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Early Prediction of Severity in Acute Pancreatitis

What can be Done in Clinical Practice?

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Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas that can lead to gland necrosis, and end-organ failure in up to 20% of cases [1]. The disease is classified into three severity categories: mild, moderate, and severe pancreatitis [2]. Mild AP occurs when there is no organ failure or local complications such as fluid collection or necrotic collection. Moderately severe AP occurs in patients with transient organ failure (<48 hours duration) and/or acute fluid or necrotic collection and/or decompensation of a comorbid condition due to AP. Severe pancreatitis occurs when organ failure persists for more than 48 hours [2]. The mild category confers low morbidity and mortality, moderately severe implies high inpatient morbidity but low mortality, and severe portends high morbidity and mortality [2]. Given the prognostic implication of severity, early prediction of severe disease thus has been a subject of intense research [3,4].

Over the last several decades, over a dozen prediction tools have been developed using various clinical parameters including examination findings, radiological features, laboratory values, and host-related characteristics [5–11]. Development of these tools paralleled advances in our understanding of some key pathophysiological markers and mediators of severe pancreatitis. For example, early intravascular volume deficit has long been shown to mediate progression of parenchymal injury to necrosis in animal models and humans [12,13]. This understanding informed exploration of surrogate markers of intravascular volume as predictors of severity, such as blood urea nitrogen and hemoconcentration [5,14]. It is well recognized that severity of host inflammatory response leads to end-organ injury especially within the first two weeks of disease onset [1,15]. Therefore, investigators studied leukocytosis, elevated C-reactive protein (CRP), and presence of systemic inflammatory response syndrome (SIRS) as predictors of severity [10,11]. Cytokines such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α have also been investigated as potential biomarkers of severity [16,17]. Prognostic significance of fat saponification and its binding to calcium led to calcium level being included in some of the scoring systems [18]. As with other illnesses, baseline reserve of vital organs has been shown to impact a patient's probability of survival [19].

Existing prediction tools (Table 4.1) attempt to assess at least one or more of the following: (i) presence of volume deficit; (ii) severity of host inflammatory response; (iii) age and comorbidity burden; (iv) risk of fat saponification; and (v) early organ dysfunction. In this chapter, we discuss each of these pathophysiological mechanisms, and prediction tools that attempt to assess these early in the course of the disease. Advantages, disadvantages, and future direction are also discussed.

Available Prediction Tools

Volume Deficit

Animal studies have long demonstrated the vulnerability of pancreatic parenchyma to ischemic insults [28,29]. This understanding is the basis for all societies' universal recommendations for early aggressive fluid resuscitation to prevent microcirculatory compromise [13,30–32]. As such, efforts have been made to find surrogate parameters that represent intravascular volume deficit early in the disease course. The best-known markers are blood urea nitrogen (BUN) and hemoconcentration (hematocrit). In a landmark observational study using large administrative data, Wu and colleagues showed that BUN elevation and its rise in the first 24 hours of admission was associated with increased mortality and this finding has been validated in multiple subsequent

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Table 4.1 Existing scoring systems for prediction of severe pancreatitis.

