Pancreatology 15 (2015) 101–104

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Classifying the severity of acute pancreatitis: Towards a way forward

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ARTICLE INFO

Article history:
Available online 2 February 2015

Keywords:
Acute pancreatitis
Classification
Severity
Organ dysfunction
Infected pancreatic necrosis
Prediction

ABSTRACT

Background: The recent development of two different severity classifications for acute pancreatitis has appropriately raised questions about which should be used. The aim of this paper is to review the two new severity classifications, outline their differences, review validation studies, and identify gaps in knowledge to suggest a way forward.

Methods: A literature review was performed to identify the purposes and differences between the classifications. Validation studies and those comparing the two different classifications were also reviewed.

Results: The Revised Atlanta Classification (RAC) and the Determinants Based Classification (DBC) both rely on assessment of local and systemic factors. The differences between the classifications provides opportunities for further research to improve the accuracy and utility of severity classification. This includes understanding how best to tailor severity classification to setting (e.g. secondary or tertiary hospital) and purpose (e.g. clinical management or research). A key difference is that the RAC does not consider infected pancreatic necrosis an indicator of severe disease. There is also the need to develop methods for the accurate non-invasive diagnosis of infected necrosis and evaluation of the characteristics of organ dysfunction in relation to severity and outcome.

Conclusion: Further improvement in severity classification is possible and research priorities have been identified. For now, the decision as to which classification to use should be on the basis of setting, validity, accuracy, and ease of use.

Introduction

The recent development of two different severity classifications for acute pancreatitis [1,2] has appropriately raised questions about which one should be used, for what purpose, by whom, and in which settings. For the last two decades the severity of acute pancreatitis has been classified using two categories based on clinical and imaging criteria [3]. Although this binary approach to severity classification goes back for more than a century [4] it was the Atlanta classification in 1992 that led to the widespread use of the mild and severe categories. While significant benefits have resulted from this original Atlanta classification (OAC) of severity, a number of deficiencies have been recognized by a better understanding of acute pancreatitis. As a result, two new classifications of acute pancreatitis have been proposed [1,2]. The aim of this paper is to review the two new severity classifications, outline their differences, review validation studies, and identify gaps in knowledge to suggest a way forward.

Purpose of severity classification

Severity classification is important for both clinical care and research, and there are several purposes in each setting (Table 1). When a clinical decision is required before severity has peaked, severity prediction is needed. When the determination of severity is required at a particular time point, severity classification is needed. Prediction is about the future while classification is about the present. Ideally an accurate prediction of the ultimate severity should be possible early in the disease course and this would enable the classification of severity at every time point along the disease course. Inaccurate prediction and classification of severity bedevils clinical research efforts. The failure of clinical trials in the field of acute pancreatitis, evidenced by the glaring lack of effective and specific treatments, can be attributed, at least in part, to misclassification error, or the failure to test treatments in accurately

DOI of original article: http://dx.doi.org/10.1016/j.pan.2015.01.005.
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http://dx.doi.org/10.1016/j.pan.2015.01.006

Table 1
Potential purposes for classifying severity in acute pancreatitis (*denotes those purposes for which prediction is more appropriate than classification).

Purposes related to clinical decision making
- Triage of patients regarding intensity of initial treatment*
- Transfer of patients to dedicated unit or ICU*
- Trajectory of patients clinical course
- Treatment early in disease course (e.g. enteral nutrition)*
Purposes related to research decision making
- Audit of outcome
- Allocation of patients to trial arm*
- Analysis of interventions

defined patients [5]. The testing of new treatments would be aided by trials using homogenous and enriched categories of patients.

New severity classifications

Recently, two new severity classifications of acute pancreatitis have been introduced: the 'determinant-based classification' (DBC) [1] and the 'revised Atlanta classification' (RAC) [2] (Table 2). Naturally, this has raised questions about which classification is more valid, which has higher utility, which should be used and in what settings. That the classifications differ is no surprise as different processes were used in their development: the foundation of the DBC was a meta-analysis of published studies while the RAC emerged through a web based iterative consultative process. And although the two classifications have been considered to have 'few differences' [6] there are some that are worth noting.

There are differences between the definition of the 'moderate' category in the DBC and the 'moderately severe' category in the RAC. The RAC includes 'exacerbations of co-morbid disease', which is not considered a determinant of severity in the DBC, but rather a consequence (Table 2). The inclusion of this raises the question as to whether severity classifications should simply describe severity and its manifestations or whether it should be based on a nomenclature using defined determinants of severity. This type of difference also occurs in cancer staging. For example it is possible to describe aspects of the disease stage like local invasion, margin status, nodal involvement, genetic markers and distant metastases. The stage of cancer (e.g. Stages 0–4) can also be defined more tightly by only using determinants of prognosis [5]. The former descriptive approach may have more merit in the clinical management of individual patients with AP, while the latter is important for testing and advancing treatments through clinical trials.

Table 2
Definitions used in the two classifications of acute pancreatitis severity: the four categories of severity in the determinants based classification (Dellinger et al., 2012) and three grades of severity in the revised Atlanta classification (Banks et al., 2013).

