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A Model to Predict the Severity of Acute Pancreatitis Based on Serum Level of Amylase and Body Mass Index

Short Title: Change in amylase and severity of Acute Pancreatitis

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Abbreviations:
Acute pancreatitis - AP
Acute Physiology and Chronic Health evaluation - APACHE-II
Area under the receiver operating characteristics curve - AUROC
Bedside index of severity of acute pancreatitis - BISAP
Body mass index - BMI
Change in amylase and body mass index score – CAB
Charleston co-morbidity index - CCI
Computed tomography scan - CT
Computed tomography severity index - CTSI
Receiver operating characteristics - ROC
Severe acute pancreatitis – SAP

Disclosures: None

Specific Author Contributions
Arthi Kumaravel – Study concept and design; interpretation of data; drafting of manuscript
Tyler Stevens - Study concept and design; interpretation of data; critical revision of manuscript for intellectual content
Georgios I. Papachristou - interpretation of data; critical revision of manuscript for intellectual content
Venkata Muddana – acquisition of data
Amit Bhatt – acquisition of data
Peter Junwoo Lee – acquisition of data
Jordan Holmes – acquisition of data

Rocio Lopez - Study concept and design; analysis; drafting of manuscript

David C. Whitcomb - interpretation of data; critical revision of manuscript for intellectual content

Mansour Parsi - Study concept and design; interpretation of data; critical revision of manuscript for intellectual content
Abstract:

**Background & Aims:** Most patients with acute pancreatitis (AP) develop mild disease but up to 20% develop severe disease. Many clinicians monitor serum levels of amylase and lipase in an attempt to predict the disease course, but this strategy has not been recommended by practice guidelines. We performed a retrospective analysis to determine whether the percent changes in amylase and lipase were associated with the severity of disease that developed in patients with AP.

**Methods:** We analyzed data collected from 182 consecutive patients with AP (21 with severe AP) admitted at the Cleveland Clinic from January 2008 through May 2010 (discover cohort). The association between 11 different factors and severity of AP were assessed by univariable analysis; multivariable models were explored through stepwise selection regression. The percent change in serum level of amylase was calculated as follows: \[ \frac{(\text{amylase day1} - \text{amylase day2})}{\text{amylase day1}} \times 100 \]. The percent change in amylase and body mass index (BMI) were combined to generate a z-score \[ z = -5.9 + (0.14 \times \text{BMI}) + (0.01 \times \text{percent change in amylase}) \], which was converted into a probability distribution called the change in amylase and BMI (CAB) score. The CAB score was validated using the AP database at the University of Pittsburgh Medical Center (140 patients, 35 with severe AP); we calculated p-scores for each patient and estimated the area under the receiver operating characteristics (AUROC) curve values.

**Results:** Univariable analysis identified percent change in serum level of amylase and other factors to be significantly associated with severity of AP \((P=0.017)\). The CAB score was best at identifying patients who developed severe AP, with an AUROC values of 0.79 in the discovery cohort (95% confidence interval, 0.71–0.87) and 0.731 (95% confidence interval, 0.61–0.84) in the validation cohort.

**Conclusion:** We developed a model to identify patients most likely to develop severe AP based on percent changes in serum level of amylase during the first 2 days after admission to the hospital and BMI.

**KEY WORDS:** pancreas; scoring system; inflammation; prognosis; risk factor
Introduction:

Acute Pancreatitis (AP) is defined as an acute inflammatory process that involves the pancreas and may also involve the peripancreatic tissues and remote organ systems (1). Multiple reports suggest that the incidence of AP is rising and ranges from 13 to 45 per 100,000 (2, 3). AP is usually a mild disease but up to 20% of patients can develop a clinically severe course (1, 4). The mortality rate for severe AP (SAP) remains high at 10-30% (5, 6). It is important to recognize patients at risk for developing SAP early as they may require transfer to an intensive care unit for more aggressive treatment, and may benefit from computed tomography (CT) imaging and early nutritional support.

