcitonin.

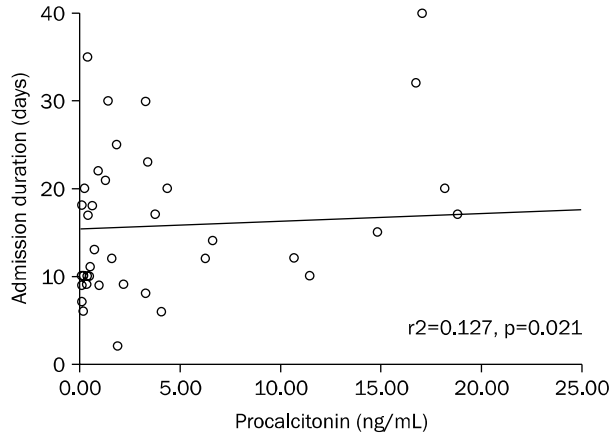

Fig. 3. Correlation between serum procalcitonin levels and duration of admission in patients with acute pancreatitis. Procalcitonin is indendent variable (x), admission duration is dependent variable (y). Coefficient B is -8.791. Coefficient of determinant (r2)=0.127, t value=2.413, dependent p-value=0.021.

tively). The range of admission duration of each patients were 4 to 41 days, and we used simple linear regression analysis to evaluate the relationship between serum PCT levels and length of hospital stay. It revealed effective p- value with low R square level, which could make only possibilty for affection of serum PCT to admission duration (r2=0.127, p=0.021, Fig. 3).

DISCUSSION

Acute pancreatitis is an increasing common abdominal emergency.[13] In patients with severe acute pancreatitis, range of mortalities is 10-30%[14] and effective treatment is relay on predictiction of severity and there is still no ideal simple predictive system or biochemical marker which can be conviniently used in clinical bases.[15] Certain predictive methods, such as the Ranson score, Glasgow score, and APACHE-II score have been established as important methods for assessing the severity of acute pancreatitis,[7,15,16] but these multifactorial scoring systems are complex and hard to use in clinical bases. Therefore, we want to set out to identify serum PCT as a single biochemical to predict the severity of acute pancreatitis. In 2000, Neoptolemos et al. reported serum CRP ($\geq$150 mg/L on admission) to be a predictor of severe acute pancareatitis with an overall accuracy of 69%.[17] In our study, the accuracy of CRP as a predictor was 68.2% similarly. However many studies have described limitation of clinical utility of CRP in early phase of acute pancreatitis, which revealed the usage of CRP alone was potentially failing to detect severe cases of acute pancreatitis.[18-21]

Serum PCT as another biochemical marker related to inflammation was introduced several years ago. PCT is a 116-amino acid protein with a molecular mass of 12,793 Da. In neuroendocrine cells (C cells of the thyroid, pulmonary and pancreatic tissues), it undergoes successive cleavages to produce 3 molecules of calcitonin (32 amino acids) and katacalcin (21 amino acids) and the N-terminal 57 amino acids.[22] During the infection, PCT is secreted into the bloodstream without increas of calcitonin, and it correlates closely with the inflammatory response of a host to microbial infections.[23] Serum PCT has also been perceived as a reliable marker for the diagnosis of infected necrosis of the pancreas,[24-26] but an increased serum PCT value in acute phase occurs regardless of cause of the triggering mechanism.[27] Some studies have focused on the increased PCT concentration in acute pancreatitis, but the results of studies were still inconclusive.[28-30] In our study, the accuracy of serum PCT as a biochemical marker was 77.3%, which was similar to the APACHE-II score, worse than the Ranson score (93.2%) and better than the Balthazar CT severity index (65.9%). We analysed 4 cut-off values for serum PCT levels (0.50, 1.00, 1.77, and 2.65 ng/mL), among them, 1.77 ng/mL value had the best accurate value and positive predictive value and likelihood ratio (77.3%, 71.4%, 13.797, respectively). Therefore we propose the level of 1.77 ng/mL could be the best cut-off value for predicting severe acute pancreatitis. Serum PCT might replace to APACHE-II score for predicting severity of acute pancreatitis. On logistic regression analysis, the Balthazar CT severity index had no significance in assessing the severity of acute pancreatitis (p=0.062), but this lack of significance might be due to small number of subjects in this study. By the Atlanta classification, serum CRP, LDH and urea levels had also significance in severe acute pancreatitis ($p < 0.05$), but serum glucose and total calcium levels were meaningless. By the analysis of accuracy, serum PCT was superior value (77.3%) than serum CRP, LDH and urea. We evaluated serum PCT and other parameters according to the severity of pancreatitis by logistic regression analysis and found that serum levels of PCT, CRP, LDH, and urea were significantly correlated with the severity of pancreatitis. There is a report of APACHE-II scoring system which had been shown to sig-

nificant relation to the length of hospital stay.[10] In this study, serum PCT did not show definite relation to the length of hospital stay but only with possibility due to low R square level (r2=0.127) even if it had effective p-value (p=0.021), and we think more studies are needed from the viewpoint of hospital stay. In this analysis, serum PCT levels (ng/mL) was used as independent variables and admission duration (days) was dependent variables. Coefficients B value of dependent variable was 1.444 and t-value was 2.43 and p-value was 0.021. In conclusion, we think that serum PCT can be a promising simple and convinient biomarker to predict severity of acute pancreatitis, which had accuracy similar to APACHE-II score and higher accuracy than the CRP, LDH and urea.

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