

Predictive factors for severe evolution in acute pancreatitis and a new score for predicting a severe outcome

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Abstract

Background Acute pancreatitis (AP) is an acute inflammation of the pancreas with an unpredictable evolution. The aim of this study was to assess the factors associated with severe evolution of AP and to create a new score for predicting a severe outcome.

Methods The initial group included 334 patients hospitalized in 2006-2009. The validation group included 195 patients admitted in 2010-2011. AP was classified according to the Atlanta criteria.

Results In the initial group, C-reactive protein (CRP), creatinine, white blood count, body mass index (BMI), age and male gender were correlated with severe evolution of AP. Using only parameters available in emergency, by multiple regression analysis we obtained in the initial group the following score for predicting severe evolution of AP: Prediction pancreatic severity I score (PPS I score) = $-1.038 + 0.119 \times \text{creatinine (mg/dL)} + 0.012 \times \text{BMI (kg/m}^2) + 0.027 \times \text{white blood count/1000 (cells/mm}^3) + 0.195 \times \text{gender (1-women, 2-men)} + 0.005 \times \text{age (years)}$. For a cut-off value >0.325 , PPS I score had 71.8% accuracy (AUC=0.790) for predicting a severe evolution of AP. In the validation group the accuracy was 71.7%. Since CRP was proven to be a good predictor of severe evolution in AP, we calculated another score, PPS II, obtained using PPS I and CRP: PPS II score = $-0.192 + 0.760 \times \text{PPS I} + 0.003 \times \text{CRP (mg/L)}$. For a cut-off value >0.397 , PPS II score had 87.1% accuracy (AUROC=0.942) in the initial group and 75.3% accuracy in the validation group for predicting severe AP.

Conclusions PPS I and especially PPS II score are accurate predictors of severe outcome in patients with AP.

Keywords Acute pancreatitis, severity score, Ranson score, APACHE II score, C-reactive protein, Atlanta criteria

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Introduction

Acute pancreatitis (AP) is an acute inflammation of the pancreas and the clinical evolution is frequently unpredictable. Multiple prognostic scoring systems have been developed to discriminate between patients with mild acute pancreatitis and those at high risk for developing severe pancreatitis: Ranson

score [1]; APACHE II (Acute Physiology and Chronic Health Evaluation) score [2-4]; combination of APACHE II score with the body mass index (BMI) - APACHE-O [5]; Balthazar computed tomography severity index (CTSI) [6]. Several single markers can be also used for predicting the severity in AP: interleukin (IL)-6, a mediator released by macrophages in response to tissue injury, responsible for synthesis of acute-phase proteins, including C-reactive protein (CRP) [7,8]; IL-8 [9,10]; pancreatitis-associated protein (PAP) [11]; trypsin activation peptide (TAP) (amino-terminal peptide) released by the activation of trypsinogen into trypsin [12]; antiproteases [13,14]; CRP [15,16]; hepatocyte growth factor (HGF) [17]; urinary trypsinogen [18]; procalcitonin [19]. Among these single markers, the most used as a prognostic factor in AP in clinical practice, is CRP.

The aim of this study was to assess the factors associated with severe evolution of AP and to create a new score for predicting severe outcome of AP.

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Patients and methods

Patients

The study was retrospective and included 712 patients diagnosed with AP and admitted to our Department during an almost 6-year period (January 2006 - December 2011). AP was defined as sudden onset of pain in the upper part of the abdomen, associated with increased serum lipase (more than 3 times the upper normal value). 183 cases were excluded because all the necessary data were not found, so 529 patients were included in the final analysis.

The 529 patients included in the study were divided in 2 categories: a. a group of 334 patients, admitted between 2006-2009, used to develop the new algorithm for predicting severe outcome in AP (initial group); and b. a group of 195 patients admitted in 2010 and 2011, used for the validation of the new score.

AP was classified as mild or severe, according to the Atlanta criteria [20]. Criteria for severity were: organ failure (shock-systolic pressure <90 mmHg, PaO₂ ≤60 mmHg, creatinine >2.0 mg/L after rehydration, or gastrointestinal bleeding >500 cc/24 h) and/or local complications (especially pancreatic necrosis, but also including abscess and pseudocyst). Early predictors of severity within 48 h of initial hospitalization included Ranson score ≥3 and/or APACHE-II score ≥8. In order to be able to classify the patients according to the Atlanta criteria, biological tests and imaging investigations [ultrasound examination, CT and/or magnetic resonance imaging (MRI) scans] were performed.

