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Research Article

Analysis of New Inflammatory Markers in Acute Pancreatitis and Confection of New Prognostic Definition Model: Panc 4

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Abstract

Introduction: Acute pancreatitis is a frequent pathology found in emergency rooms. The identification of severe forms of the disease has a great importance for the clinical approach to improve the outcome of these patients. Several classifications and scores have been proposed over the last century, but none have gained widespread international acceptance, and are difficult to memorize, costly, and have a delay to establish the prognosis. The Panc 3 score proposed by Brown., *et al*. in 2007 is fast, low cost and consists of easily and accessible parameters. Its results demonstrate good specificity, but low sensitivity. New inflammatory markers have now been discussed as predictors of acute pancreatitis severity such as urea, creatinine, and neutrophil/leukocyte, lymphocyte/neutrophil and platelet/leukocyte ratios. Therefore, the objective of this study is to add a new marker to Panc 3, making 5 proposals of a new prognostic score: Panc 4.

Methods: A prospective observational study in which 37 patients with acute biliary pancreatitis were treated at the Hospital Regional de São José. Panc3 score was applied to all patients at the time of admission, as well as complete blood count and urea and creatinine dosages. The clinical course was recorded after hospital admission and the results of Panc3 were analyzed for prognosis. Afterwards, the new markers were analyzed separately by obtaining the cut-off point with the ROC curve, and 5 combinations of markers were tested considering 2 positive variables of Panc 3 + a new positive marker.

Results: The Panc3 score obtained sensitivity of 33% and specificity of 100%. The inflammatory marker with the highest sensitivity (S) and specificity (E) was the neutrophil/leukocyte ratio with S = 88% and E = 64%. The platelet/leukocyte ratio obtained specificity of 92%. The most sensitive marker combination was Panc 3 + Urea with S = 53% and the most specific was Panc 3 + platelets/leukocytes with E = 100%.

Conclusion: Changes in the distribution of blood components showed a statistically significant sensitivity and specificity in the present study, being therefore promising markers for prognostic definition. Urea and creatinine did not obtain good results to define prognosis of pancreatitis, however Panc 3 + Urea was the combination with better result in terms of sensitivity. Panc 3 + platelets/leukocytes obtained a high specificity (E = 100%). With this we established the ideal proposal of Panc 4: Two positive variables of Panc 3 + Urea + platelets/leukocytes. This new combination of four factors has promising use in clinical practice and may present greater sensitivity and high specificity in larger series.

Keywords: *Acute Pancreatitis; Prognosis; Panc 3; Panc 4*

Abbreviations

HRSJ: Hospital Regional de São José; S: Sensitivity; E: Specificity; CT: Computed Tomography; BMI: Body Mass Index; AUC: Area under the Curve

Introduction

Acute pancreatitis is characterized by an inflammatory process of varied course and potentially lethal in severe cases. It is estimated that its incidence is of 30 - 40 cases in 100,000 individuals, being, therefore, a frequent pathology found in the emergency clinical practice.

The main causes of pancreatitis include biliary lithiasis and alcoholism. The diagnosis is made in emergency care in patients with a suggestive clinical condition and an increase in serum amylase and / or lipase levels above three times the normal value. The typical clinical presentation is characterized by intense epigastric or bar pain at the upper abdomen level, which may radiate to the back. Nausea and vomiting are often associated.

Most cases of pancreatitis occur in the mild form of the disease, in which the treatment is summarized as volume replacement, diet suspension and observation. However, the severe form of the disease is present in up to 30% of cases, in which the inflammation process extends to other organs and tissues causing organic failure at a distance. In these cases, prolongation of hospital stay and admission to intensive care units are common. Mortality rates of severe forms of pancreatitis vary by around 20 - 30% [2], corresponding to the 14th largest cause of death of gastrointestinal origin [3]. Early detection of prognosis of severity, are of fundamental importance in the management of these patients. Thus, several classifications of the degree of pancreatitis as well as criteria to define its prognosis have been proposed over the last century, including the Ranson, Glasgow, Osborne, Balthazar and APACHE-II protocols. Due to the various proposals for the classification of pancreatitis, there was no international consensus widely used for the stratification of these patients. In this context, about 40 medical authorities from 15 countries met at the International Symposium on Acute Pancreatitis in the city of Atlanta in 1992. In this event a consensus was proposed for the classification of pancreatitis, which was revised in 2012 by Banks., *et al*. [1] (Table1).

Atlanta 2012 Classification for Pancreatitis
Mild • No organic failure • No local or systemic complications
Moderately severe • Organic failure with resolution within 48h and / or • Local or systemic complications
Severe • Persistent organic failure (> 48h) - Dysfunction of one organ - Multiple organ dysfunction

Table 1.

