Hemoconcentration is a poor predictor of severity in acute pancreatitis

José M. Remes-Troche, Andrés Duarte-Rojo, Gustavo Morales, Guillermo Robles-Díaz

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory process of the pancreas with variable involvement of peripancreatic tissues or remote organ systems. Mostly, it develops as a mild and auto-limited disease, but around 25% of patients present the severe form with an elevated mortality rate (2-16%). This worrisome condition is due to the eventual development of organ failure (OF) and sepsis, both complications are associated with the concurrent development of necrotizing pancreatitis that occurs in 20-30% of the cases. Severity is currently defined according to the Atlanta International Symposium on AP by the presence of local complications (pancreatic necrosis, pancreatic pseudocyst, and pancreatic abscess) and/or OF (cardiovascular, pulmonary or renal insufficiency, and gastrointestinal bleeding). Several efforts have been made to describe prognostic factors that could help for the identification of high risk patients in order to maintain a closer vigilance, thereby providing a more aggressive medical treatment and an earlier admittance to the intensive care unit. The usefulness of multiple clinical and laboratory tests to predict severe and/or necrotizing pancreatitis has been studied. Ranson’s criteria are most widely accepted for the assessment of high risk patients; however numerous parameters need to be measured during the first 48 h after admission. Other scales like Glasgow or APACHE II are commonly used, but these also require several measurements and have not been proven superior to Ranson’s criteria. More recently, biochemical
markers, such as C-reactive protein \cite{13}, polymorphonuclear elastase \cite{14}, interleukin-6 and trypsinogen activation peptide \cite{15,16}, have been used as predictors of severity in AP. C-reactive protein is a useful marker only 48 h after the onset of acute episodes \cite{13,14} and overall usefulness of the remaining markers is restricted by their limited availability or elevated cost. Thus, so far, no early, accessible and economical predictive marker for severe AP has yet been described.

Hematocrit (Hct) is routinely assessed in every AP case at admission and is an accessible and low-cost test. Recent studies have proposed that hemoconcentration may constitute a good marker for severity of AP, but others were unable to find a significant correlation with the development of OF, pancreatic necrosis or death \cite{17-20}. Thus, the value of hemoconcentration in the initial assessment of AP patients and its implications in prognosis remain controversial. We, therefore, aimed to determine whether hemoconcentration at admission and in the following 24 h was associated with the development of severe AP, pancreatic necrosis and/or OF.

**MATERIALS AND METHODS**

Patients with a first AP episode admitted consecutively to a tertiary medical center between June 1998 and December 2001 were included in this study. AP diagnosis was confirmed by typical clinical presentation and an increase in amylase or lipase concentration at least thrice the upper limit of normal, and/or evidence of pancreatic inflammation revealed by contrast-enhanced abdominal computed tomography \cite{21}. Medical records of all the patients were reviewed retrospectively for the following variables: gender, age, etiology, Hct level at admission, Hct level at 24 h after admission, development of OF, and severity of AP (both defined according to Atlanta’s criteria) \cite{20}, evidence of necrosis in contrast-enhanced abdominal computed tomography, total hospital stay and mortality. Exclusion criteria included patients with previous AP episode(s) or with a first AP episode previously treated in other institutions.

Hematocrit levels at admission and 24 h later were compared with the severity of the pancreatitis, the presence of necrosis or OF. Categorical variables are expressed as absolute and relative frequencies and continuous variables as mean±SD. Receiver operator characteristic (ROC) curves were plotted for the range of Hct levels. Hemoconcentration was defined as an Hct level >44% for male and >40% for female patients \cite{17-20}. The t test was used to analyze continuous variables, whereas the χ² or F tests were used on categorical variables, when appropriate. A P value <0.05 was considered statistically significant. Statistical analysis was performed using commercially statistical software SPSS 10 (SPSS, Chicago, IL, USA) and NCSS-2000 (NCSS, Kaysville, UT, USA).