Name[a]	Score component	Comment	AUC for severe pancreatitis
Ranson's	Admission: age (>55 years), WBC (>16 × 10^9/l), glucose (>200 mg/dl), LDH (>350 IU/ml), AST (>250 IU/ml) 48 hours: hematocrit (decrease >10%), BUN (increase >5 mg/dl), calcium (<8 mg/dl), PaO_2 (<60 mmHg), base deficit (>4 mEq/l), fluid sequestration (>6 l)	Needs 48 hours of clinical data Requires blood gas and careful fluid balance data: not routinely available in every patient	0.69–0.72 [6,8]
Glasgow	Age (>55 years), WBC (>15 × 10^9/l), glucose (>180 mg/dl), BUN (>45 mg/dl), PaO_2 (<60 mmHg), calcium (<8 mg/dl), albumin (<3.2 g/dl), LDH (>600 IU/l)	Validated and commonly used in trials including predicted severe acute pancreatitis [20,21] Not all components routinely available or checked PaO_2 (<60 mmHg), LDH (>600 IU/l)	0.73–0.84 [6,10,22]
APACHE-II	Age, temperature, MAP, heart rate, respiratory rate, A–aPaO_2 or PaO_2, arterial pH or HCO_3, sodium, potassium, creatinine, hematocrit, WBC, GCS score, chronic health problems[b]	Cumbersome to calculate with lack of clear superiority over other models	0.77–0.80 [6,8,9]
SIRS	Temperature (<36 or >38°C), heart rate (>90 bpm), respiratory rate (>20/min or $PaCO_2$ <32 mmHg), WBC (<4 × 10^9/l, >12 × 10^9/l or >10% bands)	Extremely easy to calculate and all components widely available Reflects only one pathophysiological mechanism of severity (i.e. host inflammatory response)	0.70–0.88 [6,10,23]
Panc 3	Hematocrit (>44%), BMI (>30 kg/m^2), pleural effusion	Simple score but it requires a chest X-ray; inferior accuracy and sensitivity	0.64–0.76 [6,11]
POP	Age, MAP, PaO_2/FiO_2, arterial pH, BUN, calcium	Derived from intensive care unit patients with acute pancreatitis May not be applicable to patients on the regular nursing floor Requires an arterial gas reading	0.67–0.83 [6,24]
BISAP	BUN (>25 mg/dl), impaired mental status (GCS score <15), SIRS (≥2), age (>60 years), pleural effusion	Easy to calculate Requires chest X-ray Most extensively validated among all scores Poor sensitivity, thus low negative predictive value	0.72–0.90 [6,8,10]
JSS	Base excess (≤3 mEq/l), PaO_2 (≤60 mmHg or respiratory failure), BUN (≥40 mg/dl) or creatinine (≥2 mg/dl), LDH (≥2× upper limit of normal), platelets (≤100 × 10^9/l), calcium (≤7.5 mg/dl), CRP (≥15 mg/dl), SIRS (≥3), age (≥70 years)	More cumbersome to calculate than BISAP score without offering clear performance advantage Requires an arterial blood gas sample	0.76–0.83 [6,9]
HAPS	Abdominal tenderness, hematocrit (>43% for men or >39.6% for women), creatinine (>2 mg/dl)	Extremely simple More applicable for patients in the emergency room Designed to identify patients with "nonsevere" pancreatitis	0.62–0.85 [6,25]
PASS	Organ failure (100 points) SIRS (25 points for each criterion) Abdominal pain (5 points) Morphine equivalent dose (5 points/mg) Tolerating solid diet (yes = 0, no = 1 – 40 points)	Designed to be measured and followed over time Easy to calculate and measure Needs validation studies	0.7 [26,27]

[a] SIRS, systemic inflammatory response syndrome; Panc, pancreatitis; POP, Pancreatitis Outcome Prediction; BISAP, Bedside Index for Severity of Acute Pancreatitis; JSS, Japanese Severity Score; HAPS, Harmless Acute Pancreatitis Score; PASS, Pancreatitis Activity Scoring System.
[b] Chronic health conditions: cirrhosis with portal hypertension, New York Heart Association class IV heart failure, chronic respiratory failure, dialysis-dependent renal failure, or immunocompromised state.
AST, aspartate aminotransferase; AUC, area under the response curve; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; GCS, Glasgow Coma Scale; LDH, lactate dehydrogenase; MAP, mean arterial pressure; WBC, white blood cell count. *Source:* adapted from Mounzer et al. [6].

prospective studies using patient-level data [5,33]. Similarly, hemoconcentration and lack of hemodilution has been associated with pancreatic necrosis in several studies [34].