Determinants based classification (DBC) of AP severity (categories)	
Mild	No (peri)pancreatic necrosis No organ failure
Moderate	Sterile (peri)pancreatic necrosis ***and/or*** transient organ failure
Severe	Infected (peri)pancreatic necrosis ***or*** persistent organ failure
Critical	Infected (peri)pancreatic necrosis ***and*** persistent organ failure
Revised Atlanta classification (RAC) of AP severity (grades)	
Mild	no organ failure ***and*** no local or systemic complications
Moderately severe	transient organ failure ***and/or*** local or systemic complications ***or*** exacerbations of pre-existing co-morbidities
Severe	Persistent organ failure (single or multiple)

Another difference is that infection of local complications is not part of the definition of severe AP in the RAC [2]. The reason given is that 'infected necrosis without persistent organ failure […] has a lesser mortality rate than infected necrosis with persistent organ failure'. In contrast, the DBC includes infected (peri)pancreatic necrosis in the definition of severe AP because it is a determinant of mortality [7,8].

Comparison and validation of severity classifications

The first validation study of the DBC was a prospective study from a tertiary care center in Chandigarh, India [9]. The authors recruited 151 patients over a two-year period. The severity of AP was determined when AP was most severe, no matter which day this was. Notably, patients were excluded if they had severe pre-existing co-morbidity. The mean duration of symptoms prior to admission was 3.8 days (±2.8SD). Necrosis was detected in 68% of patients, and the overall mortality was 19%. The distribution of patients in each category of severity according to the DBC classification was mild (14%), moderate (42%), severe (39%) and critical (5%). The predictors of severity (APACHE II @24 h, CRP@48 hours, Balthazar score for necrosis and the CT severity index) increased stepwise across the categories and were all significantly different between the groups. The intervention rates and worse outcome increased significantly in step-wise fashion across the categories. This included the proportion of patients requiring percutaneous drainage and/or surgery and rates of septicemia, infected necrosis, and duration of hospital stay, ICU stay and mortality (0, 4, 34 and 87% respectively). Data from this study have been used to calculate the net reclassification improvement, a validated metric that defines the relative improvement in discriminating severity, and compares the DBC and RAC separately with the OAC [10]. It was concluded that the discriminative ability of the DBC was superior to that of RAC.

A recently published study examined the validity of the moderate category of severity in the DBC [11]. It was a retrospective analysis of prospectively collected data at the tertiary West China Hospital in Chengdu, China. They compared the outcomes of 92 consecutive patients admitted within 72 h of symptom onset, classified as severe AP by the OAC and divided into moderate category ($n = 33$) and a combined the severe/critical category ($n = 59, 51 + 8$), defined according to the DBC. The clinical outcomes were significantly different: infected necrosis (0 versus 10 patients, $p = 0.031$), ICU management (0 versus 16 patients, 0.001), hospital stay (15 ± 5 versus 27 ± 12 days, $p < 0.001$) and mortality (0 versus 7 patients, $p = 0.047$). They conclude that the moderate category is distinct from the severe/critical category, but they did not compare it with the outcomes of patients defined as 'moderately severe' by the RAC.

A retrospective validation study compared the DBC and RAC in a community setting in Spain [12]. There were 543 episodes of AP in 459 patients over a 5 year period. As expected, the distribution of patients from this setting was different: mild (71%), moderate (24%), severe (4%) and critical (0.6%) for DBC. The distribution for the RAC grades was mild (67%), moderately severe (30%) and severe (4%). The study did not find any significant differences in the distribution and outcomes between the two classifications.

The RAC and the DBC were compared in a post-hoc analysis of a prospective database of 256 patients in a University Hospital [13]. Tertiary patients comprised 49% of the cohort and the overall mortality was a low 4%. The pattern of distribution of patients across the DBC categories was different from the other reports: mild (67%), moderate (7%), severe (19%) and critical (7%). The distribution of patients across the RAC grades was mild (50%), moderately severe (25%) and severe (25%). The investigators

compared the classifications in predicting 5 different outcomes, although neither classification was designed for this purpose, and the results were mixed. Both classifications were comparable for predicting ICU admission, ICU length of stay, and mortality. The RAC was better at predicting hospital stay and DBC for predicting the need for intervention. In advising caution because of inherent biases (ascertainment, selection, and misclassification), the authors concluded that it was 'not possible to choose between' the RAC and DBC because they were 'comparable' and 'complementary'.

Research priorities in moving forward

These two classifications have been designed by different methods to achieve the same ends, and thus some differences between them are inevitable. Identifying these points of difference present research opportunities for potential improvement in classifying AP severity.

