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ORIGINAL ARTICLE

Outcome assessment in acute pancreatitis patients

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Abstract Early diagnosis and severity evaluation in patients with acute pancreatitis (AP) are very important due to its potential morbidity and mortality. Several clinical, laboratory, and radiologic factors, and many scoring systems have been proposed for outcome prediction. Although the Ranson and Acute Physiology and Chronic Health Evaluation II scoring systems have been widely used for decades, the cumbersome components partly limit their predictability. Recently, the Bedside Index for Severity in AP scoring system and series blood urea nitrogen changes, which are simple and convenient to evaluate within 24 hours after admission, have been validated for accuracy by several large-cohort studies. The presence of organ failure and systemic inflammatory response syndrome are also helpful to evaluate the severity of AP. Herein we review recent advances of the predictive methods for AP to provide an up-to-date perspective on outcome assessment of AP.

Introduction

Acute pancreatitis (AP) is a common acute inflammatory process of the pancreas that usually manifests with severe acute upper abdominal pain and elevated pancreatic enzymes. Overall, 85% of patients have interstitial pancreatitis, which is usually mild, self-limiting and has a favorable prognosis. However, a severe form of AP, necrotizing pancreatitis, develops in 15% (range 4–47%) of AP patients. One-third of these patients may have infected necrosis and subsequent complications such as sepsis, multiorgan failure, and death [1].

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The patient response to pancreatic injury in the case of AP is often variable and difficult to predict. The overall mortality in AP is approximately 5%, which can be classified into early and late death. The former is defined as $\leq$2 weeks after admission and is attributed to multiorgan failure, whereas the latter is defined as $>$2 weeks and is usually associated with septic complication due to infected necrosis [1—4]. The prevalence rates of organ failure (OF) in interstitial pancreatitis, infected pancreatitis, and sterile pancreatitis are 10%, 34—89%, and 45—73%, respectively. The mortality rates in the absence of OF, in the presence of one OF, and multiorgan failure are 0%, 3%, and 47%, respectively [5—8]. Different extents of pancreatic necrosis and its subsequent complications chiefly contribute to the occurrence of OF and/or mortality during the admission period [7,8]. Therefore, the initial assessment of severity in AP to evaluate OF and the complications of pancreatic necrosis as soon as possible is critical for the appropriate management and risk assessment in a clinical setting.

Pathophysiological mechanisms

Recent studies showed that AP is generally considered to have three phases. The first phase is characterized by trypsin activation within pancreatic acinar cells. Several pathways provoke trypsin activation, and the most important mechanisms include: (1) cleavage of trypsinogen to trypsin by the lysosomal hydrolase cathepsin B; (2) trypsin-induced trypsinogen activation (trypsinogen autoactivation); (3) a rise in intracellular Ca^{2+} and a disruption of acinar cell Ca^{2+} signaling; and (4) decreased activity of the pancreatic secretory trypsin inhibitor [1,9]. Generally, trypsin activation is the major hidden player in the scenario.

The second phase involves the activation and chemoattraction of leukocytes and macrophages in the pancreas, resulting in an enhanced intrapancreatic inflammatory reaction. Neutrophil sequestration can also activate trypsinogen. Neutrophil depletion by administration of antineutrophil serum reduced the extent of necrosis and inflammatory infiltrate in experimental studies [1,9,10].

In the third phase, there is extrapancreatic inflammation. Local release of cytokines triggers chemotaxis of activated granulocytes and macrophages. These immune cells also release cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6, activating Kupffer cells in the liver. The Kupffer cells increase cytokine levels in the blood, which in turn mediates distant organ damage such as systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome or multiorgan failure [10].

Diagnosis

Serologic tests

A diagnosis of AP requires at least two of the following three features: (1) abdominal pain characteristic of AP; (2) serum amylase and/or lipase $\geq$3 times the upper limit of normal; and (3) characteristic findings of AP on imaging studies, particularly computed tomography (CT) scan [1]. In AP, the serum amylase and lipase are usually elevated within 24 hours of onset and remains so for 3—7 days. Serum lipase level is more specific and sensitive than serum amylase level. Both values may be normal in AP, notably confounded by delayed blood sampling, underlying chronic pancreatitis, or hypertriglyceridemia. Values $\geq$3 times the upper limit of normal virtually confirm the diagnosis of AP. Some disorders may also mildly influence serum amylase level, such as renal insufficiency or salivary gland lesion. However, the extent of pancreatic enzymes elevation does not reflect the severity of AP.

