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Biological markers of severity in acute pancreatitis

Research Article

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Abstract: None of the definitions of severity used in acute pancreatitis (AP) is ideal. Many of the scoring systems used to predict and measure its severity are complex, cumbersome and inaccurate. Aim: to evaluate the usefulness of the most commonly used early markers for predicting severity, necrosis and mortality in patients with AP, and the need for surgery or Intensive Care Unit (ICU) admission. Material&methods: Prospective study was performed from March 2009 to August 2010 based on patients diagnosed with AP seen consecutively at a secondary hospital. The early prognostic markers used were Apache II score ≥8 and Ranson's score ≥3, RCP>120mg/l and Ht>44% in the first 24 hours. Results: 131 patients were prospectively enrolled. Median age was 63 years, 60% were men. The most frequent etiology of AP was biliary (68%). Fifteen patients were admitted to the ICU (11.6%) and five (3.9%) required surgery. Twelve patients (9.2%) had necrosis on CT. Four patients (3%) died , all of them in the Severe AP group. Only hematocrit>44 was predictor of mortality in univariate analysis. Conclusion: hematocrit ≥ 44% was a significant predictor of mortality. The other indicators present limitations for predicting severity, necrosis and mortality, especially in the first 24 hours.

Keywords: *Pancreatitis • Organ failure • Markers • Surgery • Review*

1. Introduction

Acute pancreatitis (AP) has an acute inflammatory process ranging from mild discomfort with localized inflammation to severe disease with multiple organ failure [1]. Between 10 and 20% of patients are qualified as severe AP (SAP) [2-5]. They have suffered an intense inflammatory response, a variety of local and systemic complications, prolonged hospital stay and significant morbidity and mortality [2]. Mortality in SAP may reach as high as 20-30% [3,4], while the mild form has a mortality of less than 5% [4].

Despite notable progress in the last six decades, our ability to accurately diagnose and estimate the severity of acute pancreatitis remains limited [6,7]. Severity assessment is essential for selection of appropriate initial treatment in the management of AP [8], and to identify the cohort of patients who require critical care support, in order to rationalize health care resources [4].

The Atlanta Classification, published in 1992, has been considered the gold standard for establishing international standards of definitions of AP. However, after recent reviewalternative definitions have been proposed.

Organ failure is a main cause of death in severe acute pancreatitis, especially in the first few days [11,13]. The pancreatic necrosis seen on the CT scan is not considered as a predictor of mortality, but infected pancreatic necrosis is a frequent cause of mortality after the first week [4].

None of the different definitions of severity used for AP are ideal. Many of the scoring systems used to predict and measureseverity are complex, cumber-

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some and inaccurate [3]. Some of them are: a) the Acute Physiology, Age and Chronic Health Evaluation (Apache II) [4,7,9,14]; b) Structured Interview of Reported Symptoms (SIRS) [4,9]; c) the Ranson score [4,7,9]; d) Bedside index for severity in AP (BISAP) (blood urea nitrogen >25mg/dl, impaired mental status, Systemic inflammatory response syndrome, age >60 years and pleural effusions) [2,3,15]; e) The Harmless Acute Pancreatitis Score (HAPS) (no rebound tenderness and/or guarding, normal hematocrit and normal serum creatinine level) allows rapid identification of patients who present mild AP in 98% of cases; f) CT severity index (CTSI) based on local complications and percentage of pancreatic necrosis seen on a CT scan [2,4,5,17,18]. Various laboratory tests and biomarkers for predicting AP outcome have been described: a) elevated C-reactive protein (CRP) [1,4,13,14,19,20]; b) elevated hematocrit (Ht) [5,7,14,21,22]; and c) high serum creatinine, as a doubtful predictor of pancreatic necrosis [23,24]. Some of the recently described individual markers of severity include procalcitonin [25-27], urinary trypsinogen activation peptide, intra-abdominal hypertension (>15mmHg) [7], angiogenic factors [28] and interleukins (IL-6 and IL-8) [29].

The aim of our study is to evaluate the usefulness of the most commonly used early markers (Apache II score, Ranson's score, CRP, Ht in the first 24 hours) for predicting (a) severity, necrosis and mortality in patients with AP, and (b) the need for surgery or Intensive Care Unit (ICU) admission.

2. Methods

This prospective study was performed from March 2009 to August 2010 based on patients diagnosed with AP seen consecutively at a secondary hospital.

The inclusion criteria were: (1) serum amylase ≥3 times upper limit of normal value, (2) abdominal pain characteristic of AP, and (3) characteristic findings on abdominal CT scan in doubtful cases. The early prognostic markers (EPMs) used were Apache II score ≥8 and Ranson's score ≥3, RCP>120 mg/L and Ht>44% in the first 24 hours.

