Predictors of Mortality in Acute Pancreatitis: A Retrospective Study

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Predictors of Mortality in Acute Pancreatitis: A Retrospective Study

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Abstract

Background: The aim of this retrospective study was to identify the association of the routinely examined laboratory indices, such as blood urea nitrogen (BUN), serum creatinine, blood glucose, leucocytes, hematocrit and the Glasgow scoring scale with mortality in acute pancreatitis patients.

Methods: This study included 271 patients with acute pancreatitis. All patients were consecutively admitted to the Second Surgery of the Pirogov Emergency Hospital from June 2000 to November 2008. Patients were divided into two groups: survivors (242) and deceased (29); for all patients, the routine laboratory parameters were determined during the first 24 hours of hospital admission.

All data were processed by the SPSS 11.0.1 software package for Windows.

Results: Non-survivors demonstrated higher BUN (P < 0.0001), serum creatinine (P < 0.0001), serum glucose (P =0.031), leucocytes (P =0.008), hematocrit (P=0.05) and Glasgow scoring scale (P < 0.0001) values, as compared to the survivor group values. The highest area under the curve (AUC) was observed for BUN (AUC=0.816, 95% CI 0.738-0.894), followed by the AUC for serum creatinine (AUC=0.798, 95% CI 0.700-0.897) and for Glasgow scores (AUC=0.744, 95%CI 0.638-0.850).

We established a statistically significant association between BUN ≥ 7.4mmol/l and mortality (odds ratio =10.018, 95% CI 3.892-25.788, P < 0.0001), between serum creatinine ≥ 107µmol/l and mortality (odds ratio=9.772, 95%CI 3.806-25.087, P < 0.0001) and between Glasgow score ≥ 2 and mortality (odds ratio=5.090, 95%CI 2.161-11.990, P < 0.0001).

Conclusion: In a retrospective study, BUN, serum creatinine and the Glasgow scoring scale were the three parameters that demonstrated the highest association with mortality in acute pancreatitis. Borderline and/or slightly elevated levels of BUN and of serum creatinine upon admission to the hospital may predict the course of the disease in patients with acute pancreatitis.

Introduction

In many cases, the clinical picture of a patient with acute pancreatitis (AP) upon admission to the hospital does not suggest the risk of the development of a severe disease (1). The severe course of the AP is characterized by the development of systemic organ failure and/or necrotic changes of the pancreas, which leads to a fatal outcome in 15-30% of cases.

The early phase of the severe AP (i.e., the first 10 days after hospitalization) is indicated by the presence of systemic inflammatory response syndrome (SIRS) and organ failure. The late or second disease phase, which begins at the end of the second week of disease onset, is usually associated with local complications of the pancreas.

It is believed that systemic organ failure is the most important early prognosticator of mortality in patients with AP (2,3).

Therefore, monitoring of patients in the first 24 hours upon hospital admission is of the utmost importance to be able to identify those cases with higher risk of developing multiple organ dysfunction (4).

The aim of this study was to establish the association between BUN, serum creatinine, blood glucose, leucocytes, hematocrit and the Glasgow scoring scale upon admission to the hospital and mortality in AP.

Patients and Methods

The data from all patients who were consecutively admitted from June 2000 to November 2008 to the Pirogov Emergency Hospital and who had a final diagnosis of acute pancreatitis were collected from the patient records.

The patients were divided into two groups of 242 survivors and 29 non-survivors.

The laboratory results obtained during the first 24 hours of admission were processed by the statistical software package for Windows, SPSS 11.0.1.

The original Glasgow scoring scale was calculated on the basis of the results collected until the 48th hour of hospital admission (6).

The diagnostics of the disease was made on the basis of the clinical picture, the sonographic and/or computed tomography (CT) findings and on the basis of clearly elevated (2 to 3 times the upper reference
limit) values of serum amylase (5,8). Moderately severe AP was determined when CT findings of pancreatic necrosis, abscess or pseudocyst could be detected. Severe AP was defined in cases of persistent organ failure (lasting for more than 48 hours) and leading to prolonged hospital stay, when there was a need for surgical intervention, and in cases of mortality (9,10).

