Prognostic scores in acute pancreatitis : A review

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Abstract

Predicting the course of an attack of acute pancreatitis still represents a challenge for the physicians.Some early interventions such as endoscopic retrograde cholangiopancreatography and sphincterotomy, admission to the intensive care unit, enteral feeding, and prophylactic antibiotics have been proven to decrease morbidity and mortality in patients of high-risk groups. However, acute pancreatitis has a potential of morbidity and mortality, and therefore early diagnosis and objective assessment of severity of the disease is fundamental. To date, many different prognostic scores have been applied to the initial management of acute pancreatitis for the evaluation of the severity of disease. However, each of the scoring systems has advantages and disadvantages. In this paper, we tried to summarize the prognostic scoring systems and their performances in assessing severity and prognosis of acute pancreatitis. (Acta gastroenterol. belg., **2016**, 79, **337-347**).

Key words : Acute pancreatitis, mortality, prognostic scores, severity

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal emergent diseases worldwide. Clinical assessment of AP remains challenging due to its course that varies from mild to severe forms. Eighty-five percentage of patients with AP have interstitial pancreatitis which has a mild course and favorable prognosis; however, %15 of patients develop necrotizing pancreatitis known as severe form of the disease (1). In other words, approximately 15-20% of patients with AP develop severe disease which complicates the clinical course and often causes an organ failure (2). The risk of mortality increases due to the presence of serious disease-specific complications (3). Approximately half of the deaths occur within the first week of the attack, as a result of multiple organ failure (3). On the other hand, septic complications are responsible for the delayed mortality (4). Therefore, identifying the severity of disease within 24-48 hours after admission is essential for planning the initial treatment and preventing complications (6).

To date, various scoring systems that aim to alert the clinicians to the severity of disease and to predict the prognosis have been reported in the literature. In this review, we try to summarize the prognostic scoring systems and their performances in assessing severity and prognosis of AP.

Estimation Of Severity

Diagnosis of AP and estimation the severity of disease were bounded with the preoperative evaluations or autopsy findings in the early time of century (7,8). Following major advances in the field of laboratory assessment, serum amylase measurement was begun to use in diagnosis of AP in 1920's. In 1965, the definition of 'severe' disease was first described as a presence of disease-specific complications with an increased risk of mortality. Multiparameter prognostic scores were then come into prominence in prediction of severe form of the disease (9,10). Ranson's criteria, described by John Ranson in 1970's, are the first widely used severity scoring system, and consist of basic laboratory data and clinical variables obtained within 48 h after hospital admission (11). Based on the same clinical point of view, Clement Imrie (12) and other investigators (13,14) also described several severity scoring systems as variants of Ranson's Criteria. For prediction of mortality in patients with AP, Acute Physiology And Chronic Health Evaluation (APACHE) II score which consists of multiple physiological parameters on admission and following days, has also been used in determining the severity and progression of the disease (15). These prognostic scores were applicated by many clinicians among the world with great acceptance, and also validated and modified in subsequent years. Nowadays, pancreatitis induced mortality, associated with the term 'severe', is explained with illness dominated by sepsis and the consequences of organ failure. According to Atlanta Symposium in 1992, severe AP was defined when the Ranson score is ≥3 points, APACHE II score is ≥8 points or evidence of organ failure (particular pulmonary insufficiency, renal failure, and shock) and/or local complications (necrosis, abscess, and pseudocysts) (16). Unfortunately, 1992 Atlanta criteria had some drawbacks between the estimated and actual disease severity, depending on the individual discrepancy of clinical course (17,18). In addition, the lack of objective definitions of the local complications, which could be easily displayed with tomographic evaluation, empowered the opinion of the need for revision and modification of the 1992 Atlanta criteria (19). Finally, in 2012, a revised Atlanta classification, which stratified the severity of AP as mild,

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moderately severe and severe depending on the absence or presence of persistent organ failure, local and systemic complications, was reported (20). Additionally, severe disease with persistent single or multiple organ failure longer than 48 h was shown to be associated with death. The definition of transient or persistent organ failure is attributed to the modified Marshall score which mainly evaluates the three organ systems including respiratory, cardiovascular and renal systems (21). Although the individualized clinical course of the disease complicates bedside evaluation and invalidates the predictive value of prognostic scores, many authors attempted to address the organ failure to better determine the severity of the disease. In this context, various organ failure-related prognostic scores such as Marshall (21), MOF/Goris (22), and the SOFA (23) scores were established.