While these parameters are readily available predictors of severity, they have limitations. BUN level is also a function of a patient's muscle mass and it decreases with age. Additionally, it is elevated at baseline in patients with chronic kidney disease. Hematocrit is affected by anemia and age, so it is not a reliable marker in such populations. Nevertheless, their simplicity and strong association with necrosis and mortality led to studies examining the impact of lowering BUN and hemodilution on AP outcomes, with mixed results [35–37].

Interestingly, existing fluid resuscitation studies failed to convincingly show that lowering BUN and hematocrit improved outcomes [38]. This could suggest that hemoconcentration and BUN elevation may simply indicate the severity of disease that has already occurred rather than being early markers, and they unfortunately do not represent a targetable end point for volume resuscitation. Additionally, intravascular volume deficit is ultimate result of complex pathophysiological events such as capillary leakage, systemic inflammation, and vascular shunting. This highlights the need for a more sensitive and specific biomarker that can detect intravascular volume deficit at the earliest stage. While novel noninvasive tools have been developed to dynamically measure volume deficit in other clinical settings, none have been extrapolated for use in AP patients [39,40].

Fluid sequestration and intra-abdominal hypertension are other important phenomena relative to AP severity. Patients often have systemic capillary leak syndrome leading to severe "third-spacing" of fluids. Age under 40 years, alcohol etiology, hemoconcentration, and presence of SIRS are risk factors for fluid sequestration and predicted severity of AP [41,42]. Aggressive fluid resuscitation in this population will eventually lead to intra-abdominal hypertension and compartment syndrome, which portends a poor prognosis [43]. As such, intra-abdominal pressure as measured via a urinary catheter has been examined as a predictor of severity with promising results [44]. At a biomarker level, angiopoietin-2, a regulator of capillary permeability, has been shown to predict severe pancreatitis [45,46].

Inflammatory Response

Starting with acinar cell injury by a variety of pancreatic toxins, systemic inflammation occurs as early as the first few hours of the inciting parenchymal injury [15]. SIRS is a clinically evident syndrome that is a manifestation of the host's exaggerated immune response to a local organ injury. SIRS secondary to sterile pancreatic inflammation is the predominant event in the first two weeks and its severity and progression to organ failure determines the fate of patients [2]. SIRS has long been recognized as a harbinger of disease severity. Several studies have shown that SIRS, especially when persistent for 48 hours or longer, is associated with increased risk of mortality [23].

At a biomarker level, white blood cell count, CRP, procalcitonin, and a variety of proinflammatory cytokines have been incorporated into different prediction models [47–51]. None of the cytokines, chemokines, damaged associated molecular pattern levels, or adipokines are routinely available for use. As such, a widely available acute-phase reactant, CRP at levels above 20 mg/dl, is a commonly used inclusion criterion for studies examining predicted severe pancreatitis [20,21]. Leukocytosis is a criterion included in the SIRS criteria, Imrie score, and Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II score. Procalcitonin has repeatedly been shown to be associated with infected necrosis and organ failure [52–54]. IL-6 is a potent proinflammatory cytokine and is the most extensively studied cytokine with a strong association with severe pancreatitis with good accuracy (Table 4.2). TNF-α is another potent proinflammatory cytokine but due to the inaccuracies inherent in its measurement, studies examining TNF-α as a predictor of severity are scarce [65].

Host-related Characteristics

Age and Comorbidity Burden

Increased age and comorbid conditions do not mediate increased pancreatitis severity, but rather reduce a patient's reserve to survive an extreme physiological stress [19]. Patients older than 75 years of age are at significantly increased risk of mortality at one and three months when compared with patients 35 years of age and younger. Similarly, a high Charlson Comorbidity Index is associated with increased mortality. While comorbidity burden is not typically included in a scoring system, age is part of most scoring systems (see Table 4.1).

