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An Overview of Acute Pancreatitis: Role of the Prediction Scores for the Assessment of Severity

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Rezumat

Pancreatita acută – o privire de ansamblu asupra rolului scorurilor de predicție în evaluarea severității

Pancreatita acută reprezintă o afecțiune inflamatorie severă a pancreasului, cu risc vital, a cărei conduită terapeutică variază în funcție de gravitatea bolii. Diagnosticul, predicția severității şi estimarea prognosticului implică, în mod obişnuit, utilizarea tehnicilor imagistice precum tomografia computerizată (CT), rezonanța magnetică (IRM) şi ecografia, alături de sisteme de scoruri clinice, precum scorul Ranson, APACHE II (Acute Physiology and Chronic Health Evaluation II) şi indicele BISAP (Bedside Index for Severity in Acute Pancreatitis). Tomografia computerizată este considerată standardul de aur datorită sensibilității şi specificității ridicate, în timp ce IRM-ul şi ecografia oferă informații utile despre eventuale obstrucții biliare şi complicații vasculare. Scorurile clinice permit stratificarea pacienților, pe baza datelor clinice şi de laborator, în forme uşoare, moderate sau severe, influențând deciziile terapeutice precum internarea în secția de terapie intensivă, inițierea precoce a alimentației enterale şi utilizarea antibioticelor. Cu toate acestea, în ciuda utilității acestor metode imagistice şi scoruri de severitate în managementul pancreatitei acute, ele se confruntă cu limitări legate de acuratețe, reproductibilitate, aplicabilitate clinică şi cost-eficiență. Aceast review de literatura îşi propune să discute relevanța clinică a principalelor scoruri de predicție utilizate în evaluarea severității acestei afecțiuni complexe.

Cuvinte cheie: pancreatită acută, scor de severitate, afecțiuni pancreatice, evaluare clinică

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Abstract

Acute pancreatitis is a serious inflammatory condition of the pancreas that can be life-threatening, with the approach to treatment depending on the severity of the disease. Diagnosing acute pancreatitis, predicting its severity, and assessing prognosis generally involve imaging techniques like computed tomography, magnetic resonance imaging and ultrasound, along with scoring systems such as Ranson, Acute Physiology and Chronic Health Evaluation II (APACHE II), and the Bedside Index for Severity in Acute Pancreatitis (BISAP). Computed tomography is regarded as the gold standard due to its high sensitivity and specificity, while magnetic resonance imaging and ultrasound offer valuable insights into biliary obstruction and vascular issues. These scoring systems help categorize patients based on clinical and laboratory data into mild, moderate, or severe levels, influencing treatment decisions like intensive care unit admission, early enteral feeding, and the use of antibiotics. However, despite the importance of these imaging and scoring methods in managing acute pancreatitis, they face challenges in terms of accuracy, consistency, practicality, and cost-effectiveness. In this review we aimed at discussing the clinical usefulness of the most important scoring systems for prediction of severity in this complex disease.

Keywords: acute pancreatitis, pancreatitis, scoring system, pancreatic disease

Introduction

Acute pancreatitis (AP) is a common condition that is becoming more prevalent; it is a multifaceted disease, with the majority of patients experiencing a mild course. However, around one-third of individuals face local or systemic complications, which are linked to higher morbidity, and in cases of persistent organ failure lasting more than 48 hours, significantly increased mortality (1). As such, accurately classifying the severity of AP is crucial for proper patient stratification, as patients can experience vastly different disease trajectories. However, the primary severity classification systems, the Revised Atlanta Classification (RAC) and the Determinant-Based Classification (DBC), both rely on the presence of local complications and organ failure at any stage of the disease, making them "post-hoc" methods (2). While these systems are useful for categorizing patients at the end of their disease course, they are not as beneficial for guiding early management. Early identification of patients at risk for severe AP is a major challenge, but predicting severity early on is critical for targeting appropriate interventions. Accurate early prediction would help determine which patients need closer monitoring, intensive care, or referral to specialized centers. Furthermore, it plays an important role in patient selection for clinical trials (3). Various approaches have been developed to predict AP severity, including scoring systems like the Ranson score and the Bedside Index for Severity in Acute Pancreatitis (BISAP), as well as general scoring systems not specific to AP, such as the Acute Physiology and Chronic Health Examination (APACHE)-II and the Systemic Inflammatory Response Syndrome (SIRS) (4). While several other tools incorporating physiological, laboratory, and radiographic parameters have been proposed, these systems generally show only moderate positive predictive values. In this review we aimed at summarizing the main features of AP and discussing the clinical usefulness of the most important scoring systems for prediction of severity in this complex disease.

