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Clinical Assessment and Biochemical Markers to Objectify Severity and Prognosis

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Introduction

Among the inflammatory digestive disorders acute pancreatitis continues to challenge physicians as the least and most difficult one to predict in terms of clinical course and outcome. Ever since the first classification system of acute pancreatitis was established in Marseille in 1965 [1] the definition of "severe" disease has been linked to disease-specific complications with an increased risk of mortality [2–5]. Stratification of severity is required for targeting individual patients for interventions against evolving complications or for referral to specialist centers on the one hand and for comparing patients for scientific purposes or recruitment into clinical trials, on the other. The type and clinical relevance of a complication rendering the course of acute pancreatitis as "severe" has been the subject of continuous development and changes. New insights into pathomechanism and natural course of acute pancreatitis, development of laboratory variables and diagnostic imaging procedures as well as novel therapeutic approaches have strongly influenced definitions and classification systems and continue to do so.

Historical Perspectives: Approaches to Severity Assessment

Attempts to stratify severity and prognosis date back to the second half of the last century and have been driven by major advances in new imaging procedures and laboratory tests. The development of serum amylase measurement in 1929 [6] was the first step toward a noninvasive diagnosis of acute pancreatitis and subsequently showed that in the majority of patients a mild course with uneventful recovery was the rule rather than the exception. Supported by the development of intensive care treatment and more restrictive indications for surgical treatment in patients with clinically severe disease, interest in prognostic assessment has gained considerable headway since the 1960s. Attempts to define objective criteria for assessing disease severity and prognosis were pioneered by John Ranson in New York [7] and Clement Imrie in Glasgow [8] in the 1970s, which found widespread application in the pancreatic community.

During the early 1980s intraoperative findings revealed local-morphological features such as presence and extent of necrosis [9,10] and infection of necrosis [11) showing an excellent correlation with systemic severity and outcome. Flanked by the introduction of contrast-enhanced computed tomography (CE-CT) and percutaneous guided fine-needle-aspiration (FNA) nonoperative assessment of these complications became possible and assigned morphology-based severity stratification a predominant role. Hence, imaging procedures have become indispensable for assessment of severity in acute pancreatitis and an integral part of new classification systems [2–4] and treatment algorithms [5,12–16] alike.

After almost two decades of mainly morphology-based severity stratification the role of systemic aspects in terms of onset, severity, and persistence of pancreatitis-related organ failure was recognized as a central determinant of severity [17–29]. Moreover, early and persisting multiorgan dysfunction syndrome (MODS) has been found to outweigh morphological factors such as necrosis and even infection of necrosis as far as nonsurvival is concerned [20,29].

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Dynamics of Organ Failure

The prognostic role of early pancreatitis-associated organ failure was already recognized during the early 1970s. Objective measurement of pulmonary failure by arterial oxygen pressure or renal failure by serum creatinine had become available and had been integrated into prognostic multiparameter scoring systems according to Ranson [7] and Imrie [8]. However, it took another three decades until pancreatologists realized that the occurrence of a temporary single organ failure does not necessarily indicate a life-threatening disease. Specific aspects such as onset, severity, and persistence of organ failure have gained special attention in the past two decades.

Early Organ Failure

The role of "early" organ failure, defined as failure of one or more organ systems within the first 3 days after onset of acute pancreatitis/hospital admission was first described by Isenmann et al. in 2001 [17]. The presence of "early" single or multiple organ failure leads to a significant increase in mortality up to 56% irrespective of whether necrosis is sterile or infected [17–19,21,22]. Early multiple organ failure represents an important risk factor for death and even seems to outweigh local morphological complications such as extent or infection of necrosis [20,29].

Persistent Organ Failure

The dynamics of organ failure in terms of response/resolution or nonresponse/persistence despite intensive care treatment has been identified as another major determinant of complications and death. In many pro- and retrospective studies resolution of organ failure within the first week of the disease resulted in mortality rates close to zero, whereas mortality rates rose to 55% if organ failure persisted beyond the first week [22–25,27]. Moreover, organ failure nonresponding to intensive care treatment closely correlates with the development of pancreatic infections and death [26,28,29].

There is little doubt that organ failure is one of the most important determinants of prognosis and mortality in acute pancreatitis. The revised Atlanta classification of 2012 [3] and the international multidisciplinary "Determinant-based classification" of 2012 [4]) therefore defined organ failure as a central criterion to differentiate up to four severity groups of acute pancreatitis (Table 19.1).

