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EDITORIAL

Predictors of Severity and In-Hospital Mortality for Acute Pancreatitis: Is There Any Role for C-Reactive Protein Determination in the First 24 Hours?

Fatores Preditivos de Mortalidade Intra-Hospitalar na Pancreatite Aguda: Haverá Algum Lugar para a Determinação da Proteína-C Reativa nas Primeiras 24 Horas?

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Acute pancreatitis (AP) is one of the most common gastrointestinal disorders, with a reported annual incidence of 13–45 cases per 100,000 persons.[1,2] It is a complex disease that can vary from a mild self-limited presentation, in approximately 80–90% of patients, to a clinically severe form in 10–20% with multiple complications and a mortality rate up to 30%.[2–5] Timely identification of patients with clinically severe AP and worse prognosis is important because they may benefit from prompt admission to a dedicated intensive or intermediate care unit, with close monitoring for the development of organ failure, they should receive aggressive fluid resuscitation and targeted therapy such as enteral feeding, endoscopic sphincterotomy, or antibiotics.[4,5] Severity stratification is also important when reporting and evaluating the results of clinical trials in AP.

The Atlanta Classification has been considered the global standard tool for the assessment of AP severity since its establishment in 1992.[6] However, this classification was somehow confusing and, in 2012, it was revised with a special emphasis on persistent organ failure, using the modified Marshall scoring system.[3]

An ideal prognostic score should be simple, non-invasive, accurate, quantitative, and the assessment methods should be easily applicable at the time of diagnosis.[7] By this moment there are different predictive scoring systems for acute pancreatitis, such as the Acute Physiology And Chronic Health Evaluation (APACHE) II, Ranson, Bedside Index for Severity in Acute Pancreatitis (BISAP), Simplified Acute Physiology Score (SAPS) II, Harmless Acute Pancreatitis Score (HAPS) and modified Glasgow score.[2,8] Persistent (>48 h) Systemic Inflammatory Response Syndrome (SIRS) is also assumed as a prognostic factor for severe acute pancreatitis. However, these scores are complex and some cannot be applied at any time. So, nowadays much effort has been concentrated on the evaluation of single serum markers (C-reactive protein, hematocrit, procalcitonin, blood urea nitrogen, creatinine, calcium, hyperglycemia, albumin, interleukin-6), clinical variables (age, body mass index, intra-abdominal pressure) and radiologic signs (pleural effusion, CT severity index) as predictive factors for worse outcome.[9]

Amongst the multiple biochemical markers the C-reactive protein (CRP) is probably the most useful.[8,10–12] It is accurate and widely available but it is generally accepted that its maximum level occurs not earlier than 72 h after the onset

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of symptoms.[8] The majority of authors/guidelines assume that a CRP level at 48 h after onset of symptoms ≥150 mg/l is a bad prognostic predictor.[8,9,13–15]

Despite the simplicity and easy availability of CRP in clinical practice, many studies have described a limitation of clinical utility of this biochemical parameter in the early phase of AP, since CRP alone can potentially fail to detect severe cases of AP at an earlier stage.[7,16,17]

In this issue of *GE Portuguese Journal of Gastroenterology*, Cardoso et al[12] report the potential utility of CRP determination in the first 24 h as a predictor of in-hospital mortality for AP. This is a retrospective study, involving 134 patients, with nine deaths (6.7%) during hospital admission. The median overall CRP level at 24 h was 104.4 (inter-quartile range, 29.2–191.2 mg/l) and this biochemical parameter was higher in patients who died during hospital stay (197.2 vs. 100.2, $p = 0.003$). In univariate analysis the odds ratio of CRP at 24 h for prediction of in-hospital mortality was 1.11 (95% CI, 1.04–1.17) and the corresponding AUC was 0.80 (95% CI, 0.65–0.95). It is interesting to notice that none of the 46 patients with CRP levels at 24 h lower than 60 mg/l died and only one of the nine patients with severe acute pancreatitis had a CRP level lower than that potential cut-off. On the other side, the addition of CRP to BISAP reduced the calculated risk of in-hospital mortality in about 42% of patients who survived but the overall effect was not statistically significant.

This study suggests that an early determination of CRP, in the first 24 h of admission, could have a good individual prognostic accuracy for in-hospital survival. Using a cut-off of 60 mg/l the sensitivity for detecting patients that will survive to this episode was 100% but the positive predictive value was only 10%. Also interesting is the suggestion that a combination of CRP and BISAP could help to reclassify patients at low risk to die from acute pancreatitis or its complications during index hospital stay, although the observed tendencies did not achieve statistical significance.

However, the results and conclusions presented by the authors had several limitations: the study is retrospective; there are only nine deaths during admission; data on organ failure were available for 70 patients; other scoring systems such as APACHE II were not considered; the authors presented no data about CRP levels at 48 h and potential differences with CRP at 24 h.

There are few studies about the clinical utility of CRP at 24 h. A recent study by Cho et al demonstrated that a CRP level ≥214 mg/l at 24 h after admission was positively associated with an increased risk of severe acute pancreatitis.[7] In the present study no clear cut-off was established and it is interesting to notice that the same authors, Cardoso et al, had already demonstrated that CRP at 48 h after hospital admission showed a good prognostic accuracy for severe acute pancreatitis and in-hospital mortality.[12] By the contrary, procalcitonin could be used as predictor of severe acute pancreatitis in the first 24 h.[18] Unfortunately, the study published today in GE did not consider this variable.

So, CRP could be an interesting alternative to more complex scoring systems. However, recent guidelines from the International Association of Pancreatology and the American Pancreatic Association discourage the routine use of single markers, such as CRP, hematocrit, blood urea nitrogen or procalcitonin alone to triage patients to an intensive care setting.[2] The guidelines from the American College of Gastroenterology also assume that no laboratory test, including CRP, is practically available or consistently accurate to predict severity in patients with acute pancreatitis.[17] Although all scoring systems have been shown to correlate with morbidity and mortality, it remains difficult to accurately identify individual patients who develop clinically severe disease on admission or early in the course of their hospitalization. However, APACHE II and persistent SIRS remain the best markers for predicting both severity and in-hospital mortality.[2,4,7,9,19,20] From the interpretation of the majority of studies we can assume that no simple scoring system is capable of reaching maximal utility for prediction of AP severity and in-hospital mortality. Unique and preferentially simple models are needed in order to achieve further improvement in this field of clinical practice. A multicentric, prospective study is urgently needed in Portugal, in order to determine which biochemical parameters, clinical variables and/or prognostic scores are best suited to identify patients with higher risk of complications and in-hospital mortality. These patients should be prematurely referred to dedicated intermediate or intensive care units, in hospitals were endoscopic, radiologic and surgical interventions are easily available.

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