Acute Pancreatitis: Assessment of Severity, Prognostic Factors, and Mortality

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ABSTRACT

Acute pancreatitis is a complex disease that results in significant morbidity and mortality. The majority of articles suggest that mortality related to acute pancreatitis has, on the whole, reduced over time. Early severity stratification remains a challenging issue to overcome to improve outcome. In this review article, we focused on recent publications related to assessment of severity of acute pancreatitis, i.e., scoring systems and individual biochemical markers and their role in predicting clinical outcomes. Based on data presented, what seems to be evident is that there is no single scoring system that can be regarded as the most useful in acute pancreatitis.

INTRODUCTION

Acute pancreatitis (AP) is a complex disease that results in significant morbidity and mortality. The majority of articles suggest that AP-related mortality has, on the whole, reduced over time (1, 2). This can be attributed to a whole host of factors, including better recognition of the signs of severity (through the assistance of severity indices), and newer therapies for the complications associated with AP (1).

Early severity stratification remains a challenging issue to overcome to improve outcome (3). In this review article, we will focus on recent publications related to assessment of severity of AP, i.e., scoring systems and individual biochemical markers and their role in predicting clinical outcomes.

Before we start presenting results of recent publications, we want to look at survey data on AP severity assessment in daily clinical practice in Switzerland (4). It is interesting that not all, but 87% of participants (193/233 from 63 hospitals) use scoring systems (4). The most frequently used are Ranson (87%) and Acute Physiology and Chronic Health Evaluation (APACHE) II (23%) scores. A majority of participants were not satisfied with the currently available tool to assess severity (59%). Only 12% of all participants use the revised Atlanta classification. The authors concluded that further efforts must be made to expand physicians' awareness of scores' existence and significance (4).

The best known, revised Atlanta classification of AP was published in 2012 to provide simple functional clinical and morphological classification. The modification (5):

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- addresses the clinical course and severity of disease,
- divides AP into interstitial edematous AP and necrotizing AP
- distinguishes an early phase (first week) and late phase (after the first week) and
- emphasizes systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF).

The goal is for radiologists, gastroenterologists, surgeons, and pathologists to use the revised classification to standardize imaging terminology to facilitate treatment planning and enable precise comparison of results among different departments and institutions (5, 6). Based on a recent survey (4), we need to put more effort to implement revised Atlanta classification in everyday practice.

The Bedside Index for Severity in Acute Pancreatitis (BISAP) was developed for prediction of in-hospital mortality in AP. Classification and Regression Tree (CART) analysis was applied on data collected from 17,992 cases of AP from 212 hospitals in 2000–2001. The new scoring system was validated on data collected from 18,625 AP cases from 177 hospitals in 2004–2005 in the United States (7). Five variables were identified for prediction of in-hospital mortality. One point is assigned for the presence of each during the first 24 hours: blood urea nitrogen > 25 mg/dL, impaired mental status, SIRS, age > 60 years or the presence of pleural effusion. The BISAP area under the curve (AUC) during revalidation was 0.82 versus APACHE II score of 0.83 (7). Since first revalidation, 12 other studies used BISAP index to determine predictive performance, and systematic review has been performed to determine prognostic accuracy of the BISAP for severe AP (7). In meta-analysis, pooled AUC was higher than in original revalidation study. It was 0.85 for BISAP and 0.92 for revised Atlanta classification (8). With high heterogeneity, BISAP has very good performance for severe AP across different patient population and aetiologies, but the impact of incorporating the BISAP into clinical practice to improve outcome in AP is still unknown (8).

The most recent paper by Vasudevan et al. (9) looked at different scoring systems and biochemical markers, and how well they predicted outcome in AP. They include the APACHE II score ≥ 7, BISAP ≥ 2, SIRS score ≥ 3 and C-reactive protein ≥ 82ng/mL predicted severity of AP. They also found that predictors of infected pancreatic necrosis were as follows: PANC 3 score ≥ 1, BISAP score ≥ 2 and Marshall score ≥ 2 and C-reactive protein ≥ 98 (9). In the same study, predictors of mortality were BISAP ≥ 2, APACHE II ≥ 10 and blood urea nitrogen ≥ 17 (9).