**RESULTS**

Three hundred and thirty-six AP cases were included in the current study. Mean age was 45±17 (range, 15-90 years) years and 55% (n = 185) of patients were females. Sixteen patients (4.7%) were anemic according to reference values established for our population \cite{17}. Mean Hct levels at admission were 41±6 for women and 46±7 for men (P = 0.00001). Biliary disease was the most common cause of the acute episode (n = 148, 44%), followed by alcohol abuse (n = 48, 14%). Other causes included: hypertriglyceridemia (9%), post endoscopic retrograde cholangiopancreatography (7%), drugs-induced (5%), post surgery (4%), obstructive disease (3%), hypercalcemia (1%), trauma (1%) and vasculitis (1%). Thirty-eight events were considered idiopathic (11%). When divided according to gender, biliary disease was more frequent in women and alcoholic pancreatitis was more frequent in men (odds ratio (OR) = 2.16; 95% CI 1.3-3.5 and OR = 40; 95% CI 9.7-243, respectively).

A mild AP episode was diagnosed in 258 (77%) patients, while the remaining 78 (23%) suffered from a severe attack. Organ failure developed in 45 (13%) patients. A contrast-enhanced abdominal computed tomography was performed during the first week after admission to assess the presence of necrosis in 150 cases. The Hct was determined in 233 (69%) patients 24 h after admission; of these, 183 patients (79%) presented with mild AP and 50 (21%) with severe AP. No differences were found in Hct levels at admission regardless of the presence of severe AP, necrosis or OF. A significant decrease in Hct levels was noted in all the patients at 24 h after admission, which was found to be independent of the severity status (Figure 1). There were no differences between the necrotizing and interstitial pancreatitis groups in terms of the fall in Hct levels after admission (7.5±4% vs 6.5±4%, respectively).

A ROC curve analysis for several cut offs of Hct levels at admission failed to show a single point combining good sensitivity, specificity, positive and negative predictive values for the detection of severe AP, necrotizing pancreatitis or OF (Figure 2).

However, the optimal cut-off values of Hct were similar to those used to define hemoconcentration (>44% for males and >40% for females). Neither the presence nor the absence of hemoconcentration at admission was associated to severity, necrosis or OF (Table 1). Hemoconcentration was present in 58% (55/96) and 61% (33/54) of patients with interstitial and necrotizing...
Besides the development of several prognostic systems for severity in AP, there are multiple biochemical tests and clinical parameters proposed as single markers for severe or necrohemorrhagic pancreatitis. Most of the laboratory assays have significant limitations in clinical practice mainly because they are expensive and not widely available. The clinical features might be the most economical and easily available parameters because they result from routine patient assessment. Among them, the presence of older age, alcohol etiology, time interval between onset of symptoms and admission, rebound tenderness/guarding, obesity, and android fat distribution have been associated with the subsequent development of severe AP. The identification of these parameters as risk factors for the development of severe AP contributed to the understanding of the disease, but their impasse of several drawbacks, such as biased clinical interpretation.

Hemoconcentration at admission as a marker for severe acute pancreatitis (AP), necrotizing AP and organ failure

|                      | Hemoconcentration (Hct ≥ 44% M, Hct ≥ 40% F) | No hemoconcentration (Hct < 44% M, Hct < 40% F) | Odds ratio (95% CI) | P value (c²) |
|----------------------|-----------------------------------------------|-----------------------------------------------|---------------------|--------------|
| Severe AP (n = 336)  |                                         |                                               |                     |              |
| Yes                  | 46                                            | 32                                            | 0.77 (0.4-1.3)      | 0.32         |
| No                   | 168                                           | 90                                            |                     |              |
| Necrotizing AP (n = 150) |                                   |                                               |                     |              |
| Yes                  | 33                                            | 21                                            | 1.17 (0.5-2.4)      | 0.64         |
| No                   | 55                                            | 41                                            |                     |              |
| Organ failure (n = 336) |                                   |                                               |                     |              |
| Yes                  | 27                                            | 18                                            | 0.83 (0.4-1.7)      | 0.58         |
| No                   | 187                                           | 104                                           |                     |              |

1Hct: hematocrit; M: male; F: female.

DISCUSSION

One of the most important actions to cope with patients suffering from AP is to quickly and accurately assess the severity of the attack. Earlier identification of patients at risk of developing pancreatic necrosis and OF potentially improves their care via prompt admission to intensive care unit.