Etiology of Acute Pancreatitis

The increasing occurrence of acute pancreatitis (AP) in adults is likely influenced by lifestyle-related factors, including dietary habits, gallstone formation, alcohol use, smoking, diabetes, and obesity (5-8). Among the various known triggers, gallstones and excessive alcohol consumption remain the most prevalent causes, accounting for approximately 45% and 20% of cases respectively, particularly in high-income nations (9-10).

Individuals with gallstones smaller than 5 mm, microlithiasis, or biliary sludge are believed to face a heightened risk of developing gallstone-induced pancreatitis. This is thought to occur when tiny stones or sludge pass from the gallbladder into the duodenum, potentially obstructing the sphincter of Oddi. Such an obstruction can lead to the reflux of bile or pancreatic secretions into the pancreatic duct, thereby damaging the pancreatic tissue and triggering AP.

Around two-thirds of patients with acute biliary

pancreatitis are female, as gallstones are more common in women (11). Epidemiological studies show an increasing prevalence of cholelithiasis with age (12), accounting partly for the increasing incidence of acute pancreatitis associated with demographic changes (13).

Heavy alcohol consumption is a well-known cause of AP, the incidence of which differs widely by geography. It is reported in the literature that alcohol is the second most common cause of AP (after the gallstone disease) in North America and Europe, accounting for up to a third of cases (14); in Eastern Europe excessive alcohol intake represents the leading cause. Alcohol-related AP tends to occur more frequently in young and middle-aged adults, potentially due to an individual sensitivity to alcohol, particularly when consumption surpasses 80 g/dL. Additional contributing factors may include variations in alcohol dehydrogenase enzyme activity within the gastric lining and liver, which can influence how alcohol is metabolized (15-17). Pathogenesis of alcohol-induced AP remains unknown, although there is evidence that ethanol may disrupt multiple biochemical pathways within acinar cells. Smoking is an independent risk factor for AP and recurrent AP most notably in heavy drinkers with an additive effect in association with alcohol (18).

In contrast, in the absence of concomitant smoking, moderate alcohol intake (less than 40 g/day) may protect against a first but not subsequent attack of AP, possibly by stimulating pancreatic ductal secretion (19).

Hypertriglyceridemia (HTG) (typically > 1000 m/dL) was found to be the cause of acute pancreatitis in ~ 9% in a recent global systematic review (20) making it the third most common cause. The Endocrine Society differentiates primary (genetic) from secondary (e.g. metabolic syndrome, diabetes mellitus, alcohol or pregnancy) hypertriglyceridemia as mild (150-500 mg/dL; 1.7-5.6 mmol/L), moderate (500-1000 mg/dL; 5.6-11.3 mmol/L) or severe (> 1000 mg/dL; > 11.3 mmol/L) dependent on serum triglyceride levels (21); much is polygenic in nature. There is an approximate 4% increase in the incidence of AP for every 100 mg/dL rise in serum triglyceride levels above 1000 mg/dL (22). HTG is associated with the highest risk of developing more severe forms of AP, including moderately severe and severe cases. A proposed underlying mechanism involves lipotoxicity caused by unsaturated fatty acids, which may lead to pancreatic tissue necrosis, multi-organ failure, and increased mortality.

Hypercalcemia is a rare cause of AP and the mechanism is not well elucidated. Some studies suggested that hypercalcemia may contribute to AP by promoting calcium deposition within the pancreatic ducts or by accelerating the activation of trypsinogen to trypsin, ultimately leading to autodigestion of pancreatic tissue.

Drugs account for less than 5% of cases of AP (23). More than 500 medications have been implicated as a cause of AP and at least 30 of them have been shown to have a definite association, meaning that they cause AP on repeated administration of the medications when other possible causes are excluded. While certain medications such as diuretics, azathioprine, sulfonamides, steroids, and drugs used to treat acquired immunodeficiency syndrome, can induce AP through direct toxic effects, the majority of drug-induced AP cases are likely due to individual hypersensitivity reactions (24). AP can result from instrumentation of the ampulla and pancreatic duct following endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS), with a risk of 5% - 10% and less than 1%, respectively (3,25).