The biliary etiology of the disease was identified when gallstones in the gallbladder were observed sonographically. The alcohol-induced etiology was diagnosed when alcohol intake before the onset of the symptoms could be established (7).

The idiopathic AP group was defined when no gallstones could be seen in the gallbladder sonographically and when there were no anamnestic data of alcohol intake before hospital admission. Patients with underlying chronic pancreatitis and those who transferred from another hospital were excluded from the study. Blood glucose results were recorded only for nondiabetic patients.

Because of the retrospective design of the study, no written consent was needed, nor was approval obtained from the ethical committee of the hospital.

Laboratory parameters:
All biochemical parameters were routinely analyzed until the 24th hour of admission to the hospital using the Synchron CX 9 ALX system (Beckman Coulter Inc., USA), using original kits obtained from the manufacturer.

Leucocytes and hematocrit were routinely measured with the hematological cell counter CELL DYN 1700 (Abbott Diagnostics, USA).

The reference limits for BUN ranged from 2.9 to 7.1 mmol/l, for serum creatinine 1 from 36 to 106 µmol/l and for blood glucose - from 4.1 to 6.4 mmol/l. The normal ranges for leucocytes were in the limits of 4.1 to 10 x 10^9/l and for the hematocrit - from 0.37 to 0.51 l/l.

Statistical analysis:
All values were expressed in medians and ranges. The comparison of the results between the survivors and the non-survivor group was performed using the Mann-Whitney test and Fisher’s exact test.

Receiver operation characteristics (ROC) analysis was performed to determine the diagnostic accuracy of the laboratory tests by using the area under the curve (AUC) for the respective analyte. Odds ratios were calculated to determine the level of association between mortality and the test value. P<0.05 was considered statistically significant.

Results

1. The demographic characteristics, etiology, duration of symptoms before admission, the entire hospital stay, laparotomy, relaparotomy and P values are given in table 1.
2. In total, 29 (11%) of 271 patients with AP admitted to the Second Surgery of the Pirogov Emergency Hospital died. Patient age among non-survivors was significantly higher as compared to survivor age (median 60 vs. 47 years, Mann-Whitney test, P=0.007).
3. We also found a statistically significant difference between non-survivors and survivors in terms of the duration of the patient’s entire hospital stay (median of 11 vs. 4 days, Mann-Whitney test, P<0.001).
4. Biliary etiology (11) and the need for laparotomy/relaparotomy were identified as risk factors that predicted disease outcome (table 1).
5. There was no difference between the non-survivor and the survivor group in terms of gender (Fisher’s exact test, P=0.823) or the duration of symptoms before admission (Mann-Whitney test, P=0.348).
6. Patients with fatal AP had significantly higher levels of BUN (P<0.0001), serum creatinine (P<0.0001), blood glucose (P=0.031), leucocytes (P=0.008), and hematocrit (P=0.05) as well as Glasgow scale scores (P<0.0001) than those with non-fatal AP (table 2).
7. The ROC analysis showed the following AUC values (table 3).
8. The highest AUC was observed for BUN (AUC=0.816, 95% CI 0.738-0.894), followed by the AUC for serum creatinine (AUC=0.798, 95% CI 0.700-0.897) and the AUC for Glasgow score (AUC=0.744, 95% CI 0.638-0.850) (table 3, figure 1, figure 2 and figure 3).
9. The lowest AUC was observed for hematocrit (AUC=0.612, 95% CI 0.484-0.741).
10. BUN ≥ 7.4 mmol/l and serum creatinine ≥ 107 µmol/l yielded the highest specificity (80 and 80%, respectively) and the highest negative predictive value (NPV) (95.9 and 100%, respectively) in predicting AP mortality (table 4).
11. Glasgow ≥ 2 points had the highest sensitivity (72%) with high NPV (95.2%), but showed the lowest specificity (66%) (table 4).
12. Blood glucose ≥ 7.7 mmol/l and leucocytes ≥ 14.8 x 10^9/l showed high specificity (74 and 72%, respectively) and high NPV (94.6 and 93.47%, respectively) but demonstrated unsatisfactory sensitivity (52 and 51%, respectively) and very low positive predictive value (16.9 and 18.07%, respectively).
13. Hematocrit ≥ 0.50 l/l demonstrated the highest
specificity (89%) but the lowest sensitivity (35%) as compared to the other indices (table 4).