Imaging modalities

To diagnose AP, there are several noninvasive imaging tests, including ultrasound (US), CT, and magnetic resonance imaging (MRI). The choice of a specific imaging modality should take the following reasons into consideration: (1) the timing of onset of symptoms; (2) the severity and complication of pancreatitis; (3) the associated biliary tract abnormalities such as biliary obstruction, gallstone or choledocholithiasis; and (4) the potential contraindication of imaging tests.

The identification of biliary gallstones by US is nearly 90%, whereas it may reach 80% in the diagnosis of choledocholithiasis [11]. US is also the most convenient and easy-to-access tool in a clinical setting. However, accurate evaluation of the whole pancreatic gland in AP remains difficult and presents some limitations. The evaluation of parenchymal perfusion and the border between parenchymal necrosis and edema are quite limited on US [11]. A dynamic ileus may also occur in AP patients, which may significantly undermine the performance of US evaluation.

Contrast-enhanced abdominal CT is the best imaging modality regarding the diagnosis of AP due to the following attributes: (1) it can be performed rapidly and urgently; (2) it is informative in the evaluation of the severity and the complication; (3) helps to approach in patients with suspected chronic pancreatitis; (4) other disorders that are clinically similar to AP can be accurately excluded; and (5) interference from bowel gas can be largely avoided. According to the CT severity index (CTSI, or Balthazar—Ranson criteria for severity) [12], CT scanning provides mortality and morbidity information (Table 1). Compared to acute physiology and chronic health evaluation II (APACHE II) score, CTSI has the advantages of: (1) better sensitivity, specificity, and negative and positive predictive values for severe pancreatitis; (2) prediction of the morbidity and mortality; and (3) being a good predictor of local complications [13,14]. Generally, CTSI is conducted 72 hours after admission, whereas the APACHE II scale is calculated at 24 hours or 48 hours. For predicting systemic OF and the need of intensive care, APACHE II is more confident than CTSI. Contrast-enhanced CT is contraindicated if there is significant renal impairment or history of significant allergy to contrast medium. Therefore, noncontrast CT scanning (if emergent) or MRI may be better choices to evaluate the severity of AP.

In the evaluation of AP, MRI has some potential advantages: (1) lack of nephrotoxicity of gadolinium as compared to an iodinated contrast; (2) application in pregnant women and children for dose-related issues or in patients with history of contrast allergy; (3) acquisition of

Table 1 The grading of acute pancreatitis and computed tomography (CT) severity index.

CT grading (unenhanced CT score)		
Grade	Findings	Scores
A	Normal pancreas	0
B	Focal or diffuse enlargement of the pancreas	1
C	Peripancreatic inflammation with intrinsic pancreatic abnormalities	2
D	Intrapancreatic or extrapancreatic fluid collections	3
E	Two or more large fluid collection or gas in the pancreas or retroperitoneum	4
Necrosis score based on contrast-enhanced CT		
The percentage of necrosis		
0		0
<30%		2
30—50%		4
>50%		6
CT grading	Mortality (%)	Morbidity (%)
Grade A+B+C (No fluid collections)	0	4
Grade D+E (Fluid collections)	14	54
Necrosis		
No necrosis	0	6
Necrosis	23	82
CTSI (CT grading + necrosis)		
0—2	0	4
3—6	6	35
7—10	17	92

MRCP sequences to evaluate choledocholithiasis-induced pancreatitis; and (4) greater ability to distinguish necrosis from fluid [1,11]. A high sensitivity (100%) and specificity (98%) of MRCP in the diagnosis of choledocholithiasis was recognized especially for stones >3 mm in diameter [11]. Patients who have early diagnosis of gallstone-induced pancreatitis can receive urgent endoscopic retrograde cholangiopancreatography, which leads to a lower rate of recurrence and complications [15]. MRI can also accurately determine disease severity and predict clinical outcome during the course of AP. Several studies showed that MR severity index, with the same grading evaluation as CTSI, possesses a performance comparable with CT and Ranson score [16—18]. MRI is also correlated well with APACHE II score in terms of mortality, morbidity, duration of hospitalization and the need for intensive care [19]. Therefore, MRI is a better alternative for AP if contrast CT is contraindicated.