Besides the above mentioned scoring systems, some pancreatic enzymes such as trypsinogen, and various systemic inflammatory markers including red cell distribution width (RDW), interleukin (IL)-1, IL-6, TNF-α, procalcitonin, and C-reactive protein (CRP), were also found to be useful and promising predictors in determining the severity of AP, especially in early phases of the disease (24-29). Although these biochemical parameters may demonstrate certain discrepancies among the clinics worldwide, they have already reached wide clinical use.

Local/general complications and mortality related to AP depend on some clinical features. First of all, the incidence of AP increases in the elderly, in parallel to the increase in human lifespan. It has been demonstrated that advanced age is strongly associated with increased risk of mortality in large population studies (30-34). In a study, late onset of the first attack of biliary AP was found to be associated with increased mortality rates in elderly patients, as a result of suspended timing of cholecystectomy (35). Besides, in another study, the authors reported that >40% of patients who did not undergo cholecystectomy on initial hospitalization would have benefited from early definitive therapy (36). Comorbid diseases such as diabetes, cardiovascular diseases and renal impairment are also other risk factors of mortality in AP (37-40). Obesity is another severity risk factor with increased morbidity and mortality in patients with AP (41). Several clinical signs and physiological parameters have been studied to clarify the individual course of the disease. Presence of hypoxemia and pleural effusions and/or pneumonic infiltrations demonstrated on chest x-ray on admission, have been shown to be predictors of poor prognosis (42,43). Intra-abdominal pressure higher than 15 mmHg was also found to be a risk factor for severe AP, and performing an urgent decompression of abdomen was shown to prolong the survival (44).

To date, many guidelines and prognostic scores based on clinical outcomes, laboratory tests, and radiologic assessments were recommended to predict fatal consequences of AP.

Table 1. — **Ranson's criteria for severity of AP**

Non-biliary etiology	Biliary etiology
At admission	At admission
Age > 55 years	Age > 70 years
Leukocytes >16 000/mm^3	Leukocytes > 18 000/mm^3
Blood glucose > 200 mg/dl	Blood glucose > 220 mg/dl
Serum LDH > 350 U/l	Serum LDH > 250 U/l
Serum AST > 250 U/l	Serum AST > 250 U/l
After 48 hours	After 48 hours
Reduction in hematocrit > 10%	Reduction in hematocrit > 10%
Increase in BUN > 5 mg/dl	Increase in BUN > 2 mg/dl
Serum calcium < 8 mg/dl	Serum calcium < 8 mg/dl
Arterial PO_2 < 60 mm Hg	Arterial PO_2 < 60 mm Hg
Base deficit > 4 meq/l	Base deficit > 5 meq/l
Estimated fluid sequestration > 6 L	Estimated fluid sequestration > 4 L

* LDH: Lactic dehydrogenase, AST: Glutamic oxaloacetic transaminase, BUN: Blood Urea nitrogen

Prognostic scores including multiple parameters

All the scoring systems used in AP can be classified into two main groups: The first group includes parameters specific to pancreatitis, and consists of Ranson and Imrie (Glasgow) scoring systems. On the other hand, the second group including Acute Physiologic and Chronic Health Evaluation System (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II (45), and the Mortality Probability Models (MPM) II (46) scores, is not specific to pancreatitis, and is originally designed for use in all critically ill patients.

Prognostic scores specific to acute panceratitis

Ranson score

Ranson score has been used to assess the severity of AP for a long time. While five parameters are assessed on admission, other six variables are evaluated during the first 48 h of hospitalization (Table 1). Therefore, total score cannot be reached until the end of 48 h. AP is defined as "severe" when the score is over three (47). Sensitivity of this score was found to be between 40% and 80%, especially among biliary etiology group in the previous studies (48-51), and thus Ranson group developed a modified index (52). Today, it is the most common scoring system used for evaluating the severity of AP. Papachristou and coauthors compared the multiparameter scores' predictive accuracies determined by area under the receiver operation characteristic curve (AUC), and found that Ranson score was the only scoring system with an AUC>0,9 (53). However, need to complete 48 h for evaluation is the main disadvantage

of this system. Despite the widespread use of the Ranson score as a guide to interventional therapies in patients with AP, it has never proved to be superior to clinical intuition or any other quantification schemes for predicting outcome or the need for any particular intervention. Prospective studies and meta-analyses have shown that the Ranson score is not as reliable as thought before in determining the severity of pancreatitis (54).