According to the etiology, AP was classified as: alcoholic, biliary and non-alcoholic, non-biliary - nonA-nonB [which included all the other etiologies of AP: hypertriglyceridemia, autoimmune, post-endoscopic retrograde cholangiopancreatography (post-ERCP), other etiologies or idiopathic AP].

Serological tests

Bioassays were performed by venous blood sampling and processed in our hospital's laboratories. All were routine biological tests and the following normal values (NV) were used: serum lipase (NV=100-300 U/L), creatinine (NV=0.6-1.1 mg/dL), white blood count (NV=4000-8000 cells/mm³), hematocrit (NV=40-44% in men; and 36-40% in women), CRP (NV=1-3 mg/L). CRP was determined at 48 h after the onset of AP symptoms and the other tests were performed on admission.

Statistical analysis

Data obtained from our patients were collected in a Microsoft Excel file. The statistical analysis was performed using the WINK SDA Software, 7th Edition (Texasoft, Cedar Hill, Texas, USA) and MedCalc Software (MedCalc program, Belgium). The distribution of numerical variables was tested by the Kolmogorov-Smirnov test. In case of numerical variables with

normal distribution, mean value and standard deviation were calculated, while in case of non-normal distribution median values and range intervals were utilized. Differences between numerical variables were analyzed by parametric (*t*-test) or nonparametric tests (Mann-Whitney or Kruskal-Wallis tests) according to the normal or non-normal distribution of variables. Spearman's rank correlation coefficient was used to assess the correlation between severe evolution of AP and serological tests, age, gender, BMI. The Chi-square (X²) test (with Yates' correction for continuity) was used for the comparison of two proportions expressed as percentages. For multivariate analysis stepwise logistic regression analysis was used. A P-value of less than 0.05 was regarded as statistically significant.

Linear multiple regression was used to calculate the new scores for predicting severe outcome in AP.

The diagnostic performance of CRP and the new scores were assessed using receiver operating characteristics (ROC) curves that we built for the detection of severe AP. Optimal cut-off values were chosen for the maximum sum of sensitivity and specificity. The sensitivity and specificity were calculated according to standard methods. 95% confidence intervals (CI) were calculated for each predictive test and used to compare AUC curves.

Results

The overall mortality rate was 4.6% (considering all the 712 patients with AP admitted in our Department between 2006 and December 2011). The main characteristics of the 529 patients included in this study are presented in the Table 1.

In the initial group, in univariate analysis, the age, male gender, BMI, white blood count, creatinine and CRP values were significantly higher in patients with severe AP as compared with those with mild AP (Table 2). In multivariate analysis all the factors mentioned above, except BMI, were independently associated with a severe outcome of AP (Table 3).

In the initial group, CRP was the best correlated parameter with a severe outcome of AP ($r=0.652$), followed by creatinine, white blood count, BMI, age and male gender (Table 4).

For a cut-off value >120mg/L, CRP had 77.2% sensitivity (Se), 89.9% specificity (Sp), 82.3% positive predictive value (PPV), 86.5% negative predictive value (NPV) and 85% accuracy for predicting a severe outcome of AP [AUC=0.888 (95% CI: 0.849-0.920), $P<0.0001$] (Fig. 1A).

Considering the variables associated with a severe outcome of AP in univariate analysis, available in emergency at admission, by using linear multiple regression analysis we obtained a new score to predict the severe outcome in patients with AP:

Prediction Pancreatitis Severity I score (PPS I score) = $-1.038 + 0.119 \times \text{creatinine (mg/dL)} + 0.012 \times \text{BMI (kg/m}^2\text{)} + 0.027 \times \text{white blood count/1000 (cells/mm}^3\text{)} + 0.195 \times \text{gender (1-women, 2-men)} + 0.005 \times \text{age (years)}$.

