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Assessment of the Severity of Acute Pancreatitis: No Room for Complacency

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Abstract
Assessing the severity of acute pancreatitis is an important initial step in the management of these patients. An ideal prognostic system or marker does not exist, and current approaches fall short of what is needed when dealing with individual patients. It is recommended that the evaluation of the performance of a particular prognostic system or marker should include the calculation of positive and negative likelihood ratios, derived from a combination of sensitivity and specificity. Knowing the pre-test probability of a particular endpoint and the likelihood ratios make it possible to derive the post-test probability for the presence or absence of that endpoint for the individual patient in that population. The change in probability from before to after the test gives an indication of the clinical usefulness of the test. Improving the performance of prognostic systems and markers remains a challenge and there is no room for complacency. There are two ways forward: either the prognostic systems and markers need to be used in a more intelligent way, with combinations, sequencing or artificial neural network techniques, or by the discovery of new markers that measure critical aspects of outcome determining pathophysiology. No lack of energy has been expended on the latter, while the former offers more immediate promise.

Three questions need to be answered when a patient is admitted with suspected acute pancreatitis. The first is whether the diagnosis is acute pancreatitis. The second is whether the acute pancreatitis is due to gallstones, alcohol or something else. The third is the most challenging and relates to determining the severity of the acute pancreatitis. It is 34 years since Ranson et al. [1] demonstrated that it is possible to stratify patients with acute pancreatitis according to their risk of dying. Since that time there have been thousands of articles promoting hundreds of prognostic markers and systems. That very few have become part of routine clinical practice suggests that we still have not found what we are looking for. This article is a commentary on our search for the ideal prognostic marker or system [2].

There are several reasons for wanting to accurately assess the severity of acute pancreatitis. The ultimate reason is to select individual patients for a specific treatment, still to be discovered. Another reason for an accurate, practical and useful prognostic marker or system is to allow triage of patients because of the 'implications for management, prognostication and the allocation of health care resources' [3]. More specifically it allows the identification of patients who require early aggressive intravenous fluid resuscitation in high dependency or intensive care environments, those who would benefit from expeditious transfer to an expert center, and those who would require specific intervention, such as endoscopic

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sphincterotomy or stenting [4]. The ongoing assessment of severity helps to determine the response to treatment, to identify the development of complications, delineate the clinical trajectory of the patient and to help predict the outcome. Another important reason for being able to assess the severity of pancreatitis is the importance of comparing groups of patients, between centers and between clinical trials [5]. One can but wonder how many of the clinical trials evaluating specific treatments for acute pancreatitis have been negative because of deficiencies in the assessment of severity and risk stratification.

Although the ideal prognostic marker or system has yet to be found, it can be described. For a start it would be a single safe test that was simple, quick and cheap to measure. It would be done on admission to hospital, be readily available in all settings where patients with acute pancreatitis are seen and assessed, and would be easily repeated for monitoring purposes. It would be reproducible, observer independent and not affected by concomitant disorders. But probably most important, the ideal test would accurately identify *individual* patients with severe pancreatitis. This is the glaring deficiency of all current approaches to severity assessment. They have been developed using groups of patients and when used to assess individual patients there is an 'inbuilt and unquantified inaccuracy' [6]. Much work remains to be done before prognostic markers or systems will have a sufficiently high utility for individual patient use [7]. Current approaches to severity assessment correctly classify only 60–80% of patients. There is no room for complacency because that is simply not good enough for assessing the severity of individual patients.

An intrepid investigator, seeking to discover an ideal prognostic marker or system, faces a number of challenges. As a syndrome, acute pancreatitis has a range of clinical manifestations each of which have a different range of severities and prognostic significance [8]. Furthermore, there are different prevalence rates of severe disease in different populations, different determinants of severity [9], and different definitions of severity [10]. And there are temporal challenges as well. Patients present at different times after the onset of symptoms and this may or may not coincide with an optimal testing window for the particular prognostic marker or system, let alone be prior to a therapeutic window when an intervention might be most effective. A further challenge is that organ failure has a bimodal distribution, similar to mortality, with early and late organ failure. There are also different endpoints for the prediction of severity, including death, pancreatic complications, and the degree of systemic inflammatory response, extent of organ dysfunction, intervention rates, intensive care and hospital stay. The latest guidelines state that the 'development of organ failure defines severe acute pancreatitis' [11] and it is now accepted that the degree of organ failure is more important than the extent of necrosis in defining severity [10]. It is also appreciated that 'not all organ failure is equally morbid' with early, persistent and multiple organ failures being the most important markers of clinical outcome [11].

Evaluating the performance of a prognostic marker or system is important, but the methods of reporting have not always been particularly useful. The 2×2 contingency table, the cornerstone of clinical decision analysis, is the starting point. It is commonplace to quote sensitivities and specificities, positive and negative predictive values and accuracy. But there are two ways to combine sensitivity and specificity into a single measure, and both of these are particularly useful when comparing prognostic markers and systems. The ROC curve (plotting sensitivity against 100 – specificity) allows the comparison of different tests by calculating the area under the curve. It is also useful in defining the optimal cutoff for that particular test. The second way is to calculate likelihood ratios (LRs), and it is pleasing to see other authors advocating their use [12].

There are three steps to using a LR. The first is to determine the prevalence of the endpoint in the population of patients. This is known as the pre-test probability. The second step is to calculate the LRs, which can be positive (LR+ = sensitivity/100 – specificity) or negative (LR– = 100 – sensitivity/specificity). The third step is to use this information to read off the post-test probability from a likelihood nomogram (fig. 1) [13]. This tells you the likelihood of the endpoint in the population after the test has been applied. The change in the probability from before to after the test provides a helpful and useful indication of the performance of the test.

Evaluating the performance of commonly used prognostic markers and systems has been generally disappointing [11]. The paper evaluating urinary trypsinogen activation product (uTAP) as a potential prognostic marker is a useful example [14]. The pancreatic enzyme activation cascade is triggered by the cleavage of this short peptide from trypsinogen, and this makes the significant elevation of uTAP an ideal diagnostic test. As a prognostic test for severe acute pancreatitis it performs poorly, in keeping with the understanding that the extent of pancreatic enzyme elevation does not correlate well with severity. This illustrates that diagnostic tests are not necessarily useful in predicting severity or measuring the