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Predicting the severity of acute pancreatitis: Current approaches and future directions

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ABSTRACT

Acute pancreatitis (AP) is a sudden-onset inflammatory disease of the pancreas. The severity of AP is classified into mild, moderate, and severe categories based on the presence and persistence of organ failure. Severe acute pancreatitis (SAP) can be associated with significant morbidity and mortality. It requires early recognition for appropriate timely management. Prognostic scores for predicting SAP incorporating many clinical, laboratory, and radiological parameters have been developed in the past. However, all of these prognostic scores have low positive predictive value for SAP and some of these scores require >24 h for assessment. There is a need to develop biomarkers that can accurately identify patients at risk for SAP early in the course of the presentation. In this review, we aim to provide a summary of the most commonly utilized prognostic scores for AP and discuss future directions.

Introduction

Acute pancreatitis (AP) is a sudden onset inflammatory condition of the pancreas that is associated with an overall mortality rate of 3–5 % [1,2]. Most patients with AP experience mild disease with a self-limited course. However, approximately 20 % of AP patients experience moderate or severe disease characterized by local complications (pancreatic necrosis, fluid collections, splanchnic vein thrombosis, and pseudoaneurysms) and organ failure (respiratory, cardiovascular, and renal). In a systematic review, severe acute pancreatitis (SAP) was found to be associated with mortality rates of 20–40 % [3,4]. Over the past decade, the mortality associated with SAP has not increased in proportion to the rising incidence of AP which is likely secondary to earlier recognition of SAP, avoidance of early invasive therapies, use of enteral nutrition and intensive care units (ICU) management [5]. Multi-organ failure (MOF) involving <2 organ systems and persistent (<48 h) organ failure (POF) are associated with a higher risk of death and local complications, especially pancreatic necrosis [6]. Therefore, early identification of patients at risk of developing SAP is essential for triaging patients to the appropriate site of care and initiating management [7–9].

Several prognostic scoring systems have been developed to predict SAP since the early 1970s, but they have limited clinical applicability due to low positive predictive values (PPV) of 11–23 % [10]. Most of these scoring systems take >24 h for the complete assessment of disease severity, which can lead to delays in appropriate care. These scores were developed to predict mortality, as opposed to organ failure, which is problematic due to the reductions in observed mortality of AP over the last decade [11]. In this review, we aim to summarize and discuss the existing literature surrounding commonly used severity prediction scores and the potential future directions in this field.

Methods

In this narrative review, we searched PubMed for all relevant English-language original clinical studies, systematic reviews and meta-analyses published over the last 10 years using the terms '*acute pancreatitis*', '*severity scores*', '*radiologic scores*', '*laboratory scoring*' and '*prognostic scores*'. However, we did include relevant earlier studies. We excluded case reports and case series.

Current approaches used to predict the severity of AP

Defining severe acute pancreatitis

The first definition of SAP was proposed by the Atlanta classification (AC) in 1992 [6] (Table 1) (Fig. 1). It had been the standard severity assessment criteria for almost two decades until improved diagnostic

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List of abbreviations

AP	Acute Pancreatitis
SAP	Severe Acute Pancreatitis
PPV	Positive Predictive Values
MOF	Multi-Organ Failure
POF	Persistent Organ Failure
AC	Atlanta Classification
RAC	Revised Atlanta Classification
DBC	Determinant-based Classification
GPS	Glasgow Pancreatitis Score
APACHE II	Acute Physiology and Chronic Health Enquiry II
SIRS	Systemic Inflammatory Response Syndrome Score
BISAP	Bedside Index for Severity in Acute Pancreatitis
HAPS	Harmless Acute Pancreatitis Score
HCT	Hematocrit
CRP	C-reactive protein
BUN	Blood urea nitrogen
Cr	Creatinine
CT	Computed Tomographic
CTSI	CT severity index
MCTSI	Modified CT severity index
PSI	Pancreatic Size Index
EPIC	Extra-pancreatic Inflammation on CT score
MOP	Mesenteric Edema and Peritoneal Fluid score
CLS	Capillary Leak Syndrome
NAPP	Non-albumin Plasma Protein
TP	Total Protein
ANG I	Angiopoietin-1
ANG II	Angiopoietin-2
AUC	Area Under the Curve

imaging and understanding of the pathophysiology of necrotizing pancreatitis and organ failure provided the necessary impetus for revising the AC [6]. The AC was updated as the revised Atlanta Classification (RAC) in 2012 based on consensus across 11 national and international pancreatic societies. It provided more objective terms to describe the local complications of AP by differentiating AP into interstitial edematous and necrotizing pancreatitis, and classification of collections into acute peripancreatic fluid and necrotic collections. The RAC also stratified AP severity into mild, moderate, and severe disease largely on the presence and duration of organ failure (Table 2) [6].