The Imrie/Glasgow score

Imrie and co-authors developed Glasgow severity score in their study regarding the Trasylol therapy of AP (55). Glasgow severity score, as a variant of Ranson's criteria, was also validated on patients with gallstone and alcohol induced AP, and modified by reducing the prognostic factors into nine parameters in 1980s (56,57). Glasgow score's accuracy in the diagnosis of severe form of the disease seems to be almost equal to the Ranson score (11), with a sensitivity below 80% and a positive predictive value less than 70% (48,50,54,58).

Bedside Severity Index of AP (BISAP)

BISAP score is a new scoring system, and consists of five variables including blood urea nitrogen >25 mg/dl, impaired mental status, systemic inflammatory response syndrome, age >60 years, and pleural effusion detected by imaging methods. One point is assigned for each variable within 24 h of presentation, and is added for a composite score of 0 – 5 (59). BISAP score ≥3 indicates severe AP (60). This score is also able to identify patients at increased risk of mortality prior to the onset of organ failure. Papachristou et al also demonstrated that main advantages of BISAP score were its high accuracy rate and usefulness for predicting the severity within 24 h of hospital admission (53). However, lack of some parameters including etiology, presence of recurrent attack of AP, and obesity are the disadvantages of this score. Some authors tried to insert obesity into the BISAP score; however, they also indicated that prospective clinical trials with large populations are required to describe the exact association between BISAP score and obesity (61).

Japanese Severity Score (JSS)

JSS, first described in 1991, was composed of 18 complicated parameters, and therefore, its clinical use could not be widespread in comparison to other prognostic scores (62). For this reason, in 2008, JSS was revised to a simple form with nine prognostic factors including base excess (BE), partial pressure of arterial oxygen ($PaO_{2)}$, blood urea nitrogen (BUN), serum lactate dehydrogenase (LDH), platelet count, calcium (Ca), CRP, systemic inflammatory response syndrome (SIRS), and age (63). In Ueda study, the AUC for the prediction of the mortality rate in the new JSS was found to be 0.822, similar to Ranson score (0.820) (63).

Simple prognostic markers

Fan et al. provided extremely a simple score known as Hong Kong criteria including two prognostic parameters, urea and glucose. Urea greater than 7.4 mmol/L and glucose greater than 11.0 mmol/L were the indicators of severe form of the disease. They declared that the results were comparable to the Glasgow score in predicting the severity of AP, with 75.0% sensitivity, 80.3% specificity and 79.3% accuracy (64). However, the major drawback of the score is that some authors have found them to be inaccurate (65-67).

Ueda et al also developed a simple score for the prediction of severe AP, with three determinants; serum BUN≥ 25 mg/dL, serum LDH≥ 900 IU/L, and contrast-enhanced computed tomography (CT) findings compatible with pancreatic necrosis. Prognostic scores were analyzed by AUC between the conventional prognostic scores, and no significant difference was found in the predictive accuracy of the scores (68).

General severıty of ıllness scores

APACHE score

APACHE score was first described by Kanus et al in 1981 for ICU patients (69). It was modified to APACHE-II system by reducing the number of parameters from 35 to 12, and thus an easier score was formed by the same authors (70). APACHE-II system for predicting the severity of AP was first used by Larvin et al in 1989 (15). In that study, sensitivity and specificity of initial (at admission) APACHE-II score for predicting the severity of acute pancreatitis were found to be high, with rates of 63% and 81% respectively. Additionally, the 48 h APACHE-II had also high sensitivity (75%) and specificity (92%). According to these data, the APACHE II score at 24 h was better than the Ranson and Imrie scores at 48 h. Domínguez-Muñoz JE et al (71) supported these findings by publishing data that demonstrated 70.4% sensitivity and 79.1% specificity. In a study conducted in 2000, similar results were obtained; however, calculation of APACHE-II score at 24th and 48th hours were proven to be more accurate than admission calculations (27). The main advantage of the APACHE system is that the clinicians can follow the progression of the disease daily through the data obtained from 12 physiological variables on admission and on each day thereafter. However, Kaya et al (72) indicated one potential weakness of APACHE II was that patients older than 65 years had very high scores and there was a possibility of a false-positive score in that age group. They also found no association between age and disease severity, morbidity or mortality.