There are several clinical, laboratory-based and image-based scoring systems currently available, such as the Ranson’s score (7, 8), the Acute Physiology and Chronic Health evaluation (APACHE-II) (9), the bedside index of severity of AP (BISAP) (10, 11), the computed tomography severity index (CTSI) (12), and blood urea nitrogen (BUN) (13). However, each has certain shortcomings. APACHE-II score is complex and hard to use. BISAP and Ranson scores were developed to predict mortality rather than assess severity of AP. CTSI requires a computed tomography (CT) scan, which is expensive and not recommended in most patients with AP. Furthermore, all these scores have been found to predict SAP with moderate accuracy (14). In light of the shortcomings of these currently available parameters and tools, there remains an unmet need for an easy and accurate method of predicting AP severity.
Serial monitoring of serum pancreatic enzymes is a common clinical practice but is not recommended as the changes in levels are not thought to correlate with the severity or outcomes of AP (1). In this study, we sought to determine the association of serum amylase and lipase levels with outcomes in AP. We developed a model incorporating the percent change in serum amylase, which predicted SAP, and tested the model in a validation cohort from a second independent center.

**Methods:**

The diagnosis of AP was based on ACG criteria and required the presence of at least two of the three following factors: 1. abdominal pain characteristic of AP, 2. serum amylase and/or lipase ≥ 3 times the upper limit of normal, 3. CT findings characteristic of AP (1). Only patients with at least two serum amylase and lipase levels measured within the first 48 hours after admission were included in the study. Patients were classified as having SAP if they had organ failure, defined as modified Marshall score ≥ 2 for cardiovascular, pulmonary or renal system that persisted for > 48 hours (15).

Two independent cohorts of patients were utilized. Demographic and clinical data on consecutive patients with AP admitted at the Cleveland Clinic between January 2008 and May 2010 were retrospectively collected, which served as our discovery cohort. This database has IRB approval. For patients that were transferred to our institution, the charts were obtained from the time of admission for data entry. Initially, 11 different factors were assessed by univariable analysis as predictors of SAP: Age, gender, body mass...
index (BMI), first vs. recurrent episode, chronic pancreatitis, Charlson co-morbidity index (CCI), transfer patient, BISAP, BUN and percent change in amylase or lipase from admission to day 2 were consider for inclusion in the models. The percent change in serum amylase levels was calculated as: [(amylase day 1 – amylase day 2)/amylase day 1 * 100].

Subsequently, multivariable models were explored through stepwise selection regression. The amylase percent change and Body mass index (BMI) were combined to generate a z-score, which was then converted into a probability distribution.

The final model to predict severity of AP was subsequently validated using the AP database at the University of Pittsburgh Medical Center (UPMC) by calculating the p-score for each patient and estimating the area under the receiver operating characteristics curve (AUCROC). The UPMC database collected data prospectively on consecutive patients admitted with AP. The diagnosis of AP and the classification of SAP were made using the same criteria described above in this database. This prospective database was also approved by the IRB.

**Statistical analysis:**

Data are presented as mean ± standard deviation, median [25th, 75th percentiles] or N (%). Univariable analysis was performed to assess associations with outcomes of interest. Student’s t-tests or the non-parametric Wilcoxon rank sum tests were used for continuous factors and Pearson’s chi-square tests were used for categorical variables. In addition, a
Receiver Operating Characteristics (ROC) analysis was performed to assess the use of change in amylase and or lipase from admission to day 2 for prediction of outcomes of interest. The final number of factors included in each model was determined with the 10 events per variable rule. For each outcome, an automated stepwise variable selection method performed on 1000 bootstrap samples was used to choose the final models; variables with inclusion rates >20% were further assessed and the combination with highest AUCROC was selected. A p < 0.05 was considered statistically significant. SAS version 9.2 (The SAS Institute, Cary, NC) and R version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used to perform all analyses.

Results:
Baseline characteristics of the discovery and the validation cohorts are presented in Table 1. The rule out selection bias, the included and excluded patients from the discovery cohort were compared and had similar age, etiology, CCI and BISAP score on day 1 of admission.

Discovery Cohort
One hundred and eighty-two patients were included in the discovery cohort, of which 21 had SAP. The univariable analysis revealed several statistically-significant predictors of severe AP (Table 2). The percent change in amylase was a statistically-significant predictor (p=0.017). For every 10% decrease in percent of amylase the odds of SAP decreased by 10. Neither the magnitude of lipase or amylase, nor the percent change in lipase was predictive.
Multivariable models were explored through stepwise selection regression (Table 3). A final model comprised of Change in Amylase and BMI (CAB) provided optimal prediction of SAP (AUC 0.79). The final multivariable logistic regression model (z) was defined as follows:  
\[ z = -5.9 + (0.14 \times \text{BMI (kg/m}^2) + (0.01 \times \text{Percent change in amylase day 2}) \]  
where Percent change in amylase day 2 is defined as [(amylase day 2 - amylase day 1)/amylase day 1]*100. This z-value was then converted into a probability distribution (p) with a value between 0 to 100 by the following formula:  
\[ p = 100 \times \exp(z)/(1 + \exp(z)) \]. The probability calculator is available at [http://www.r-calc.com/calculator.aspx?calculator_id=XY5L5ROMY](http://www.r-calc.com/calculator.aspx?calculator_id=XY5L5ROMY).