Severe AP is defined by the presence of POF and moderate AP is defined by the presence of transient (<48 h) organ failure and/or local complications [6]. The determinant-based classification (DBC) system was developed at the same time as the RAC and was based on a survey of 249 pancreatologists from 49 different countries. The DBC classification system defined severity by the presence of necrosis (pancreatic and peripancreatic) and organ failure [12]. The key difference between the RAC and DBC is that the latter accords greater importance to the presence of infected necrosis as a determinant of severity. The RAC, however, offers a broader overview of AP than DBC in terms of defining the diagnosis, duration of illness, and individual local complications and is, therefore, has become the global standard for defining and reporting the severity of AP. A prospective study compared these three systems and concluded that DBC and RAC were equally superior to the AC and that POF was the most significant determinant of severity [13].

Scoring systems

Ranson criteria

The Ranson criteria was the first prognostic scoring system developed for AP in 1974, at a time when surgical laparotomy was commonly employed to manage severe AP [14]. The criteria included 11 objective parameters for predicting the severity and mortality of AP [15]. Of these parameters, 5 are assessed at admission and 6 are assessed after 48 h. The Ranson score predicts AP organ failure, necrosis, mortality, and severity with AUCs of 0.84, 0.56, 0.80, and 0.810, respectively [14,16]. Scores of <3, ≥3 and ≥ 6 indicate a mortality of 0–3 %, 11–15 % and 40 %, respectively [17–20].

A major limitation of the Ranson criteria is that it cannot be determined until 48 h after admission, thereby precluding early identification of SAP and potentially delaying treatment. Another limitation is that it was based on eleven parameters among which several are not routinely collected in clinical practice (Table 1). Ransons criteria was also found to have a poor predictive power of SAP in a more recent meta-analysis that looked at 110 studies [21] and moreover, it failed to accurately differentiate between sterile and infected necrosis [22,23].

Glasgow Pancreatitis Score (GPS)

Due to the complexity of the Ranson Criteria and the need for a simpler scoring system, Blamley et al. developed the Glasgow Pancreatitis Score (GPS) in 1984. It was based on 9 parameters and a GPS ≥2 was considered to commensurate with severe AP while a GPS ≥3 increased the likelihood of ICU admission [24]. A prospective study found that the GPS correlates with increased 28-day mortality in AP (OR = 3.025, 95 % CI 1.230–7.442, $p = 0.016$) [25]. In contrast to the Ranson criteria, the GPS can be evaluated within 48 h, is simpler to use, and measures albumin instead of measuring hematocrit, base deficit, and sequestration of fluid [16,26]. Albumin is a determinant of plasma oncotic pressure and plays a central role in maintaining intravascular volume and tissue perfusion. There is inflammatory endothelial damage in AP causing leakage of albumin into interstitial spaces resulting in third-space fluid loss. This phenomenon of capillary leak is central to the pathogenesis of organ failure in SAP [27]. Therefore, albumin is a key laboratory parameter that can help in the comprehensive assessment of severity as well as prognosis. Both the GPS and Ranson criteria have similar accuracy in predicting the severity of AP with GPS's AUC of 0.78 for SAP [24]. Similar to the Ranson criteria, the GPS has many variables that can make its calculation cumbersome.

Acute Physiology and Chronic Health Enquiry II (APACHE II)

APACHE II is a revised version of the prototype APACHE classification system that has been successfully used to predict AP outcomes [16]. It was developed on the presumption that the severity of acute illness can be measured by quantifying the degree of abnormality across multiple physiologic variables [28]. It was originally developed to classify patients who needed treatment in an ICU setting and is not specific for AP [20]. The original APACHE score included 34 physiological parameters which were later reduced to 12 in the APACHE II score [28] (Table 1). A score < 8 had a predicted mortality of <4 % whereas a score > 8 had a predicted mortality of 11–18 % [16]. In comparison to Ranson's criteria, APACHE II can be evaluated in the first 24 h and each day thereafter to reassess disease severity. Decreasing values during the first 48 h suggest an improving clinical course while increasing values signify worsening disease severity. In a study comparing APACHE II and Ranson score, the APACHE II score had a PPV of 43 % and a NPV of 86 % for SAP 24 h after disease onset, while at 48 h, the Ranson score had a PPV and NPV of 48 % and 93 %, respectively [29]. Obesity is an important component in predicting mortality in AP, so the APACHE-O score was developed as an upgradation of the existing score to include BMI to the APACHE-II score [30] One point was added to the APACHE-II score for a BMI between 26 and 30, while 2 points are added when BMI >30. This was thought to lead to an improved categorical prediction of SAP but this was later refuted [31]. A major disadvantage of the APACHE II score

Table 1
Current clinical scores used in AP.