Table 19.1 (a) Definition of three grades of severity in acute pancreatitis according to the revised Atlanta classification 2012. *Source:* [3]/BMJ Publishing Group Ltd.

* **Mild acute pancreatitis:**	• no organ failure • no local or systemic complications
* **Moderately severe acute pancreatitis:**	• organ failure that resolves within 48 h (transient organ failure) *and/or* • local or systemic complications without persistent organ failure
* **Severe acute pancreatitis:**	persistent organ failure >48 h • single organ failure • multiple organ failure

(b) Definition of four grades of severity in acute pancreatitis according to the "Determinant-based classification" 2012. *Source:* Adapted from [4].

* **Mild acute pancreatitis:**	• no organ failure • no peri-/intrapancreatic necrosis
* **Moderate acute pancreatitis:**	• organ failure that resolves within 48 h (transient organ failure) *and/or* • sterile peri-/intrapancreatic necrosis
* **Severe acute pancreatitis:**	• persistent organ failure >48 h *or* • infected peri-/intrapancreatic necrosis
* **Critical acute pancreatitis:**	• persistent organ failure >48 h *and* • infected peri-/intrapancreatic necrosis

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS), defined as intra-abdominal pressure >20 mmHg and newly developed organ failure [30], was re-recognized as a determinant of prognosis more than a decade ago. Abdominal hypertension (intra-abdominal pressure >15 mmHg) is observed in up to 75% of patients with severe acute pancreatitis [31–33] and ACS in about 25–38% [33–35]. Several studies revealed a strong association between intra-abdominal hypertension and the development of multiple organ dysfunction, which occurred in more than 90% of patients [18,31]. Multiple organ dysfunction in turn carries excessively high mortality rates. Clinical evidence suggests that "early" multiple organ failure may be the result of undiagnosed ACS arising from the extensive inflammatory process in the retroperitoneum and an aggressive fluid resuscitation. Beyond its prognostic role, the diagnosis of abdominal compartment syndrome has therapeutic implications that have been shown well in a few studies [36,37].

Multiparameter Scoring Systems

Analysis of numerous objective clinical and biochemical variables associated with complications and death led to the development of the very first multiple parameter scores by John Ranson [7] and Clement Imrie [8]. Both systems still offer a good level of accuracy, but have the disadvantage that valid calculation is restricted to primary admissions within the first 48 hours of treatment, whereas recalculation beyond 48 hours is impossible. Since their original description, the requirements of researchers and clinicians have changed and are driven by the need for speed and simplicity more than ever. Supported by the recognition of organ failure as a major determinant of outcome, scoring systems such as the Marshall [38] and sequential organ failure assessment (SOFA) [39] score, which have all been developed and validated in the intensive care setting, have led to more flexible and practicable assessments of severity and prognosis in acute pancreatitis.

The APACHE II Score

Dissatisfaction with the temporal applicability of the Ranson and Imrie systems led pancreatologists to search for more flexible scoring systems. One of the first multiple parameter scores applied in acute pancreatitis was the acute physiology and chronic health evaluation (APACHE) score in the early 1980s. A modification of the initial system [40] by the Intensive Care Research Group from Washington, DC, USA reduced the number of physiological variables from 35 to 11 and was termed APACHE II score [41], which, despite further modifications, remains the most commonly used version. Larvin et al. from Leeds, UK published the first evaluation in 290 attacks of acute pancreatitis [42]. Initial APACHE II scores of 10 or more revealed a sensitivity of 63% and a specificity of 81% (PPV 46%, NPV 90%) in predicting "severe" disease. By 24 hours APACHE II scores >10 provided a sensitivity of 71% and a specificity of 91% (PPV 67%, NPV 93%), which further rose to a sensitivity of 75% and a specificity of 92% (PPV 71%, NPV 93%) at values >9 after 48 hours. The APACHE II scores at 24 hours outperformed both the Ranson and Imrie scores at 48 hours. The results of the Leeds study have been confirmed exhaustively in subsequent years [43–48].

The advantage of the APACHE II system is clearly its flexibility and greater speed with possible recalculation at any time throughout the course of the disease for monitoring purposes. Conversely, calculation of this score is complex and time-consuming and carries the risk of miscalculations.

