Ukrainian Journal of Clinical Surgery. 2025. November/December; 92(6):61-80
DOI: 10.26779/2786-832X.2025.6.61

Acute pancreatitis 2025: shaping the future of care. Part 1

S. M. Chooklin, S. S. Chuklin
Surgical Center, Saint Paraskeva Medical Center, Lviv, Ukraine

Introduction

Acute pancreatitis (AP) is one of the most common acute gastrointestinal conditions requiring hospitalization, and its global incidence continues to rise. Recent epidemiological studies report annual rates between 13 and 45 per 100,000 population, with marked geographic variation influenced by gallstone prevalence, alcohol consumption, obesity, and metabolic syndrome [1]. Although the majority of cases follow a mild and self-limiting course, approximately one-fifth develop into moderately severe or severe disease characterized by local complications and organ dysfunction, with a mortality risk that remains substantial in the setting of infected necrosis [2]. This variability in clinical course underscores the unpredictable nature of AP and its importance as a subject of continued clinical and scientific interest.

The significance of AP extends far beyond the acute phase. Survivors are increasingly recognized as being at risk for chronic sequelae that substantially affect health and daily functioning. Among the most prominent complications are post-pancreatitis diabetes mellitus (PPDM), which develops independently of initial disease severity and reflects sustained pancreatic endocrine dysfunction [3], and exocrine pancreatic insufficiency (EPI), particularly frequent after necrotizing forms, leading to maldigestion and nutritional deficiencies [4]. In addition, long-term quality of life is often reduced due to persistent abdominal pain, functional impairment, and psychosocial distress [5]. Beyond metabolic and nutritional consequences, a higher risk of pancreatic cancer has been demonstrated, particularly in the first two years after an episode of AP [6]. Collectively, these findings reinforce the notion that AP is not a transient disorder but a condition with enduring clinical impact.

From a socioeconomic perspective, AP imposes a disproportionate burden relative to its frequency. Severe forms often necessitate intensive care unit admission, prolonged hospitalization, and interventional procedures, thereby driving significant healthcare costs [7]. Furthermore, indirect costs associated with loss of productivity, long-term disability, and reduced quality of life add to the overall impact, making AP a major public health concern.

Diagnostic frameworks have evolved over the past decades to standardize case definition and stratify risk. The Revised Atlanta Classification (2012) remains the cornerstone, combining clinical features, biochemical enzyme elevation, and imaging findings. However, contemporary evidence has highlighted limitations in its ability to reflect the full heterogeneity of disease presentation [8]. The most recent International Association of Pancreatology (IAP) Revised Guidelines of 2025 preserved this structure while emphasizing contextual interpretation, comprehensive etiological assessment, and integration of patient-reported perspectives [4]. Importantly, patients prioritized non-invasive diagnostic options, transparent communication regarding prognosis, and consideration of psychosocial consequences such as the implications of genetic testing for insurance and financial security.

Despite advances in classification and guideline development, significant gaps remain. Early prediction of disease severity continues to pose challenges, as no single biomarker or scoring system achieves complete reliability. The underlying biological complexity of AP – including intracellular calcium dysregulation, mitochondrial dysfunction, and systemic inflammatory activation – creates variability in individual trajectories and complicates prognosis [9]. Furthermore, long-term follow-up strategies require refinement to ensure timely recognition and management of PPDM, EPI, and cancer risk.

Given its multifaceted nature, AP demands a multidisciplinary approach. Optimal outcomes require the coordinated expertise of gastroenterologists, surgeons, radiologists, intensivists, endocrinologists, and nutrition specialists. At the same time, advances in molecular biology, systems medicine, and high-resolution imaging continue to refine the understanding of disease mechanisms and hold promise for more accurate diagnosis and prognostication [10].

Acute pancreatitis is increasingly recognized as a disease of major clinical and societal importance, extending well beyond the acute hospitalization. Its unpredictable course, risk of severe complications, long-term sequelae, and substantial economic burden highlight the need for ongoing scientific exploration. Contemporary international guidelines have established a unified diagnostic and etiological framework while incorporating patient-centered perspectives, yet unresolved challenges in risk prediction and long-term sur-

veillance remain. These factors underscore the relevance of AP as a central topic in gastroenterology and justify continued research into its epidemiology, pathophysiology, and chronic consequences.