Scoring system	Purpose summary	Year	Parameters used for scoring	Key limitations	Key advantages
Ranson [72]	Determine role of operative treatment, with a focus on multi-organ failure, SIRS, and vascular leak	1974	At admission, Age > 55 y WBC count > 16,000 LDH > 350 AST > 250 Glucose > 200 mg/dL After 48 h, fall in HCT > 10 % Increase BUN > 5 mg/dL Calcium < 8 mg/dL PaO2 < 60 mm Hg Base deficit >4 mEq/L fluid loss > 6 L	Requires 48 h for prognostication Time consuming Not all variables are routinely collected	Most parameters are readily available
Glasgow Pancreatitis Score	Acute pancreatitis, used internationally	1984	Age > 55 y WBC count > 15,000 Glucose > 180 mg/dL Urea > 16 mmol/L PaO2 < 60 mm Hg Calcium < 2 mmol/L LDH > 600 AST > 200 Albumin < 32 g/L	Time consuming	Simpler to use compared to Ranson Incorporates albumin as a variable
Simplified prognostic criteria [73]	Criteria of physiologic risk factors based on major organ functions to evaluate patients with acute pancreatitis	1986	BP < 90 mm Hg Tachycardia > 130/min PO2 < 60 mm Hg Urinary output 40 mL/h Metabolic Calcium < 8 mg/dL Albumin < 3.2 g/dL	Further prospective studies are needed to confirm the reliability of this system	Fewer Lab measurements are required compared to other scores More cost effective
The Acute Physiology and Chronic Health Examination II scores (APACHE)-II [74,75]	Predicting severity of pancreatitis, mortality, and need for ICU admission	1989	Temperature, MAP, heart rate, respiratory rate, Pao2, arterial pH, HCO3, sodium, potassium, creatinine, hematocrit, WBC, Glasgow Coma Score, age, chronic health points	Requires parameters which may not be available outside the ICU Few parameters may be irrelevant to the prognosis. Better used for research purposes rather than for clinical care.	evaluated in the first 24 h and each day thereafter to assess the clinical course of the disease
SIRS score	Used in emergency department settings as a screening tool to identify sepsis	2002	Heart rate (>90 beats per minute), respiratory rate > 20/min or PCO2 < mm Hg, core temperature (<36 or >38), and white blood cell count (<4000/mm^3 or >12,000/mm^3)	SIRS criteria may be fulfilled in patients without AP Cannot differentiate between inflammation and infection	Simple to calculate, inexpensive, and can be measured repeatedly. Can be used for prognosis as well as dynamic clinical assessment of the disease course.
Multiple organ dysfunction score [76]	An objective scale to measure the severity of the multiple organ dysfunction syndrome as an outcome in critical illness.	1995	PaO_2/FiO_2 Platelets Bilirubin Hypotension Glasgow Coma Score Creatinine	Developed as an outcome measure rather than a predictive index	Reflects organ dysfunction developing during the ICU stay
Sequential organ failure assessment score (SOFA) [77]	Mortality prediction tool based on six organ systems, widely used as a mortality stratification tool in ICU	1996	PaO_2/FiO_2 Platelets Bilirubin Hypotension Glasgow Coma Score Creatinine	Developed to evaluate ICU patients with ventilatory and aminergic support and has not been validated specifically in patients with acute pancreatitis	Describes the extent of organ dysfunction at the time of evaluation
Logistic organ dysfunction score (LOD) [78]	Evaluates severity during the first day in ICU	1996	Glasgow Coma Score Heart rate, beats/min <30 or Systolic blood pressure Serum urea or Serum urea nitrogen Creatinine Urine output Pao2 (mm Hg)/Fio2 on MV or CPAP or No ventilation; White blood cell count, Platelets Bilirubin Prothrombin time	Cannot be used past the first day in ICU	Takes into account the relative severity among organ systems and the degree of severity within an organ system.
Japanese severity score (Original) [79]	Classification system for AP	2002	BE ≤ 3 mEq/L Hct ≤ 30 % after hydration BUN ≥ 40 mg/dL or creatinine ≥ 2 mg/dL Ca ≤ 7.5 mg/dL FBS ≥ 200 mg/dL Pao2 ≤ 60 mm Hg (room air) LDH ≥ 700 IU/L Total protein ≤ 6 g/dL Prothrombin time ≥ 15 s	Multiple parameters that are not always done in every acute pancreatitis patient as standard of care.	Introduced the concept of systemic inflammatory response syndrome