Periampullary tumors, pancreatic head masses and cystic lesions of the pancreas can cause obstruction of the pancreatic duct, impeding the flow of pancreatic enzymes, which may lead to inappropriate enzyme activation within the pancreas. Pancreas divisum and pancreatic strictures can also obstruct the pancreatic duct and cause pancreatitis. The etiology of AP is not identified in many cases. Mutations, up-regulation, and genetic variants in several genes have been involved in AP, such as the trypsinogen gene (PRSS1) and trypsin inhibitor (SPINK1), cystic fibrosis transmembrane regulator (CFTR) variants, and endothelial ion/water channel CLDN2 risk allele (26). Several risk factors, in addition to the mentioned smoking, associated with AP include obesity, older age, type 2 diabetes, and HIV positive status.

Autoimmune pancreatitis is a rare (<1%), distinct form of chronic pancreatitis that may present acutely. It is a largely lymphocytic inflammatory process that lead to final organ fibrosis and altered function (3). Increased levels of pancreatic enzymes, such as amylase and lipase, in the bloodstream result from the leakage of these enzymes from damaged acinar cells into the surrounding interstitial tissue, after which they are absorbed into the circulatory system.

However, there are differences in half-life

between the two pancreatic enzymes. Various biomarkers such as serum immunoreactive trypsin, chymotrypsin, elastase, phospholipase A2, alpha2-macroglobulin, methemalbumin, and carboxypeptidases, have been proposed as diagnostic tools for AP. However, these tests are not routinely performed in clinical practice and are not widely available for commercial use. Although serum and urinary enzyme measurements are commonly used to confirm the diagnosis of AP, they do not provide reliable information regarding disease severity or help predict its clinical progression. IgG4 levels are helpful when autoimmune pancreatitis is suspected. Imaging exams are generally not needed in emergency when the clinical features and laboratory exams are suggestive of AP. When the clinical presentation is typical the blood exams are not conclusive, imaging techniques like as contrast enhanced computed tomography (CECT), magnetic resonance imaging (MRI) and ultrasound (US) are mandatory. Imaging still plays a fundamental role in the early assessment of AP, aiding in the identification of severe forms, prediction of prognosis, and guiding treatment strategies. Precise imaging interpretation is especially important in conditions like AP, where effective management relies on accurate diagnosis. According to the modified Japan Pancreas Society Criteria, diagnosing AP involves characteristic imaging features on CT, MRCP, or ERCP, along with either serologic markers (such as IgG4 or total IgG) or related pancreaticobiliary or systemic manifestations, including sialadenitis, nephritis, or IgG4-associated pneumonitis (27).

Chronic pancreatitis is a fibroinflammatory disease that can be complicated by episodes of acute pancreatic inflammation (acute on chronic pancreatitis). A recent study from the Hungarian Pancreatitis Study Group found that ~ 50% of patients who had suffered three or more episodes of AP had coincident chronic pancreatitis, confirming that recurrent AP helps to identify early chronic pancreatitis. Alcohol is the most common etiology to account for these scenarios, smoking and hypertriglyceridemia are other causes of this progression (28). Current guidelines recommend, on admission of the patient, identification of the causes of AP, as early as possible, to project the need of definitive treatment (e.g. gallstone disease) and to avoid recurrence (e.g. alcohol intake, HTG) (29-30). If risk factors for AP vary according to age group, a tailored strategy may be needed for the prevention of AP in each age group.

Pathophysiology

The development of AP involves the premature activation of trypsinogen and the subsequent damage to pancreatic secretory cells. This process triggers the systemic release of cytokines and inflammatory mediators, which in turn activate immune cells and may lead to fever and multiple organ failure (MOF). Additional mechanisms contributing to the pathogenesis include calcium overload, mitochondrial dysfunction, disrupted autophagy, endoplasmic reticulum stress, and the involvement of exosomes (31). Edema of the pancreas and surrounding tissues, along with fat necrosis, is commonly observed across all forms of AP, ranging from mild to severe. However, in severe cases, hemorrhagic changes within the pancreas may also occur. While pancreatic necrosis is typically absent in mild and moderately severe AP, it becomes a prominent feature in severe forms. This necrosis arises from compromised microcirculation within the pancreas and generally takes about 4 to 7 days to fully develop after symptom onset. Nevertheless, its progression can vary, potentially continuing over the first two weeks. Initially, pancreatic necrosis is usually sterile, and infection during this early stage is rare. Beyond the first week or two, however, secondary infection, often resulting from the translocation of gut bacteria, can occur, significantly increasing the risk of complications, morbidity, and mortality (32).