Definition and Clinical Relevance

Acute pancreatitis is an acute inflammatory disease of the pancreas, typically presenting with severe abdominal pain, biochemical evidence of pancreatic enzyme elevation, and signs of local or systemic inflammation. The Revised Atlanta Classification (2012) remains the standard diagnostic framework, requiring at least two of the following three features: (1) sudden and persistent epigastric pain, frequently radiating to the back; (2) serum lipase or amylase levels elevated to more than three times the upper limit of normal; and (3) characteristic radiologic findings on contrast-enhanced CT, MRI, or abdominal ultrasound [8]. This classification further differentiates two morphological forms: interstitial-edematous pancreatitis, defined by diffuse glandular swelling without necrosis, and necrotizing pancreatitis, characterized by non-viable pancreatic and/or peripancreatic tissue. Approximately 80% of cases are interstitial-edematous, while necrotizing pancreatitis accounts for about 20% and is strongly associated with persistent organ failure and worse clinical outcomes [2, 4].

The American College of Gastroenterology (ACG, 2024) recommends serum lipase as the diagnostic enzyme of choice, given its superior sensitivity, specificity, and longer diagnostic window compared with amylase. Imaging should not be performed routinely but reserved for atypical cases or when complications are suspected [11]. Similarly, the World Society of Emergency Surgery (WSES, 2019) consensus endorses the Atlanta criteria, emphasizing that diagnosis should primarily rely on clinical and biochemical findings, with imaging restricted to specific indications [12]. Contemporary analyses consistently confirm that lipase outperforms amylase in diagnostic accuracy and persistence, reinforcing its role as the most reliable biochemical marker for AP [13].

The IAP 2025 revised guidelines retain the Atlanta framework but underscore its limitations. Enzyme elevations below the threefold threshold do not exclude AP, while higher values may occasionally derive from non-pancreatic etiologies. Thus, accurate diagnosis requires integration of biochemical, clinical, and imaging data [4].

The guidelines also stress the importance of early etiological assessment during hospitalization. Clinical evaluation should explore gallstones, alcohol intake, medications, hypertriglyceridemia, trauma, and recent ERCP, supported by laboratory tests of liver function, calcium, and triglycerides, together with transabdominal ultrasound. If the cause remains unclear, further investigation with endoscopic ultrasound or MRCP is advised. In recurrent or idiopathic cases, genetic testing should be considered, particularly in younger patients or those with a family history of pancreatic disease [14].

From a prognostic perspective, the persistence of systemic inflammatory response syndrome (SIRS) beyond 48 hours remains one of the most reliable early markers of severity, particularly when combined with elevated CRP or IL-6 levels. Persistent organ failure lasting more than 48 hours continues to be the strongest predictor of adverse outcomes and mortality. Patients at high risk should be referred to specialized high-volume centers whenever comprehensive multidisciplinary expertise is unavailable [4].

For the first time, the IAP 2025 guidelines integrated patient perspectives. Patients emphasized transparent communication regarding etiology, diagnostic strategies, and treatment options, and often preferred less invasive modalities such as MRI over EUS unless strongly indicated. They also highlighted concerns about access to tertiary care and the broader psychosocial and financial consequences of genetic testing, including implications for insurance coverage and mortgage eligibility [4].

In conclusion, the contemporary definition of AP combines clinical features, biochemical testing, and selective imaging, reinforced by international consensus. This integrative approach not only standardizes diagnostic practice but also reflects patient-centered priorities and emerging evidence, providing a robust foundation for early recognition, risk stratification, and clinical management.

Clinical Relevance

The importance of acute pancreatitis (AP) lies in its unpredictable clinical trajectory, its potential for high mortality, and the lasting health consequences it can produce. Around four out of five cases follow a mild, self-limiting course, but approximately 20% evolve into moderately severe or severe disease, accompanied by local complications, organ dysfunction, or a systemic inflammatory response. Severe AP is defined by organ failure persisting beyond 48 hours and may carry mortality rates approaching 30%, particularly when complicated by infected pancreatic necrosis [8, 14]. The 2025 IAP consensus highlights persistent organ failure as the most reliable predictor of fatal outcome, recommending referral of such patients to specialized, high-volume centers whenever multidisciplinary expertise is not available [4].

The impact of AP extends well beyond the acute illness. One of the most significant chronic sequelae is PPDM, a distinct form of diabetes reflecting damage to the endocrine pancreas. Survivors face nearly a twofold increase in diabetes risk compared with the general population, regardless of initial disease severity [14]. Consequently, the IAP

2025 guidelines advise systematic metabolic follow-up, with HbA1c and fasting glucose testing initiated 3–6 months after recovery and repeated annually [4].

Exocrine pancreatic insufficiency represents another frequent long-term complication. It manifests as maldigestion, steatorrhea, progressive weight loss, and deficiencies of fat-soluble vitamins. Evidence from systematic reviews suggests that nearly one-third of patients experience EPI after an AP episode, with the highest incidence among those with necrotizing disease [4]. Current recommendations advocate pancreatic enzyme replacement therapy for patients showing clinical signs of maldigestion and reduced fecal elastase after necrotizing AP [4].

