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Predicting death and severity in acute pancreatitis: A retrospective study

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Predicting death and severity in acute pancreatitis:

A retrospective study

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Abbreviations

AP: Acute Pancreatitis

AC12: Revised Atlanta Classification 2012

ALT: Alanine aminotransferase

APACHE II: Acute Physiology and Chronic Health Evaluation

AST: Aspartate aminotransferase

AUC: Area under curve

BISAP: Bedside Index for Severity in Acute Pancreatitis

BUN: Blood urea nitrogen

CECT: Contrast enhanced computer tomography

CHUC: Centro Hospitalar e Universitário de Coimbra

CRP: C-reactive Protein

DBC: Determinant Based Classification

GGT: Gamma-Glutamyl Transferase

mCTSI: Modified Computer Tomography Severity Index

NPV: Negative predictive value

PPV: Positive predictive value

ROC: Receiver operating characteristic

SIRS: Systemic Inflammatory Response Syndrome

WBC: White blood cells

Abstract

Introduction: Several different clinical scoring systems and biomarkers have been proposed to predict acute pancreatitis (AP) severity at admission. The aim of this study was to assess the ability of the Bedside Index of Severity in Acute Pancreatitis (BISAP), Systemic Inflammatory Response Syndrome (SIRS), Ranson's, modified Computer Tomography Severity Index (mCTSI), C-reactive protein (CRP) at 48 hours, lactates, blood urea nitrogen (BUN), haematocrit, white blood cells (WBC), glycaemia, prothrombinemia, amylase, lipase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and bilirubin in predicting the severity and mortality for AP.

Methods: A retrospective study was performed including all patients with AP admitted into the Gastroenterology Department of Centro Hospitalar e Universitário de Coimbra between January/2012 and December/2013. The severity of AP was defined using the Revised Atlanta Classification of 2012 (AC12) and data regarding aetiology, clinical parameters, radiology and patient's demographics were collected. The outcomes defined were survival or death and mild or moderately severe/severe AP.

Results: This study included 197 patients (Male-119; Mean age-62 ± 17 years). There were 9 deaths (4.6%) and 84 cases of moderately severe/severe AP (42.6%). CRP at 48 hours was the best parameter for predicting both mortality (AUC=0.943, $p<0.001$) and severity (AUC=0.741, $p<0.001$). Lactates was the best biochemical parameter at admission for predicting mortality (AUC=0.911, $p<0.001$). Lactates≥1.64 mmol/L at admission and CRP at 48 hours ≥27.4 mg/L had 100% sensitivity for predicting mortality. Prothrombinemia and haematocrit's accuracy were acceptable (AUC=0.793 and AUC=0.760) for predicting mortality. Haematocrit≥46.9% and prothrombinemia≤71.5% were associated with much higher risk of death (OR 25.11 and 11.66). BUN was the best

predictor for severity (AUC=0.670, p<0.001) at admission, with acceptable accuracy for predicting mortality (AUC=0.720, p=0.035). SIRS and BISAP≥3 were associated with much higher risk of mortality (OR 14.95 and 11.84) and mild increases in risk of AP being moderately severe/severe (OR 3.48 and 5.28). Ranson≥3 determined mild increases of risk in both severity (OR 3.28) and mortality (OR 4.56). WBC and glycaemia had acceptable accuracy on predicting mortality (AUC=0.701 and AUC=0.720) and poor accuracy for predicting severity (AUC=0.642 and AUC=0.642). Being the first episode of AP was also associated with increased risk of severity.

Conclusion: Glycaemia, WBC count, BUN, SIRS, BISAP and Ranson's criteria have shown some capability in predicting both mortality and severity at admission. Elevated lactates at admission and CRP at 48 hours were the best predictors of mortality. Elevated haematocrit, decreased prothrombinemia, presence of SIRS and BISAP≥3 were associated with much higher risk of mortality.

Keywords: Acute pancreatitis, Prognostic markers, Mortality, Lactates, C-reactive protein

Resumo

Introdução: Vários sistemas de pontuação clínica e biomarcadores foram propostos para prever a gravidade da pancreatite aguda (PA) á admissão. O objetivo deste estudo é avaliar a capacidade dos sistemas de pontuação Bedside Index of Severity in Acute Pancreatitis (BISAP), Systemic Inflammatory Response Syndrome (SIRS), Ranson's, modified Computer Tomography Severity Index, e dos seguintes biomarcadores proteína c reativa (PCR) às 48 horas, lactatos, azoto ureico (AU), hematócrito, leucócitos, glicemia, protrombinemia, amílase, lípase, aspartato aminotransferase, alanina aminotransferase, gama-glutamil transferase, fosfatase alcalina e bilirrubina na sua capacidade de prever a gravidade e a mortalidade na PA.