Tailoring severity classification to setting and purpose

Whether the approach to severity classification should be the same across different clinical settings and for different purposes should be further explored. The requirements of clinicians in secondary and tertiary settings are probably different. There are notable differences in the distribution of patients between severity categories in secondary and tertiary centers. The low numbers in severe and critical categories in secondary centers supports the use of a binary approach. A non-specialist clinician in a smaller center has to decide whether a patient should be transferred to a dedicated unit or not. In this setting only two categories are sufficient; either the patient has mild disease and can be managed locally or has sufficiently severe disease to warrant transfer. In contrast, specialists who accept transferred patient will be interested in more than two categories. Audit, outcome and treatments studies are best conducted on homogenous subgroups with distinct outcomes as we move towards tailored treatment. For example, in a trial of a new treatment for organ failure analysis of the outcomes would not be helped if patients who will respond promptly (e.g. transient organ failure) are mixed in with those who cannot (e.g. no organ failure) or may not (e.g. persistent organ failure). Further, if the purpose were to interrupt deterioration to persistent organ failure, then it would be desirable to include all patients. If the purpose were to reverse established organ failure, then patients with transient organ failure would need to be excluded. In this type of setting, multiple categories of severity are desirable. This suggests that a dichotomous classification of severity is sufficient for the generalist, but that a specialist requires a more stratified approach.

One of the challenges besetting clinical studies is the question about how to deal with transferred patients. This is because the effect of a variable delay in admission introduces a selection bias. One approach to this challenge would be to develop whole of region prospective studies, simultaneously capturing patients in both secondary and tertiary settings and to report separately on the performance of classification systems and treatment strategies.

There is also the need for more clarity around whether, depending on the purpose, it is more appropriate to predict severity or classify severity. For instance, the early allocation of individual patients to the arms of a clinical trial may require the use of prediction and not classification. But even in this setting it would be ideal, at any time point during the course of the disease, that the severity of AP can be accurately determined, mapped and stated. It may be more useful to develop the concept of a 'provisional classification' of severity, rather than attempting to predict severity early in the disease course. As the disease progresses the provisional classification can be modified, reflecting the dynamic disease course. The use of severity classification to map the trajectory of a patient's clinical course needs to be investigated, and whether this offers any advantage over serial SOFA or Marshall scores needs to be determined.

Local complications

The RAC has improved the characterization of local collections and this provides an opportunity to examine their natural history and the extent to which they contribute to disease course and outcome. Some of the questions that might be answered relate to the prognostic significance of acute pancreatic fluid collections [5], the frequency of infection within these collections and the frequency of pseudocysts in the absence of necrosis.

There are a number of outstanding issues in relation to the diagnosis of necrosis and infected necrosis. The relative clinical significance of pancreatic and extra-pancreatic necrosis requires prospective study [14]. With the less frequent use of routine CT scanning and fine needle aspiration for bacteriologic culture, alternative and accurate methods for the diagnosis of necrosis and infected necrosis are required. Contrary to the concerns raised by recent authors [6,13], infected necrosis can be diagnosed in the majority of patients on the basis of clinical signs and imaging [15]. Any clinical deterioration should prompt a septic screen to seek the locus of infection. This will include a CT scan that will reveal any significant change in the morphology of local complications or direct signs of infection. The significant clinical deterioration of a patient and the diagnosis of a collection (especially one containing gas) will almost certainly result in percutaneous (or transgastric) catheter drainage, especially when empiric utilization of intravenous antibiotics does not improve the clinical status. This will allow definitive proof of infection in the majority of patients. Preliminary experience with diffusion-weighted magnetic resonance imaging for the non-invasive detection of infection in acute pancreatic and acute necrotic collections is promising and requires further evaluation [16]. Given that it is unusual to alter clinical management on the basis of the diagnosis of necrosis per se, it may be more important to focus on developing an accurate approach to diagnosing infected necrosis.

Organ dysfunction

The term 'organ failure' has become embedded in the pancreatology lexicon, but has been removed from the critical care literature [17] where the terms 'organ dysfunction' and 'multiple organ dysfunction' have been adopted. Further studies are necessary to determine whether it is better to classify dysfunction by individual organs or a composite score such as SOFA or Marshall. The risk of mortality appears to be significantly higher if persistent organ dysfunction occurs within the first week of the onset of symptoms, compared with later in the disease course [18]. There is much more to understand about different characteristics of organ dysfunction and their relative importance in relation to severity and outcome. These characteristics include the effect of timing of the onset (for instance within 24 h of the onset of symptoms, within the first 48 h, within the first week, after several weeks), duration of organ dysfunction (for instance for 24 h, for 48 h, for 72 h, for one week), the optimal timing cut-off between persistent and transient organ failure, the number of organs affected, the degree of organ dysfunction, the ease of reversibility, the specific combination of organ dysfunctions, and the sequence of different organ dysfunctions [19]. Data on these dimensions may define other useful subgroups of severe and critical acute pancreatitis.

Conclusions

Advances in the care of patients with AP will require improvements on current methods used for predicting and classifying severity. There may be different requirements for severity classification depending on the whether it is used in the secondary or tertiary settings. Ultimately, improvements in this field will come from the discovery of early biomarkers of severity that accurately reflect the key changes in the pancreas, peri-pancreatic tissues, and distant organs within the first few hours after disease onset. For now we are reliant on the presence of organ dysfunction and the detection of the presence of infection in local complications. The two new classifications of severity both rely on these factors, but there are important differences, as discussed, and these highlight areas where further research should yield improvements. The decision as to whether the RAC or DBC is used to classify severity should be on the basis of the setting, validity, accuracy, and ease of use.

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