In order to evaluate the clinical utility of the CAB score, it was compared to other scoring systems routinely used to estimate the severity of acute pancreatitis. In the discovery cohort, we compared the CAB score to BISAP, change in BUN and BUN >20 on admission and the CAB score had the highest AUC (0.79). (Figure 2) Change in BUN had an AUC of 0.73, BUN >20 on admission had an AUC of 0.65 and BISAP > 2 on admission had an AUC of 0.67.

Using a cutoff of CAB score > 9 %, the sensitivity of the score to predict AP was 75% with a specificity of 65.4%. The negative predictive value was 95.3% and positive predictive value was 21.7%.

**Validation Cohort**
One hundred and forty-four patients were included in the UPMC validation cohort and 35 patients had SAP. Both cohorts were comparable except for percentage of patients with SAP in the validation cohort (Table 1). The AUCROC for the CAB score in the validation cohort was 0.731 (95% C.I 0.61 – 0.84). The AUCROC curves for the CAB score in the discovery cohort and the validation cohort are shown in Figure 1.

The CAB score was compared to other scoring systems in the validation cohort and had the highest AUC (0.73) in this cohort as well. (Figure 3) Change in BUN had an AUC of 0.69, BUN >20 had an AUC of 0.62 and BISAP >2 on admission had an AUC of 0.61.

Using the same cutoff point in the validation cohort (CAB score > 9%), the sensitivity and specificity of the model to predict SAP were 82.6% and 67.6% respectively. The negative predictive value was 92.3% and positive predictive value was 45.2%.

Only 106/182 patients in the original cohort and 97/154 patients in the validation cohort had amylase levels checked on day 3 after admission. In a model using the percent change in the serum amylase levels from day 1 to day 3 and BMI, the AUCROC was 0.805 (95% C.I 0.69 – 0.91) in the discovery cohort and 0.781 (95% C.I 0.67 – 0.88) in the validation cohort.

**Discussion:**
This is a dual center study aiming to design a multivariable logistic regression model, which accurately predicts SAP. We designed a novel multivariable model based on percent changes in serum amylase levels during the first 2 days of admission and BMI, which accurately predicted severity of AP. The initial findings using the discovery cohort were subsequently validated by an independent cohort of AP patients.

Serum amylase levels have long been used for the diagnosis of AP. In early animal studies the serum amylase levels was shown to correlate with the histological changes of AP (16). However, the serum amylase levels have not been shown to correlate with severity of disease in human subjects and severity scores were developed based on markers of inflammatory response and complications in other organ systems. Several reports suggested that the serum amylase levels were inversely associated with severity of pancreatitis and pancreatic necrosis as production of the enzymes ceased with destruction of the gland (17-19). However, later studies suggested that the initial amylase levels did not correlate with the severity of disease as defined by presence of organ failure (20, 21). However, previous studies have not assessed the predictive value of the trend in serum amylase. Amylase is thought to be a more responsive indicator of pancreatic inflammation than lipase, with a quicker rise and fall. The lipase values tend to remain elevated for a longer period of time than the amylase values and may be the reason the trend in lipase values was not predictive of the severity of AP. The initial amylase value depends on the time from onset of symptoms to the time that serum amylase is measured. As such, we are measuring the slope of the decline in serum amylase levels and a more pronounced decline in amylase may suggest improvement in pancreatic inflammation.
The data from the current study supports this hypothesis, in that the percent change in the amylase values from day of admission (day 1) to day 2 predicted the severity of the episode. The percentage change in amylase levels from day one of admission to day 3 was found to be an even stronger predictor in our analysis, but this has to be interpreted with caution due to smaller number of patients with the day 3 values available.

The strong association between obesity and severity of AP has been previously reported (22-30). There have been attempts to include BMI in predictive scores such as APACHE-O score with limited success (31, 32). It has been proposed that obesity increases the risk of SAP due to amplification of the inflammatory response to pancreatic injury as a result of up-regulation of adipokines in obese individuals (32). Another hypothesis suggests that increased fat levels predispose the pancreatic and peripancreatic tissues to necrosis (26, 30). Finally, recent studies in both humans and animal models suggests that release of excess triglycerides from fat, which are then hydrolyzed by pancreatic lipase to release toxic unsaturated free fatty acids, may directly add to injury and worsen the severity of acute pancreatitis (33). Regardless of mechanism, the addition of BMI significantly improved the predictive power of the model. The CAB score based on the combination of the percentage change in serum amylase values from day 1 to day 2 and the BMI performed better than the traditional scoring systems (BISAP, BUN >20 on admission and change in BUN) in both the discovery and validation cohorts. The negative predictive value of the score was also consistently high in both cohorts.