Métodos: Realizou-se um estudo retrospetivo, incluindo todos os pacientes, admitidos no Departamento de Gastroenterologia do Centro Hospitalar e Universitário de Coimbra entre Janeiro/2012 e Dezembro/2013. A gravidade da AP foi definida utilizando a Classificação Revista de Atlanta de 2012 (AC12) e os dados referentes à etiologia, parâmetros clínicos, exames de imagiologia e dados demográficos dos pacientes foram colhidos. Os desfechos definidos foram sobrevivência ou morte e PA ligeira ou moderadamente severa a severa.

Resultados: Este estudo incluiu 197 pacientes, com uma media de idades de 62 ± 17 anos e predomínio masculino com 119 casos. Houve 9 óbitos (4,6%) e 84 casos de PA moderadamente grave a grave (42.6%). A PCR às 48 horas foi o melhor parâmetro para predizer a mortalidade (AUC=0,943, p<0,001) e gravidade (AUC=0,741, p<0,001). Os lactatos foram o melhor parâmetro bioquímico à admissão para predizer a mortalidade (AUC = 0,911, p <0,001). os lactatos≥1,64 mmol/L à admissão e PCR às 48 horas≥27,35 mg/L apresentaram uma sensibilidade de 100% para prever mortalidade. A protrombinemia e o hematócrito tiveram precisão aceitável (AUC=0,793 e AUC=0,760)

para predizer a mortalidade. Hematócrito≥46,9% e protrombinemia≤71,5% foram associados com risco muito elevado de óbito (OR 25,11 e 11,66). O AU foi o melhor preditor à admissão para a gravidade (AUC=0,670, p<0,001) e teve precisão aceitável para predizer a mortalidade (AUC=0,720, p=0,035). SIRS e BISAP≥3 foram associados com risco aumentado de mortalidade (OR 14,95 e 11,84) e ligeiro aumento no risco de a PA ser moderadamente severa a severa (OR 3,48 e 5,28). Ranson≥3 determinou aumento ligeiro de risco tanto para a gravidade (OR 3,28) como para a mortalidade (OR 4,56). Os leucócitos e a glicemia apresentaram precisão aceitável na predição de mortalidade (AUC=0,701 e AUC=0,720) e baixa precisão na predição da gravidade (AUC=0,642 e AUC=0,642). Ser o primeiro episódio de PA esteve também associado com risco aumentado de severidade.

Conclusão: Glicemia, contagem de leucócitos, AU, SIRS, BISAP e Ranson demonstraram alguma capacidade de previsão de mortalidade e gravidade à admissão. A elevação dos lactatos à admissão e PCR às 48 horas foram os melhores preditores de mortalidade. Hematócrito elevado, diminuição da protrombinemia, presença de SIRS e BISAP≥3 estão associados a um risco muito maior de óbito.

Palavras Chave: Pancreatite Aguda, Marcadores de Prognóstico, Mortalidade, Lactatos, Proteína C Reativa.

Introduction

Acute pancreatitis (AP) is a clinical entity with an annual incidence of 13-45 cases per 100,000 inhabitants[1]. A United States study showed that AP was the most common single gastrointestinal diagnosis with an estimated cost of 2.6 billion dollars per year in inpatient costs[2].

AP is considered to have two distinct clinical phases that may overlap: the early phase and the late phase.[3–5] The early phase usually lasts 1 week and is due to the systemic manifestations of the disease secondary to the cytokine cascade and the systemic inflammatory response syndrome (SIRS). It is during this phase that organ failure may appear.[3] The late phase is characterized by the persistence of ongoing inflammation and by the presence of local and systemic complications.[3] There is a peak of mortality in each phase, with organ failure being the most common cause of death in the early phase and infections in the late phase. The inflammation may settle spontaneously or may progress to necrosis of the pancreas or surrounding fatty tissue[6]. Mortalities range from 1% in all cases of AP up to 40% in severe cases with persistent organ failure, showing the clinical heterogeneity and unpredictable outcome of AP [1,7].

To better differentiate which cases require intensive care management and which cases can potentially be treated on a regular ward, several different severity classification systems have been developed, the two most widely used to date are the Revised Atlanta Classification (Atlanta 2012)[3,8–10] and the Determinant Based Classification (DBC)[4,10,11]. The Atlanta 2012 divides AP into mild, moderately severe and severe depending on the presence of transient or persistent organ failure and/or local complications[3,8,9]. The DBC divides AP into mild/medium, moderate, severe and critical by taking into account the presence or absence of peripancreatic or pancreatic necrosis, sterile or infected necrosis

and transient or persistent organ failure[4,11]. A recent study concluded that both classification systems perform equally well for classification of disease severity[12].

However, both classifications suffer from the same drawback since both require more than 48 hours to fully define the severity of the disease. Considering that AP's clinical course varies wildly, it is important to predict severe cases on admission to initiate more aggressive therapies, such as early intensive care admission[13]. With that purpose in mind, several different clinical scoring systems and biomarkers have been developed and tested, such as the Bedside Index for Severity in Acute Pancreatitis (BISAP)[14], Ranson's criteria[15], Modified Computed Tomography Severity Index (mCTSI)[15], haematocrit upon admission[15] and others with the aim of predicting the disease severity at presentation. There is still a lack of a clear indication of which scoring system and biomarker is the best for clinical use.