Methods and scoring systems for severity assessment in AP

The initial assessment of severity in AP is critical for the appropriate triage and management of patients due to its high mortality and morbidity in severe cases. Criteria of severe AP, including early prognostic signs, OF, and local complication, were initially established in 1992 (Table 2) [1].

There are several simple predictors to evaluate the prognosis on admission or in the emergency department. Old age, defined as age over 75 years, is a definite predictor for poorer prognosis [1]. Frey et al. demonstrated that as compared with patients aged 35 years or under, patients over 75 years carried a more than 15-fold and 22-fold of death within 2 weeks and 91 days, respectively [20]. Older age is also associated with mortality in the first 48 hours of AP occurrence but it is not related to the development of persistent or deteriorating multiorgan dysfunction syndrome [21].

Several studies have found that obesity (body mass index > 30) is a risk factor for disease progression in AP [1]. In a meta-analysis study with 739 patients, obese patients developed significantly more severe AP [odds ratio (OR) 2.9, 95% confidence interval (CI) 1.8—4.6], systemic

Table 2 Severe acute pancreatitis as defined by the Atlanta Symposium.

Item	Comment
Early prognostic signs	1. Ranson criteria ≥3 points, *or* 2. APACHE II ≥8 points
or	
Organ failure	1. Shock: systolic blood pressure <90 mmHg 2. PaO_2 ≤60 mmHg 3. Creatinine >20 mg/L after rehydration 4. Gastrointestinal bleeding >500 mL/24 h
and/or	
Local complication	1. Pancreatic necrosis 2. Abscess 3. Pseudocyst

complications (OR 2.3, 95% CI 1.4—3.8), local complications (OR 3.8, 95% CI 2.4—6.6), and showed a higher mortality (OR 2.1, 95% CI 1.0—4.8) than their counterparts [22]. Patients with android fat distribution (central or visceral obesity) also had a relative risk of 4.36 or more in developing severe AP [23]. The combination of APACHE-II and obesity (APACHE-O) measured within the first 24 hours of admission improved the prediction of severity (BMI score, <26: score = 0, 26—30: score = 1 and >30: score = 2). At a cut-off of >8, APACHE-O had a sensitivity of 82%, a specificity of 86%, a positive predictive value of 74%, a negative predictive value of 91% and an overall accuracy of 85% [24].

SIRS is defined by two or more of the following criteria: (1) pulse >90 beats/min; (2) respiratory rate >20/min or PCO_2 <32 mmHg; (3) rectal temperature <36°C or >38°C; and (4) white blood count $<4 \times 10^9$/L or $>12 \times 10^9$/L or > 10% bands. The presence of SIRS on admission, at 24 hours and 48 hours as well as persistent SIRS (defined as SIRS present for the entire 48 hours) has a significantly higher mortality rate as compared with the absence of SIRS in patients with severe AP [25]. Persistent SIRS leads to a strong risk of persistent or deteriorating multiorgan dysfunction syndrome development [21]. In addition, patients with persistent SIRS have higher rate of persistent OF, pancreatic necrosis, and greater need of intensive care, compared to those with transient or no SIRS [26].

OF, an advanced and extreme consequence of inflammatory processes, is also a good predictor for mortality and local complication in AP, especially during the 1st week (i.e. early OF). There is a strong association between persistent OF (>48 hours) and local complication [4]. Transient OF (< 48 hours) was also associated with a mortality rate of 1.4 %, in contrast to 35% of persistent OF. Meanwhile, the presence of early OF has a lower survival rate than the absence of OF, and persistent as well as deteriorating OF have a higher mortality rate than transient, resolved OF [25]. The occurrence of OF combined with infected pancreatic necrosis suggests a grave outcome [27].

Ranson criteria

Ranson criteria have been used since 1974 to evaluate the severity and mortality of AP (Table 3). Severe AP is defined when the Ranson score is ≥3 points. Mortality was 0—3% when the score was <3, 11—15% when the score was ≥3, and 40% when the score was ≥6 [1]. Five factors are assessed at admission and the other six factors are assessed during the next 48 hours. However, Ranson criteria are cumbersome, laborious and not clinically practical. Complete evaluation after 48 hours may miss the golden time for therapy. A meta-analysis of 110 studies also found that the Ranson score has very poor positive and negative predictive value for severe AP [28]. Therefore, there has been a continuous need for an easy-to-access and useful method for decades.