Patients were classified as mild or severe AP based on the Atlanta Classification published in 1992: (1) organ failure included shock (systolic blood pressure ≤90mmHg), pulmonary insufficiency (arterial PO2≤60mmHg), renal failure (serum creatinine level >2 mg/L after rehydration) and gastrointestinal bleeding >500cc/24h; (2) local complications such as necrosis, abscess and pseudocyst; (3) early prognostic signs including Apache II score ≥8 and Ranson's signs ≥3.

2.1 Statistics

After data collection, the following statistical studies were performed: a) a descriptive analysis presenting continuous variables as medians and categorical data as proportions; b) a bivariate analysis matching individual EPMs regarding the severity, necrosis and mortality; c) a univariate analysis between individual EPMs regarding mortality, risk of surgery and risk of ICU admission; d) a multivariate analysis matching EPMs and ICU admission. A multivariate analysis of the mortality and surgery was not performed because of the low number of patients in these groups; e) Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for individual EPMs.

We used the statistical program SPSS v19.0, with Chi-Square and Fisher Test for qualitative variables and the Mann Whitney-U and Student's 't' test for quantitative variables.

3. Results

3.1. Patients' characteristics

One hundred and thirty patients were prospectively enrolled between March 2009 and August 2010. Median age was 63 years (range 27-94); 60% were men and 40% women. The etiologies of AP were biliary (68%), alcoholic (18%) and others (14%) including post-endoscopic retrograde cholangiopancreatography, hypertriglyceridemia and idiopathic. Forty-eight patients (36.9%) underwent early CT scan because of poor evolution or diagnostic doubt. Fifteen patients were admitted to the ICU (11.6%) and five (3.9%) required surgery. Twelve patients (9.2%) had evidence of necrosis on CT scan. The median length of stay was 9 days (range 1-80), being 9 days ± 5 for mild AP (cholecystectomy was performed in the same admission period) and 21 days ± 19 for SAP ($p<0.001$). Four patients (3%) died during hospitalization, all of them in the SAP group.

Based on the Atlanta Classification 29 patients (22.3%) were defined as SAP. Fifty-two patients (40%) were classified as SAP by EPMs, 16 patients (12%) by Ranson's score, 21 (16%) by CRP, and 50 (38%) by Ht.

3.2 Comparison of EPMs in predicting severity, necrosis and mortality

In the bivariate analysis of EPMs and severity, necrosis and mortality, 28% of patients with Apache II ≥8 were classified as SAP by Atlanta, 9.6% had necrosis, and 5.8% died. Among the patients with Ranson's score ≥3, 25% were classified as SAP by Atlanta, 6.3% had necrosis and 6.3% died. Among the patients with CRP

≥120mg/L, 47.6% were classified as SAP by Atlanta, 23.8% had necrosis and 4.7% died. Of the patients with Ht ≥44%, 26% were classified as SAP by Atlanta, 12% had necrosis and 8% died (Table 1).

Table 1. Bivariate analysis of EPMs and severity, necrosis and mortality.

	N	% Severity	% Necrosis	% Mortality
Apache II				
< 8	78	18%	8.9%	1.3%
≥ 8	52	28.8%	9.6%	5.8%
Ranson				
< 3	114	22%	9.6%	2.6%
≥ 3	16	25%	6.3%	6.3%
CRP		p<0.05	p<0.05	
< 120	109	17.4%	6.4%	2.7%
≥ 120	21	47.6%	23.8%	4.7%
Ht				p<0.05
< 44%	80	20%	7.5%	0
≥ 44%	50	26%	12%	8%

The sensitivity, specificity, PPV and NPV of various EPMs predicting severity, necrosis and mortality are seen in Table 2.

Table 2. Sensitivity, specificity, PPV and NPV of various EPMs predicting severity, necrosis and mortality.

	SENSITIVITY	SPECIFICITY	PPV	NPV
SEVERITY				
Apache II	51%	63%	28%	82%
Ranson	14%	88%	25%	78%
CRP	65%	99%	90%	91%
Ht	45%	63%	26%	80%
NECROSIS				
Apache II	42%	60%	9.6%	91%
Ranson	8.3%	87%	6.2%	90%
CRP	41%	94%	24%	94%
Ht	50%	62%	12%	93%
MORTALITY				
Apache II	75%	61%	5.7%	99%
Ranson	25%	88%	6.3%	97%
CRP	25%	84%	4.7%	97%
Ht	100%	63%	8%	100%

3.3 Comparison of EPMs predicting mortality, risk of surgery and risk of ICU admission

In the univariate analysis of EPMs, age and sex regarding mortality, survivors and non-survivors presented statistically significant differences with regard to age and Ht (Table 3). No differences were found with regard to surgery (Table 4). With regard to ICU admission, Apache II and Ranson's scores presented statistically significant differences between admitted and non-admitted patients, and CRP presented a trend towards significance (Table 5).