(*continued on next page*)

is that it requires the collection of many parameters, which may not be available outside the ICU and some parameters may be less relevant to AP such as the inclusion of chronic health conditions [17]. Necrotizing pancreatitis has worse outcomes in comparison to interstitial pancreatitis but the APACHE II score does not account for morphological differentiation of the disease [32]. Another important limitation of the APACHE II score was that it does not differentiate between infected and non-infected necrosis [22,23,33].

Systemic inflammatory response syndrome score (SIRS)

Systemic inflammatory response syndrome (SIRS) in AP is characterized by a systemic immune response to a pancreatic injury involving

Table 1 (*continued*)

Scoring system	Purpose summary	Year	Parameters used for scoring	Key limitations	Key advantages
			Platelet count ≤ 100,000/mm^3 CT grade IV or V		
BALI score [80]	Predict disease severity when used at admission or anytime during the first 48 h of hospitalization	2006	BUN ≥ 25 mg/dL Age ≥ 65 years LDH ≥ 300 IU/L IL-6 ≥ 300 pg/mL	Must be used during the first 48 h of hospitalization	Less parameters than other scores
Early warning score [81]	Scoring system to monitor patient progress in critically unwell patients	2006	Blood pressure Urine output Respiratory rate Pulse rate Level of consciousness	Does not measure pancreas-specific variables, but rather an accurate measure of the SIRS response in acute pancreatitis.	Parameters are readily available
Mortality probability model	Developed to estimate the probability of hospital mortality among patients in ICU	2007	Metastatic Cancer Cirrhosis Diuresis < 150 mL/8 h Creatinine > 2 mg/dL Coma (GCS 3–5) Intracranial Mass Effect Vasoactive Drug ≥ 1 h Mechanical Ventilation PaO2 < 60 mm Hg Proven Infection PT > Standard + 3 s	Requires collection of variables within 1 h of admission to ICU	Useful for ICU patients
Panc 3 score [82]	Score designed to predict whether the patient would have a longer length of stay at ICUs	2007	Measures three variables obtained within the first 24 h after diagnosis of AP: 1) serum hematocrit (>44 mg/dL) 2) body mass index (BMI) (<30); 3) pleural effusion on the chest X-ray.	Does not account for comorbid conditions in assessing prognosis	Easy application and rapid results
The Pancreatitis Outcome Prediction (POP) [83]	Based on six readily available physiologic and biochemical indicators gathered within the first 24 h after ICU admission.	2007	Age MAP Pao2:Fio2 Arterial pH BUN Calcium	Utilizes parameters that are not measured in all patients as standard of care	The six variables are collected within the first 24 h of ICU admission and are readily available
The Bedside Index for Severity in AP (BISAP) [84]	Predicts mortality More variables associated with higher mortality	2008	BUN > 25 Impaired mental status SIRS (2 or more criteria) Age > 60 y Pleural effusion	Has a low PPV and most studies have validated its performance within 24 h of admission	Simple to calculate
Simple prognostic score [85]	Helps physicians stratifying the severity of AP	2009	Age > 65 years Leucocytes > 13,000/mm [3] Albumin < 2.5 mg/dL Calcium < 8.5 mg/dL C reactive protein > 150 mg/dL	72 h to calculate rather than the 48 h, can delay prognostication Requires further validation to be widely applicable	All variables are routinely collected
The Harmless Acute Pancreatitis Score (HAPS) [41]	Identify mild Cases of AP	2009	No rebound tenderness Normal hematocrit Serum creatinine < 2 mg/dL	Predicts mild disease course, thereby implying a poor PPV in predicting severity	Can be calculated within 30 min after admission
The Japanese Severity Score	Predicts severe AP	2009	Shock (low BP or base excess) PaO2 < 60 mm Hg, BUN > 40 mg/dL or Cr > 2.0 mg/dL or oliguria LDH > 2× normal Platelet count < 100,000/mm^3 Ca < 7.5 mg/dL CRP > 15 mg/dL SIRS criteria > 3 Age > 70 years	High accuracy in predicting severe AP	Several variables and more complicated to calculate
The Pancreatitis Activity Scoring System (PASS)	Uses dynamic measure to quantify AP activity and capture the disease's progressive nature through its dynamic manifestations	2017	Organ failure (×100 per organ), Oral intolerance (×40), systemic inflammatory response syndrome (SIRS) (×25 per criterion), morphine equivalent dose or MED (×5) and pain score (×5)	Not uniformly applicable as opioids are variably prescribed in different centers	Includes variables not used in other scoring systems
Predicting Severe Acute Pancreatitis at Admission (ASAP) [86]	Uses identified parameters at admission associated with severe pancreatitis and developed a predictive severity score	2022	Oxygen saturation Hypothermia Serum albumin Serum creatinine	Still a new score not validated in other centers	Easy to use with easily accessible parameters at patient admission