The aim of this study is to assess the ability of some scoring systems like BISAP≥3, presence of SIRS, Ranson≥3 and mCTSI>6 and some biomarkers, C reactive protein (CRP) at 48 hours, lactates, blood urea nitrogen (BUN), haematocrit, white blood cells (WBC), glycaemia, prothrombinemia, amylase, lipase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin and direct bilirubin in predicting the severity and mortality in patients admitted for acute pancreatitis. Other factors like gender, and first episode of AP were also analysed.

Methods

Data Collection

A retrospective study was performed including all patients with the diagnosis of AP, admitted into the Gastroenterology Department of Centro Hospitalar e Universitário de Coimbra (CHUC) between January of 2012 and December of 2013, whose discharge notes contained the words "Pancreatitis" and "Acute". All cases were reviewed and excluded if AP was misdiagnosed or if it was AP as complication of endoscopic retrograde cholangiopancreatography. The remaining cases were included and the corresponding discharge notes, emergency department notes, laboratory analysis and imagiological exams were reviewed and the following information was collected: age (years), gender, length of hospital stay (days), time from symptoms onset until arrival at the emergency department (hours), AP aetiology, body temperature in Celsius, heart rate (pulse per minute), respiratory rate, arterial blood lactate (mmol/L), partial pressure of oxygen in arterial blood (mmHg), partial pressure of carbon dioxide in arterial blood (mmHg), systolic blood pressure (mmHg), haematocrit (%), CRP at 48 hours after disease onset (mg/dL), WBC ($x10^9$/L), platelets ($x10^9$/L), prothrombinemia (%), glycaemia (mg/dL), creatinine (mg/dL), BUN (mg/dL), lactate dehydrogenase (LDH) (U/L), AST (U/L), ALT (U/L), GGT (U/L), alkaline phosphatase (U/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), triglycerides (mg/dL), amylase (U/L), lipase (U/L), presence of pleural effusion, presence of infection and presence of local complications (acute pancreatic fluid collection, pseudocyst, acute necrotic collection, walled-off necrosis). Using the data collected the following scores and classifications were determined retrospectively: AC12, BISAP, Ranson's admission criteria, SIRS and mCTSI. The outcomes defined for this study were survival or death and mild or moderately severe to severe AP.

Definitions

The diagnosis of AP was defined by the presence of at least 2 of the following 3 criteria: (A) Characteristic upper abdominal pain with or without radiation to the back; (B) Serum Amylase or Lipase three times the upper limit of normality; (C) Characteristic findings of AP on abdominal contrast enhanced computer tomography (CECT), magnetic resonance or transabdominal ultrasonography[4,5]. The aetiology of AP was considered biliary when gallstones or bile duct stones were encountered, alcohol induced when severe exposure to alcohol was present (defined as a daily intake of at least 50 grams over the course of at least 5 years.), hypertriglyceridemia when serum triglycerides were above 1000mg/dL, AP caused by rarer aetiologies (drugs, pregnancy, cancer among others), was classified as others and all AP in which the aetiology could not be discerned were classified as undetermined.

The severity of AP was established using the AC12 that divides AP into mild, moderately severe and severe. Mild AP entails no local complications and no organ failure, moderately severe AP has either transient organ failure (less than 48 hours) or local complications, Severe AP is defined by persistent organ failure (more than 48 hours). Organ failure was assessed using the modified Marshal classification that considers the three major organ systems affected in AP: cardiovascular, renal and pulmonary system[16]. To better stratify the patients, we decided to consider only two groups: mild AP and moderately severe/severe AP.

BISAP score was calculated by the sum of the presence of the following conditions, each worth 1 point: presence of SIRS, impaired mental status, BUN over 25 mg/dl, presence of pleural effusion and age over 60 years. SIRS was deemed present when 2 of the following 4 criteria were met: (A) temperature of <36ºC or >38ºC; (B) partial pressure of arterial carbon dioxide <32 mmHg or respiratory rate >20 breaths per minute; (C) pulse

>90 beats per minute; (D) WBC count < 4000 cells/mm^3 or >12000 cells/mm^3 or >10% immature bands. A cut-off value of ≥3 was used for the BISAP score.

Ranson's criteria was calculated only using the five parameters at admission: age >55 years; serum glucose >200 mg/dl; WBC count >16000 cells/mm^3; AST >250 U/L and LDH >350 U/L. A cut-off value of ≥3 was used for the Ranson's admission criteria.