They also suggested that BISAP and APACHE II were comparable in predicting outcome, but unlike APACHE II, BISAP predicted all three outcomes with the same cut off and hence is robust scoring system (9). Despite this finding, APACHE II score remains gold standard in assessing severity of AP.

Early Warning Score (EWS) has been extensively used in the United Kingdom, as a score that facilitate early detection of unwell patients on medical wards with the aim to start treatment on time. Jones et al. (10) compared EWS score with different variables and APACHE II score by including 629 patients with AP. They found EWS was the best predictor of adverse outcomes (AUC values 0.81, 0.84 and 0.83 for days 1, 2 and 3, respectively) and was the most accurate predictor of mortality on both days 2 and 3 (AUC values 0.88 and 0.89, respectively). Multivariate analysis revealed that a EWS ≥ two was independently associated with severity of pancreatitis, adverse outcome, and mortality (10).

Another general scoring system, Emergency General Surgery disease grading system to measure anatomical severity, although recently introduced in clinical practice (by American Association for the Surgery of Trauma), has shown initial validity for prediction of length of hospital stay and increased rates of readmission in AP patients (11).

Recent study conducted by Beduchi et al. and another study conducted by Paanda et al., both

aimed to assess the efficacy of PANC 3 score to predict AP severity (haematocrit, body mass index (BMI) and pleural effusion) by including 64 and 74 patients, respectively, in the studies (12, 13). They both found PANC 3 score easy and quick to use, with 50% sensitivity and 100% accuracy, with 91% positive and 100% negative predictive value (12). Beduchi's et al. study performed in Brazil agrees with Jekura's et al. study performed in Japan conducted on 116 patients with AP (14). Multiple logistic regression analysis revealed that BMI of 25 kg/m2 was associated with significant mortality. They suggested to add BMI > 25 kg/m2 as an additional parameter to a Japanese prognostic factor score to enhance predictive value of the prognostic factor score for AP-related mortality (14).

However, the role of BMI is not as clear-cut from the literature as it might seem – the findings of many papers would appear to suggest that higher BMI increases one's risk of AP (14), yet a recent analysis by Kim et al. found lower BMI to be closely associated with mortality in AP (15). While it seems plausible that the comorbidities associated with a higher BMI may put one at risk of a poorer prognosis from AP (such as fatty liver), the findings of Kim et al. arguably mean that the relationship between BMI and prognosis in AP would be worth elucidating further (15).

Promising multivariate prediction model for patients with AP in intensive care unit that has better AUC than APACHE II (0.91 versus 0.80), has been recently presented (16). Variable with statistical significance in multivariate analysis were age, no alcoholic and no biliary etiology, development of shock, development of respiratory failure, need of continuous renal replacement therapy and intra-abdominal pressure (16). The only issue with this scoring system is that patients were already admitted to the intensive care unit and they already developed SIRS and MOF. When AP patients already reach intensive care unit stage, it is very obvious that the outcome may be poor.

BIOCHEMICAL MARKERS AS PREDICTORS OF SEVERITY OF ACUTE PANCREATITIS

Recent study conducted by Hong et al. showed that albumin levels within 24 hours of patient admission correlate with the development of persistent organ failure and mortality in AP (17). As levels of serum albumin decrease, the incidence of organ failure is 3.5%, 10.6%, and 41.6% in patients with normal albumin, mild and severe hypoalbuminemia, respectively. Decreased albumin levels were also proportionally associated with prolonged hospital stay ($p < 0.001$) and the risk of death ($p < 0.001$). Multivariate analysis suggested that biliary etiology, chronic concomitant diseases, hematocrit, blood urea nitrogen, and the serum albumin level were independently associated with persistent organ failure (17). All these factors have already been looked at as indicators of severity of AP (8, 9, 10) and they have been included in different scoring systems (8, 9, 10). In Hong's et al. study, blood urea nitrogen and the serum albumin level were also independently associated with mortality. Area under receiver operating characteristic curves of albumin for predicting organ failure and mortality were 0.78 and 0.87, respectively (17).