Organ Failure-Related Scoring Systems

Organ failure-related intensive care scores such as the Marshall [38] and the SOFA [39] scores have been applied in AP by a number of studies to assess organ failure or outcome [23,26,28,46,49,50–53]. The two scores belong to the newer generation of organ failure-related systems, which can describe the evolution of individual and multiple organ dysfunction over time. Both scoring systems rely on six major organ systems: pulmonary, cardiocirculatory, renal, hepatic, and neurologic function, as well as coagulation. Failure of each organ system is scored as absent or up to 4 points with escalating severity. The SOFA score is a further development of the Marshall score, because specific treatment such as ventilation and vasopressors are included, thus reflecting clinically relevant severity of organ failure [39].

Marshall Score

The first detailed validation study of the Marshall score was published by Halonen et al. in a large series of Finnish patients with severe acute pancreatitis. This scoring system provided a sensitivity of 59% and a specificity of 91% in predicting mortality within 72 hours of hospital admission, comparable results were obtained using the APACHE II system (sensitivity 65%, specificity 91%) [52]. In another retrospective study of the same group in 113 patients with severe acute pancreatitis admitted to the intensive care unit both admission and peak Marshall scores were as accurate as SOFA scores in assessing the risk of hospital mortality. Unfortunately no information about optimum cutoff levels, sensitivity, and specificity

was provided [51]. A modification of the Marshall score excluding hepatic and neurologic function has been applied in two prospective studies [23,24] and the original score in a retrospective study [25] from the UK to quantify organ failure. The components for pulmonary, cardiocirculatory, and renal function match well with the definitions of the original Atlanta classification, but hepatic (bilirubin), neurologic (Glasgow coma scale), and coagulation parameters (platelet function) may further increase total scores, even if true organ failure is absent. The revised Atlanta classification of 2012 has adopted the Marshall components for pulmonary, cardiocirculatory, and renal function to define and quantify early pancreatitis-associated organ failure [3].

SOFA Score

Two detailed evaluation studies in acute pancreatitis are available for the SOFA score. In a prospective international multicenter study, SOFA scores >4 were predictive of death with a sensitivity of 86% and a specificity of 79% (PPV 27%, NPV 98%) 48 hours after onset of symptoms [53]. Corresponding results have been reported by a Finnish study for admission scores in an ICU population-based cohort at a cutoff level >8 [51]. Among the critical care scoring systems the SOFA system offers obvious advantages since it includes therapeutic requirements such as mechanical ventilation and inotropic substances. The SOFA score is an integral means for severity stratification of sepsis and septic shock in the critical care community worldwide and is therefore a valid tool in severely ill patients with acute pancreatitis requiring intensive care treatment [54].

The advantage of organ failure scores clearly lies in their widespread implementation in critical care medicine, which allows a good comparison with other critically ill patients (e.g., patients with sepsis). The introduction of the modified Marshall score in the revised Atlanta classification has overcome the problem of erroneously high scoring points by omitting the hepatic and neurologic components. The latter are truly problematic in acute pancreatitis, because high bilirubin values or delirium tremens are frequent features of biliary or alcoholic pancreatitis, albeit not representing organ failure.

Bedside Index of Severity in Acute Pancreatitis (BISAP)

Considering both the cumbersome calculation of multiparameter scoring systems and the 48-hour delay of pancreatitis-specific scoring systems, the BISAP score was dedicated to estimate pancreatitis-related mortality within 24 hours of hospital admission. It includes five easy to obtain parameters: blood urea nitrogen (BUN), mental status, SIRS, age, and presence of pleural effusions reaching scores from 0 to 5 points [48,55]. The score was initially developed and validated in two multicenter patient cohorts of around 18,000 cases with acute pancreatitis [55]. In the validation cohort the BISAP score reached an area under the curve (AUC) of 0.82 in the receiver operating characteristic (ROC) analysis, which was equal to the APACHE II score with an AUC of 0.83. Mortality rates ranged from 0.1% in patients with 0 up to 9.5% in patients with 5 points [55]. A systematic review confirmed the BISAP score as a reliable tool to identify patients at high risk for unfavorable outcomes. Compared with the Ranson criteria and APACHE II score, the BISAP score outperformed in specificity, but showed a suboptimal overall sensitivity for prediction of mortality and of a severe course of acute pancreatitis [56].