Since CECT is usually only performed with the intention of either diagnosing AP, diagnosing the aetiology or to investigate potential local complications, the CECT data was not available to all patients and didn't follow specific time rules.

mCTSI is a point based system accessed through an abdominal CECT and is divided as follows: (A) Regarding to the degree of pancreatic inflammation 0 points are given if the pancreas is normal, 2 points if there are intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat and 4 points for the presence of pancreatic or peripancreatic fluid or peripancreatic fat necrosis. (B) Depending on the degree of pancreatic necrosis, 0 points are given if there is none, 2 points if it is below 30% of the total pancreatic parenchyma and 4 points if it exceeds 30%. (C) 2 points are given for the presence of extrapancreatic complications such as pleural effusion, ascites, vascular complications, parenchymal complications and gastrointestinal involvement. A cut-off value of >6 points was used.

Appendix 1 contains all the scoring systems and classifications used in this study.

Statistical analysis

Categorical variables were described by absolute and relative frequencies. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data were reported using means and standard deviation and non-normally distributed data were reported using medians with their interquartile range.

Comparison between patients with mild AP and those with moderately severe to severe was performed using t-Student test and for comparing patients who survived and those who died the Man-Whitney U test was used, in agreement with results of normality assessments. Statistically different parameters were highlighted in both analysis. For comparing paired nominal data

For the study of the capability of predicting the severity and mortality of AP, continuous variables (CRP at 48 hours, lactates, BUN, haematocrit, WBC, glycaemia, prothrombinemia, amylase, lipase, AST, ALT, GGT, alkaline phosphatase, total bilirubin and direct bilirubin) were analysed with receiver operating characteristic (ROC)[17] analysis in order to calculate their area under the curve (AUC). Both categorical data (BISAP≥3, Ranson≥3, mCTSI>6, male gender, first episode, comorbidities and SIRS) and the best cut-off value of continuous variables (calculated using the youden index[18]) were analysed with either chi-squared test or Fisher's exact test and the respective sensitivity, specificity, and odds ratio were calculated. The analysis was performed on IBM SPSS Statistics 23. The significance value adopted was 0.05.

Results

This study included 197 patients, with 119 males and 78 females. The mean age was 62 ± 17 years. The mean age for males was 60 ± 17 years while for females was 66 ± 17 years. The median waiting period for a CECT scan was 7 days which was performed on 93 patients in total. **Table 1** provides a quick summary of the study sample.

Table 1 Demographic and clinical characteristics of the study sample

Parameter	*Frequency (Percentage)*
Male	119 (60.4)
Female	78 (39.6)
Age	62 ± 17
First episode	133 (67.5)
Deaths	9 (4.6)
Organ Failure	49 (24.9)
Aetiology	
Biliary	76 (38.6)
Alcohol	45 (22.8)
Hypertriglyceridemia	7 (3.6)
Other	6 (3)
Undetermined	63 (32.0)

Severity study

In total 42.6% of all AP were moderately severe to severe, of which 18.8% were severe and 23.9% were moderately severe. Considering male gender, 48.7% were at least moderately severe (moderately severe – 26.9%; severe – 21.8%), while in female gender, 33.3% were at least moderately severe (moderately severe – 18.2%; severe – 15.1%). By aetiologies, hypertriglyceridemia had the highest percentage of at least moderately severe AP with 71.5% (moderately severe – 42.9%; severe – 28.6%), followed by biliary aetiology with 42.1% (moderately severe – 15.8%; severe – 26.3%), then undetermined AP at 41.3% (moderately severe – 28.6%; severe – 12.7%), next comes alcohol abuse with 40% (moderately severe – 26.7%; severe – 13.3%) and lastly the others group that had 33.3% of at least moderately severe AP (moderately severe – 16.7%; severe – 16.7%). **Table 2** shows the comparison between patients that had mild AP and those with moderately severe to severe disease regarding the parameters tested in this study.

The ROC analysis of continuous parameters for severity prediction is presented on **Table 3**. Haematocrit, amylase, lipase, AST, ALT, GGT, alkaline phosphatase, total bilirubin, direct bilirubin didn't reach statistical significance therefore were not presented. No parameter tested showed excellent test results, the best one being CRP 48 hours after admission with an acceptable accuracy (AUC=0.741). BUN, lactates, WBC, glycaemia and prothrombinemia all presented poor accuracy for predicting severity.

The risk analysis for categorical parameters regarding the risk of AP being at least moderately severe is presented in **Table 4**. Most parameters were only associated with mild increases in risk of moderately severe and severe AP. CRP at 48 hours after admission≥18.6 mg/L was the best parameter with an OR of 6.25 while BISAP≥3 was the most relevant score at admission with an OR of 5.28. Glycaemia≥150.5 mg/dL and

lactates≥1.64 mmol/L slightly outperformed both the Ranson's admission criteria≥3 and the presence of SIRS

Table 2 Baseline characteristics of the mild AP population vs. moderately severe to severe AP.