Table 3. Univariate analysis regarding mortality.

MORTALITY			
	NO (n=126)	YES (n=4)	p
Age	62.6±19.3	73.75±3.8	0.002 (p<0.05)
Sex			
Women	40.5%	25%	0.649
Men	59.5%	75%	
Apache ≥ 8	38.9%	75%	0.301
Ranson ≥ 3	11.9%	25%	0.414
CRP ≥ 120	17.5%	25%	0.546
Ht ≥ 44	36.5%	100%	0.020 (p<0.05)

Table 4. Univariate analysis regarding surgery.

SURGERY			
	NO (n=125)	YES (n=5)	p
Age	62.78±19.2	67±18.6	0.644
Sex			
Women	40%	40%	1.000
Men	60%	60%	
Apache ≥ 8	38.4%	80%	0.157
Ranson ≥ 3	12%	20%	0.487
CRP ≥ 120	16.8%	40%	0.214
Ht ≥ 44	36.8%	80%	0.072

Table 5. Univariate analysis regarding ICU.

ICU			
	NO (n=115)	YES (n=15)	p
Age	62.49±19.3	65.94±18.3	0.490
Sex			
Women	41.6%	29.4%	0.339
Men	58.4%	70.6%	
Apache ≥ 8	35.4%	70.6%	0.006 (p<0.05)
Ranson ≥ 3	9.7%	29.4%	0.037 (p<0.05)
CRP ≥ 120	15%	35.3%	0.080
Ht ≥ 44	36.3%	52.9%	0.188

Since the ICU group was the only one with enough cases to perform a multivariate analysis, we applied logistic regression analysis calculating the odds ratio with the EPMs that had a p<0.1 in the multivariate analysis (Table 6).

Table 6. Early independent predictor markers of ICU admission in patients with AP. Logistic regression analysis.

MARKER	OR	IC 95% (OR)	p
Apache			
< 8	1		
≥ 8	3.422	1.069-10.954	0.038
Ranson			
< 3	1		
≥ 3	2.489	0.68-9.109	0.168
RCP			
< 120	1		
≥ 120	2.656	0.818-8.621	0.104

4. Discussion

In this study the percentage of patients with SAP reflected that described in other literature reports [2-5,19], as did the high percentage of biliary etiology [2,5,13].

The mortality obtained is also comparable to previous studies, since all our non-survivors (14%) belonged to the group with SAP [2-5,19].

Comparison with the Atlanta Classification indicated that the Apache II score overclassifies patients as SAP. This is because age accounts for a major part of the Apache II score, and our subjects had a high median age. In terms of sensitivity, specificity, PPV and NPV (in our study 51%, 63%, 28%, 82% respectively) the results are comparable to those of another study (sensitivity 52%, specificity 77%, PPV 46%; NPV 84%) [13] which, like us, used the Atlanta Classification, but poorer than another (sensitivity 70.3%, specificity 71.9%, PPV 40%, NPV 90.1%) [2] that used organ dysfunction for at least 48h as a definition of SAP. In our study as in others [5], the Apache score was not a reliable predictor of necrosis, presenting low sensitivity and specificity even when it is calculated after 24 hours of admission [13]. Comparing our results for the Apache II score as a predictor of mortality (sensitivity 75%, specificity 61%, PPV 5.7% and NPV 99%) with the literature (sensitivity 65-81%, specificity 77-91%, PPV 23-69% NPV 86-99%) [4], the results are similar, except for PPV (lower in our study due to the small number of deaths). In the literature three studies [30-32] found a significant association of Apache II with mortality, but conflicting results were found in the multivariate analysis, and in only two [31,32] of these studies was the score highly correlated with death.

In our study the Ranson's score underestimated the severity of the disease in the first 24 hours, with low sensitivity, specificity, PPV and NPV (14%, 88%, 25% and 78% respectively) compared with literature reports [2,33]. This is because we calculated the Ranson's score in the first 24 hours; its predictive value of organ failure is known to increase after the full 48 hours [2]. Nor was the score a good predictor of necrosis, providing poor sensitivity and moderate specificity, again because the score's accuracy increases when calculated after 48h. As a predictor of mortality, Ranson's score had low sensitivity (25%) and low PPV (6.3%) because of the low number of deaths, but had reasonable specificity (88%) and NPV (97%) compared with other reports (sensitivity 65%, specificity 70%, PPV 20-63% and NPV 86-94%) [4].