the innate immune system [34]. In a prospective study of AP patients, SIRS on day 1 had a sensitivity of 85–100 % and a negative predictive value (NPV) of 98–100 % for predicting severe disease [35]. The most important advantage of the SIRS score is that it is simple to calculate, inexpensive, and can be measured several times during hospitalization. Therefore, it can be used for prognosis as well as dynamic clinical assessment of the disease course which led to SIRS being incorporated in the Pancreatitis Activity Scoring System (PASS) [26]. However, its specificity as a prognostic score is low as only 20–60 % of patients with AP present with SIRS and it is impossible to differentiate whether SIRS is due to AP or infection, as the latter is seen in nearly 24 % of patients [35–37]. Procalcitonin may help to differentiate between inflammation and infection in AP based on the results of a recent single center randomized trial but this will need to be validated. [38]

Bedside Index for Severity in Acute Pancreatitis (BISAP)

The BISAP score was developed in 2008 using classification and regression tree (CART) analysis to identify patients at elevated risk for mortality early during AP [39]. A total of 17,922 cases of AP from 2000 to 2001 were used to develop the score and this was validated in a separate cohort of 18,256 cases from 2004 to 2005. It is a composite of five parameters, one point assigned for each, including blood urea nitrogen (BUN) level > 25 mg/dL, impaired mental status, SIRS, age > 60 years, and presence of pleural effusion measured 24 h after hospitalization [39]. If no criteria were met, mortality was <1 %, whereas if a patient had a score of 5, the mortality was 22 %. Gao et al. found that the BISAP score was a reliable tool to identify AP patients at high risk for unfavorable outcomes when compared with the Ranson criteria and APACHE II score. The BISAP score had a high specificity of 91 % (95 % CI, 90 %–91 %) but low sensitivity 56 % (95 % CI, 53 %–60 %) for mortality as well as severe AP [39]. A BISAP score of ≥3 seems to be reliable to identify those AP patients at risk of developing POF and mortality since a score of 7.4 (95 % CI 2.8–19.5) predicts organ failure and a score of 3.8 (95 % CI, 1.8–8.5) predicts pancreatic necrosis. Similar to the SIRS score, the BISAP score is easy to calculate and requires clinical data that is routinely collected within 24 h of presentation. The most important limitation of BISAP is its low PPV and sensitivity in predicting mortality in comparison to the Ranson and APACHE II scores [39] and this is likely due to the fact that many patients present with age >60, BUN elevations, and SIRS with improvement of the latter two after modest fluid resuscitation.

Harmless acute pancreatitis score (HAPS)

The harmless acute pancreatitis score (HAPS) was developed as a scoring system to determine which AP patients are likely to have a mild or "harmless" disease course. The system was based on a combination of readily available clinical and laboratory parameters that include serum creatinine, hematocrit, and clinically elicited rebound tenderness that can be calculated as early as within 1 h of admission [40]. The score is used to stratify patients into low-risk and high-risk categories. Patients with low HAPS score may be candidates for less aggressive management while those with higher scores may require closer monitoring and more intensive management. Based on this premise, the HAPS score was found be an appropriate prognostic tool in rapidly triaging patients that may need to be transferred to an ICU setting [16]. Lankisch et al. showed that the HAPS could accurately identify those patients with AP who would experience a mild disease course with a high specificity (97 %) and PPV (98 %) [41]. However, it could be argued that many other prognostic scoring systems perform similarly as they can accurately predict a mild course thus limiting the use of the HAPS [42]. Moreover, the score lacks robust validation in predicting outcomes such as length of hospitalization and development of complications in patients with AP.