14. The highest association to mortality was identified for BUN (odds ratio = 10.018, 95% CI 3.892-25.788), for serum creatinine (odds ratio = 9.772, 95% CI 3.806-25.087) and for Glasgow (odds ratio = 5.090, 95% CI 2.161-11.990) (table 5).

15. Blood glucose (odds ratio 3.571, 95% CI 1.431-8.911), leucocytes (odds ratio 3.162, 95% CI 1.407-7.103) and hematocrit (odds ratio 3.235, 95% CI 1.409-7.426) also showed satisfactory results in association with mortality in AP (table 5).

**Discussion**

In a retrospective study, we demonstrated the possibility that not only high but also borderline and/or slightly elevated levels of some routinely measured parameters upon admission to the hospital could play a predictive role in identifying AP patients. All indices included in the study showed significantly higher levels in the non-survivor group as compared to the survivor group.

The data from our study demonstrated high sensitivity and high specificity for BUN and for serum creatinine in predicting the mortality in AP.

Elevated BUN levels upon admission are caused by a decrease in the intravascular volume due to fluid loss and the development of prerenal azotemia (4). It is believed that BUN > 39 mg/dl (13.9 mmol/l) on admission to the hospital is related to mortality in AP patients (12).

According to another study, blood urea nitrogen (BUN) increase of 5 mg/dl (1.8 mmol/l) during the first 24 hours upon hospital admission is associated with high AP mortality, irrespective of admission BUN levels (4). Another investigation demonstrated that peak serum creatinine > 1.8 mg/dl (159 µmol/l) during the first 48 hours after hospitalization is indicative of the development of pancreatic necrosis (13).

Serum creatinine ≥1.5 mg/dl (133 µmol/l) upon hospital admission is an indicator of the progress towards acute renal failure (ARF). Acute renal failure in AP is caused by the release of vasoactive compounds, enzymes and cytokines from the necrotic pancreatic tissue into the circulation (14).

Additionally, hypovolemia, decreased kidney blood flow, activated intravascular coagulation and infection contribute to the development of ARF in these patients (14).

Serum creatinine > 2 mg/dl (177 µmol/l) on admission as well as admission blood glucose > 250 mg/dl (13.88 mmol/l) were identified to be strong predictors of mortality in AP patients (15). Blood glucose > 125 mg/dl (6.95 mmol/l) on hospital admission correlate strongly with high Ranson, Glasgow and Balthazar scores, as well as with prolonged hospital stay and with the development of a pancreatic pseudocyst, but not with organ failure, surgery or mortality (16).

Hematocrit ≥ 44% on hospital admission and the no decrease during the following 24 hours as well as admission leucocytes ≥ 15.9 x 10^9/l have proven to be markers for necrotizing/and or life-threatening AP and organ failure (17,1).

We found a significant correlation between high blood glucose levels and mortality, between moderately high Glasgow and mortality and between high leucocytes and mortality in patients with AP.

The significantly higher blood glucose levels in the non-survivor AP group in our study are probably related to damage of the endocrine pancreas, as determined by the extent of the pancreatic necrosis. The high leucocyte levels in the non-survivor AP group as well as the high hematocrit values in the same group are related to the development of the early inflammatory response and increased hemoconcentration in the setting of necrotizing AP.

It is believed that early death in AP is caused by the development of multiple organ failure during the first two weeks after hospitalization, while the late AP death occurring later in the disease course is associated with local complications due to pancreatic necrosis (18,19).