The addition of an obesity measure to our score impacted the clinical utility of the score, in spite of the fact that an obesity measure has not significantly impacted the utility of
APACHE. There are several potential reasons for this discrepancy. First, APACHE II is a binary discriminator based on a score exceeding a threshold value such as 7. In the APACHE-O score, for example, the time obesity has any relevance is when the APACHE II score is just below threshold (e.g. 7) and an additional point or two tips the balance to a severe score (e.g. 8). Otherwise it makes no difference in classification. Furthermore, if obesity is a pre-injury predictor of the inflammatory response, and the APACHE II score is a measure of the inflammatory response, then the APACHE II score already contains the effects of obesity on inflammation. In contrast, the CAB score includes amylase level changes – likely a marker of pancreatic injury, and an obesity measure (BMI) as a predictor of the magnitude of the inflammatory response to a given injury. Both amylase and BMI are continuous variables, both contribute to the final score, and each represent different, but complementary domains. Together, this approach has a high predictive value (Figure 3)

This study has several strengths. The study design was such that the model used to predict SAP was generated in a “discovery cohort” and validated in an independent validation cohort from another institution. In addition the predictive model has only two variables (amylase levels and BMI) and thus easy to use. Furthermore, the model does not require expensive tests.

One limitation of the study is the relatively small number of patients with SAP in both cohorts. This limited the number of variables that could be included in the final model and in a larger cohort with more patients with severe AP a model which included BUN
along with BMI and percent change in amylase could be evaluated. Another limitation is that the model requires an amylase value 24 hours from admission so it cannot be used to triage patients upon presentation. In a recent study in which the existing scoring systems were compared in a training cohort and a validation cohort all the scoring systems performed comparably with only modest ability to predict severity of disease (14). The current model has good negative predictive values but it is possible that our ability to predict SAP may be enhanced in the future by incorporating genetic, molecular and other physiologic markers of severity to the existing model.

In conclusion, in humans with acute pancreatitis the percentage change in serum amylase levels over the first 24 hours correlates with disease severity, and may reflect the severity of pancreatic injury. We confirm that BMI is a pre-injury predictor of acute pancreatitis severity, and may reflect a greater inflammatory response to injury. The CAB score is a new, validated mathematical model using only amylase levels and BMI that more accurately predicts severity of acute pancreatitis than most other models. The score has a high negative predictive value which could aid in triaging patients to step down units. However, as this requires a change in the monitoring of patients with AP (i.e., trending of the serum amylase) the score needs further validation in a cohort with a large number of patients with severe AP.
Legends:

Table 1: Baseline characteristics of the discovery cohort and the validation cohort

Table 2: Results of univariable logistic regression analysis in the discovery cohort

Table 3: Prediction of Severe acute pancreatitis: Receiver Operating Characteristics (ROC) analysis

Figure 1: ROC of the model to predict severe acute pancreatitis in discovery cohort and validation cohort

Figure 2: Comparison of the different scoring systems to predict severe acute pancreatitis in the discovery cohort

Figure 3: Comparison of the different scoring systems to predict severe acute pancreatitis in the validation cohort
References


20. Lankisch PG, Burchard-Reckert S, Lehnick D. Underestimation of acute pancreatitis: patients with only a small increase in amylase/lipase levels can also have or develop severe acute pancreatitis. Gut 1999;44:542-4.


Table 1: Baseline characteristics of the discovery cohort and the validation cohort

<table>
<thead>
<tr>
<th>Factor</th>
<th>Discovery cohort (N = 182)</th>
<th>Validation cohort (N = 154)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.7±17.0</td>
<td>53.1±19.5</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.2 ± 6.7</td>
<td>28.4 ± 7.2</td>
<td>0.83</td>
</tr>
<tr>
<td>Male</td>
<td>104 (57%)</td>
<td>83 (54%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Severe AP</td>
<td>21 (11%)</td>
<td>35 (22%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Etiology of AP</td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>- Gallstones</td>
<td>54 (30%)</td>
<td>58 (38%)</td>
<td></td>
</tr>
<tr>
<td>- Alcohol</td>
<td>36 (20%)</td>
<td>20 (13%)</td>
<td></td>
</tr>
<tr>
<td>- Idiopathic</td>
<td>46 (25%)</td>
<td>39 (25%)</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>46 (25%)</td>
<td>37 (24%)</td>
<td></td>
</tr>
</tbody>
</table>