The revised Atlanta criteria are the current major tool for classifying forms of pancreatitis. This protocol considers clinical evolution, organic dysfunction and local complications for stratification of disease severity. Thus, acute pancreatitis is classified as mild, moderately severe and severe. Mild pancreatitis is the most common form in which there is no organ failure, local or systemic complications, and usually resolves within a week. The moderately severe form exhibits transient organ failure (< 48h), local complications or exacerbation of preexisting comorbidity. Severe pancreatitis is defined by persistent organ failure (> 48h). Local complications include peripancreatic collections, pseudocysts and pancreatic necrosis (sterile or infected).

The early determination of severity plays a key role in the management of pancreatitis, anticipating the necessary measures and improving the outcome of patients who develop the severe form of the disease [4]. The Ranson, Balthazar, and APACHE-II protocols establish criteria for prognosis. However, they are difficult to memorize, require more than 48 hours for complete stratification and depend on not widely available tests (serial tomography, interleukin-6). A meta-analysis of 100 studies demonstrates that the Ranson score does not have good results for predicting severe pancreatitis with low positive and negative predictive values [12]. In this context, in 2007 Brown., *et al*. set the Panc 3 score [5]: a quick and simple tool to predict severity in pancreatitis, which can be applied early in hospital admission. The Panc3 score is formed by the following parameters: Hematocrit above 44%; Pleural effusion on a single chest X-ray and a body mass index greater than 30 kg/m^2. Patients who meet the 3 criteria of Panc 3 have a 99% probability of developing severe disease, demonstrating the high specificity of this combination. However, it presents sensitivity results of only 31% [6]. Recent studies have shown that increased serum urea and creatinine levels, as well as alterations in the distribution of white blood cells, reflect the severity of the inflammatory process in patients with pancreatitis [7-9]. Thus, the objective of this study is to add new variables to the Panc 3 score, establishing a new tool for gravity prediction, supposedly more sensitive and equally easy and quick to access in any emergency room. The variables to be tested and added are: urea, creatinine, neutrophil / leukocyte ratio, neutrophils / lymphocytes and platelets / leukocytes.

Materials and Methods

The main objective of this study is to establish a new tool for determining the severity prognosis in acute pancreatitis to be used in a large scale in the emergency room. The Panc 3 score is very specific for pancreatitis severity; however its results demonstrate low sensitivity, around 31% in a study performed in this hospital in 2012 [6]. The hypothesis of this study considers that the complementation of Panc 3 with other inflammatory markers increases the sensitivity of the test, without undermining its already consolidated specificity. The present research is characterized as an observational, prospective study in which 37 patients diagnosed with acute biliary pancreatitis, attended by the General Surgery Service of the São José Regional Hospital from November 2015 to September 2016, were evaluated. All the patients participated in the research of their own free desire, being in agreement with the informed consent term. The present study was submitted for evaluation by the Ethics Committee in Research through the Brazil Platform, and was approved by means of the consubstantiated opinion no 1,876,508.

The diagnosis of acute biliary pancreatitis was established in all patients in the study, considering the suggestive clinical condition associated with serum amylase greater than 3 times the limit of normality and / or tomographic findings compatible with acute pancreatitis. The biliary etiology occurred in 100% of the patients, proven with bile lithiasis on previous abdominal ultrasonography. Computed tomography (CT) is not a routine method for the diagnosis of pancreatitis in the General Surgery service, and the cases that were admitted with abdominal CT at the time of diagnosis were referred from the Medical Clinic service.

At hospital admission, a laboratory evaluation was performed with complete blood count, urea and creatinine dosages, simple chest radiography and BMI calculation. The clinical evolution of the patients was observed after hospital admission and clinical outcomes were classified according to the revised Atlanta consensus (Table 1).

The exclusion criteria of the study were patients with biliary lithiasis and a clinical condition suggestive of pancreatitis, but with an increase in amylase below that specified, as well as patients with acute pancreatitis from other institutions and without access to laboratory tests of admission.

Panc 3 score variables were analyzed (Table 2) as well as analysis of the new variables included in the study using the ROC curve for the identification of the most sensitive and specific cutoff point (CP). The MedCalc software was used to obtain the ROC curve for each of the variables, as well as the area under the curve (AUC), confidence interval and p value calculation. AUC greater than 0.5 was considered statistically significant. After analyzing the univariables, we performed sensitivity tests (S) and specificity (E) of five combinations in which we considered: two Panc3 positive variables plus one new positive inflammatory marker (Table 3).

Panc 3 criteria
Hematcrit > 44%
BMI > 30Kg/m^2
Pleural effusion on simple chest x-ray

Table 2.

Prognostic marker proposed combinations
Panc 3 (2 or more criteria) + Urea above the CP
Panc 3 (2 or more criteria) + Creatinine above CP
Panc 3 (2 or more criteria) + neutrophils / leukocytes above the CP
Panc 3 (2 or more criteria) + neutrophils / lymphocytes above the CP
Panc 3 (2 or more criteria) + platelets / leukocytes below the CP

Table 3.