Although APACHE-III system was defined in 1991, the commonly used system is still APACHE-II (73). Williams and Simms (74) demonstrated that APACHE III score assessed at 96 hours after ICU admission predicted late complication. In contrast, Eachempati

et al (75) showed that Ranson score was similar to the APACHE III score in predicting mortality and development of organ dysfunction. Besides, in the recent years, it has been argued that APACHE-O system which was modified according to obesity indicated better predictive values than APACHE-II (76-78). One and two points are added to obese patients with body mass index between 26-30 kg/m^2 and >30 kg/m^2 respectively should be separated. APACHE-O system has been validated by several authors, and has been confirmed as better in terms of severity prediction.

Besides APACHE systems, SAPS II and MPM II systems have been studied to evaluate the severity of AP. These systems are especially provided for an estimation of death risk for ICU patients without a specified primary diagnosis (45,46). Similar to the APACHE system, SAPS II and MPM II systems comprise of multiple variables such as age, type of admission, the presence of underlying disease, and various physiological variables. Although there are few prospective studies assessing the severity of AP with these exclusive criteria's, Gocmen et al. (79) described that MPM II model predicted mortality better than the Ranson, APACHE and SAPS II systems. On the other hand, Anglade et al (80) suggested that prognostic scores specific to the AP have the same predictive efficiency as general severity of illness prognostic scores including APACHE II, SAPS I and II systems.

Artificial Neural Networks (ANNs)

During last 10 years, a class of techniques inspired by the workings of biologic neurons, ANNs, have been proposed as a supplement or alternative to standard statistical techniques for predicting complex biologic phenomena. Briefly, ANNs are a class of nonlinear mathematical models characterized by a complex structure of interconnected computational elements, the neurons. These computational elements aggregate a series of inputs (factors that influence the outcomes of acute biliary pancreatitis) by using a summation operation and produce an output, such as the severity of acute biliary pancreatitis (81).

Several authors have used ANNs to develop predictive models for the management of patients with AP, with varying degrees of success (82). Pofahl et al (83), by using the ANN model, found that the ANN was reasonably accurate in predicting inpatient stays of longer than 7 days, which was used as a surrogate marker of disease severity. The accuracy of the ANN model obtained from their study, however, was similar to the APACHE II and Ranson scores. Keogan et al (84) used six clinical and radiological variables in an ANN to identify pancreatitis patients whose hospital stay exceeded the mean hospital stay of 8.4 days. They did not find any difference between the groups in terms of the predictive ability of the ANN. Halonen et al (39) used 10 clinical and laboratory variables to develop the ANN from a retrospective review of 253 patients with severe pancreatitis. In the validation set, the predictive accuracy, determined by the AUC, was 0.847 for the ANN model using eight variables, 0.817 for APACHE II, 0.655 for Ranson score, and 0.536 for Imrie score, but they did not find any difference in accuracy between the ANN model and the logistic regression model. In a recent publication, Mofidi et al (82) created a feed-forward ANN for predicting severity and mortality of AP. They found that ANN was more accurate than APACHE II and Glasgow severity prognostic scores in predicting progression to a severe course, development of multi organ dysfunction syndrome and death from AP. Yoldas et al (85) showed a predictive advantage of ANN over conventional prognostic scores in patients with AP.

In summary, the ANNs offer a number of advantages, including requiring less formal statistical training, ability to implicitly detect complex nonlinear relationships between dependent and independent variables, ability to detect all possible interactions between predictor variables, and the availability of multiple training algorithms (86).

Radiologic scores

Each of prognostic scores discussed above has shortcomings depending on the lack of radiological evaluations. In revised Atlanta classification, AP was classified as acute interstitial edematous pancreatitis and necrotizing pancreatitis (20). The complications defined in CT examination for moderately severe disease are acute peripancreatic fluid collections (APFCs), pancreatic pseudocysts, acute necrotic collections (ANCs), and walled off necrosis (WON). Extra pancreatic complications include colonic necrosis, splenic/portal vein thrombosis and gastric outlet dysfunction. While fluid collection and interstitial edema are the imaging signs of early phases of pancreatic inflammation, reduced perfusion or infarction of the pancreas are accepted as the gold standard radiological evidences in severe AP (87-89). Due to natural clinical course of the disease, severe pancreatitis proved with pancreatic necrosis is rarely presented within 24 h after the presentation. Although initial evaluation of the patients with contrast enhanced CT still remains controversial in critically ill patients, some authors have reported that early use of non-enhanced CT can predict mortality in severe AP (90-92). In addition to CT, magnetic resonance imaging is also used in the evaluation of the severity of AP (93).