Table 2
Severity categories of the Atlanta 1992, Revised Atlanta Classification (RAC) 2012, and Determinant Based Classification (DBC).

Severity category	Atlanta 1992	Revised Atlanta classification 2012 (RAC)	Determinant based classification (DBC)
Mild	No Local Complications No Organ Failure	No Local Complications No Organ Failure	No (Peri)Pancreatic Necrosis No Organ Failure
Moderate		Local Complications and/or Transient Organ Failure and/or Exacerbation of Comorbid Disease	Sterile Peri (Pancreatic) Necrosis and/or Transient Organ Failure
Severe	Local Complications and/or Organ Failure and/or APACHE II ≥ 8 or Ranson's Score ≥ 3	Persistent Organ Failure	Infected Peri (Pancreatic) Necrosis or Persistent Organ Failure
Critical			Infected Peri (Pancreatic) Necrosis and Persistent Organ Failure

Laboratory indicators of severity

A wide array of laboratory markers as predictors of SAP have been studied and most of them are incorporated into the prognostic scores discussed above. However, a few of these markers have been found to be individually significant in the prediction of SAP.

Hemoconcentration. Hemoconcentration is a parameter incorporated into several severity scores (e.g., APACHE-II, HAPS, PANC 3, Ranson) and has been found to correlate with pancreatic necrosis and MOF [43]. This is due to AP induced third space intravascular fluid loss which leads to hemoconcentration. Studies have shown variable results using HCT as

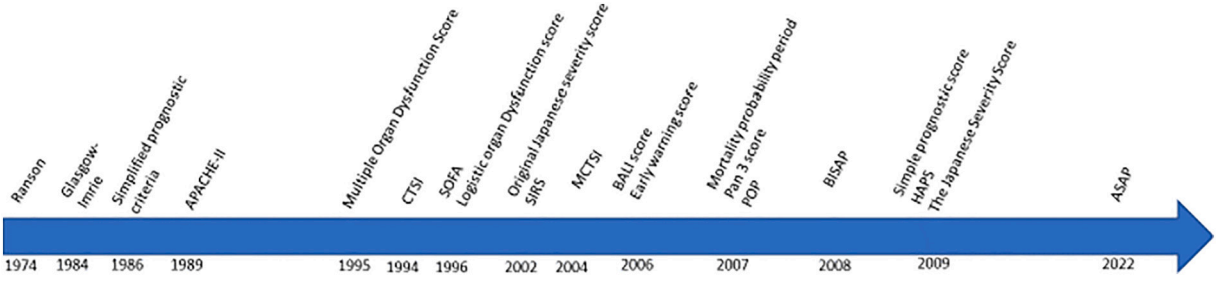

Fig. 1. Timeline of prognostic scores:
Legend: APACHE-II (Acute Physiology and Chronic Health Enquiry), CTSI (CT severity index), SIRS (Systemic inflammatory response syndrome score), SOFA (Sequential organ failure assessment score), SIRS (Systemic inflammatory response syndrome), MCTSI (modified CTSI) POP (Pancreatitis Outcome Prediction), HAPS (The Harmless Acute Pancreatitis Score), BISAP (Bedside Index for Severity in Acute Pancreatitis), ASAP (Predicting Severe Acute Pancreatitis at Admission).

a predictor of the severity of AP because the baseline HCT is variable across the population which can affect the cut-off HCT values used to define hemoconcentration in individual studies. In addition, the timing of sample collection were different for each study due to referral bias [44]. A normal or low HCT at admission and during the first 24 h is associated with a milder clinical course. Patients with MOF and pancreatic necrosis had incremental increases in HCT from their baseline, suggesting that population-based cutoff values for HCT are of limited value. Therefore, the changes in HCT from baseline would be better indicators of hemoconcentration secondary to dehydration and third space fluid loss [45]. Despite these caveats and limitations, HCT levels may be monitored and interpreted in conjunction with other clinical and laboratory parameters to assess severity and guide management in AP patients.

C-reactive protein. C-reactive protein (CRP) is an acute-phase reactant produced by the liver due to stimulation by interleukin-1 and 6. It has been found to be a predictor of pancreatic necrosis, infected pancreatitis, SIRS and SAP [46]. However, CRP levels are influenced by liver disease [47], which may be present in many patients with AP who may have concomitant alcoholic or obesity-related non-alcoholic liver disease. CRP levels also peak at 72–96 h after symptom onset which can limit its prognostic accuracy since patients typically present at variable times during their clinical course [48,49]. CRP levels above 150 mg/L at 48 h can help to distinguish severe from mild disease with a sensitivity and specificity of 80 % and 76 %, respectively [50]. The main advantage is that it is inexpensive to measure and testing is readily available to help predict the severity of pancreatitis, especially at 48 h [7,9]. CRP levels can be serially monitored to assess response to treatment and resolution of inflammation, thereby enabling evaluation of the trajectory of the disease. Declining levels may indicate successful improvement in pancreatic inflammation, whereas increasing levels may suggest ongoing inflammation or development of complications that may require further intervention [51].