Even in patients who achieve apparent clinical recovery, quality of life (QoL) often remains impaired. Persistent abdominal pain, decreased physical performance, chronic fatigue, and psychological distress are common. Recent meta-analyses demonstrate that QoL deficits can endure for months or even years, particularly in individuals who have experienced severe disease [5]. The 2025 IAP guidelines formally recognize QoL as a key clinical outcome, underscoring the need for structured long-term follow-up [4].

An additional concern is the observed association between AP and pancreatic ductal adenocarcinoma (PDAC). The risk appears to be highest within the first two years after an acute episode, as confirmed by large population-based studies showing a significantly increased incidence compared with matched controls [6]. While the causal relationship remains debated, the IAP 2025 recommendations advise targeted imaging, including cross-sectional modalities and endoscopic ultrasound, especially in older patients and in those with idiopathic pancreatitis, to rule out underlying malignancy [4].

In summary, AP is not only a common acute abdominal emergency but also a disease with long-term metabolic, nutritional, oncological, and psychosocial consequences. Contemporary guidelines therefore call for structured surveillance programs, encompassing regular screening for endocrine and exocrine dysfunction, selective evaluation of malignancy risk, and multidisciplinary care aimed at improving both survival and long-term quality of life.

Etiology

The origins of AP are multifactorial, yet three etiologies dominate globally: gallstones, alcohol consumption, and hypertriglyceridemia. Biliary pancreatitis arises when gallstones or biliary sludge obstruct the ampulla of Vater, leading to impaired pancreatic juice outflow, increased intraductal pressure, and premature activation of pancreatic enzymes. This sequence explains why gallstone disease remains the most frequent trigger of AP, particularly during a first attack [15].

Alcohol-related pancreatitis represents the second leading cause, especially in Western countries. Prolonged ethanol exposure exerts direct cytotoxic effects on pancreatic acinar cells, enhances oxidative stress, and increases the gland's sensitivity to cholecystokinin stimulation. Alcohol not only precipitates initial acute attacks but also predisposes to recurrent episodes and progression toward chronic pancreatitis when consumption persists [16].

Hypertriglyceridemia-induced pancreatitis contributes to roughly 4–10% of cases worldwide, with higher incidence in individuals with uncontrolled diabetes, metabolic syndrome, or in pregnant women. Excess triglyceride hydrolysis by pancreatic lipase generates large quantities of free fatty acids that are highly toxic to acinar cells and vascular endothelium. These metabolites exacerbate ischemia and necrosis, often resulting in a more aggressive disease phenotype [17].

Alongside these principal causes, numerous less frequent but clinically relevant etiologies must be considered. Post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis remains a significant iatrogenic complication despite advances in prophylactic measures. Drug-induced pancreatitis, although rare, has been attributed to over 100 agents, including azathioprine, valproic acid, statins, and tetracyclines, with causality supported by case–control data and structured classification systems [18]. Additional contributors include metabolic or endocrine disorders (e.g., hypercalcemia, hyperparathyroidism), anatomical anomalies such as pancreas divisum or periampullary tumors, and genetic predispositions involving PRSS1, SPINK1, and CFTR variants. These mutations are particularly relevant in recurrent or early-onset disease. Even after comprehensive evaluation, 20–30% of AP cases are initially categorized as idiopathic, though advanced diagnostics frequently uncover microlithiasis, subtle structural abnormalities, or genetic factors [8].

From a clinical standpoint, identifying the underlying cause is crucial, as etiology directly influences recurrence risk, treatment strategies, and long-term prognosis. For instance, biliary pancreatitis carries a substantial risk of recurrence unless cholecystectomy is performed during the index admission, a practice strongly endorsed by current guidelines [11]. Alcohol-related disease has one of the highest recurrence rates and recurrent episodes are strongly linked to chronic pancreatitis with both endocrine and exocrine insufficiency, profoundly affecting quality of life [19]. Hypertriglyceridemia-related AP is particularly severe, with triglyceride levels above 1000 mg/dL on admission predicting necrosis and prolonged hospital stay [17]. Iatrogenic AP, such as post-ERCP pancreatitis, underscores the value of prophylactic measures including rectal NSAIDs and pancreatic duct stenting [20]. Genetic predisposition has deep-

ened understanding of recurrent and idiopathic AP, and genetic testing for PRSS1, SPINK1, and CFTR mutations can inform prognosis, guide counseling, and shape follow-up strategies [21].

The 2025 IAP consensus strongly advocates a structured etiological evaluation at the time of first admission. Universal transabdominal ultrasound is recommended, followed by selective MRCP or endoscopic ultrasound when initial studies are inconclusive. For recurrent or idiopathic cases, conditional genetic testing is advised, particularly in younger patients or those with a family history of pancreatic disease [4]. Importantly, idiopathic pancreatitis should be treated as a provisional diagnosis, prompting advanced evaluation to identify occult causes, since establishing etiology markedly reduces recurrence and improves outcomes [4].