A direct, linear, strong correlation (Spearman coefficient

Table 1 Patients' characteristics. Numerical variables with normal distribution are presented as mean value \pm standard deviation, while variables with non-normal distribution are presented as median values and range intervals

Parameter	Initial group (334 patients)	Validation group (195 patients)	P value
Age (years)	54.3 \pm 16.4	55 \pm 14.8	0.65
Gender	women: 129 (38.6%) men: 205 (61.4%)	women: 83 (42.5%) men: 112 (57.5%)	0.42 0.42
Severity	mild: 207 (61.9%) severe: 127 (38.1%)	mild: 116 (59.4%) severe: 79 (40.6%)	0.63 0.63
Etiology	alcoholic: 124(37.1%) biliary: 139 (41.6%) nonA-nonB: 71 (21.3%)	alcoholic: 53 (27.2%) biliary: 107 (54.9%) nonA-nonB: 35 (17.9%)	0.02 0.004 0.40
BMI (kg/m ²)	27 \pm 5.1	28.1 \pm 5.1	0.01
Serum lipase (U/L)	4428 (920-133400)	7534 (1245-187326)	0.0005
White blood count (cells/mm ³)	11350 (2400-31900)	11700 (1760-32100)	0.15
Hematocrit (%)	40.7 \pm 5.5	41.7 \pm 5.1	0.03
Serum creatinine (mg/dL)	0.9 (0.3-9.9)	0.8 (0.2-8.4)	<0.0001
CRP (mg/L)	90 (1.2-498)	84 (2-464)	0.88
Days of hospitalization	6.5 (1-41)	6 (1-30)	0.70
Patients who required surgery	43 (12.8%)	5 (2.5%)	0.0001
Patients who required ERCP	36 (10.7%)	14 (7.1%)	0.22

BMI, body mass index; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; nonA-nonB, non-alcoholic, non-biliary

$r=0.503$) was found to exist between the PPS I score and a severe outcome of AP ($P<0.0001$).

PPS I score had a pretty good value for predicting a severe outcome of AP, with an AUC=0.790 (95% CI: 0.751-0.840, $P=0.0001$), the best cut-off value being >0.325 (Fig. 1B).

The performance of PPS I score in the initial group and in the validation group (195 patients admitted in 2010-2011), for the same cut-off value (>0.325) are presented in Table 5.

Considering PPS I score and CPR, by using linear multiple regression analysis, we obtained a second new score to predict

Table 2 Factors associated with the severe outcome of AP in univariate analysis in the initial group. Numerical variables with normal distribution are presented as mean value \pm standard deviation, while variables with non-normal distribution are presented as median values and range intervals

Parameter	Mild AP (207 patients)	Severe AP (127 patients)	P
Age (years)	52.5 \pm 16.6	57.2 \pm 15.8	0.01
Sex	women: 90 (43.5%) men: 117 (56.5%)	women: 39 (30.7%) men: 88 (69.3%)	0.02 0.02
Etiology	alcoholic: 77 (47.2%) biliary: 82 (39.6%) nonA-nonB: 48 (23.2%)	alcoholic: 47 (37%) biliary: 57 (44.9%) nonA-nonB: 23 (18.1%)	0.93 0.40 0.33
BMI (kg/m ²)	26.3 \pm 4.7	28.1 \pm 5.7	0.01
Serum lipase (U/L)	4094 (1315-88674)	5124 (920-133400)	0.08
White blood count (cell/mm ³)	10100 (3430-31900)	13100 (2400-29800)	<0.0001
Hematocrit (%)	40.8 \pm 4.7	40.5 \pm 6.6	0.62
Creatinine (mg/dL)	0.8 (0.3-4.1)	1.2 (0.5-9.9)	<0.0001
CRP (mg/L)	42 (1.2-297)	179 (7.3-498)	<0.0001

AP, acute pancreatitis; BMI, body mass index; CRP, C-reactive protein; nonA-nonB, non-alcoholic, non-biliary

Table 3 Factors associated with the severe outcome of AP in multivariate analysis in the initial group