APACHE scores

The APACHE II score was originally developed for critically ill patients in intensive care units (Table 4). A higher APACHE-II score at admission and during the first 72 hours is correlated with a higher mortality (<4% with an APACHE-II < 8 and 11—18% with an APACHE-II > 8) [1]. However, APACHE II score is also complex and more cumbersome than Ranson criteria. Furthermore, it does not differentiate well between interstitial and necrotizing pancreatitis and between sterile and infected necrosis [1]. Therefore, the clinical role of APACHE II score for AP severity assessment is declining compared to other predictors such as MR severity index and SIRS [19,26].

Bedside index for severity in AP

The Bedside Index for Severity in AP (BISAP) score is a new scoring system first described in 2008. Development of the BISAP score was based upon 17,922 cases of AP from 212 hospitals in 2000—2001 and validated in 18,256 cases from 177 hospitals in 2004—2005 [29]. In this study, several candidate risk factors were proposed: (1) individual Ranson criteria; (2) pleural effusion (on chest radiology or CT); (3) SIRS; (4) OF; (5) altered mental status; and (6) hemoglobin and hemoconcentration. The worst vital signs and positive findings of physical examination were also utilized. All risk factors were analyzed by classification and regression tree (CART) analysis. However, the serum calcium, lactate dehydrogenase, PaO_2 and aspartate aminotransferase

Table 3 Ranson criteria for severity prediction of acute pancreatitis.

0 hour	Comment
Age >55 y	1. Each item means one point.
White blood cell count $>16 \times 10^9$/L	2. Severe pancreatitis:
Blood glucose >2.0 mg/L (11.1 mM)	Ranson criteria ≥3 points
Lactate dehydrogenase (LDH) >350 U/L	3. Mortality:
Aspartate aminotransferase (AST) >250 U/L	0—2 Points: 0—3%
48 hours	3—5 Points: 11—15%
Hematocrit decrease by ≥10%	6—11 Points: ≥40%
Blood urea nitrogen increase by ≥50 mg/L (1.8 mM) despite fluids	
Serum calcium <80 mg/L (2 mM)	
pO_2 <60 mmHg	
Base deficit >4 MEq/L	
Fluid sequestration >6 L	

Table 4 Acute physiology and chronic health evaluation II (APACHE II) score.

	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal temperature (°C)	≥41	39–40.9		38–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
MAP (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (/min)	≥180	140–179	110–139		70–109		55–69	40–54	≤40
Respiratory rate (/min)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
If FiO_2 ≥50%, check A-a gradient; if FiO_2 <50%, PaO_2									
A-a gradient	≥500	350–499	200–349		<200				
PaO_2 (mmHg)					>70	61–70		55–60	<55
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.3–7.49		7.25–7.3	7.15–7.2	<7.15
Na (mM)	≥180	160–179	155–159	150–154	130–149		120–129	111–19	≤110
K (mM)	≥7	6–6.9		5–5.9	3.5–4.9	3–3.4	2.5–2.9		<2.5
Creatinine(mg/L)	≥35	20–34	15–19		6.0–14		<6.0		
Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count(10^9/L)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1

Glasgow coma score (GCS): 0–12 points = 15–GCS

Age (y)	Points
<44	0
45–54	2
55–64	3
65–74	5
>75	6

Chronic health (history of chronic conditions)[a]	Points
None	0
If patient is admitted after elective surgery	2
If patient is admitted after emergency surgery or for reason other than after elective surgery	5

A-a gradient = alveolar-arterial oxygen difference; K = serum potassium; MAP = mean blood pressure; Na = serum sodium; WBC = white blood cell.

[a] Chronic health conditions: liver, cirrhosis with portal hypertension or encephalopathy; cardiovascular, class IV angina (at rest or with minimal self-care activities); pulmonary, chronic hypoxemia or hypercapnia, polycythemia, ventilator dependent; kidney, chronic peritoneal or hemodialysis; immune, immunocompromised host.

measurements were excluded due to their failure to meet the pre-specified 85% collection rate threshold.

The risk points of BISAP score includes blood urea nitrogen (BUN) > 250 mg/L, impaired mental status, SIRS (≥2 criteria), age > 60 years, and pleural effusion within 24 hours after admission. In the derivation cohort after CART analysis, BUN was identified as the most efficient first splitting variable. Age and SIRS further discriminated between high- and low-risk cases. Both the mortality rate and the area under curve (AUC) were comparable between the derivation and the validation cohorts and APACHE-II score were similar (AUC: 0.83, 0.82 and 0.83 of the derivation cohort, validation cohort, and APACHE-II score, respectively). The BISAP score also had performance characteristics for mortality prediction, which were comparable with the APACHE II score. However, in this study, the BISAP score can only be a predictor for in-hospital mortality of AP.