In summary, while gallstones, alcohol, and hypertriglyceridemia explain most AP cases, recognition of less common etiologies remains essential. Each cause carries distinct therapeutic and prognostic implications. International guidelines therefore endorse a comprehensive diagnostic approach, integrating imaging, biochemical testing, and – when indicated – genetic analysis.

Pathophysiological Mechanisms

The development of acute pancreatitis begins within the acinar cell of the pancreas, where the balance of intracellular signaling and organelle function is disturbed. One of the earliest abnormalities is the inappropriate colocalization of zymogen granules with lysosomal hydrolases, which initiates premature intrapancreatic activation of trypsinogen. This event triggers a chain reaction of protease activation that rapidly overwhelms endogenous inhibitors such as pancreatic secretory trypsin inhibitor, leading to progressive acinar damage [9].

A central driver of this process is the disruption of calcium homeostasis [22] (Figure 1). Under physiological circumstances, acinar secretion depends on short-lived oscillations of cytosolic calcium. In pancreatitis, however, sustained calcium influx from extracellular sources and depletion of intracellular stores result in pathologic calcium over-

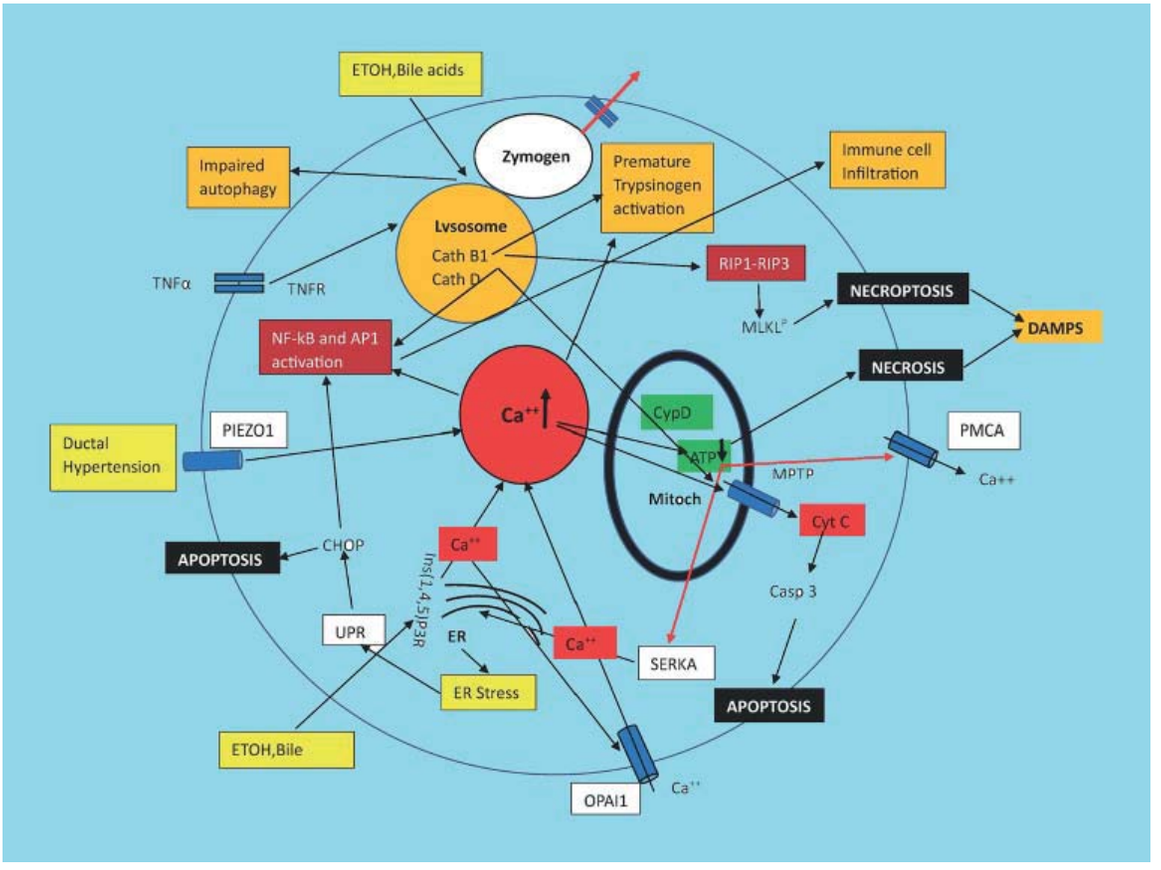

Fig. 1.
Schematic representation of the pathogenesis of PD.
Black arrows indicate activation, red arrows indicate inhibition.
ER – endoplasmic reticulum; MPTP – mitochondrial transitional permeability-transient pore; ATP – adenosine triphosphate; DAMPS – damage-associated molecular patterns; ETOH – alcohol; SERCA – smooth muscle calcium channels; PMCA – plasma membrane calcium channels; UPR – unfolded protein response.
Reproduced from: I. Tsomidis, A. Voumvouraki, E. Kouroumalis. The Pathogenesis of Pancreatitis and the Role of Autophagy. Gastroenterology Insights. 2024;15(2):303–41 [22]. © MDPI Basel, Switzerland.
Distributed under a Creative Commons Attribution License, CC BY 4.0).

load. Persistently elevated calcium concentrations open the mitochondrial permeability transition pore, collapse the mitochondrial membrane potential, and compromise ATP synthesis. The resulting energetic failure prevents cells from maintaining ionic gradients and protein-folding capacity, favoring necrotic rather than apoptotic death [23].

Defective autophagy adds to this pathological cascade. Normally, autophagy removes damaged organelles and aggregates of misfolded proteins, thereby preserving cellular integrity. In acute pancreatitis, this process is impaired, leading to the accumulation of autophagic vacuoles that become abnormal sites for trypsinogen activation. At the same time, unresolved stress within the endoplasmic reticulum provokes an unfolded protein response. When this response is prolonged or severe, adaptive signaling transitions into pro-apoptotic and necrotic pathways, further amplifying acinar destruction [22, 23] (Figure 1).