Another biochemical marker that has potential to predict organ failure or death in patients with AP is cortisol. Study performed to assess whether copeptin, pro-atrial natriuretic peptide, proadrenomedullin, and cortisol are associated with disease severity in patients with AP included 142 patients with AP (18). Disease severity was rated by the Atlanta 1992 and 2012 criteria and organ failure by the modified Marshall score. The aforementioned laboratory markers, C-reactive protein, and procalcitonin were measured. Patients with moderate to severe AP showed significantly higher plasma concentrations of all biomarkers than did those with mild AP. Mortality from severe AP was as high as 21%. All biomarkers except cortisol had only modest discriminatory ability, with areas under the receiver operating characteristic curve between 0.44 and 0.66. Cortisol showed an AUC of 0.78 compared with the APACHE

II score with an AUC of 0.75. Authors concluded that cortisol was the best predictor of organ failure or death (18). All biomarkers were associated with disease severity to a similar degree as C-reactive protein, the criterion-standard marker in AP.

Intestinal fatty acid binding protein (IFAB) is another promising prognostic marker in AP. Based on prospective study that compared 94 AP patients with 100 control patients, that has found significantly higher IFAB in AP group ($p<0.001$) and also higher IFAB level of IFAB in patients with severe AP versus mild AP ($p=0.03$, the authors propped a model by which IFABP > 350 pg/mL and citruline < 18mcg/L can predict poor prognosis in 34% of patients with AP (19).

Total serum calcium and albumin-corrected calcium measured within 24 hours of AP are also useful severity predictors in AP (20).

It is well known that coagulation disorders can develop with severe AP. Plasma thrombin-antithrombin III complex (TAT) levels are markers of coagulation disorder. When measuring TAT in 46 patients with AP and 30 healthy volunteers, Fidan et al. found plasma TAT level significantly higher in severe AP group compared with AP group and healthy control. Based on this study, coagulation disorder is more pronounced as severity of disease increased (21).

Based on data presented, what seems to be evident is that there is no single scoring system that can be regarded as the most useful in AP. A systematic review by Gravante et al. found that, except APACHE II, most do not have a high degree of sensitivity, specificity or predictive value (22). Moreover, one of the criticisms of the use of APACHE II in the management of AP is that it requires the collection of a large number of parameters, many of which are unlikely to be relevant in AP (7). It seems likely, therefore, that the use of scoring systems in AP will continue to be an extensively debated and studied area in the literature.

Arguably the commonest mode of death in AP is MOF, which can be defined as 'the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention' (23). The SIRS is commonly associated with MOF, and its persistence is known to be a risk factor for the development of MOF and death in AP (24). It is, however, important to note that organ dysfunction in AP is a process and that the stage at which a patient is in this process can determine their overall mortality – early organ dysfunction usually has no significant effect on mortality, but deteriorating organ dysfunction has high mortality (25). Early, prompt management can, therefore, have a tremendous impact on patient outcomes.

Arguably the most important risk factor in AP is infected pancreatic necrosis – it occurs in up to 70% of patients with AP during the natural disease course (26), and the mortality rate is more than 20% (27). However, the use of prophylactic antibiotics to prevent this complication occurring is highly controversial, with some articles suggesting that antibiotic prophylaxis reduces mortality in AP (28, 29), and others demonstrating no significant beneficial effect of antibiotic prophylaxis (30). Current management guidelines do not definitively commit one way or another on the issue of antibiotic prophylaxis in AP – indeed; guidelines from the United Kingdom Working Party on Acute Pancreatitis recommend that if antibiotics are used at all, they should be given for a maximum of 14 days (27). Interestingly, a recent study by Baxter et al. found that the routine use of nonsteroidal anti-inflammatory drugs in AP might help prevent some of the complications associated with AP, including pancreatic necrosis (although it was found to make no significant difference on mortality) (30). While the use of nonsteroidal anti-inflammatory drugs as a therapeutic measure in AP is something that needs to be explored. Further, this finding offers a potential breakthrough in the prevention of this highly fatal complication.

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