However, it is still not clearly established how much persistent organ failure contributes to the extent of the pancreatic necrosis, if it does. The mechanism by which pancreatic necrosis could contribute to the development of multiple organ dysfunction is not completely understood (18).

Despite these uncertainties, a patient admitted to the hospital with suspected AP should be examined carefully.

The application of a novel scoring system, such as the bedside index for severity in acute pancreatitis (BISAP), will be of help in the early identification of cases at higher risk (20).

The inclusion of additional results, retrieved from the patient records, will most likely be of much help in understanding the disease pathology. In conclusion, our study demonstrated that not only clearly elevated but also borderline and/or moderately high admission levels of BUN and of serum creatinine are related to AP mortality.

High admission hemoconcentration is characterized by high specificity and a high negative predictive value in predicting AP mortality.
A Glasgow score ≥2 points is associated with the development of multiple organ failure in AP.

**Conclusion**

In conclusion, our study demonstrated that not only clearly elevated but also borderline and/or moderately high admission levels of BUN and of serum creatinine are related to AP mortality.

High admission hemoconcentration is characterized by high specificity and a high negative predictive value in predicting AP mortality.

A Glasgow score ≥2 points is associated with the development of multiple organ failure in AP.

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12. Faisst M, Wellner UF, Utsolino S et al., Elevated blood urea nitrogen is an independent risk factor of prolonged intensive care unit stay due to acute necrotizing pancreatitis., J Crit Care, 2010,25: 105-11
Illustrations

Illustration 1

Table 1: Age, gender, total hospital stay, duration of the symptoms before admission, etiology (biliary, alcoholic, idiopathic and other), laparotomy and relaparotomy in patients with AP

<table>
<thead>
<tr>
<th></th>
<th>Survivors (N=242)</th>
<th>Non-survivors (N=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47 (20-83)</td>
<td>60 (23-84)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>159/83</td>
<td>21/8</td>
<td>0.823**</td>
</tr>
<tr>
<td>Total hospital stay, days</td>
<td>4 (1-48)</td>
<td>11 (1-47)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Duration of symptoms to admission, days</td>
<td>1 (&lt;1-14)</td>
<td>1 (&lt;1-7)</td>
<td>0.348*</td>
</tr>
<tr>
<td>Biliary AP, n (%)</td>
<td>84 (34)</td>
<td>19 (66)</td>
<td>0.0028**</td>
</tr>
<tr>
<td>Alcoholic AP, n (%)</td>
<td>56 (23)</td>
<td>4 (14)</td>
<td>0.923**</td>
</tr>
<tr>
<td>Idiopathic AP, n (%)</td>
<td>99 (41)</td>
<td>5 (17)</td>
<td>0.997**</td>
</tr>
<tr>
<td>Other etiology, n (%)</td>
<td>3 (1)</td>
<td>1 (4)</td>
<td>0.365**</td>
</tr>
<tr>
<td>Laparotomy, n (%)</td>
<td>20 (8)</td>
<td>21 (73)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Relaparotomy, n (%)</td>
<td>3 (1)</td>
<td>7 (24)</td>
<td>&lt;0.0001**</td>
</tr>
</tbody>
</table>

P*- Mann Withney test
P**- Fisher’s exact test

Age, entire hospital stay and duration of symptoms prior to admission are presented as medians and ranges (in parenthesis)
Illustration 2

Table 2: Medians and ranges for blood urea nitrogen, serum creatinine, blood glucose, leucocytes, hematocrit and Glasgow for the non-survivor and the survivor AP groups.