Classification Systems of Severity

There are two classification systems of severity of AP: the Determinant-Based Classification of Acute Pancreatitis Severity (DBC) and the Revised Atlanta Classification 2012 (RAC) with the latter most commonly used (2).

The RAC 2012 (defining clinical diagnosis, CT manifestation and the disease course of AP) distinguished two morphologically different subtypes of AP: interstitial edematous pancreatitis and necrotizing pancreatitis. Interstitial edematous pancreatitis involves inflammation and swelling of both the pancreatic tissue and surrounding areas. When this condition advances to include tissue death in the pancreas or nearby regions, it is classified as necrotizing pancreatitis. The RAC defines acute AP in three severity levels: mild, moderately severe, and severe. The DBC includes these same three categories but introduces an additional fourth level (Critical Severity Grade) based on two key factors that influence mortality:

persistent organ failure and the presence of pancreatic or peripancreatic necrosis. The combination of sustained organ failure and infected necrosis is linked to the highest mortality risk.

So far, there is no consensus on whether AP should be classified into three (RAC) or four categories (DBC). However, the DBC is not as widely used as the revised Atlanta. Based on the RAC 2012, AP severity can be categorized into three groups: mild, moderately severe and severe (2). Mild AP, or interstitial pancreatitis, is characterized by the absence of organ failure and the absence of local or systemic complications. Moderately severe AP is characterized by the presence of transient organ failure (resolving within 48 hours) and/or local or systemic complications without persistent organ failure (>48 hours). Severe AP is characterized by persistent organ failure (>48 hours) that may involve one or more organ systems.

Organ failure, which may be single or multiple, develops during the early phase of AP in set in motion by the activation of cytokine cascades resulting in systemic inflammatory response syndrome (SIRS). When the levels of toxins and inflammatory mediators are high, SIRS may progress to a more critical condition known as multiple organ dysfunction syndrome (MODS). Persistent organ failure lasting more than 48 hours is the primary contributor to morbidity in acute pancreatitis, affecting approximately 50% of patients with pancreatic necrosis and up to 66% of those who develop secondary infections. Pancreatic necrosis occurs in about 20% of cases, and among these, 30–70% progress to infected necrosis, which carries a mortality rate of 20–30% (33). Fungal infections, often following bacterial involvement, are linked to high mortality rates in both primary and secondary infected necrosis and typically require prompt and intensive antifungal treatment. Mortality in acute pancreatitis generally follows a biphasic pattern: during the first week, deaths are primarily due to persistent multiple organ failure, whereas later fatalities are more often the result of local complications, particularly infected necrosis. A systematic review and meta-analysis involving 6,970 patients reported a mortality rate of 35.2% in individuals with both infected necrosis and organ failure, compared to 19.8% in those with sterile necrosis and organ failure, and just 1.4% in patients with infected necrosis without accompanying organ failure (34). SIRS can become overwhelming leading to an early multiple organ failure (MOF). Multiple organ failure includes shock (systolic blood pressure < 90 mmHg), pulmonary insufficiency ($PaO2 \leq 60$ mmHg), acute kidney injury (serum creatinine level > 2 mg/dL) and gastrointestinal bleeding (2). Both forms of AP (interstitial edematous pancreatitis and necrotizing pancreatitis) may be associated with local complications that occur in cases of moderately severe AP and severe AP.

Local complications of AP include acute peripancreatic fluid collections (APFCs), pancreatic pseudocysts (PPs), acute necrotic Collections (ANCs) and walled-off necrosis (WONs) (2). APFCs develop within 4 weeks of disease onset and contain mostly fluid; ANCs develop in necrotizing pancreatitis and contain solid and fluid components. Acute intrapancreatic collections are a result of necrotizing pancreatitis and are referred to as ANCs. APFCs and ANCs that persist after 4 weeks from onset of disease are referred to as pseudocysts and WONs respectively. Peripancreatic and pancreatic collections may be secondarily infected and described as infected ANC and infected WONs.