In our study a CRP ≥120mg/L emerged as a statistically significant predictor of severity with a high specificity (99%), but a low sensitivity (65%), and of necrosis (specificity 94% and sensitivity 41%). CRP was not a statistically significant predictor of mortality, with a specificity of 84% and sensitivity 25%. It has been identified as a predictor of severity in AP, but it increases late (during the first 24-48 hours), directly related with the degree of the necrosis [19]. Other authors consider that it is a sensitive predictor of the progression of severity from moderate to severe [14]; the results of its accuracy in predicting severity and mortality vary in different studies according to the time of measurement and the cutoff value used to measure it [7,8,9,14,19,26]. Plasma levels above 150mg/L within the first 72 hours of disease correlate with the presence of necrosis with a sensitivity and specificity that are both >80% [9].

In severe acute pancreatitis, there is considerable extravasation of intravascular fluid into third spaces as a result of inflammatory mediators. The reduction in intravascular volume may lead to a decrease in the perfusion of the microcirculation of the pancreas and result in pancreatic necrosis [9]. As a result, it is has been suggested that hemoconcentration caused by dehydration may be a predictor of pancreatic necrosis and organ failure [14]. In our study, hematocrit ≥44% was not a good predictor of severity (sensitivity 45%, specificity 63%), or of necrosis (sensitivity 50%, specificity 62%). In the literature the results vary according to the time of measurement (on admission or after 24 hours) and the cutoff value [9,21,22]. Other reports do not confirm that hemoconcentration is associated with necrosis [5,34]. However, it is agreed that the likelihood of necrotizing pancreatitis is very low in the absence of hemoconcentration on admission, as we demonstrate in our study with a NPV of 80% for severity and 93% for necrosis. In predicting mortality there was a statistically significant difference between the patients who presented Ht ≥44% and those with lower figures. Sensitivity, specificity, PPV and NPV scores were 100%, 63%, 8% and 100% respectively; the low PPV is because of the small number of deaths, as in the case of the other EPMs.

Regarding mortality, apart from Ht ≥44%, a statistically significant difference was observed with age, since the decrease in the physiological reserve of elderly people makes them more susceptible to this (and any other) disease.

No EPM was able to predict the need for surgery at time of admission.

Regarding the need for ICU admission the Apache II score and Ranson's score presented statistically significant differences and a trend towards significance was found with CRP ≥120 mg/L. These are the independent predictors we use in our protocol to monitor need for ICU admission. Among them, the Apache II score was the only one to maintain statistical significance in the logistic regression model.

In conclusion, in our study hematocrit ≥44% was a significant predictor of mortality. All the other indicators present limitations for predicting severity, necrosis and

mortality, especially in the first 24 hours. The search for early predictors must continue and it should be based on the understanding of the pathophysiological mechanism of AP, considering predisposing risk factors and identifying biomarkers that activate these mechanisms, in order to obtain more accurate predictions.

Conflict of interest statement

Authors state no conflict of interest.