Obesity and Hypertriglyceridemia

Obesity has long been recognized to be a risk factor for pancreatic necrosis, organ failure, and mortality but its precise mediatory mechanism remained elusive until recently [66,67]. The differential significance of visceral, intrapancreatic and peripancreatic distribution of fat has been illustrated in multiple studies [68,69]. Lipolysis of triglycerides contained within and around the pancreatic parenchymal adipose tissue releases unsaturated free fatty acids that mediate end-organ injury by causing mitochondrial failure [67,69,70]. Body mass index (BMI) has been incorporated into existing prediction systems such as APACHE-II scores, with modest performance improvement [71]. Free fatty acids also bind to calcium, which

Table 4.2 Cytokines, chemokines, and adipokines examined in studies for prediction of severe pancreatitis or mortality.

Name of cytokine, chemokine or adipokine	Function	AUC for severe pancreatitis or mortality
Interleukin-1β	Proinflammatory cytokine: stimulates macrophages, causes lymphocyte maturation; induces acute-phase protein production; facilitates leukocyte trafficking	74–82% [55]
Interleukin-6	Proinflammatory cytokine: regulates T lymphocytes activation and differentiation, causes lymphocyte maturation; induces acute-phase protein production; facilitates neutrophil trafficking to the site of injury; strongly associated with acute lung injury in acute pancreatitis	75–88% [55–57]
Interleukin-8	Proinflammatory cytokine	73–76% [55,57]
TNF-α	Proinflammatory cytokine: induces acute-phase protein production; activates neutrophils and macrophages	81% [58]
Angiopoietin-2	Autocrine peptide regulator of vascular permeability	74–81% [46,59]
Resistin	Adipokine: induces production of IL-1β, IL-6 and TNF-α	76–80% [60,61]
Visfatin	Adipokine: induces production of IL-1β, IL-6 and TNF-α	74% [62,63]
Monocyte chemotactic protein-1	Chemokine secreted early in the disease course to recruit monocytes, lymphocytes, mast cells, and eosinophils	88% [64]

explains the decreased calcium level often seen during severe necrotizing pancreatitis, and calcium level is part of existing scoring systems such as Ranson's. Similar mechanisms likely explain why hypertriglyceridemic patients are at increased risk of developing severe pancreatitis [72].

Degree of Parenchymal and Extra-parenchymal Injury

The prognostic significance of parenchymal and extra-parenchymal injury was first illustrated in 1985 by Balthazar et al. [73]. These authors demonstrated that the degree of edema, and number of pancreatic fluid collections, determined the risk of infection of pancreatic fluid collections and death in 83 patients with acute pancreatitis. Subsequently, presence and degree of pancreatic parenchymal necrosis were recognized to be significant predictors of morbidity and mortality [74]. The most commonly recognized cross-sectional imaging-driven prediction tools are computed tomography severity index (CTSI) and modified CTSI. These depend on the availability of contrast-enhanced CT and assess severity by degree of pancreatic edema and pancreatic collections, as well as presence and extent of parenchymal necrosis (Table 4.3). It is worth noting that pancreatic fluid collections (necrotic and non-necrotic) are not independent mediators of mortality unless they become infected [4]. On the other hand, the degree of parenchymal and extra-parenchymal injury strongly correlates with both inpatient and outpatient morbidity [75,76]. This is not surprising because morbidity from acute pancreatitis is determined by the compressive effects of fluid collections on surrounding organs or infection of the collections.

Scoring Systems

Currently available scoring systems are shown in Table 4.1. Of these, SIRS and the Bedside Index of Severity in Acute Pancreatitis (BISAP) are the most commonly used and easy to calculate (Table 4.1). Using SIRS criteria to risk-stratify has advantages over BISAP score because it does not need a chest X-ray to calculate, and its predictive performance is fairly comparable to BISAP. One in two patients meeting all four criteria for SIRS on admission required transfer to the intensive care unit (ICU) within the first week in a prospective study of 252 patients with AP [23]. Other systems are more cumbersome to calculate (APACHE-II) or rely on data availability over 48 hours (Ranson). The Harmless Acute Pancreatitis Score aims to identify patients predicted to have a mild course, with high sensitivity and specificity [77,78]. The Pancreatitis Activity Scoring System (PASS) score (see Table 4.1) is the most recently developed score [26]. While originally designed and developed

Table 4.3 Components of computed tomography severity index (CTSI) and modified CTSI.