Results and Discussion

Of the 37 patients, 28 (75.6%) presented the mild form of the disease, obtaining spontaneous resolution with the supportive treatment and submitted to cholecystectomy after resolution of the inflammatory condition. Seven patients (18.9%) developed a moderately severe form and two patients (5.4%) had severe pancreatitis. Death occurred in one of the patients (2.7%) with the severe form of the disease.

The Panc 3 score was analyzed in all the patients of the study. Twelve patients (32.4%) had a hematocrit greater than 44%. Pleural effusion on the chest X-ray was observed in six patients (16.21%). The Body Mass Index was higher than 30 kg/m^2 in thirteen patients (35.13%). The three components of the Panc 3 score were present in three patients (8.1%), who developed moderately severe (one patient) and severe (2 patients) forms. Thus the Panc 3 score obtained a sensitivity of (33%) and specificity of (100%) for moderately severe and severe pancreatitis. Its positive predictive value was (100%) and negative predictive value (82%) (Table 4).

Positivity of the Panc 3 criteria for moderately severe / severe PA			
Criteria	**Number of patients**	**Sensitivity**	**Especificity**
Hematocrit > 44%	12	66%	78%
Pleural effusion	6	44%	92%
BMI > 30 Kg/m^2	13	66%	75%
All the criteria	3	33%	100%

Table 4.

The study variables were analyzed through the ROC curve, identifying the most sensitive and specific cut-off point for the following outcomes: moderately severe pancreatitis and severe pancreatitis. Urea was shown to have area under the curve (AUC) of 0.653 (CI 95% 0.479 - 0.801) and its best cutoff point at the dosage > 29 mg/ml. Creatinine obtained AUC of 0.506 (CI 95% 0.377 - 0.674) and a better cutoff point at a dose greater than 0.98mg/dl. The Neutrophil/Leukocytes ratio presented a AUC of 0.738 (CI 95% 0.568-0.868), a better cutoff value above 0.82. Neutrophils/Lymphocytes obtained AUC of 0.750 (CI 95% 0.581-0.877), ideal cut point values above 12.72. Platelets/Leukocytes presented a AUC of 0.679 (CI 95% 0.505-0.822), with a better cutoff value below 11.4 (Figure 1).

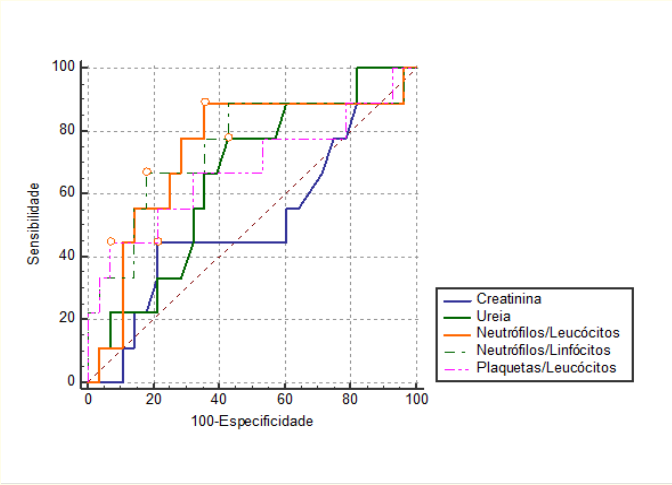

Figure 1: *Comparison of ROC curves of new markers.*

Sensitivity and specificity tests were performed for each of the variables, considering the positive outcomes in cases of moderately severe or severe pancreatitis. The results are shown in Table 5.

Isolated analysis of the new inflammatory markers through the ROC curve					
Varable	**Cut-off point**	**Sensitivity**	**Specificity**	**AUC (Área = 0.5)**	**p**
Urea	> 29 mg/ml	77.7%	57.1%	0.653 (CI 95%0.479 - 0.801)	0.13
Creatinine	> 0.98 mg/dl	44.4%	78.5%	0.506 (CI 95% 0.337 - 0.674)	0.96
Neutrophils/Leukocytes	> 0.82	88.8%	64.2%	0.738 (CI 95% 0.568 - 0.868)	0.02
Neutrophils/Lymphocytes	> 12.72	66.6%	82.1%	0.750 (CI 95% 0.581 - 0.877)	0.02
Platelets/Leukocytes	< 11.40	44.4%	92.8%	0.679 (CI 95% 0.505 - 0.822)	0.03

Table 5.

With the obtaining of the best cut-off points for the study variables, five combinations of prognostic markers were elaborated, as described in table 3. The results are shown below in table 6.