Parameter	Mild AP (n = 113)	Moderately severe to severe AP (n = 84)	P value
Age (years)	61.6 ± 16.8	62.7 ± 16.8	0.661
Gender (M/F)	61/52	58/26	**0.032**
First Episode(yes/no)	67/46	66/18	**0.004**
SIRS (yes/no)	27/81	44/38	**<0.001**
BISAP >3 (yes/no)	12/101	32/51	**<0.001**
Ranson (yes/no)	24/89	39/44	**<0.001**
mCTSI >6 (yes/no)	0/30	12/51	**0.008**
BUN (mg/dL)	18.4 ± 7.7	27.7 ± 17.3	**<0.001**
Haematocrit (%)	40.7 ± 5.1	40.7 ± 7.1	0.964
WBC ($x10^9$/L)	11.7 ± 3.9	14.2 ± 5.5	**<0.001**
Prothrombinemia (%)	85.4 ± 13.6	78.4 ± 17.8	**0.004**
Glycaemia (mg/dL)	131.2 ± 45.4	160.0 ± 75.7	**0.002**
AST (U/L)	228.5 ± 351.5	205.6 ± 253.0	0.614
ALT (U/L)	218.2 ± 311.2	171.9 ± 213.0	0.218
Alkaline phosphatase (U/L)	160.8 ± 152.7	175.2 ± 198.4	0.564
GGT (U/L)	315.9 ± 351.6	398.4 ± 421.7	0.139
Total bilirubin (mg/dL)	2.5 ± 3.1	2.3 ± 2.5	0.540
Direct bilirubin (mg/dL)	2.1 ± 2.5	1.6 ± 1.8	0.222
Amylase (U/L)	1225.5 ± 1241.5	1432.4 ± 1382.4	0.272
Lipase (U/L)	1330.3 ± 2118.4	1753.7 ± 2296.2	0.462
Lactates (mmol/L)	1.28 ± 0.72	1.85 ± 1.39	**0.001**
CRP at 48 hours (mg/L)	11.5 ± 9.6	20.7 ± 11.0	**<0.001**

BISAP: Bedside Index for Severity in Acute Pancreatitis; SIRS: Systemic Inflammatory Response Syndrome; mCTSI: Modified Computed Tomography Severity Index; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; WBC: White Blood Cell. AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma-Glutamyl Transferase.

Table 3 Receiver operator curve analysis of continuous parameters for predicting disease severity

SEVERITY			
Parameter	AUC [95% CI]	p value	Best cut-off
CRP at 48h	0.741 [0.668-0.814]	p<0.001	≥18.6
BUN	0.670 [0.591-0.749]	p<0.001	≥20.9
Lactates	0.643 [0.557-0.729]	p=0.002	≥1.64
WBC	0.642 [0.564-0.721]	p=0.001	≥11.5
Glycaemia	0.642 [0.564-0.721]	p=0.001	≥150.5
Prothrombinemia	0.610 [0.525-0.694]	p=0.012	≤71.5

AUC: Area Under Curve; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; WBC: White Blood Cells. Severe disease was defined as moderately severe or severe acute pancreatitis. The best cut-off value was calculated using the youden index.

Table 4 Risk analysis for predicting disease severity.

Severity					
Parameter	n (%)	Odds Ratio	p value	Sensitivity	Specificity
CRP at 48h≥18.6 mg/L	66(38)	6.25	p<0.001	60%	80.6%
BISAP≥3	44(22)	5.28	p<0.001	39%	89%
Glycaemia≥150.5 mg/dL	60(30)	3.80	p<0.001	46.4%	81.4%
Lactates≥1.64 mmol/L	52(33)	3.77	p<0.001	47.4%	80.7%
SIRS	71(37)	3.48	p<0.001	54%	75%
Prothrombinemia≤71.5%	41(23)	3.39	p=0.001	35.1%	86.3%
Ranson≥3	63(32)	3.28	p<0.001	47%	79%
BUN≥20.9 mg/dL	82(43)	3.00	p<0.001	58%	69.4%
WBC≥11.5 x10^9/L	103(52)	2.81	p<0.001	66.7%	58.4%
First Episode	133(68)	2.51	p=0.004	79%	41%
Male gender	119(60)	1.90	p=0.032	32%	46%
mCTSI>6	12(13)	1.59	p=0.008	19%	100%

BISAP: Bedside Index for Severity in Acute Pancreatitis; SIRS: Systemic Inflammatory Response Syndrome; mCTSI: Modified Computed Tomography Severity Index; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; WBC: White Blood Cell.

Mortality Study

Overall mortality was 4.6%, while mortality among severe AP was 24.3%. There were 9 deaths in total of which 6 (66.7%) were due to respiratory failure and 3 (33.4%) to multiple organ failure. Eight deaths occurred among males (6.7% mortality) and only 1 was female (1.3% mortality). Among aetiologies AP caused by hypertriglyceridemia showed the highest mortality rate, 14.3%, however it must be noted that there were only 7 cases with 1 death. Alcohol abuse induced AP had the second highest mortality rate, 6.6%. Undetermined AP had 4.8% mortality rate and biliary AP mortality rate was of 2.6%. There were no deaths in the others group. **Table 5** contains the comparison between patients that survived the episode of AP and those who died.