Balthazar score

In 1985, Balthazar et al. described the usefulness of early CT examination in AP patients as a prognostic indicator of morbidity and mortality (94). The patients were ranked into five groups from Grade A to E, depending on the findings of fluid collections and degree

of inflammation. Due to the lack of contrast utilization, Balthazar score is unable to demonstrate the ANCs and WON as severity predictors.

CT Severity Index

Balthazar CT severity index is the first contrast-enhanced CT evaluation of pancreatic necrosis in AP patients (95). Initial tomography was shown to be useful in predicting the serious complications in patients with more than 30% necrosis. Thus, a CT severity index was developed based on a combination of peripancreatic inflammation, phlegmon and degree of pancreatic necrosis, and the patients were divided into three groups; those with ≤30 %, >30–50 %, and >50 % necrosis. The final score was calculated by adding additional points for each of the findings. CT severity index score >7 was found to be associated with a mortality rate of 92% (Table 2). Several authors concluded that the CT severity index was superior to other prognostic scores in all outcome measures, especially in prediction of severe disease and pancreatic necrosis (96, 97). Mortele et al (98) modified the CT severity index to evaluate the extra pancreatic complications and to foresee the correlation between development of organ failure and the predictive value of new severity index. This modified index is superior to the original index in terms of the disease outcomes, overall hospital stay, the need for surgical and percutaneous procedures, and the development of infectious complications. Compared with APACHE II, both CT indexes more accurately diagnose clinically severe disease and better correlate with the need for intervention and pancreatic infection. However, no significant differences were noted between the original and modified forms of CT severity indexes in evaluating the severity of AP (99).

Table 2. — **Balthazar CT Severity Index**

CT findings	Points
Grade of AP	
Normal pancreas	0
Pancreatic enlargement	1
Inflammation involving pancreas and peripancreatic fat	2
Single fluid collection or phlegmon	3
Two or more fluid collections or phlegmons	4
Degree of AP	
No necrosis	0
Necrosis of one third of pancreas	2
Necrosis of one half of the pancreas	4
Necrosis of more than one half of the pancreas	6
Severity Index	Mortality/ Complication (%)
0-1	0% / 0%
2-3	3% / 8%
4-6	6% / 35%
7-10	17% / 92%

Other CT-based prognostic scores

Kempainen et al (90) described Helsinki score by dividing the pancreatic tissue necrosis into four groups, according to the anatomical sites. The study demonstrated that the clinical course of the disease with entire pancreatic necrosis was as severe as necrosis limited to the head of pancreas. The authors suggested that the correct localization of the pancreatic necrosis by an immediate contrast-enhanced CT could give an additional information about the disease severity, and therefore should be used for prognostic scoring.

In addition to the presence and extent of pancreatic necrosis, extra pancreatic evaluation is also essential in determining the severity of disease. In 2007, De Waele et al (92) categorized the extra pancreatic manifestations as pleural effusion, ascites, retroperitoneal and mesenteric inflammation, and developed the ExtraPancreatic Inflammation on CT (EPIC) score. The calculated AUC values for estimation of disease severity and mortality were 0.91 and 0.85 respectively. EPIC score features a better accuracy with a high sensitivity and specificity rates in contrast to Balthazar and CT severity index. As a non-contrast evaluation performed within 24 h after administration to the hospital, EPIC score can be used securely in patients at risk of acute kidney injury. King et al (100) also emphasized that the presence of mesenteric edema (MO) and peritoneal fluid (P) findings on CT should be used for a simple score (MOP score) as a predictor of disease severity in AP.