Besides the development of several prognostic systems for severity in AP, there are multiple biochemical tests and clinical parameters proposed as single markers for severe or necrohemorrhagic pancreatitis. Most of the laboratory assays have significant limitations in clinical practice mainly because they are expensive and not widely available. The clinical features might be the most economical and easily available parameters because they result from routine patient assessment. Among them, the presence of older age, alcohol etiology, time interval between onset of symptoms and admission, rebound tenderness/guarding, obesity, and android fat distribution have been associated with the subsequent development of severe AP. The identification of these parameters as risk factors for the development of severe AP contributed to the understanding of the disease, but their impasse of several drawbacks, such as biased clinical interpretation.

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underlined the role of cytokines (e.g., tumor necrosis factor-α and interleukin-1, -6, and -8) and other inflammatory response mediators (e.g., platelet activating factor) in this propagating process. Interestingly, the inflammatory response is always accompanied by the increase in vascular permeability that produces extravasation of

Table 2 Hemoconcentration at 24 h as a marker for severe acute pancreatitis (AP), necrotizing AP and organ failure

| Groups                      | No hemoconcentration (Hct <44% M, Hct <40% F) | Odds ratio (95%CI) | P value(χ²) |
|-----------------------------|-----------------------------------------------|--------------------|-------------|
| Severe AP (n = 233)         |                                               |                    |             |
| No                          | 125                                           | 58                 | 0.64        | 0.23        |
| Yes                         | 29                                            | 21                 | (0.3-1.2)   |             |
| Necrotizing AP (n = 100)    |                                               |                    |             |
| No                          | 39                                            | 24                 | 0.9         | 0.97        |
| Yes                         | 22                                            | 15                 | (0.4-2)     |             |
| Organ failure (n = 233)     |                                               |                    |             |
| No                          | 139                                           | 68                 | 0.68        | 0.47        |
| Yes                         | 15                                            | 11                 | (0.3-1.5)   |             |

1 Hct: hematocrit; M: male; F: female.

Table 3 Accuracy of hemoconcentration at admission and at 24 h later as a marker for severe acute pancreatitis (AP), necrotizing AP and organ failure

| Groups                      | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%)  |
|-----------------------------|-----------------|-----------------|---------|----------|
|                             | Admission       | 24 h            | Admission | 24 h |
| Severe AP                   | 59              | 58              | 35       | 31      | 21 | 18 | 74 | 73 |
| Necrotizing AP              | 61              | 59              | 42       | 38      | 37 | 36 | 66 | 61 |
| Organ failure               | 60              | 58              | 36       | 32      | 13 | 10 | 85 | 86 |

PPV: positive predictive value; NPV: negative predictive value.

Table 4 Prognostic values of hemoconcentration in previous studies

| Studies                     | n    | Prognostic criteria                                           | sensitivity (%) | specificity (%) | PPV (%) | NPV (%) |
|-----------------------------|------|--------------------------------------------------------------|-----------------|-----------------|---------|---------|
| Baillargeon et al[c]        | 64   | Necrosis ≥47% at admission                                   | 34              | 91              | 44      | 87      |
|                             |      | Failure to decrease at 24 h Necrosis                        | 81              | 88              |         |         |
| Brown et al[36]             | 128  | >44% at admission                                            | 72              | 83              | 68      | 85      |
|                             |      | Failure to decrease at 24 h Necrosis                        | 94              | 69              | 61      | 96      |
|                             |      | Organ failure >44% at admission                              | 60              | 75              | 26      | 93      |
|                             |      | Failure to decrease at 24 h Necrosis                        | 87              | 65              | 27      | 97      |
| Goulis et al[37]            | 63   | >44% at admission                                            | 78              | 83              | 50      | 94      |
| Lankisch et al[34]          | 316  | Necrosis >43% for male and >39.6% for female at admission    | 74              | 45              | 24      | 88      |
| Pezzilli et al[38]          | 158  | Necrosis ≥43.8 at admission                                  | 52.3            | 74.6            |         |         |
| Khan et al[39]              | 58   | Severity                                                     | 0               | 92              | 0       | 65      |
|                              |      | >47% at admission                                            | 32              | 82              | 46      | 71      |
|                              |      | >44% at admission                                            | 21              | 66              | 24      | 63      |
| Present study               | 336  | Severity                                                     | 59              | 35              | 21      | 74      |
|                              |      | >44% for male and 40% for female at admission                | 61              | 42              | 37      | 66      |
|                              |      | >44% for male and 40% for female at admission                | 60              | 36              | 13      | 85      |