The receiver operator curve analysis of continuous parameters for mortality prediction is presented on **Table 6**. Amylase, lipase, LDH, AST, ALT, GGT, alkaline phosphatase, total bilirubin, direct bilirubin didn't reach statistical significance therefore were not presented. CRP at 48 hours after admission and lactates' results were excellent (AUC=0.943 and AUC=0.911 respectively). Prothrombinemia and haematocrit's accuracy were acceptable (AUC=0.793 and AUC=0.760 respectively) and were both superior to glycaemia (AUC=0.720), BUN (AUC=0.720) and WBC (AUC=0.701).

The risk analysis for categorical parameters regarding risk of mortality is presented in **Table 7**. All parameters except for male gender and first episode of AP showed an increased risk of death when positive. Both lactates≥1.64 mmol/L and CRP at 48 hours after admission≥27.4 mg/dL showed a 100% sensitivity in predicting mortality. mCTSI>6, haematocrit≥46.9%, SIRS, BISAP≥3 and prothrombinemia≤71.5% were all associated with a much higher risk of death.

Table 5 Baseline characteristics of the patients that survived vs. the patients that died.

	Mortality		
Parameter	Survived (n = 188)	Deaths (n = 9)	p value
Age (years)	64 (IQR=27)	63 (IQR=33)	0.568
Gender (M/F)	111/77	8/1	0.090
First Episode(yes/no)	126/62	7/2	0.721
SIRS (yes/no)	63/118	8/1	**0.002**
BISAP >3 (yes/no)	38/150	6/2	**0.002**
Ranson (yes/no)	57/130	6/3	**0.032**
mCTSI >6 (yes/no)	7/79	5/2	**<0.001**
BUN (mg/dL)	19.0 (IQR=11.0)	30.0 (IQR=25.0)	**0.035**
Haematocrit (%)	40.3 (IQR=8.1)	47.0 (IQR=2.1)	**0.008**
WBC ($x10^9$/L)	11.6 (IQR=6.1)	15.1 (IQR=5.0)	**0.042**
Prothrombinemia (%)	83.0 (IQR=23.0)	63.0 (IQR=22.0)	**0.005**
Glycaemia (mg/dL)	126.0 (IQR=48.0)	151.0 (IQR=56.0)	**0.026**
AST (U/L)	116.0 (IQR=257.0)	164.0 (IQR=144.0)	0.398
ALT (U/L)	88.0 (IQR=214.0)	151.0 (IQR=106.0)	0.702
Alkaline phosphatase (U/L)	110.0 (IQR=128.0)	81.0 (IQR=22.0)	0.139
GGT (U/L)	233.0 (IQR=435.0)	382.0 (IQR=312.0)	0.307
Total bilirubin (mg/dL)	1.4 (IQR=2.0)	1.4 (IQR=0.8)	0.988
Direct bilirubin (mg/dL)	0.8 (IQR=2.3)	0.8 (IQR=0.4)	0.344
Amylase (U/L)	890.0 (IQR=1361.0)	1190.0 (IQR=1605.0)	0.141
Lipase (U/L)	542.0 (IQR=1275.0)	2168.5	0.118
Lactates (mmol/L)	1.20 (IQR=0.86)	3.14 (IQR=3.82)	**<0.001**
CRP at 48 hours (mg/L)	13.7 (IQR=16.0)	33.8 (IQR=10.0)	**<0.001**

BISAP: Bedside Index for Severity in Acute Pancreatitis; SIRS: Systemic Inflammatory Response Syndrome; mCTSI: Modified Computed Tomography Severity Index; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; WBC: White Blood Cell. AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma-Glutamyl Transferase. IQR: Interquartile Range.

Table 6 Receiver operator curve analysis of continuous parameters for predicting mortality.

	Mortality		
Parameter	AUC [95% CI]	p value	Best cut-off
CRP at 48h	0.943 [0.899-0.988]	p<0.001	≥27.35
Lactates	0.911 [0.832-0.991]	p<0.001	≥1.635
Prothrombinemia	0.793 [0.645-0.942]	p=0.005	≤71.5
Haematocrit	0.760 [0.545-0.975]	p=0.008	≥46.85
Glycaemia	0.720 [0.568-0.872]	p=0.026	≥142
BUN	0.720 [0.532-0.909]	p=0.035	≥25.5
WBC	0.701 [0.513- 0.888]	p=0.042	≥13.95

AUC: Area Under Curve; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; WBC: White Blood Cells. Severe disease was defined as moderately severe or severe acute pancreatitis. The best cut-off value was calculated using the youden index.

Table 7 Risk analysis for mortality prediction.