Taken together, premature enzyme activation, sustained calcium dysregulation with mitochondrial collapse, defective autophagy, and unresolved endoplasmic reticulum stress form the core mechanisms of acinar cell injury. These events are rapidly initiated following exposure to noxious stimuli such as gallstone obstruction, ethanol metabolites, or lipotoxic injury from elevated triglycerides, thereby establishing the basis for subsequent inflammatory amplification [15, 17].

Following acinar injury, a strong local inflammatory response is rapidly established. Activation of transcription factors such as NF-κB induces the expression of proinflammatory mediators including tumor necrosis factor-α, interleukins IL-1β, IL-6, and IL-8. These cytokines drive the recruitment of neutrophils and macrophages, thereby sustaining a self-amplifying cycle of inflammation [24]. At the same time, damaged acinar cells and their mitochondria release danger-associated molecular patterns (DAMPs) such as mitochondrial DNA, extracellular ATP, and HMGB1. These signals are recognized by innate immune receptors, including Toll-like and NOD-like receptors, which initiate inflammasome assembly, caspase-1 activation, and the maturation of IL-1β and IL-18. This pathway not only intensifies cytokine production but also promotes pyroptotic cell death, thereby amplifying the inflammatory cascade [22].

Neutrophils are key mediators of parenchymal injury. Upon infiltration, they release reactive oxygen species, proteolytic enzymes, and form neutrophil extracellular traps (NETs), all of which exacerbate necrosis and damage to the microvasculature. Macrophages exhibit a dual role depending on disease stage: they initially adopt a proinflammatory phenotype that fuels tissue injury, but later transition into a reparative state that facilitates clearance of necrotic debris and promotes resolution [10].

The microvascular compartment plays a pivotal role in linking local pancreatic injury with systemic disease progression. Inflammatory mediators disrupt endothelial integrity, increase vascular permeability, and promote leukocyte adhesion. These processes cause interstitial edema, reduced pancreatic perfusion, and expansion of necrosis. Oxidative stress, derived both from infiltrating immune cells and dysfunctional mitochondria, further aggravates endothelial dysfunction. Reactive oxygen species destabilize intercellular junctions, perpetuate vascular leakage, and drive additional inflammatory signaling [22, 25].

Clinically, the 2025 IAP guidelines emphasize that early systemic inflammatory response syndrome (SIRS), persistently elevated C-reactive protein at 48 hours, and rising interleukin-6 levels are among the most reliable early indicators of progression to severe disease. These biomarkers capture both the magnitude of local pancreatic injury and the degree of microvascular inflammation, making them valuable for early risk stratification and guiding treatment decisions [4].

As pancreatic inflammation escalates, mediators enter the systemic circulation and initiate a widespread inflammatory cascade. This transition is marked by a cytokine storm, characterized by endothelial activation, microthrombus formation, and diffuse capillary leakage. These systemic processes underlie the development of systemic inflammatory response syndrome (SIRS) and ultimately lead to multi-organ dysfunction, which is the major determinant of patient outcomes [26].