CTSI
CT grade
Normal: 0 points
Focal or diffuse enlargement: 1 point
Intrinsic change or fat stranding: 2 points
One ill-defined fluid collection: 3 points
Multiple fluid collections or gas: 4 points
Necrosis score
None: 0 points
One-third of pancreas: 2 points
Half of pancreas: 4 points
More than half of pancreas: 6 points
CTSI: Severe >6 points (CT grade + necrosis)
Modified CTSI
CT grade
Normal: 0 points
Intrinsic pancreatic abnormalities with/without inflammatory changes in peripancreatic fat: 2 points
Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis: 4 points
Necrosis score
None: 0 points
<30%: 2 points
≥30%: 4 points
Extrapancreatic complications (one or more of pleural effusion, ascites, vascular complications, parenchymal complications or gastrointestinal involvement): 2 points
Modified CTSI: 0–2 mild; 4–6, moderate; 8–10, severe

to measure "activity" of AP, the authors also recently tested its predictive function [27].

Limitations and Future of Current Scoring Systems and Predictive Markers

While many scoring systems and markers have been recognized and validated, most have only modest accuracy (see Table 4.1) [6]. For practicing clinicians, a severity prediction tool should ideally help change management of a patient based on the prognostic forecast given by the tool. An excellent example of a useful prediction tool is the Model for End-Stage Liver Disease (MELD) score in patients with cirrhosis [79,80]. MELD score had long been used as a tool to assign priorities for liver transplants, and appropriately risk-stratify cirrhotic patients undergoing surgery and transjugular intrahepatic portosystemic shunt [79,80]. In contrast, it is not known if any of the existing acute pancreatitis severity prediction tools influence clinical management.

Given the abundance of scoring systems, the next priority is to examine which of the systems directly impact management in real clinical settings. While SIRS score represents the most promising candidate for such practical use, there is lack of data on which is most useful at a clinical practice level. Even in patients with severe pancreatitis as defined by Revised Atlanta Classification, many could be managed on a regular nursing floor if the end-organs do not require inotropes, mechanical ventilation, or renal replacement therapy. In a large multicenter prospective cohort study, 28% of severe AP patients were managed on the regular nursing floor [81]. In this context, some practical end points could include "impending" need for ICU admission or organ support requirement, need for a full admission from the emergency room, progression to multisystem organ failure, and early death. Almost all existing scoring systems predict in-hospital mortality. While relevant, they do not consider where in the course of disease the death occurs.

Artificial Intelligence and Biomarkers: the Future?

While an extensive number of cytokines, adipokines and chemokines have been tested, none are routinely available, and none outperform existing clinical scoring systems. The most notable cytokines are IL-1β, IL-6, TNF-α, resistin, visfatin, angiopoietin-2, and MCP-1 (see Table 4.2). Table 4.2 is a list of the most promising biomarkers that have been tested for their predictive performance in AP patients, but it is not exhaustive as many other markers have been associated with AP severity [82,83]. In the future, combining biomarkers with clinical scoring systems can be examined to see if prediction performance can be enhanced.

Machine learning algorithms are increasingly tested to aid clinical decision-making [84–87]. Similarly, in pancreatology, deep learning could be integrated into patients' electronic medical records to build more accurate models that will continue to refine themselves automatically with time. For example, using machine learning models the risk of "under-triaging" patients in the emergency room was significantly less than the human triage system [85]. Deep learning could also be employed to incorporate cytokine, chemokine, and adipokine data as well as clinical data to develop better prediction tools that clinicians can use.

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