Parameter	Coefficient	Standard error	P value	Odds ratio	95% Confidence Interval
Age	0.030	0.013	0.003	1.1	1.01-1.4
Male gender	0.47	0.12	0.02	1.61	0.69-3.72
Etiology	0.0002	0.266	0.99	1.0002	0.59-1.08
BMI	-0.015	0.042	0.71	0.98	0.90-1.06
Serum lipase	0.002	0.0009	0.07	1.002	0.98-1.01
White blood count	0.010	0.004	0.01	1.4	1.002-1.7
Hematocrit	-0.018	0.038	0.62	0.98	0.91-1.05
Creatinine	1.35	0.32	<0.0001	3.87	2.04-7.36
CRP	0.024	0.003	<0.0001	1.2	0.97-1.42

BMI, body mass index; CRP, C-reactive protein

severe outcome in patients with AP after 48 h from the onset of symptoms:

Prediction Pancreatitis Severity II score (PPS II score): $-0.192 + 0.760 \times \text{PPS I} + 0.003 \times \text{CRP (mg/L)}$.

A direct, linear, strong correlation (Spearman coefficient $r=0.743$) was found to exist between PPS II score and a severe outcome of AP ($P<0.0001$).

PPS II score had a very good predictive value for severe outcome of AP, with an AUC=0.942 (95% CI: 0.910-0.963, $P=0.0001$), the best cut-off value being >0.397 (Fig. 1C).

The performance of PPS II score in the initial group and in the validation group for the same cut-off value (>0.397) is presented in Table 5.

In the initial group, the AUROC curve for CRP was significantly better than that for PPS I score, but lower than the AUROC curve for PPS II score (Table 6).

In the whole cohort of 529 patients, the AP subjects with

Table 4 Parameters and correlation with the severe outcome of AP in the initial group

Parameter	Spearman r correlation coefficient
CRP	0.652, $P<0.0001$
Creatinine	0.355, $P<0.0001$
White blood count	0.332, $P<0.0001$
BMI	0.151, $P=0.005$
Age	0.130, $P=0.01$
Sex: men	0.127, $P=0.01$
women	-0.127, $P=0.01$
Serum lipase	0.107, $P=0.07$
Hematocrit	-0.007, $P=0.88$
Etiology: alcoholic	-0.001, $P=0.97$
biliary	0.05, $P=0.34$
nonA-nonB	-0.06, $P=0.27$

BMI, body mass index; CRP, C-reactive protein; nonA-nonB, non-alcoholic, non-biliary

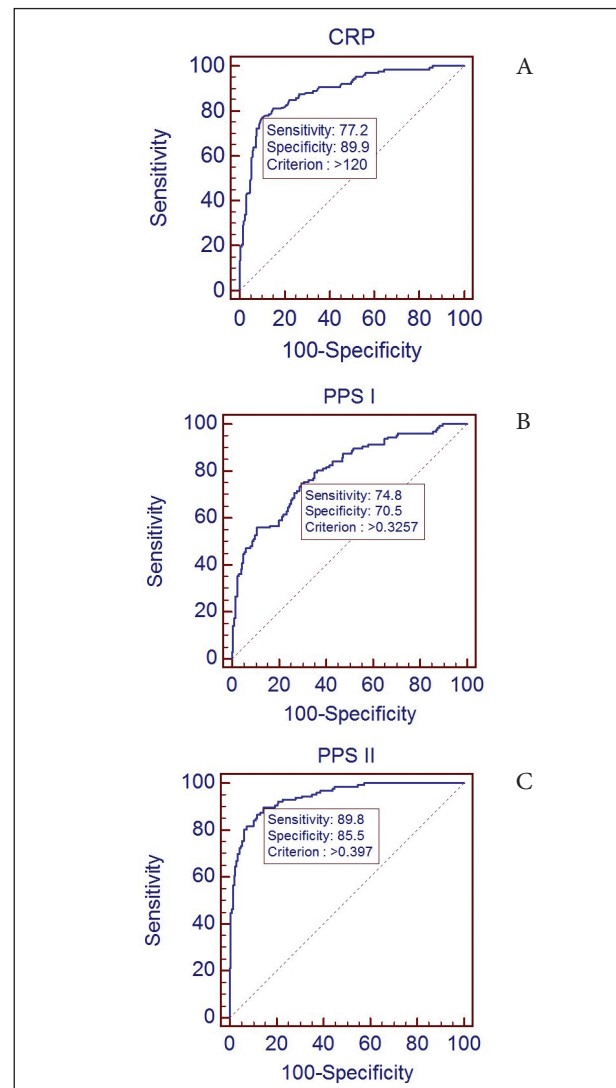


Figure 1 Predictive values of CRP (A), PPS I (B) and PPS II (C) score for a severe outcome of acute pancreatitis
CRP, C-reactive protein; PPS I score, prediction pancreatitis severity I score; PPS II score, prediction pancreatitis severity II score