Laboratory Variables

In the mid-1960s, the first evidence arose that acute pancreatitis is reflected by abnormalities of many serum/plasma variables [57]. Hence, a multitude of laboratory markers have been identified that allow early stratification of patients at risk to develop complications such as necrosis, infection of necrosis, organ failure, and death. Beyond the potential to predict disease severity, many of these parameters were found to be determinants of disease progression and subsequent complications in the pathomechanism of acute pancreatitis such as proteases, cytokines, chemokines, adhesion molecules, and acute phase proteins. An ideal laboratory test to assess severity of acute pancreatitis should be simple in test performance, readily available under routine and emergency conditions, accurate, and cost-effective. However, despite a large array of potentially useful parameters, their large-scale clinical use is frequently limited by moderated accuracy, and time-consuming and expensive assay procedures. Consequently, only a few tests have passed the threshold to routine clinical application.

Routine Laboratory Variables

Since the introduction of Ranson and Imrie scores, single routine laboratory components such as hematocrit, creatinine or blood urea nitrogen, and blood glucose have been extensively investigated, either alone or in combination, to predict complications and thus "severe" disease.

Hematocrit

Admission hematocrit and its subsequent changes during fluid resuscitation still represent a simple and good prognostic estimate. An admission hematocrit >44% was found to be closely associated with complications in terms of necrosis and organ failure [58] or pancreatic infection [59]. An overall high negative predictive value of around

90% excluding "severe" acute pancreatitis at admission hematocrit <44% [58] and <40% [60] was reported by some authors. However, admission hematocrit of >41% to >44% failed to predict severity, organ failure or death in other large studies [43,60]. In a recent international multicenter analysis in 1,612 patients with acute pancreatitis admission hematocrit ≥44% and increasing BUN levels at 24 hours were able to predict persistent organ failure and pancreatic necrosis in 54% and 60% of patients, respectively [61]. Hematocrit is one of three variables of the "harmless acute pancreatitis score [HAPS]," which allows a fast and accurate identification of patients with nonsevere acute pancreatitis [62]. Taken together, hematocrit serves as a widely available and good estimate to exclude severe attacks, but is not a reliable means to predict severity or any other specific complications accurately.

Serum Creatinine and Blood Urea Nitrogen (BUN)

Creatinine and blood urea nitrogen (BUN) are surrogate laboratory tests that indicate and define renal failure. Renal failure, defined as creatinine >2 mg/dl (177 µmol/l) by the Atlanta classification belongs to the most serious of organ complications in AP and has been shown to be an independent risk factor for fatal outcome [51,52,63]. However, the widely used cutoff level >2.0 mg/dl is frequently not reached on the day of hospital admission, which limits the use of this variable for "early" risk estimation. As far as disease severity in terms of local or systemic complications is concerned, admission BUN achieved no satisfactory test performance [48,64,65] reaching a maximum sensitivity of 79% and a specificity of 67% (PPV 43%, NPV 91%) only [64]. In the largest patient cohort ever published, rising BUN within 24 hours after admission achieved a sensitivity of <60% in predicting persistent organ failure or pancreatic necrosis [61], but revealed increasing diagnostic accuracy rates beyond 48 hours after admission [66].

Acute-Phase Proteins

Acute-phase proteins constitute a family of inflammatory proteins, which are mainly synthesized in the liver in response to infectious and noninfectious stimuli. The most famous member is C-reactive protein (CRP), which has become the most widely established single laboratory marker for biochemical severity stratification of acute pancreatitis. The availability of fully automated immunoassays for CRP is an essential feature for its large-scale routine application.

C-Reactive Protein

Severity stratification of acute pancreatitis by CRP has a long tradition and still represents the "gold standard" for both early severity stratification and monitoring the course of the disease [65,67,68,69,70,71]. CRP is the laboratory variable of choice to differentiate necrotizing from interstitial edematous acute pancreatitis. However, the majority of the studies focused on the discrimination between mild and severe acute pancreatitis according to the original Atlanta classification of 1993. Therein, CRP achieves diagnostic accuracy rates of between 70% and 80% at a cutoff level >150 mg/l within 48 hours after disease onset [71]. As has been well documented for all acute phase proteins CRP is not useful for prediction of infected necrosis, organ failure or death within the first week after disease onset [65,72]. Another shortcoming of CRP is the relatively long delay of its induction with systemic peak values at 72 to 96 hours after disease onset thus making very early severity assessment impossible.

In contrast to CRP, SAA failed to show any relevant benefit over CRP in estimating severity or prognosis of acute pancreatitis [67,69].