Results of prognostic marker combinations				
Combination	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Panc 3 + Urea	55,3%	92%	71%	76%
Panc 3 + Creatinine	44%	96%	80%	84%
Panc 3 + Neut/Leuk	44%	96%	80%	84%
Panc 3 + Neut/Linp	33%	96%	75%	81%
Panc 3 + Plae/Leuk	22%	100%	100%	80%
PPV Positive predictive value, NPV: Negative predictive value				

Table 6.

The definition of severity of acute pancreatitis has always caused great discussions among specialists because of their great variability of presentation and clinical evolution. The most widely accepted severity classification and severity model is the Atlanta criteria, reviewed at an international conference in 2012. This was the tool used to classify severity in 100% of the study patients.

Although most patients with acute pancreatitis present the mild form of the disease, cases of severity require greater attention and care due to their high morbidity and mortality. Therefore, the early detection of the prognosis of these patients is fundamental to anticipate adequate support, with optimization of oxygenation and tissue perfusion, admission to intensive care units and continuous monitoring.

The current trends in the approach of patients with acute pancreatitis are the stratification of the prognosis in an early manner, that is, in hospital admission. The Panc 3 score was described as a test of high accuracy and high positive predictive value in its original description, but it is a retrospective study. Panc 3 prospective analyzes demonstrated high specificity (100%) but low sensitivity (31.25%) [6], results also found in the present study. It is evidenced the high positive predictive value of Panc3 for severity in acute pancreatitis. However, the number of false negatives remains high, making it necessary to add one more variable that can increase its sensitivity.

New inflammatory markers have been proposed to define the prognosis. Renal failure with increased creatinine levels and reduction of glomerular filtration rate is related to pancreatic necrosis in tomographic studies [9]. Increased urea dosages are associated with increased mortality [8]. Leukogram deviation for neutrophil counts as well as reduction in platelet count is related to the severity of the inflammatory process [7].

The cut-off points for urea and creatinine were > 29 and > 0.98, respectively. Sensitivity and specificity for these cut-off points were not statistically significant. As a small sample, few cutoff points could be evaluated and conclusions cannot be drawn regarding the discard of renal function markers in the prediction of severity in pancreatitis.

Statistically significant sensitivity and specificity values were found for blood counts. Neutrophil/leukocyte values above 0.82 (82% neutrophils) presented considerable sensitivity (88.8%) for the severity of pancreatitis. Neutrophils/lymphocytes above 12.72 obtained specificity of 82%, corroborating with the reports of reduction of the number of lymphocytes and neutrophilia in severe inflammatory processes. The reduction in platelet count associated with leukocytosis, that is, platelets/leukocytes < 11.4, was shown to be the most specific univariate (92.8%) for severe forms of acute pancreatitis.

In order to elaborate a more accurate tool for the prognosis of severity, a new inflammatory marker was added to the already consolidated Panc3 (table 3). The application of the marker combinations occurred at hospital admission, since the variables of the present study are easy to obtain in the emergency room. Each combination is considered positive in patients who had two or more positive Panc 3 criteria and the positive new marker. The combination of the highest sensitivity found was in the combination Panc 3 + urea with S = 55.3% (Table 6), despite the non-statistical significance of urea as an isolated variable. Panc 3 + platelets/leukocytes obtained specificity of 100%, being therefore an alternative to be used in clinical practice and tested in larger series. The other 4 combinations obtained similar results to Panc 3, with high specificity (96 - 100%) and low sensitivity (22 - 44%). Due to the good results of the blood component ratios as isolated prognostic markers, there is a high probability that combinations of markers including neutrophils/lymphocytes or neutrophils/leukocytes have better sensitivity results in larger series.

Considering the most sensitive combination (Panc 3 + Urea) and the more specific combination (Panc 3 + platelets/leukocytes) we propose a score of Panc 4: Two Panc3 markers + urea + platelet/leukocyte. Like Panc 3, the Panc 4 proposed in this work is easy to perform and provides a prognosis of severity at hospital admission, but possibly with better results in terms of sensitivity and maintaining specificity around 100%.

Conclusion

Achieving high accuracy in a test of easy execution and access is possible. In the present study, we obtained combinations of inflammatory markers with greater sensitivity and similar specificity to Panc 3.

The results of the present study demonstrate that there is no need to have the three Panc 3 criteria to achieve high specificity, since other markers were equally specific when associated with only 2 Panc 3 criteria, highlighting the combination 2 Panc3 + platelet/leukocytes. In addition, a better sensitivity result was obtained with the association of 2 Panc3 + urea criteria compared to the original Panc 3. Thus, the proposed Panc 4 (2 Panc3 + urea + platelets / leukocytes) criteria is a more accurate score for the prognosis of severity, but it needs to be tested in larger series to prove good results also in large scale and diffuse its use in clinical practice.

Conflict of Interest

There is no conflict of interest in this study.

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