Table 5 The performance of PPS I and PPS II score for predicting the severe outcome of AP in the initial and the validation group

PPS I score					
Group	Se(%) (95%CI)	Sp(%) (95%CI)	PPV(%) (95%CI)	NPV(%) (95%CI)	Accuracy(%) (95%CI)
Initial	74.8 (66.3-82.1)	70.5 (63.8-76.6)	60.3 (53.2-62.5)	82.8 (76.3-89.6)	71.8 (65.6-79.1)
Validation	72.1 (63.8-80.5)	71.5 (65.6-78.7)	63.3 (56.7-69.8)	79.1 (73.8-87.4)	71.7 (65.1-79.8)
PPS II score					
Group	Se(%) (95%CI)	Sp(%) (95%CI)	PPV(%) (95%CI)	NPV(%) (95%CI)	Accuracy(%) (95%CI)
Initial	89.8 (82.2-93.8)	85.5 (80-90)	79.1 (73.8-83.8)	93.1 (89.7-96.9)	87.1 (81.9-92.1)
Validation	73.4 (68.8-78.2)	76.6 (71.5-81.4)	68.2 (62.4-72.1)	80.9 (75.6-85.8)	75.3 (70.1-79.8)

PPS I score, prediction pancreatitis severity I score; PPS II score, prediction pancreatitis severity II score; AP, acute pancreatitis; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

PPS I score >0.325 and those with PPS I score up to 0.325 had similar rates of need for surgery or ERCP: 10.1% vs. 8.3%, $P=0.57$ and 9.6% vs. 9.2%, $P=0.99$, respectively.

AP patients with PPS II score >0.397 had a significantly higher need for surgery as compared with those with PPS II score up to 0.397: 12.8% vs. 6.2%, $P=0.01$. These two categories of patients had a similar need for ERCP: 9.3% vs. 9.5%, $P=0.94$.

Discussion

Predicting the severity and outcome of AP still represents a challenge for the physician. Although there are multiple scoring systems and single markers to predict a severe outcome in AP, there is no consensus regarding the use of one or another in clinical practice.

The aim of our study was to create a score able to accurately predict a severe outcome in AP at admission (in the Emergency Department), using inexpensive and easy to measure parameters, available in any hospital. Since CRP was proven to be a good predictor of severe evolution in AP, we calculated another score that includes CRP evaluated 48 h after AP onset.

Several studies and meta-analyses showed that a severe outcome should be expected in overweight and obese patients [5,21,22]. Also, in our current study, BMI was correlated with the severity of AP.

Some studies concluded that the evolution of AP is more

severe in cases of alcoholic etiology [23,24]. In our study, in a large cohort of patients, the severity of the disease was not influenced by the etiology.

The severe outcome of AP was also correlated in our study with age and male gender. In the study of Lankish *et al* [25], the age influenced the evolution of the disease, but the influence was only limited.

In our study, in the initial group, the alcoholic etiology of AP was significant higher in men as compared with women (58% vs. 9.3%) and maybe this is one of the causes of the more severe evolution of AP in men, despite non-correlation between alcoholic etiology and the severe outcome of AP.

In clinical practice, probably the most used prognostic factor in AP is CRP, but it is useful only if it is measured after at least 48 h following the onset of AP. Values greater than 120 mg/L can detect between 67 and 100% of pancreatic necroses [15]. Others authors proposed a cut-off value of 150 mg/L [26,27]. In the study of Gurleyik *et al* [27], for a cut-off value of 150 mg/L, CRP had 84.6% Se, 73.8% Sp, 50% PPV, 93.9% NPV and 76.4% accuracy to predict a severe outcome of AP. In the study of de la Pena *et al* [28], for a cut-off value of 100 mg/L, CRP had 100% Se and 86% Sp to predict a severe outcome of AP. In our study, the best cut-off value of CRP to predict a severe AP was 120 mg/L, with an accuracy of 85%. Also, CRP was the best correlated test with the severe outcome of disease.