Cytokines and Chemokines

A wealth of experimental and clinical studies during the 1990s have convincingly outlined that cytokines and chemokines play a key role in the pathophysiology of acute pancreatitis by promoting local tissue destruction and mediating distant organ complications [73,74]. Therefore, cyto- and chemokine measurement was thought to offer an excellent approach to biochemical severity assessment. Despite the development of fast and fully automated assay techniques, the vast majority of the cytokine and chemokine family members play no role as biochemical markers for acute pancreatitis in the clinical setting. So far, only the cytokine interleukin-6 (IL-6) has passed the threshold from pathophysiological importance to clinical application.

Interleukin-6

Systemic concentrations of IL-6 have been found to be early and excellent predictors of severity. A large number of clinical studies have uniformly shown that IL-6 is dramatically increased in complicated attacks [65,70,71,75–77]. IL-6 concentrations generally rise 24–36 hours earlier than CRP levels and remain significantly elevated as long as complications persist. One of the first series in 24 patients from Glasgow found a sensitivity of 100% and a specificity of 71% (PPV 71%, NPV 100%) at a cutoff level >130 IU/ml for IL-6 in predicting a severe attack within 36 hours of symptom onset [75]. Beyond discriminating mild from severe attacks, IL-6 closely correlates with evolving organ failure [65,70,76]. A recent systematic review indicated superiority of IL-6 for the early prediction of moderate to severe acute pancreatitis compared with 29 other biochemical markers [71]. IL-6 has been introduced as routine parameter in some

laboratories and represents an easy and rapid means to select patients at risk to develop severe disease. However, a large-scale use of IL-6 measurements in acute pancreatitis has never been reached.

Procalcitonin

Ever since its first description in 1993 [78] procalcitonin (PCT) has become an established marker for predicting bacterial/fungal infections, sepsis, and septic shock in the intensive care and emergency surgery settings [13,54,79,70]. A close correlation between elevated PCT concentrations and the development of infected necrosis was first described in a cohort study comprising 51 patients with acute pancreatitis by our group in 1997. At a cutoff level of >1.8 ng/ml PCT was able to predict this complication with a sensitivity and specificity of more than 90% within the first days after onset of symptoms [72]. An international multicenter trial in 104 patients with severe acute pancreatitis has shown that PCT is able to predict serious complications such as pancreatic infections or death with a sensitivity of 79% and a specificity of 93% (PPV 65%, NPV 97%) at a cutoff level >3.8 ng/ml within 48–96 hours after onset of symptoms [80]. This observation was confirmed by a number of subsequent studies which have been subjected to a meta-analysis and a systematic review. Herein, PCT reached a cumulative sensitivity of 80% and a specificity of 90% for predicting infected necrosis in acute pancreatitis [66,81]. Notably, PCT is of little or no value for simple stratification of patients as "mild" or "severe" according to the original Atlanta classification of 1993. The international guidelines for the management of sepsis and septic shock and the World Society of Emergency Surgery guidelines recommend the use of PCT as the most sensitive laboratory test to detect sepsis/pancreatic infections [13,54].

PCT measurements are available as fully automated assay for routine use, a semiquantitative strip test is an alternative for a fast and easy quantification. On the basis of the data available, PCT is a valuable tool for an early stratification and consecutive monitoring of patients at risk to develop the most serious complications in acute pancreatitis.

Table 19.2 provides an overview of relevant multiparameter scoring systems and laboratory markers for severity stratification and prediction of specific complications in acute pancreatitis.

Table 19.2 Relevant multiparameter scoring systems and laboratory markers for severity stratification and prediction of specific complications in acute pancreatitis.

Variable	Severity	Pancreatic infection	Overall prognosis
Ranson-/Imrie Score	++ (48 h)	–––	++ (48 h)
APACHE II Score	++	–––	+++ (>7 d)
SOFA-/Marshall Score	++	–––	+++ (>7 d)
BISAP Score	++ (24 h)	–––	++ (24 h)
Hematocrit	++ (48 h)	–––	–––
Creatinine/blood urea nitrogen	+	–––	++ (>7 d)
IL-6	+++ (<48 h)	–––	–––
CRP	+++ (72–96 h)	–––	–––
PCT	–––	+++ (72–96 h)	+++ (72–96 h, > 7 d)

Optimum accuracy after symptom onset of acute pancreatitis:
<48 h: within less than 48 h after symptom onset
48 h: within 48 h after symptom onset
72–96 h: within 72 to 96 h after symptom onset
>7 d: beyond the first week after disease onset.
APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; IL-6: interleukin-6; CRP: C-reactive protein; PCT: procalcitonin.

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