The systemic immune response is largely orchestrated through transcriptional activation of NF-κB and MAPK pathways within both pancreatic acinar cells and infiltrating leukocytes. This activation drives robust production of proinflammatory cytokines such as tumor necrosis factor-α, IL-1β, IL-6, IL-17, and multiple chemokines, thereby sustaining immune cell recruitment and prolonging inflammation [24].

Microcirculatory failure represents a critical step in the transition from local pancreatic injury to systemic disease. Disruption of endothelial barrier function, intravascular microthrombi, and impaired oxygen delivery create hypoxic regions not only within the pancreas but also in distant organs. Inflammatory mediators and reactive oxygen species exacerbate endothelial dysfunction, increase vascular permeability, and amplify leukocyte adhesion. These alterations compromise tissue perfusion in vital organs and establish a mechanistic link between pancreatic necrosis and systemic organ failure [22].

Oxidative stress further amplifies systemic involvement. Reactive oxygen species disrupt endothelial integrity, initiate lipid peroxidation, and impair mitochondrial function in extrapulmonary tissues. This redox imbalance accelerates vascular leakage, perpetuates inflammation, and drives

progression to multi-organ injury.

Different forms of regulated cell death (RCD) have emerged as central determinants of acute pancreatitis severity. Pyroptosis, mediated through NLRP3 inflammasome activation and caspase-1 cleavage, promotes the release of IL-1β and IL-18, thereby amplifying inflammation and fueling further immune cell recruitment [27]. Ferroptosis, an iron-dependent process characterized by uncontrolled lipid peroxidation, has been linked to severe and hyperlipidemia-associated pancreatitis; pharmacologic inhibition of this pathway reduces tissue necrosis and organ dysfunction in experimental models [28]. Defective autophagy accelerates these destructive processes, as impaired clearance of damaged mitochondria promotes oxidative stress and facilitates ferroptotic injury [29]. Together, these mechanisms establish a vicious cycle of acinar cell damage, inflammation, and organ failure.

The 2025 IAP guidelines recognize that regulated cell death pathways are not merely mechanistic phenomena but clinically relevant determinants of outcome. Biomarkers reflecting inflammasome activation, ferroptosis-related lipid metabolites, and autophagy dysfunction are highlighted as potential prognostic indicators and may inform early therapeutic decision-making. This recognition underscores the translational importance of incorporating RCD biology into clinical practice.

Beyond destructive processes, the clinical trajectory of acute pancreatitis is shaped by the host's ability to engage resolution programs. Normally, macrophages undergo a phenotypic shift from proinflammatory M1 states to anti-inflammatory M2 phenotypes, supporting clearance of necrotic material and tissue repair. Specialized pro-resolving mediators (SPMs) such as lipoxins, resolvins, and protectins further promote recovery by limiting neutrophil infiltration, restoring vascular barrier function, and facilitating regeneration. In severe disease, however, these resolution mechanisms are inadequately activated, prolonging systemic inflammation, sustaining organ dysfunction, and worsening prognosis [30, 31].

Accordingly, the 2025 IAP consensus reframes acute pancreatitis as more than a process of uncontrolled necrosis. It is a dynamic disorder shaped by the interplay of destructive RCD pathways and impaired resolution. Future therapeutic strategies are therefore envisioned to pursue a dual approach: inhibiting deleterious processes such as inflammasome activation and ferroptosis, while simultaneously enhancing pro-resolving pathways through macrophage reprogramming and supplementation with SPMs. Such interventions may shorten the inflammatory course, limit multi-organ involvement, and ultimately improve long-term outcomes [4].

In summary, the pathophysiology of acute pancreatitis represents a complex, multi-step cascade that begins with acinar cell injury and premature enzyme activation, progresses through calcium overload, mitochondrial dysfunction, impaired autophagy, and endoplasmic reticulum stress, and then expands into local and systemic inflammation. Once inflammatory mediators and DAMPs escape into the circulation, they drive widespread immune activation, endothelial dysfunction, and microcirculatory collapse, which set the stage for systemic inflammatory response syndrome and multi-organ dysfunction. Superimposed on these destructive processes are distinct forms of regulated cell death, including pyroptosis and ferroptosis, which further amplify tissue injury.

At the same time, the severity of disease is not determined solely by the intensity of injury, but also by the host's capacity to initiate resolution. Effective resolution requires timely macrophage reprogramming, clearance of necrotic material, and production of specialized pro-resolving mediators. When these pathways fail, inflammation persists, systemic damage accumulates, and clinical outcomes worsen.

Thus, acute pancreatitis should not be regarded merely as a localized necrotizing disorder but rather as a systemic disease arising from the dynamic interplay between intracellular stress, immune activation, regulated cell death, and impaired resolution. This integrated framework explains why some patients experience self-limiting disease while others progress to multi-organ dysfunction. It also provides the conceptual basis for future therapies, which must simultaneously restrain destructive cascades and reinforce endogenous resolution programs in order to shift the balance toward recovery [32].