Values presented as Mean ± SD with ANOVA; Median [P25, P75] with Kruskal-Wallis test, or N (%) with Pearson's chi-square test.
Table 2: Results of univariable logistic regression analysis in the discovery cohort

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (5 year increase)</td>
<td>1.2 (1.01, 1.4)</td>
<td>0.036</td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>1.00 (0.40, 2.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI (1 kg/m^2) increase</td>
<td>1.1 (1.05, 1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent vs. First attack</td>
<td>3.0 (0.85, 10.7)</td>
<td>0.086</td>
</tr>
<tr>
<td>Chronic Pancreatitis History</td>
<td>0.67 (0.14, 3.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>CCI (1 unit increase)</td>
<td>1.08 (0.89, 1.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Transfer Patient</td>
<td>0.02 (0.001, 0.11)</td>
<td>0.95</td>
</tr>
<tr>
<td>BISAP score at Day 1 (1 unit increase)</td>
<td>2.7 (1.7, 4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BISAP 2+ day 1</td>
<td>7.3 (2.8, 19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN admission (5 mg/dl increase)</td>
<td>1.09 (1.01, 1.2)</td>
<td>0.027</td>
</tr>
<tr>
<td>BUN&gt;20 on admission</td>
<td>3.7 (1.4, 9.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Percent change in amylase day 2 (10% decrease)</td>
<td>0.93 (0.87, 0.98)</td>
<td>0.017</td>
</tr>
<tr>
<td>Percent change in lipase day 2 (10% decrease)</td>
<td>1.0 (0.94, 1.06)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Table 3: Prediction of Severe acute pancreatitis: Receiver Operating Characteristics (ROC) analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Severe AP AUCROC (95% C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase on admission</td>
<td>0.556 (0.429, 0.683)</td>
</tr>
<tr>
<td>Lipase on admission</td>
<td>0.566 (0.440, 0.692)</td>
</tr>
<tr>
<td>BUN on Admission</td>
<td>0.733 (0.622, 0.844)</td>
</tr>
<tr>
<td>BUN &gt; 20 on Admission</td>
<td>0.652 (0.538, 0.766)</td>
</tr>
<tr>
<td>BISAP &gt; 2 on Admission</td>
<td>0.669 (0.561, 0.776)</td>
</tr>
<tr>
<td>Change in BUN (24 hr - admission)</td>
<td>0.692 (0.532, 0.851)</td>
</tr>
<tr>
<td>Pct change in amylase day 2</td>
<td>0.726 (0.628, 0.823)</td>
</tr>
<tr>
<td>Pct change in amylase day 3</td>
<td>0.699 (0.584, 0.814)</td>
</tr>
<tr>
<td>Pct change in lipase day 2</td>
<td>0.390 (0.298, 0.483)</td>
</tr>
<tr>
<td>Pct change in lipase day 3</td>
<td>0.595 (0.471, 0.719)</td>
</tr>
<tr>
<td>Pct change in amylase day 2 + BMI</td>
<td>0.793 (0.711, 0.874)</td>
</tr>
<tr>
<td>Pct change in amylase day 2 + BUN &gt; 20</td>
<td>0.752 (0.637, 0.867)</td>
</tr>
<tr>
<td>Pct change in amylase day 2 + BUN</td>
<td>0.778 (0.674, 0.882)</td>
</tr>
<tr>
<td>Pct change in amylase day 2 + Change in BUN</td>
<td>0.737 (0.601, 0.874)</td>
</tr>
<tr>
<td>Pct change in amylase day 2 + BISAP &gt; 2</td>
<td>0.775 (0.667, 0.883)</td>
</tr>
</tbody>
</table>
AUC (95% CI)

- Discovery cohort: 0.79 (0.71, 0.87)
- Validation cohort: 0.73 (0.62, 0.84)

Prediction of Severe AP based on model containing BMI and % change from baseline to day 2 in amylase
AUC (95% CI)
- CAD Score: 0.79 (0.71, 0.87)
- BUN: 0.73 (0.62, 0.84)
- BUN > 20: 0.65 (0.54, 0.77)
- BISAP > 2: 0.67 (0.56, 0.78)