References

[1] Triester SL, Kowdley KV. Prognostic factors in acute pancreatitis. J Clin Gastroenterol 2002;34:167-176
[2] Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, Apache II and CTSI Scores in predicting organ failure, complications and mortality in acute pancreatitis. Am J Gastroenterol 2010; 105: 435-441
[3] Shailendra C, Forsmark CE. The difficulty in predicting outcome in acute pancreatitis. Am J Gastroenterol 2010;105:443-445
[4] Gravante G, Gracea G, Ong SL, et al. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. Pancreatology 2009;9:601-614
[5] Lujano LA, Pérez JL, Duran EG, Serralde AE. Correlación entre criterios clínicos, bioquímicos y tomográficos para evaluar la gravedad de la pancreatitis aguda. Rev Esp Enferm Dig 2010;102(6):376-380
[6] Pannala R, Kidd M, Modlin IM. Acute Pancreatitis. A Historical perspective. Pancreas 2009;38:355-366
[7] Talukdar R, Vege SS. Recent developments in acute pancreatitis. Clin Gastroenterol Hepatol 2009;7:S3-S9
[8] Pezzilli R, Zerbi A, Di Carlo V, et al. Practical guidelines for acute pancreatitis. Pancreatology 2010;10(5):523-553
[9] Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379-2400
[10] Bollen TL, van Santvoort HC, Besselink MG, et al. The Atlanta Classification of acute pancreatitis revisited. Br J Surg 2008;95:6-21
[11] Vege SS, Gardner TB, Chari ST, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include "moderately severe acute pancreatitis". Am J Gastroenterol 2009;104(3)710-715
[12] de Madaria E, Soler-Sala G, Lopez-Font I, et al. Update of the Atlanta Classification of severity of acute pancreatitis: should a moderate category be included? Pancreatology 2010;10(5)613-619
[13] Poves I, Fabregat J, García Borobia FJ, et al. Early onset of organ failure is the best predictor of mortality in acute pancreatitis. Rev Esp Enf Dig 2004;96(10):705-713
[14] Hirota M, Takada T, Kawarada Y, et al. JPN Guidelines for the management of acute pancreatitis: severity assessment of acute pancreatitis. J Hepatobiliary Pancreat Surg 2006;13:33-41
[15] Singh VK, Wu BU, Bollen TL, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. Am J Gastroenterol 2009;104(4):966-971
[16] Lankisch PG, Weber-Dany B, Hebel K, et al. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. Clin Gastroenterol Hepatol 2009;7:702-705
[17] Retiz S, Slam K, Lowell W, et al. Biliary, pancreatic and hepatic imaging for the general surgeon. Surg Clin N Am 2011;91:59-92
[18] Heiss P, Bruennler T, Salzberger B, et al. Severe acute pancreatitis requiring drainage therapy: findings on computed tomography as predictor of patient outcome. Pancreatology 2010;10:726-733
[19] Betancour P, Villagrá D, Jorquera N, et al. Determinación de Proteína C Reactiva como predictor de severidad en Pancreatitis Aguda. Revista Anacem 2009;3(2):37-40
[20] Wang X, Cui Z, Li H, et al. Nosocomial mortality and early prediction of patients with severe acute pancreatitis. J Gastroenterol Hepatol 2010;25(8):1386-1393
[21] Brown A, Orav J, Banks PA. Hemoconcentration is an early marker of organ failure and necrotizing pancreatitis. Pancreas 2000;20/4):367-372
[22] Lankisch PG, Mahlke R, Blum T, et al. Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? A critical appraisal. Am J Gastroenterol 2001;96(7):2081-2085
[23] Muddana V, Whitcomb DC, Khalid A et al. Elevated serum creatinine as a marker of pancreatic necrosis in acute pancreatitis. Am J Gastroenterol 2009;104:164-170
[24] Lankisch PG, Weber-Dany B, Maisonneuve P, Lowenfels A. High Serum Creatinine in Acute Pancreatitis: a marker for pancreatic necrosis? Am J Gastroenterol 2010;105(5):1196-1200
[25] Rau BM, Kemppainen EA, Gumbs AA, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalci-

tonin (PCT). Ann Surg 2007;245(5):745-754
[26] Gurda-Duda A, Kusnierz-Cabala B, Nowak W, et al. Assessment of the prognostic value of certain acute-phase proteins and procalcitonin in the prognosis of acute pancreatitis. Pancreas 2008;37(4):449-453
[27] Woo SM, Noh MH, Kim, BG, et al. Comparison of Serum Procalcitonin with Ranson, Apache II, Glasgow and Bathazar CT Severity Index Scores in Predicting Severity of Actue Pancreatitis. Korean J Gastroenterol 2011;58(1):31-37
[28] Espinosa L, Linares PM, Bejerano A, et al. Soluble angiogenic factors in patients with acute pancreatitis. J Clin Gastroenterol 2011;45(7):630-7
[29] Aoun E, Chen J, Reighard D, et al. Diagnostic accuracy of interleukin-6 and interleukin-8 in predicting severe acute pancreatitis: a meta-analysis. Pancreatology 2009;9(6):777-785
[30] Kong L, Santiago N, Han TQ, et al. Clinical characteristics and prognosis factors of severe acute pancreatitis. World J Gastroenterol 2004;10:3336-3338
[31] Bourgaux JF, Defez C, Muller L, et al. Infectious complications, prognostic factors and assessment of anti-infectious management of 212 consecutive patients with acute pancreatitis. Gastroenterol Clin Biol 2007;31:431-435
[32] Mofidi R, Lee ac, Madhavan KK, et al. Prognostic factors in patients undergoing surgery for severe necrotizing pancreatitis. World J Surg 2007;31:2002-2007
[33] Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. Gastroenterology 2007;132(5):2022-2044
[34] Wu BU, Conwell DL, Sing VK, et al. Early hemoconcentration is associated with pancreatic necrosis only among transferred patients. Pancreas 2010;39(5):572-576