Symptoms and Physical Findings

The clinical recognition of AP begins with a careful assessment of presenting complaints, as patient-reported history remains fundamental to diagnosis alongside biochemical and imaging investigations. In the Revised Atlanta Classification, abdominal pain consistent with pancreatitis is considered a mandatory diagnostic feature, but it must be accompanied by either elevated pancreatic enzyme levels or characteristic radiological findings [8].

Abdominal pain is nearly universal in AP. It usually arises abruptly, localizes to the epigastrium, and frequently radiates posteriorly toward the back. The pain is constant, severe, and often worsens after meals, particularly those rich in fat. Many patients describe transient relief when sitting upright or leaning forward, positions that reduce tension on the inflamed gland. Associated gastrointestinal symptoms such as nausea and vomiting are common and reflect visceral irritation caused by pancreatic inflammation [33].

Systemic manifestations vary depending on severity. In mild disease, they are generally limited to low-grade fever,

malaise, and anorexia. In contrast, severe cases are often accompanied by tachycardia, tachypnea, fever, and hypotension – features consistent with SIRS. When SIRS persists for more than 48 hours, it is strongly predictive of organ dysfunction and adverse outcomes [11, 12].

On physical examination, localized epigastric tenderness is the most typical finding and may be accompanied by abdominal wall guarding. Abdominal distension can arise from paralytic ileus, while bowel sounds are frequently reduced or absent. In advanced disease, diffuse tenderness with peritoneal signs may suggest complications such as necrosis or fluid collections [13].

Although uncommon, several distinctive but clinically meaningful physical signs have been described. Cullen's sign (periumbilical ecchymosis) and Grey Turner's sign (flank discoloration) result from subcutaneous tracking of blood-stained exudates from the retroperitoneum. These findings are rare, occurring in fewer than 3% of patients, and typically appear after 48–72 hours. Their presence correlates with necrotizing pancreatitis and increased mortality, serving more as indicators of severity than primary diagnostic markers [34].

Respiratory involvement represents the most frequent extra-abdominal manifestation, particularly in severe AP. Tachypnea, hypoxemia, and basal crackles may reflect diaphragmatic irritation, systemic inflammatory injury, or the development of acute lung injury. Pleural effusions, usually left-sided, are the most common thoracic complication. They correlate with severity indices such as BISAP and APACHE II, and meta-analyses have shown that their presence significantly increases the risk of organ failure and death [35]. A multicenter study further demonstrated that the volume of pleural effusion quantified by CT independently predicts severity, intensive care unit admission, and prolonged hospitalization [36].

Jaundice and scleral icterus can occur in biliary pancreatitis, typically due to gallstone obstruction of the distal common bile duct. In this setting, jaundice should prompt evaluation for cholangitis or persistent obstruction, as timely biliary intervention may be required. Thus, jaundice functions both as a diagnostic clue and as a therapeutic signal [37].

Other systemic manifestations are largely driven by the inflammatory and hemodynamic burden of AP. Fever, tachycardia, and hypotension often appear within the first 48 hours. Prolonged hypotension suggests significant third-space fluid loss and capillary leakage, while confusion or agitation may reflect hypoxemia or developing encephalopathy. Clinical examination may also reveal dehydration, with signs such as dry mucous membranes and reduced skin turgor. Collectively, these findings contribute to early bedside risk stratification. Persistent SIRS beyond 48 hours remains one of the most reliable indicators of progression to severe disease and multi-organ dysfunction [14].

Although physical signs are rarely diagnostic in isolation, they retain important prognostic relevance. The Bedside Index for Severity in Acute Pancreatitis (BISAP) incorporates systemic parameters such as SIRS and altered mental status, along with radiological evidence of pleural effusion, into a five-point score. Large population studies consistently validate BISAP as a robust early predictor of severity and mortality [38, 39].

The 2025 IAP guidelines reaffirm that careful evaluation of presenting symptoms and bedside examination are indispensable not only for diagnosis but also for early prognostication. They recommend systematic assessment of pain intensity, systemic inflammatory features, and extra-abdominal signs such as pleural effusion or jaundice, emphasizing that these should be integrated with laboratory and imaging data into structured severity scoring systems like BISAP or the modified Marshall score. This approach informs fluid resuscitation strategies, monitoring intensity, and decisions regarding referral to specialized centers [4].