In another prospective study with 397 cases [30], the trend for increasing mortality with increasing BISAP score was statistically significant ($p < 0.0001$, and AUC was 0.82). Of 397 cases, 230 were admitted with their first episode of AP, and mortality was also significant ($p < 0.0001$) with increasing BISAP score in this subgroup. Patients with a BISAP score ≥ 3 were 7.4, 12.7, and 3.8 times more likely to develop OF (after 24 hours), persistent OF (>48 hours), and pancreatic necrosis, respectively.

The BISAP score was compared to Ranson scores, APACHE II scores, and CTSI scores in another prospective study [31]. The AUCs for BISAP, Ranson, APACHE-II, and CTSI in predicting severe AP are 0.81, 0.94, 0.78, and 0.84, respectively. However, the BISAP score has lower sensitivity, but similar or higher specificity than the other three traditional scoring methods.

In summary, the BISAP score is more reliable than the traditional scoring systems due to the following advantages: (1) it is easily memorable; (2) it can be used within 24 hours for severe AP exclusion; and (3) two variables (i.e. BUN and SIRS) can be evaluated continuously for the development of complications, such as mortality and persistent OF, at 24 hours and 48 hours. Further studies should focus on how to increase post-test probability of severe disease (or pancreatic necrosis or death), making the BISAP score a powerful predictor in AP.

Serial BUN levels and other laboratory tests

In all risk factors, BUN was identified as the most efficient splitting variable by CART analysis [29]. The relationship between series BUN levels and AP complications has been consistently addressed. In a large hospital-based cohort [32], serial BUN measurements were the most reliable single routine laboratory test to predict the mortality in AP. The adjusted odds ratio for mortality was 2.2 for every increase in the BUN of 50 mg/L during the first 24 hours, whereas it was 1.0 for every increase in the hemoglobin

(Hb) of 10 g/dL during the first 24 hours. There was a significant correlation between the extent of BUN change and the risk of mortality. Increasing AUC of BUN was also significantly observed between admission and 24 hours after admission, but not between 24 hours and 48 hours after admission. A BUN level of ≥200 mg/L at admission was associated with an increased risk of death compared with a BUN level of <200 mg/L. Any increase in BUN at 24 hours was also associated with an increased risk of death. Moreover, among patients with an elevated BUN level at admission (>200 mg/L), a decrease of at least 50 mg/L at 24 hours after admission was associated with reduced risk of in-hospital death [33].

A higher hematocrit level (hemoconcentration) subsequent to fluid loss in the third space is considered as a single reliable severity predictor in AP. AP patients with hematocrit level <44–47% at admission and failure to recover 24 hours later have a high possibility to develop necrotizing pancreatitis [34,35]. Hemoconcentration is also a predictor of OF, and patients with hematocrit criteria should be admitted urgently to an intensive care unit for vigorous fluid resuscitation [36]. The absence of hemoconcentration usually excludes a suspicion of pancreatic necrosis, and a contrast-enhanced CT may not be necessary. However, inconsistent results have been postulated in spite of consistent findings of a high negative predictive value of hemoconcentration for necrosis and OF. The absence of hemoconcentration at admission and during the first 24 hours is generally suggestive of a benign clinical course. However, hematocrit is not