Organ failure related scores

Failure of the two or more organ systems among the cardiovascular, respiratory, renal, hepatic, hematological and neurological systems is defined as multi organ dysfunction syndrome (MODS). MODS and septic complications are responsible for late mortality in AP, especially between first and third weeks of onset of disease. However, SIRS and MODS may also cause mortality in the early phase (namely within the first week) (1, 4, 101, 102). Revised Atlanta Criteria suggest that disease severity shows a compatibility with persistent organ failure for longer than 48 h (103, 104). Glasgow group also showed that organ failure, or deterioration of organ function, which persists for more than 36 h, was associated with mortality rates of 50% to 60%, whereas patients with only transient organ dysfunction rarely died from the disease (101). Several stratification systems have been utilized to assess the AP severity by evaluating the functional status of these organ systems. MODS/Marshall score and Sequential Organ Failure Assessment (SOFA) score are the most accepted systems in routine clinical practice. While both prognostic scores evaluate six organ systems, SOFA score also criticizes

the cardiovascular system and definitive individual inotrop administration.

MOF/Goris score

MOF/Goris score depends on clinical deterioration in seven major organ systems including the renal, respiratory, cardiovascular, hepatic, central nervous, haemopoeitic, and gastrointestinal systems (105). Roumen et al (22) demonstrated in 39 patients with necrotizing pancreatitis that APACHE II system displayed good performance in grading the severity, whereas Goris score was superior for monitoring the degree of organ dysfunction and the intensity of supportive treatment. In contrast, de Beaux et al (31) displayed that higher Goris scores between 5-9 showed great relationship with higher mortality rates of 67%.

Marshall score

MODS score was first described by Marshall and co-authors in 1995 (21). Since then, Marshall score was modified by excluding the parameters of hepatic function in several clinical trials (6, 101). The modified Marshall system evaluates respiratory, cardiovascular, and renal organ systems affected by severe AP (Table 3). Persistent organ failure is defined objectively as a score of 2 or more for longer than 48 h for 1 (or more) of the 3 organ systems. Transient organ failure is also important in the classification of moderately severe AP, and involves a score of 2 or more for 1 (or more) of the 3 organ systems that are present for longer than 48 h. The modified Marshall score can be reevaluated during the course of the disease to reclassify the severity.

SOFA score

SOFA score was essentially defined for the assessment of the incidence of organ dysfunction/failure in ICU patients. Halonen et al (39) studied the predictive values of organ dysfunction scores on hospital mortality in patients with severe AP, compared with APACHE II system. In this study, all of the prognostic scores showed better predictive values over mortality than the age and APACHE system. However, SOFA score showed the highest discrimination rates which were not statistically different from other organ dysfunction scoring systems. In a prospective study, SOFA scores >4 predict mortality with a sensitivity of 86% and specificity of 79% 48 h after onset of symptoms (107). SOFA score, thanks to some additional advantages such as easy applicability and individualized evaluation schemes, has come into prominence among other organ failure prognostic scores.

Miscellaneous markers of the severity and inflammation

In recent years, multiorgan failure has been acknowledged as a major determinant of mortality (6, 108-111). Several studies identified the markers which have contributed to the inflammatory process. Nowadays, prognostic markers such as CRP, TNF-α, IL-1, and IL-6 have been widely used to determine the disease severity.

Hemoconcentration is accepted as an important factor for the development of severe AP. For this reason, hematocrit levels on admission can be assumed as a novel predictor of severity of the disease. Some studies have indicated that hematocrit level over 50% is a sign of severity (112). Other studies carried out in this field have demonstrated that hematocrit level over 44% is associated with complications in AP (113,114). However, whether changes in hematocrit levels during the follow up could be used to assess the severity is still unknown. Recent studies have implicated that, raised hematocrit level on admission or within the first 24 h, is a satisfactory single prognostic variable in predicting the severity of AP, when compared to the Ranson criteria's and APACHE system (112,113,115,116).

RDW is reflective of systemic inflammation, and is a remarkable prognostic marker to determine the risk of mortality in a wide range of clinical manifestations (117-121). Senol et al (122) demonstrated in a study that increased RDW value at admission was an independent predictor of mortality in patients with AP. In that study, RDW>14,8% at onset of the disease displayed more distinct correlation in predicting mortality than the other novel prognostic markers in the literature.