<table>
<thead>
<tr>
<th></th>
<th>Median, (non-survivors/survivor)</th>
<th>Range, (non-survivors/survivors)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN, mmol/l</td>
<td>9.4/4.2</td>
<td>3.8-16.75/1.2-35.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine, µmol/l</td>
<td>133/84</td>
<td>69-320/21-290</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>8.0/6.1</td>
<td>3.6-13.5/2.4-17.0</td>
<td>0.031</td>
</tr>
<tr>
<td>leucocytes, x10^9/l</td>
<td>16.5/12.5</td>
<td>3.8-28.2/3.2-33.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Hematocrit, l/l</td>
<td>0.47/0.44</td>
<td>0.33-0.58/0.21-0.65</td>
<td>0.05</td>
</tr>
<tr>
<td>Glasgow, points</td>
<td>3/1</td>
<td>0-6/0-6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

P value*- Mann-Whitney test
BUN- blood urea nitrogen
Illustration 3

Table 3: Area under the curve (AUC), 95% confidence interval (CI) and P values of blood urea nitrogen, serum creatinine, blood glucose, leucocytes, hematocrit and Glasgow, differentiating non-survivors from survivors in AP.

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>0.816</td>
<td>0.738-0.894</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.798</td>
<td>0.700-0.897</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>0.642</td>
<td>0.506-0.779</td>
<td>0.031</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>0.654</td>
<td>0.533-0.775</td>
<td>0.009</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.612</td>
<td>0.484-0.741</td>
<td>0.052</td>
</tr>
<tr>
<td>Glasgow</td>
<td>0.744</td>
<td>0.638-0.850</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BUN - blood urea nitrogen
Illustration 4

Table 4: Diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for BUN, serum creatinine, blood glucose, leucocytes, hematocrit and for the original Glasgow scoring system for the non-survivor and the survivor AP groups.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity,%</th>
<th>Specificity%</th>
<th>PPV,%</th>
<th>NPV,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN≥7.4mmol/l</td>
<td>70</td>
<td>80</td>
<td>29.82</td>
<td>95.9</td>
</tr>
<tr>
<td>Serum creatinine≥107µmol/l</td>
<td>70</td>
<td>80</td>
<td>28.81</td>
<td>100</td>
</tr>
<tr>
<td>Blood glucose≥ 7.7 mmol/l</td>
<td>52</td>
<td>74</td>
<td>16.9</td>
<td>94.6</td>
</tr>
<tr>
<td>Leucocytes≥ 14.8 x 10^9/l</td>
<td>51</td>
<td>72</td>
<td>18.07</td>
<td>93.47</td>
</tr>
<tr>
<td>Hematocrit≥ 0.5 l/l</td>
<td>35</td>
<td>89</td>
<td>21.56</td>
<td>92.16</td>
</tr>
<tr>
<td>Glasgow≥ 2 points</td>
<td>72</td>
<td>66</td>
<td>20.38</td>
<td>95.2</td>
</tr>
</tbody>
</table>

BUN- Blood urea nitrogen
Illustration 5

Table 5: Odds ratios, 95% confidence interval (CI) and P values of BUN, serum creatinine, blood glucose, leucocytes, hematocrit and the Glasgow for the prognostics of patients with AP.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN≥7.4mmol/l</td>
<td>10.018</td>
<td>3.892-25.788</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine≥107µmol/l</td>
<td>9.772</td>
<td>3.806-25.087</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose≥7.7mmol/l</td>
<td>3.571</td>
<td>1.431-8.911</td>
<td>0.01</td>
</tr>
<tr>
<td>Leucocytes≥14.8x10⁹/l</td>
<td>3.162</td>
<td>1.407-7.103</td>
<td>0.007</td>
</tr>
<tr>
<td>Hematocrit≥0.5l/l</td>
<td>3.235</td>
<td>1.409-7.426</td>
<td>0.009</td>
</tr>
<tr>
<td>Glasgow≥2</td>
<td>5.090</td>
<td>2.161-11.990</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

P*- Fisher’s exact test
Illustration 6

Figure 1: ROC curve of BUN, differentiating deceased AP and survivor AP patients.
Illustration 7

Figure 2: ROC curve of the serum creatinine in differentiating deceased from survivor AP patients.
Illustration 8

Figure 3: ROC curve for the Glasgow scoring scale for the deceased and the survivor patients with AP.
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