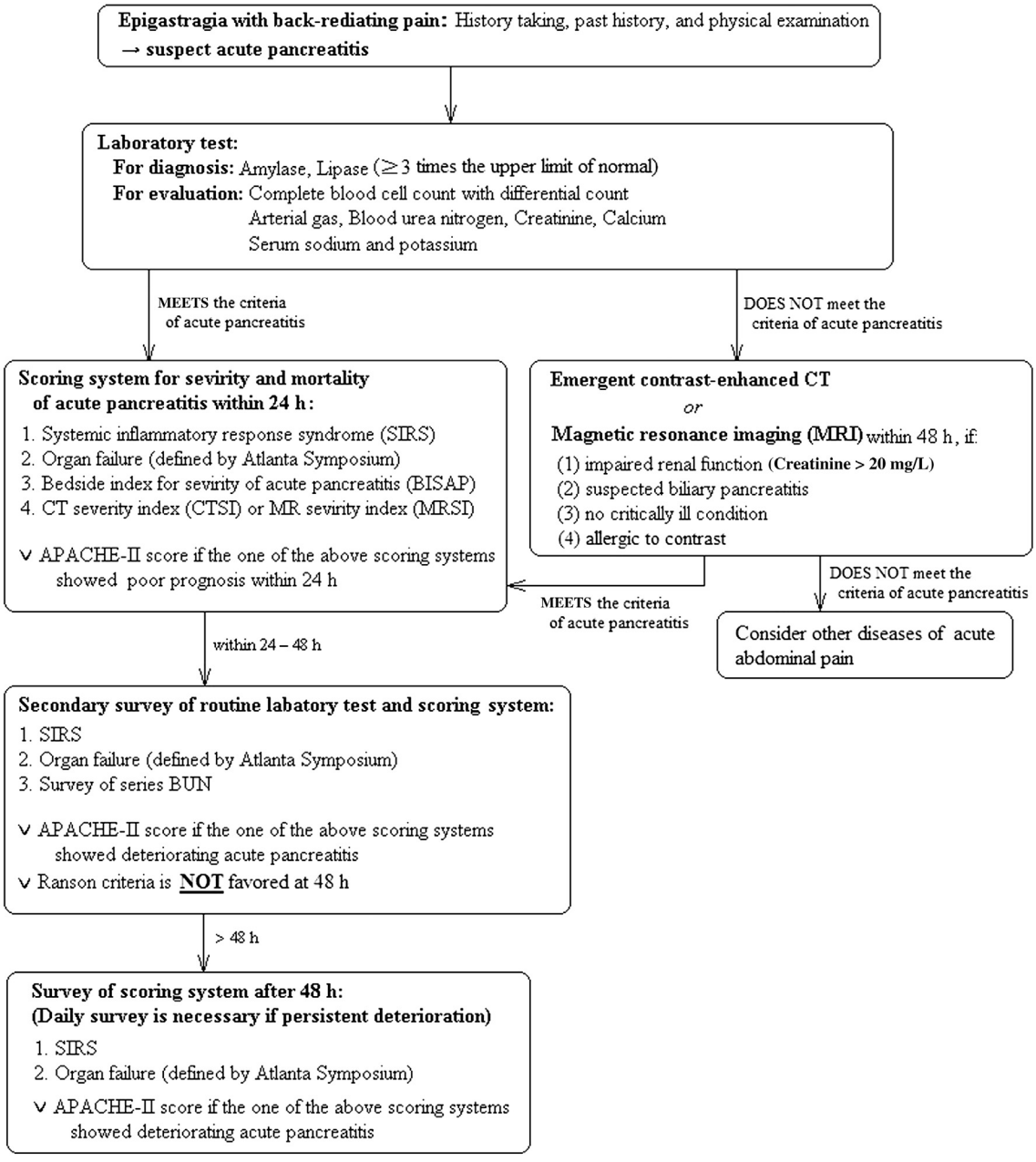

Figure 1. Flowchart for acute pancreatitis diagnosis and severity assessment.

a single reliable predictor for OF, mortality, and severity in AP.

Hypocalcemia, one item of Ranson criteria calculated at 48 hours of AP development, is associated with severity and necrosis of AP. The precise pathogenesis is incompletely understood. It may be attributed to binding of calcium during the process of fat necrosis and altered levels of circulating parathyroid hormone in AP [37,38]. Serum calcium level as well as plasma interleukin-10 and serum glucose were identified as independent predictors of OF in

Table 5 Summary of clinical, laboratory, radiologic risk factors and scoring systems for acute pancreatitis.