Many investigators studied the potential role of acute renal failure (ARF) in the course of AP (123-125). It is well known that mortality rate is high in AP patiens who develop ARF (125). In addition, another fact is that ARF is directly influenced by severity of pancreatitis (123). In a study, sensitivity and specificity of elevation of BUN for predicting the severity of AP was found 79% and 70%, respectively (126). It should be noted that BUN and creatinine are among the routine laboratory tests,

Table 3. — **Modified Marshall scoring system**

Organ system	0	1	2	3	4
Respiratory (PO_2/FIO_2)	>400	301-400	201-300	101-200	≤100
Renal (serum creatinine, mg/dl)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular (SBP*, mmHg)	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2

*SBP: Systolic blood pressure

and hence can be easily used in the evaluation of severity of AP.

CRP levels over 150 mg/dl are broadly recognized as an indicator of severity 48 h after the disease onset, when other causes of inflammation such as cholangitis and pneumonia are ruled out (127-130). Sensitivity and positive predictive value of serum CRP level in patients with severe pancreatitis were reported to be 83-90% and 75-86%, respectiveley. Additionally, CRP level was found to significantly increase in the early phase of severe AP, suggesting as an early indicator of the progression of disease (129).

IL-6 is the major mediator of CRP, and is mainly released from macrophages. Its high serum levels at admission have a sensitivity and specificity of 69-100% and 70-86% respectively, for distinguishing severe and mild pancreatitis (131). IL-6 rises with the beginning of symptoms and makes the peak on the 3rd day. As it has a short plasma half-life, the degradation during the course of the disease can be used as an indicator of progression.

IL-8 is a neutrophil activating cytokine, and can be used as an early predictor of severity and complications of AP (131). A variety of results on predicting the infected necrosis in AP (sensitivity 72-100% and specificity75-81%) have been reported to date (26, 132). Despite the high prediction rates, it still has a limited use in daily clinical practice.

IL-10 is a well-known anti-inflammatory cytokine. Even though a study has reported a sensitivity of 67% and specificity of 100% with IL-10 for predicting the severity on the first day of AP (133), other studies have stated less reliable results when compared with IL-6 and IL-8 (129).

TNF-α, which is primarily produced by macrophages, is a cytokine that stimulates the acute phase reaction. Many clinicians have investigated its role in predicting the severity of AP; however, the outcomes of these studies are not very promising (134, 135). As a result of its rapid clearance, TNF-α seems to be less useful than other cytokines in prediction of disease severity.

Serum procalcitonin level is known as a reliable marker of infection and sepsis (136). It has high sensitivity and specificity rates on detecting the infected necrosis of AP. In a review, it has been reported that procalcitonin had an overall sensitivity of 80% and specificity of 91% in the diagnosis of infected necrosis (137). In another study, procalcitonin level higher than 0.5 ng/mL was found to be associated with the presence of infected necrotizing pancreatitis (138). On the other hand, the main handicap of this marker is that it is not a preferable laboratory data for daily use.

Urinary trypsinogen activation peptide (uTAP) is liberated during the activation of trypsinogen to trypsin. According to 1992 Atlanta Criteria, uTAP is a rapid and reliable test in predicting severity of AP (16). In recent years, several studies have demonstrated significant correlation between the uTAP level and severity of disease. In a study published in 1997, uTAP>10 ng/ml at admission was found to be a predictor of disease severity, with sensitivity and specifity rates of 100% and 85% respectively (139). However, other studies conducted in the following years have revealed different sensitivity (58-100%) and specificity (65, 8-77%) levels for different cut-off values of uTAP (27,140,141). The increased level of uTAP is that may give information about the severity of disease at admission, but it does not still seem as a diagnostic marker.

Conclusion

AP, as one of the most frequent gastrointestinal emergent diseases worldwide, still has a significant overall mortality rate despite the recent advances in diagnosis and treatment. Therefore, early diagnosis and predicting of severity of the disease take an important place in reducing morbidity and mortality. To date, many clinical and radiological prognostic markers and scoring systems have been recommended to predict its clinical course. However, none of those seems to be an ideal marker for early assessment of severity in AP. In our opinion, large-scale multi-centre clinical studies that can discover new, easy-to-use, effective and non-complicated biomarkers and/or grading systems are needed for predicting the severity of this annoying disease.

Prospects for future research

Each passing day, new markers are recommended to determine the severity and prognosis of AP. The efficacy of these promising indicators can be clarified with large-scale clinical studies, and thus more effective scoring systems can be improved.

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