	Mortality				
Parameter	N (%)	Odds Ratio	p value	Sensitivity	Specificity
CRP at 48h≥27.4 mg/L	33(19)	-	p<0.001	100%	85%
Lactates≥1.64 mmol/L	52(33)	-	p<0.001	100%	71%
mCTSI>6	12(13)	28.21	p<0.001	71%	92%
Haematocrit≥46.9%	30(15)	25.11	p<0.001	78%	88%
SIRS	71(37)	14.95	p=0.002	89%	65%
BISAP≥3	44(22)	11.84	p=0.002	75%	80%
Prothrombinemia≤71.50 %	41(23)	11.66	p=0.002	75%	80%
WBC≥14.0 x10^9/L	67(34)	7.47	p=0.008	78%	68%
Glycaemia≥142.0 mg/dL	75(38)	6.18	p=0.028	78%	64%
BUN≥25.5 mg/dL	47(24)	5.64	p=0.022	63%	77%
Ranson≥3	63(32)	4.56	p=0.032	67%	70%

CRP: C Reactive Protein; mCTSI: Modified Computed Tomography Severity Index; SIRS: Systemic Inflammatory Response Syndrome; BISAP: Bedside Index for Severity in Acute Pancreatitis; WBC: White Blood Cell; BUN: Blood Urea Nitrogen.

Discussion

The importance of an accurate prediction of AP's severity upon admission is to be able to safely select patients in whom early, aggressive intervention is indicated[19] and also the selection of mild cases in whom treatment can be less aggressive and hospital stay potentially shortened. An ideal prognostic test should be usable on admission, cheap and with high sensitivity to quickly select the patients in whom severe pancreatitis is extremely unlikely and treatment can be restrained, then a costlier exam with higher specificity could potentially be used to select those who are best treated in intensive care units. However most prognostic scores and parameters currently used fall under the second category and a higher sensitivity prognostic factor at admission is still needed.

The present study demonstrated that most continuous parameters tested show better results when predicting mortality than severity, this is likely due to severity including cases of moderately severe AP that only had local complications and no significant hemodynamic repercussions.

CRP at 48 hours revealed the best overall performance when predicting both mortality and severity but, since it requires a waiting period of 48 hours, it can't be used as an at admission stratification approach. Lactate levels at admission seemed to be almost as good as CRP at 48 hours, with no deaths occurring for values under 1.64 mmol/L. Thus, arterial blood gas measurement on patient admission is an excellent method to quickly select those who are at highest risk of death.

BUN showed to be a capable predictor of both mortality and severity and given the simplicity to obtain such parameter in an emergency department it should be part of the initial assessment. Nonetheless, it isn't sufficient on its own to reliably stratify patients. A recent meta-analysis of 3 studies that evaluated the capability of BUN to predict

mortality in AP showed an accuracy of 0.84 (AUC, 0.72-0,92)[20], a value higher than the one obtained in our study most likely due to the fact that the meta-analysis also included a measurement of BUN at 24 hours that increases overall efficacy. The same meta-analysis considered a cut-off of≥20 mg/dL[20] while in our study the best cut-off for predicting mortality was≥25.5 mg/dL.

A 2006 study on prediction of mortality in biliary pancreatitis by serum glucose at admission reported a sensitivity of 88% and specificity of 63% for glucose≥8.3 mmol/L (≈ 150 mg/dL)[21] compared to our study's 77.8% sensitivity and 63.8% specificity for glucose≥142 mg/dL which probably means that glucose is a good overall predictor of mortality in AP but is more accurate in the specific group of biliary pancreatitis patients.

Haematocrit at admission appears to be a good single parameter predictor for mortality, outperforming BUN, WBC and glycaemia. A 2004 study found that haematocrit at admission≥50% was a predictor of severe AP (OR-14.5)[22]. Unfortunately, this study used a different method to classify AP as severe. Another study showed that haemoconcentration (defined in the study as a haemoglobin≥14.6 mg/dL) in the first 24 hours after admission showed no increased risk of death (OR-1) in the overall sample but a much higher risk of death (OR-7.2) when only transferred cases (patients that had to undergo transportation from primary care hospitals to more specialized ones) were considered[23]. The conflicting results regarding haematocrit's role in predicting severity and mortality has been address in several review articles[15,24] and perhaps this is due to the lack of a robust prospective study evaluating this single parameter.

Prothrombinemia also showed a good capability of predicting mortality and no other study that evaluated its prognostic capabilities was found on the literature. A study evaluating the utility of d-dimer (another biomarker related to coagulation derangements that elevates with thrombotic events) found that it was also a useful biomarker in

predicting severity and mortality[25]. Perhaps the degree of coagulation derangement is closely related to the prognostic outcome. It must be noted however that no data was collected to whether patients were on anticoagulation therapy or not and this may be a confounding variable.

The risk analysis performed shows that the BISAP score is a highly specific scoring system for both severity and mortality and Ranson's criteria also appear to have high specificity for predicting both outcomes. While we didn't perform a direct comparission between both scoring systems a recent meta-analysis[26] demonstrated that BISAP had higher specificity on predicting mortality while Ranson had higher sensitivity[26]. This leads to the conclusion that neither scoring system can be considered superior and used at the expense of the other.