Item	Mortality	Severity	Pancreatic necrosis	Persistent organ failure	Comments, Pros and Cons	Reference
Characteristics of patients						
Old age	S				The older age, the higher mortality	20, 21
Obesity	S	S			Definition of obesity: body mass index $>$ 30 kg/m^2 Central or visceral obesity is more significant	22—25
Single laboratory test						
Series BUN	S				The mortality is higher if the initial BUN level is $>$ 200 mg/L and the following BUN level increases at 24 h Pros: Easy evaluation Cons: only significant in mortality the AUC of 24 h and 48 h are not different	34, 35
Hematocrit			S		Hematocrit $\geq$ 44% Pros: easy to evaluate Cons: cannot evaluate mortality	36—40
Calcium				S	Pros: good predictor in organ failure Cons: cannot evaluate mortality	42
Imaging scores						
CTSI	S	S	S		The only one scoring system is proven to be superior to Ranson criteria and APACHE II Pros: easy to perform accurately diagnose pancreatic necrosis Cons: contraindicated in patients with allergy to contrast, impaired renal function, or pregnancy	12—14, 32,44
MRSI	S	S	S		Pros: alternative if contrast CT is contraindicated better diagnosis for biliary pancreatitis good predictor in length of hospitalization & need for ICU Cons: cannot be performed rapidly and urgently	11, 15—19
Other scoring system						
SIRS	S	S	S	S	Can be evaluated once per day according to clinical condition Patients with persistent SIRS, SIRS within 1 d, and 3 or 4 SIRS criteria have higher complication and mortality	4, 21, 27
Organ failure	S	S		S	Can be evaluated once per day according to clinical condition Patients with persistent or early organ failure have higher complication and mortality	4, 28
BISAP	S	S	S	S	Pros: early predictor within 24 h easily accessible BUN and SIRS can be evaluated continuously	30—33
APACHE-II	S	S			Pros: good predictor for intensive care Cons: cumbersome and laborious	1, 19 27
Ranson score	S	S			Pros: has been used and validated for 40 y Cons: cumbersome, laborious and not clinically practical may miss the golden time of therapy after 48 h	1, 29

AP = acute pancreatitis; APACHE-II = Acute Physiology and Chronic Health Examination II; APACHE-O = APACHE-II and obesity; BISAP = Bedside Index for Severity of AP; BUN = blood urea nitrogen; CRP = C-reactive protein; CTSI = computed tomography severity index; ICU = intensive care unit; MRSI = magnetic resonance severity index; OF = organ failure; S = significantly predictable; SIRS = systemic inflammatory response syndrome.

AP [39]. The combination of an elevated interleukin-10 concentration (>50 pg/mL) and a decreasing calcium concentration (<65 mM or <68 g/L) was a significantly better predictor than any single marker or APACHE II score, with a sensitivity of 88% and specificity 93%. Hypocalcemia has been widely adapted as an important predictor within 72 hours for disease severity [38,40].

Other serum markers have been studied for predicting the severity of AP including the following: serum c-reactive protein, urinary trypsinogen activation peptide, procalcitonin, polymorphonuclear elastase, pancreatic-associated protein, procarboxypeptidase-B, carboxypeptidase B activation peptide, serum trypsinogen-2, phospholipase A-2, serum amyloid protein-A, substance P, antithrombin III, platelet activating factor, interleukins-1, 6, 8, and 10, tumor necrosis factor-α, or soluble tumor necrosis factor receptor, and various genetic polymorphisms. However, most serum markers were not widely available in the clinical setting because of their limitations of predictability and accessibility.

Future perspectives and conclusion

Early diagnosis and evaluation for the severity and mortality of AP are very important (Fig. 1). Severe AP can be predicted by using clinical, laboratory, imaging, and/or many scoring systems (Table 5). In various scoring systems and laboratory tests, the Ranson and APACHE-II scoring systems have been used widely for decades. However, these are cumbersome in intent and may delay treatment implementation due to limited predictability. BISAP scoring system and series BUN changes have been validated for accuracy by several large-cohort studies [29,32]. Meanwhile, both tests are simple and convenient to evaluate within 24 hours after admission. However, a complementary application of the assessment methods is essential because a single method does not reliably predict the development of morbidity and mortality. For example, imaging scoring has good evaluation for pancreatic necrosis but it is a poor predictor for OF. Only SIRS and OF can evaluate the severity after 48 hours. Therefore, to find a simple and easy-to-access panel and/or biomarkers over the whole clinical course is the further research goal. Further validation among AP patients of different etiologies, race and regions will be mandatory in order to elucidate the diverse outcomes of the disease. For example, previous study in Taiwan demonstrated that CTSI is superior to Ranson criteria and APACHE II score [40]. Patients with CTSI $\geq$ 5 have higher mortality, longer duration of hospitalization ($\geq$20 days), and complications. In addition, host susceptibility regarding genetic and proteomic studies is helpful for clarification of the whole pathogenic context of AP. It will also be informative to assess various outcome measurement tools based on personalized medicine in the future.

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