data obtainment, controversial results and low sensitivity and/or specificity, and the results have been controversial. AP is considered as a consequence from an insult to the pancreatic parenchyma that generates a local inflammatory reaction which then propagates and gives place to a generalized inflammatory response. Multiple studies have
intravascular fluid into the peritoneal cavity\cite{15,16}. The fluid loss significantly decreases the perfusion pressure into the pancreas leading to microcirculatory changes that contribute to pancreatic necrosis\cite{17} Thus, it has been proposed that hemoconcentration resulting from this fluid loss might well be associated with AP severity.

Gray and Rosenman\cite{18} in 1965 reported that hemoconcentration at admission was a poor prognostic sign in patients with AP, but Talamin\ et\ al\cite{19} did not find significant differences of Hct levels obtained within 24 h of admission in survivors and non-survivors of AP. On the other hand, the classic study of Ranson\cite{20} found that a fall in Hct level by greater than 10% during the initial 48 h of therapy correlates with severity and mortality. Thereafter, Baillegron\ et\ al\cite{21} in a retrospective study reported that an admission Hct ≥ 47% or, opposed to Ranson's finding, a failure of Hct to decrease at 24 h were predictive of necrosis but not of OF. The same group of authors in a subsequent prospective study of 128 patients with AP established an admission Hct ≥ 44% and a failure to decrease after 24 h as the best binary predictor for necrosis and OF\cite{22}. Both studies may have a referral bias in patient selection because the included patients transferred from other hospitals may correspond to sicker cases with a delay or less vigorous hydration. In some of the subsequent studies\cite{23-25}, elevated values of admission Hct were reported in necrotizing pancreatitis and also associated with serious complications but in all the studies, neither hemoconcentration at admission nor an Hct not decreasing after 24 h were able to predict severity (Table 4). In the current study, we could not find differences in the admission Hct between severe and mild cases. In every case, independently of the presence or absence of necrosis and/or systemic complications, there was a significant decrease in Hct levels at 24 h after admission. This finding might be explained by the common practice of aggressive fluid resuscitation in most of our patients with AP. The mean Hct fall at 24 h was under 10%, being non-significantly lower in necrotizing pancreatitis as expected in agreement with Ranson. According to our results, the accuracy of hemoconcentration at admission and at 24 h later as a marker for severe AP, necrotizing pancreatitis or OF lies in its high negative predictive value, mainly for OF (85% and 86%, respectively), as has been found in the previous reports (Table 4).

We analyzed a series of consecutive patients, including 4.7% of them with anemia, in order to test the utility of the Hct in a realistic clinical setting as was done by Khan\ et\ al\cite{26}. Our results were similar to those found by them, unlike our higher mean Hct levels. Admission Hct was analyzed separately in males and females as done by Lankisch\ et\ al\cite{27}, but in addition to their approach, we also analyzed the Hct at 24 h after admission. Since Hct levels may differ according to atmospheric oxygen pressure (higher in high altitudes) and to gender (lower in females)\cite{28}, we constructed ROC curves that displayed cutoff values of Hct to define hemoconcentration at risk for severity in agreement with those previously reported by others\cite{29,30,31}. Thus, anemia does not seem to play a role in the poor predictive accuracy of Hct in our study.

Our study is the only one that proves that hemoconcentration analyzed according to gender at admission and at 24 h is not a good predictor for severity in AP. We consider that our findings of the poor prognostic value of Hct at admission in AP cannot be attributed to sample bias. However, this is a retrospective study and only 69% of the patients had Hct determination at 24 h after admission; thus the lack of utility of the Hct at this time cannot be established strongly.

In conclusion, the sole clinical application that follows from the current study and several previous reports could be that patients without hemoconcentration have a very low likelihood of developing pancreatic necrosis or organ failure. However, we consider that in spite of the consistent findings of high negative predictive value of hemoconcentration for necrosis and/or OF, there is no prognostic gain because of the pre-existing 75% prevalence of mild AP.

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