In addition to pancreatic collections and pancreatic necrosis, other local complications also include gastric outlet dysfunction, splenic or portal vein thrombosis, disruption of the main principal duct, involvement of contiguous organs due to necrotizing pancreatitis, colonic necrosis, abdominal compartment syndrome and pseudoaneurysm. Systemic complications of severe AP are disseminated intravascular coagulation, acute distress respiratory syndrome (ARDS), hypocalcemia, hyperglycemia, gastrointestinal hemorrhage, renal failure, cardiovascular complication.

The majority of cases of adult AP are categorized as mild (60-75%), 20-30% as moderate, and 5-10% as severe. The overall mortality is of 1-5% (35,36): mortality is low (1%) in mild AP but it can be as high as 50% in severe AP.

Most cases of acute pancreatitis (AP) in children are mild; however, approximately 15–34% progress to moderately severe or severe forms, which are associated with increased risk of complications and mortality. Ranson's criteria, one of the earliest tools developed to predict AP severity, has proven difficult to apply in everyday clinical settings. It requires the assessment of five variables at admission and an additional six within 48 hours, making it cumbersome for routine use. A meta-analysis of 110 studies found it to have limited accuracy in predicting disease severity, with a notably high false-positive rate (21). In contrast, the APACHE II score can be calculated upon admission and reassessed daily during the first 72 hours. It is widely used in intensive care units globally and is based on 12 physiological variables (including the

Glasgow Coma Scale, white blood cell count, hematocrit, creatinine, electrolytes, pH or bicarbonate, respiratory parameters, heart rate, mean arterial pressure, and body temperature) along with additional points for age and chronic health conditions. An initial and 72-hour APACHE II score below 8 is associated with a mortality rate under 4%, while scores of 8 or higher raise the risk to 11–18% (37). Monitoring changes in the APACHE II score is valuable for assessing disease progression: a rising score within the first 48 hours strongly indicates severe AP, whereas a declining score is suggestive of a milder course. Despite its utility, the APACHE II system has limitations, including its inability to reliably differentiate between interstitial and necrotizing forms of AP.

The BISAP score is considered one of the most accurate and practical tools for predicting the severity, mortality, and organ failure in AP, mainly due to its simplicity. It includes five variables: blood urea nitrogen levels > 25 mg/dL, impaired mental status or Glasgow Coma Scale (GCS) < 15, Systemic Inflammatory Response Syndrome (SIRS), age > 60 years, and the presence of pleural effusion on imaging. Mortality rates range from 1% for a BISAP score of 0 to 22% for a score of 5.

A study by Mounzer et al. (38) compared various scoring systems, including APACHE II, BISAP, Glasgow, HAPS, JSS, Ranson, and SIRS, in predicting persistent organ failure. The study found that these systems had moderate accuracy, with area under the curve (AUC) values ranging from 0.62 to 0.84 in the training cohort and 0.57 to 0.74 in the validation cohort. Interestingly, the Glasgow score emerged as the most accurate classifier on admission in both cohorts.

In another retrospective study involving 161 patients, significant cutoff values for predicting severe AP were found to be: APACHE II ≥ 8, Ranson ≥ 3, BISAP ≥ 2, CTSI ≥ 3, and serum C-reactive protein (CRP) levels after 24 hours ≥ 21.4 mg/dL. Among these, APACHE II had the highest accuracy for predicting severe AP.

A meta-analysis revealed that the Balthazar CT Severity Index (CTSI) was comparable to BISAP, Ranson, and APACHE II for predicting severity, though it was less accurate than APACHE II for predicting mortality.

The MOF/Goris score evaluates clinical decline across seven key organ systems: renal, respiratory, cardiovascular, hepatic, central nervous, hematopoietic, and gastrointestinal. In a study involving 39 patients with necrotizing pancreatitis, Roumen et al. found that while the APACHE II system was effective in assessing disease severity, the Goris score was more useful for tracking organ dysfunction and guiding the level of supportive care required (39). Conversely, research by de Beaux et al. indicated that patients with Goris scores ranging from 5 to 9 had a significantly higher mortality rate, reaching up to 67% (40).