Blood urea nitrogen and serum creatinine. Blood urea nitrogen (BUN) and serum creatinine are markers of renal function and can be elevated in various conditions including dehydration, renal failure, gastrointestinal bleeding and certain medications. Studies have found serial BUN measurements to be reliable predictors of mortality in AP [30,39,52]. Consequently, BUN levels have been included as components of previously discussed severity systems including Ranson criteria, BISAP and APACHE II. A study including 5819 patients from 69 different institutions showed that for every 5 mg/dL increase in the BUN during the first 24 h, the adjusted odds ratio (OR) for mortality was 2.2 [52]. Another study with 1043 patients showed that a BUN level of 20 mg/dL or higher at admission was associated with a greater risk of mortality compared with a BUN level of <20 mg/dL (OR 4.6) [53].

Similarly, elevated serum creatinine within the first 48 h was found to be a predictor of the development of pancreatic necrosis and severity of disease [36]. In a study of 129 patients, a peak creatinine of >1.8 mg/dL during the first 48 h had a PPV of 93 % for the development of pancreatic necrosis [54]. However, a study from Germany instead showed that normal creatinine had a high NPV for the development of pancreatic necrosis [55]. The authors suggested that a normal creatinine in the absence of complications obviated the need for an abdominal CT scan. The difference between the two studies could be attributed to a decreased incidence of pancreatic necrosis in the German study, resulting in a lower PPV. It is important to note that in a context of AP, elevated BUN and creatinine can be due to dehydration, third space fluid loss, hypoperfusion, renal dysfunction or protein catabolism. Therefore, these markers have limited isolated prognostic value and should be interpreted in conjunction with other clinical and laboratory markers. Additionally, individual patient factors and comorbidities should be considered when interpreting these results.

Others. Several other markers have been studied to predict SAP. Procalcitonin is commonly found to be elevated in patients with infections and MOF. Procalcitonin measured at the time of hospitalization has been reported to be a better predictor of SAP than CRP levels or the APACHE II and Ranson scores. A procalcitonin strip test has shown 86 % accuracy in predicting SAP [56]. In addition, urinary trypsinogen activation peptide (TAP) was shown to be elevated in patients with severe AP. When trypsin is activated, TAP is released from the amino-terminal end of trypsinogen, and it is the most widely explored activation peptide in AP. Within 24 h of symptom onset, urinary TAP was found to have a sensitivity and specificity of 58 % and 73 %, respectively, and was helpful in predicting the SAP [57]. Other markers include, polymorphonuclear elastase; pancreatic-associated protein; procarboxypeptidase-B; carboxypeptidase-B actitivation peptide; serum trypsinogen-2; phospholipase A-2; serum amyloid protein-A; substance-P; antithrombin III; platelet activating factor; interleukins 1 and 6; tumor necrosis factor (TNF)-alpha or soluble TNF receptor; angiopoietin-2, and various genetic polymorphisms [54,58–60]. However, the majority of the tests for these markers' have not yet been validated for clinical application, and are limited to a few studies.

Radiological scoring systems

The first CT-based scoring system was developed by Balthazar in 1990 which could objectively predict the severity of AP based on the extent of necrosis and inflammation. Contrast-based studies are required for accurate determination of the extent of inflammation and necrosis. The CT severity index (CTSI) scores for inflammatory changes, fluid collections, and necrosis. Modified CT severity index (MCTSI) incorporates five additional extrapancreatic changes including ascites, pleural effusion, gastrointestinal involvement, and vascular and parenchymal complications. There was no difference noted between CTSI and MCTSI for prognostication of AP [61]. Other CT-based scoring systems that have been developed for severity assessment and prognostication of AP include pancreatic size index (PSI), extra-pancreatic CT score on inflammation on CT score (EPIC), mesenteric edema and peritoneal fluid score (MOP) and Balthazar grading. A comparative analysis of radiological and clinical scoring systems including APACHE II and BISAP showed no significant difference in predicting the severity of AP [62]. A CTSI score 0–3 points was associated with a 3 % mortality rate, while a score of 7–10 points was associated with a 17 % mortality [63].