Several studies concluded that the best method to predict a severe AP is Balthazar computed tomography severity index [27,29,30]. This method has some disadvantages: it is expensive,

Table 6 Comparison of AUC curves of CRP, PPS I and PPS II score for prediction of severe outcome of AP in the initial group

AUC curves	Difference between areas	Standard error	95% Confidence Interval	P
CRP vs. PPS I: 0.888 vs. 0.790	0.088	0.032	0.024 to 0.153	0.007
PPS II vs. CRP: 0.942 vs. 0.888	0.053	0.013	0.028 to 0.079	<0.001

AUC curves, area under receiver operating curves; CRP, C-reactive protein; PPS I score, prediction pancreatitis severity I score; PPS II score, prediction pancreatitis severity II score; AP, acute pancreatitis

irradiant and it cannot evaluate all the patients (a CT scan is needed for this score, but CT scans should not be performed in mild forms of AP). However, it should be specified that CT scan is a valuable tool that can provide extremely important information, especially in severe forms.

The PPS I score proposed by this study to predict a severe outcome of AP at admission is inexpensive (the only needed laboratory data are the white blood count and creatinine levels) and available in any hospital. The accuracy of PPS I score, in the initial as well as in the validation group, was good (71.8% and 71.2% respectively). This score can be a useful tool to select on admission the patients with a high risk of developing severe AP and who need to be hospitalized in the Intensive Care Unit.

PPS score I was less accurate than CRP to predict a severe outcome of AP, but it is available at admission, while CRP is available only 48 h after the onset of symptoms of AP.

PPS II score, that includes PPS I score and CRP, was significantly better than CRP alone to predict a severe outcome in the initial group of patients with AP: AUC=0.942 vs. AUC=0.888, $P<0.001$. A logical conclusion is that patients with PPS II >0.397 should be more carefully monitored and, maybe a CT scan should be performed in these patients. It should also be specified that even if PPS II is lower than 0.397, but the clinical evolution is not favorable, a CT scan should be performed.

For both PPS I and II scores we obtained a very good NPV, both in the initial and in the validation group, so if the values of these scores are under the specified cut-off values, we can estimate with 80-90% confidence that the AP will not have a severe outcome.

The PPS I score could not predict the need for surgery or ERCP, but in patients with PPS II score >0.397 , the need for surgery was significantly higher (double) as compared with patients with PPS II score up to 0.397.

One of the limitations of our study is its retrospective nature. Another limitation is the fact that PPS I and PPS II scores were not compared with Ranson or APACHE II scoring system, but the laboratory tests included in these scores are inexpensive and available in emergency, to all patients. CRP also, included in the PPS II score, is a simple and cheap laboratory test, available in any hospital. The PPS I score can be rapidly and easily calculated in small hospitals, so that cases with a high score can be referred to secondary or tertiary centers. It should be specified that a limitation of PPS I and PPS II scores is the fact that white blood cells count or CRP can also be elevated due to other causes unrelated to AP, for example infections unrelated to AP. External validation of these scores may be required, in comparison with other prognostic scores and these are the next steps that we propose.

In conclusion CRP, creatinine, white blood count, BMI, age and male gender were correlated in different degrees with severe outcome of AP. PPS I score (available at the admission of patients) and especially PPS II score, had a good accuracy to predict severe outcome in patients with AP (AUC=0.790, and 0.942, respectively).

Summary Box

What is already known:

- Multiple prognostic scoring systems have been developed to discriminate between patients with mild acute pancreatitis (AP) and those at high risk for developing severe AP
- C-reactive protein (CRP) is the best known single simple serological predictor of severity in AP

What the new findings are:

- PPS I score can predict easily, cost-effectively and with good accuracy the severe outcome of AP on admission of patients
- PPS II score is a simple and cheap serological score with better accuracy than CRP for predicting the severe outcome of AP after 48 h from patient admission.
- Patients with PPS II >0.397 need careful monitoring

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