Marshall et al. first introduced the MODS score in 1995; in subsequent clinical studies, a modified version of the score was adopted, often omitting hepatic function parameters. This modified Marshall scoring system focuses on assessing dysfunction in the respiratory, cardiovascular, and renal systems, particularly in cases of severe AP. Persistent organ failure is identified by a score of 2 or higher in any of these three systems lasting more than 48 hours.

Transient organ failure, also defined by a score of 2 or more, plays a role in classifying moderately severe AP, even if the dysfunction does not persist beyond 48 hours. The modified Marshall score is designed to be reassessed throughout the disease course to help update the classification of severity (41,42).

The SOFA score was originally developed to evaluate the presence and extent of organ dysfunction or failure in patients admitted to intensive care units. In a study by Halonen et al., the predictive ability of various organ dysfunction scoring systems was compared to the APACHE II system in patients with severe acute pancreatitis. The results indicated that all organ dysfunction scores provided better predictions of mortality than age or the APACHE II score. Among these, the SOFA score demonstrated the highest discriminatory power, although the difference was not statistically significant when compared to the other organ dysfunction scoring tools (43).

Additionally, a prospective study found that a SOFA score greater than 4 within 48 hours was associated with a mortality prediction sensitivity of 86% and a specificity of 79% (44). Due to its ease of use and the ability to tailor assessments to individual patients, the SOFA score has gained recognition as a prominent tool among various organ failure prognostic scoring systems. The quick SOFA (qSOFA) score is based on three parameters: respiratory rate, systolic blood pressure, and the Glasgow Coma Scale. In a longitudinal study spanning 17 years and involving 1059 patients, ROC curve analysis showed that the AUC values for predicting outcomes in infected patients were 0.713 for APACHE II, 0.744 for SOFA, and 0.662 for qSOFA (45). Qin et al. concluded that qSOFA,

thanks to its ease of use and rapid data collection, could be a practical tool for evaluating the prognosis of ICU patients with infections (46). Its straightforward nature makes it especially suitable for initial assessments in emergency settings.

However, while qSOFA offers quick prognostic insights in cases of acute pancreatitis, its predictive power is somewhat limited. Supporting this, a cohort study by Rasch et al. involving 203 patients found that qSOFA was useful in identifying individuals at risk for ICU admission and developing multiple organ dysfunction syndrome in the context of AP (47).

Future Directions of Research

A key feature of MOF in AP is the irreversible leakage of plasma proteins through compromised endothelial barriers. Changes in plasma albumin, total protein (TP), and non-albumin plasma protein (NAPP; calculated as TP minus albumin), which are essential for sustaining plasma oncotic pressure, could serve as indirect markers of capillary permeability. Given the progressive nature of the inflammatory response over time, early identification of patients at risk for developing capillary leak syndrome (CLS) and subsequent MOF is crucial. Monitoring these biomarkers may provide insight into the disease course before MOF fully develops, enabling timely intervention in patients with AP (48).

Langmead et al. identified five cytokines, angiotensin II (ANG II), hepatocyte growth factor (HGF), interleukin-8 (IL-8), resistin, and tumor necrosis factor receptor 1 (TNF-R19), as key indicators reflecting different aspects of the pathophysiological processes in AP. These biomarkers were shown to effectively predict persistent organ failure within 24 hours of symptom onset. Notably, their predictive accuracy surpassed that of traditional laboratory markers and clinical scoring systems commonly used for assessing the risk of persistent organ failure (49). Genetic research could offer a promising avenue for enhancing the prediction of AP. Identifying genetic risk factors could help clarify individual susceptibility to recurrent AP and the likelihood of progression to more severe forms, such as infected necrotizing pancreatitis and persistent organ failure (50).

Conclusions

Studies show that the widely used scoring systems for predicting AP tend to be ineffective and are not helpful in making clinical decisions. These systems appear to have reached their limits in accurately predicting persistent organ failure in AP cases. Although more advanced predictive models may offer better accuracy, they are complex and difficult to implement in practice, limiting their clinical value. It is unlikely that our ability to predict the severity of acute pancreatitis will improve in the near future without new methods or approaches.

Author's Contributions

GE, MV: conceptualization, writing and draft preparation; GB: conceptualization, supervision, review and editing; FRE, GAR, GM, GM, VDA: writing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The Authors declare no conflict of interest regarding the research, authorship and/or publication of this article.

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