Future directions

Plasma proteins

The pathophysiological hallmark of MOF in AP is the irreversible capillary leakage of plasma proteins between damaged endothelial cells. The dynamic variations in plasma albumin, total protein (TP), and non-albumin plasma protein (NAPP; i.e., TP minus albumin) that are responsible for maintaining the plasma oncotic pressure can be used as surrogates for capillary permeability [27,64]. Since the inflammatory process intensifies and evolves with time, identifying patients which are likely to develop capillary leak syndrome (CLS) and MOF consequently, is critical [27]. These biomarkers can be utilized to predict the overall disease trajectory within the pre-MOF window, allowing for early treatment for patients with AP [65].

The antagonistic autocrine peptides angiopoietin-1 (ANG I) and angiopoietin-2 (ANG II), which are expressed solely in endothelial cells, also regulate capillary permeability at the endothelial level and therefore, can be potential biomarkers of severity in AP [66]. ANG I inhibit capillary leakage by stabilizing the endothelium, whereas ANG II enhances it by preparing the endothelium to respond to inflammatory cytokines.

Studies have shown that plasma albumin levels have a good correlation with MOF and poor outcomes in AP [67,68]. AP patients with MOF showed a decline in both plasma albumin and NAPP levels

indicating a severe irreversible form of endothelial injury. On the other hand, patients without MOF showed decreased plasma albumin levels only with a reversible form of endothelial injury unless complicated by pancreatic necrosis or infection [27].

Other cytokines and biomarkers

Langmead et al. discovered that five cytokines, ANG II, HGF, IL-8, resistin, and TNF-R1 represent various parts of the pathophysiologic mechanisms of AP and reliably predict POF as early as 24 h after symptom onset. These cytokines outperformed commonly used laboratory and clinical scoring systems in predicting POF with much higher accuracy [9]. Cytokine elevation likely occurs before any physiologic changes related to POF can be detected by laboratory parameters and clinical scores. This 5-cytokine panel is currently being evaluated in a multicenter prospective cohort study funded by the NIDDK (see NCT05878236) [9,69].

Genetic markers

Genetic studies are another way to improve the prediction of AP in the future and genetic risk factors can provide insight into susceptibility for recurrent AP as well as disease progression toward (infected) necrotizing pancreatitis and POF [69].

In a systematic review and meta-analysis of genetic association studies in AP, Van den Berg et al. discovered 17 variants reported by more than two articles, and a meta-analysis showed three weak correlations with disease severity in CXCL8, GSTP1, and TNF [70]. They also found nine positive gene associations with disease severity in the genes TLR3, TLR4, TLR6, CD14, NFKBIA, PKA2G7, PPARG, and SERPINE1; however, these were not replicated in another study. Although the limited data on other disease phenotypes did not allow for pooled analyses, positive associations were identified for infectious complications (TLR4, CD14, DEFB1, IL10, REN), systemic complications (TNF, TNFAIP3, PLA2G7), pancreatic necrosis (HMOX1), mortality (REN) and surgery (TLR2) [70].

The lack of reproducibility and small sample sizes are two major drawbacks of genetic association studies in complicated disorders since large sample sizes are needed to establish a causal relationship, and as a result, the majority of small-scale studies are underpowered and risk missing true associations (type II error). Another limitation regarding genetic markers is that they cannot be used as a bedside predictor of severity since the time from sample collection to availability of results is too long. However, the results could be useful for further management after discharge from the hospital. Future genetic research must be adequately powered to ensure that enough patients across the spectrum of disease severity to delineate a potential variant(s) that may differentiate risk of severe AP from the numerically larger group of patients with mild AP.

Conclusion

AP is a complex disease with a dynamic course and variable presentation depending on the time between symptom onset and clinical evaluation. The lack of reliable methods to predict severe AP early in the disease course has limited further advances in clinical therapy and the conduct of clinical trials [9]. An ideal disease activity index should be able to reflect the changing clinical manifestations of the illness and be reproducible across different clinical settings [71]. Patients with SAP are usually identified later in the course of their disease, often beyond 48 h at a point in the natural history when the inflammatory cascade may be less amenable to intervention. Early diagnosis and severity stratification with the timely institution of appropriate treatment are the principal goals of AP management. There are many biomarkers under evaluation that hold promise for improved early prediction of severe AP.

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CRediT authorship contribution statement

Aida Metri: Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nikhil Bush:** Data curation, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Vikesh K. Singh:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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