The mCTSI>6 clearly shows a much higher risk of death, but given that most patients didn't perform a CECT at admission, its' value as a predictor for mortality when used at admission can't be extrapolated from the present study. A 2009 manuscript analysed the prediction capabilities of the computed tomography severity index, a different score but similar to mCTSI, only on patients that performed CECT on the first 48 hours after admission[27]. It found promising results with an OR of 14.7 and 15.4 for predicting severe AP and mortality respectively, however it must be noted that the classification used to define the severity of patients was different to AC12.

Only the AP being a first occurrence showed a decent sensitivity for predicting disease severity (79%). One possible explanation is, perhaps, due to the diagnosis of AP being more easily suspected if there is history of a previous one, which might incite earlier treatment, leading to less severe cases overall. Another possible explanation is patients being more aware of the symptomology associated with AP and the time from pain onset to hospital admission being much shorter consequently. Further studies are required in

this field to be able to conclude if a first episode of AP is an independent risk factor for disease severity.

Overall, most parameters tested had decent prediction capabilities and several parameters not included in BISAP and Ranson's criteria like lactates, haematocrit and prothrombinemia have shown good results and a prospective study in which these parameters are included in these prognostic scores or perhaps the creation of a new scoring system could potentially reveal better results than BISAP and Ranson's criteria have shown so far.

Regarding study limitations, firstly this was a retrospective analysis based on discharge notes and laboratory notes, therefore we can't assume that a standard procedure was followed for every single case and potentials errors might exist in the registry of subjective matters like presence of comorbidities. Secondly this is a single centre study and the results can't be safely extrapolated to the general population. Finally it should also be noted that there are many more proposed and accepted parameters and scoring systems for predicting mortality and severity among the literature that weren't used in this study, like for example: hypertriglyceridemia[28], urinary trypsinogen activation peptide[29], the prealbumin-to-fibrogen ratio[30], serum procalcitonin[15,24,31], the harmless acute pancreatitis score (HAPS)[24], the APACHE II score[15,32], radial endoscopic ultrasound[33] and the Glasgow score[15].

Conclusion

Glycaemia, WBC count, BUN, SIRS, BISAP and Ranson's criteria have shown some capability in predicting both mortality and severity at admission. Elevated lactates at admission and elevated CRP at 48 hours were the best predictors of mortality. Elevated haematocrit, decreased prothrombinemia, presence of SIRS and BISAP≥3 are associated with much higher risk of mortality while most parameters tested showed mild increases in risk of AP being moderately severe to severe. The only clinical parameter that showed decent sensitivity for predicting severity was AP being a first episode.

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Appendix 1. Tables of Scoring and Classification Systems in Acute Pancreatitis

Revised Atlanta Classification of 2012

Parameter	Mild AP	Moderately Severe AP	Severe AP
Organ Failure	Absent	Transient (<48 hours)	Persistent (> 48 hours)
Local Complications	Absent	Present	May be absent or present

AP: Acute Pancreatitis. Organ failure defined as a score of ≥ 2 in any parameter of the modified marshal scoring system (see below).

Modified Marshall Scoring System

Organ: Parameter	0	1	2	3	4
Respiratory: $Pa0_2/Fi0_2$.	>400	301-400	201-300	101-200	≤101
Renal: Serum Cr (mg/dL).	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular: SBP (mmHg).	>90	<90 fluid responsive	<90, not fluid responsive	<90 + pH<7.3	<90 + pH<7.2

Cr: Creatinine; SBP: Systolic Blood Pressure: A score of 2 or more in any organ defines the presence of organ failure.

Bedside Index for Severity in Acute Pancreatitis		*Ranson's Admission Criteria*	
Age above 60 years old.	1 Point	Age above 55 years old.	1 Point
Blood urea nitrogen ≥25 mg/dL	1 Point	Serum glucose >200 mg/dl.	1 Point
Impaired mental status	1 Point	White blood cell count >16000 cells/$mm^{3.}$	1 Point
Pleural Effusion	1 Point	Aspartate aminotransferase >250 U/L.	1 Point
Presence of SIRS (see below)	1 Point	Lactate dehydrogenase >350 U/L.	1 Point

Systemic Inflammation Response Syndrome

Parameter	
White blood cells	<4000 cells/mm^3 or >12000 cells/mm^3 or >10% immature bands
Temperature	<36 °C or >38 °C
Heart Rate	>90 beats per minute
Respiratory rate	>20 breaths per minute or $PaCO_2$ <32 mmHg

Positive if at least two of the above parameters are present.

Modified Computer Tomography Severity Index

		Points
Pancreatic Inflammation	Absent.	0
	Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat.	2
	Peripancreatic necrosis.	4
Pancreatic Necrosis	Absent.	0
	Below 30%.	2
	Above 30%.	4
Extrapancreatic Complications	Pleural effusion, ascites, vascular complications, parenchymal complications and gastrointestinal involvement.	2