In conclusion, the clinical picture of AP is dominated by sudden, severe epigastric pain, often radiating to the back and accompanied by nausea and vomiting. Physical examination commonly reveals localized tenderness, distension, and diminished bowel sounds, while systemic signs may include fever, tachycardia, and hypotension. Rare cutaneous markers such as Cullen's and Grey Turner's signs denote severe disease, whereas respiratory complications – particularly pleural effusions – are of strong prognostic value. The appearance of jaundice indicates a biliary etiology and the need for targeted intervention. While no single sign suffices for diagnosis, the constellation of symptoms and examination findings provides essential information for diagnosis, risk stratification, and clinical decision-making, an approach now firmly embedded in the 2025 IAP consensus [4].

Laboratory Markers

Serum pancreatic enzymes remain the biochemical cornerstone of diagnosing acute pancreatitis. Among these, serum lipase is the preferred test due to its higher specificity, longer duration of elevation, and diagnostic reliability in situations where amylase may be normal, such as alcohol- or hypertriglyceridemia-associated disease. Both the 2024 ACG guideline and contemporary international consensus identify lipase as the single most important biochemical marker while advising against repeated enzyme measurements once the diagnosis is established, as serial values provide no prognostic or therapeutic guidance [4, 11]. Lipase levels usually increase within 4–8 hours after symptom onset, peak within 24 hours, and can remain elevated for one to two weeks, thus outperforming amylase, which may be either normal or nonspecifically elevated in sever-

al other conditions.

Because the early phase of acute pancreatitis is highly dynamic, simple laboratory tests obtained within the first 24–48 hours are invaluable for risk stratification and fluid management. Among these, blood urea nitrogen (BUN) has consistently emerged as one of the most reliable predictors of mortality. A rising BUN reflects intravascular volume depletion, third-space losses, and renal hypoperfusion. Frequent measurement, ideally every 6–12 hours during the initial resuscitation period, is recommended to monitor adequacy of fluid replacement [11]. The 2025 IAP consensus emphasizes admission BUN and its trajectory as practical and widely applicable indicators of severity across healthcare settings [4].

Hematocrit (Hct) at admission, and especially failure of Hct to decline with resuscitation, signals hemoconcentration and correlates with an increased likelihood of necrosis and organ dysfunction. Persistent Hct values of 44% or higher after fluid therapy should prompt reassessment of fluid adequacy and careful monitoring for evolving complications. Hypocalcemia, which usually develops in severe disease due to fat saponification and tissue necrosis, should be recognized as a marker of severity rather than an etiological factor [4, 11].

C-reactive protein (CRP) remains the most validated single inflammatory biomarker in acute pancreatitis. Concentrations above 150 mg/L at approximately 48 hours after onset have long been associated with necrotizing or severe disease, supporting its role in early risk stratification when interpreted in conjunction with clinical severity scores [40]. This application is fully supported by international consensus [4].

Interleukin-6 (IL-6) rises earlier than CRP, often within hours of symptom onset, and has shown promise as an early predictor of severe outcomes. Comparative analyses suggest that IL-6 may outperform CRP in identifying patients at risk for infected necrosis and mortality, although the lack of standardized thresholds has limited its widespread adoption [41]. Current international guidelines recognize IL-6 as a valuable adjunct where available but not as a substitute for established markers [4].

Procalcitonin (PCT) serves as a robust indicator of bacterial infection and is particularly helpful in guiding antibiotic use in uncertain cases. In the PROCAP randomized trial, PCT-guided protocols significantly reduced unnecessary antibiotic exposure without compromising patient safety, supporting its selective application when infection is suspected but unconfirmed [42]. International consensus therefore positions PCT as a decision-support tool rather than a routine test [4].

Complete blood count–derived ratios such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) provide inexpensive surrogates of systemic inflammation. These indices have been linked to severe disease at admission in multiple studies [43, 44]. However, because of variability across patient populations, such ratios are best regarded as supplementary tools rather than replacements for established markers such as CRP, BUN, or hematocrit [4].

Beyond the conventional diagnostic and prognostic markers, several novel biomarkers provide additional insight into the pathobiology of acute pancreatitis. These are not yet routine but may augment clinical assessment in selected patients or research settings.

Urinary trypsinogen-2 (UT-2) rapid dipstick testing offers a simple bedside method with high specificity for early diagnosis, particularly when venipuncture is challenging, such as in pediatric cases. Trypsinogen activation peptide (TAP), released during the activation of trypsinogen, reflects intrapancreatic protease activity. Both urinary and plasma TAP levels have been shown in multicenter studies to correlate with early severity, thus offering prognostic information at a stage when clinical decisions are most critical [45, 46]. Although promising, these tests remain limited by availability and a lack of standardized use protocols [4].

At presentation, laboratory evaluation should simultaneously establish the diagnosis, define etiology, and provide early indicators of severity to guide fluid therapy. A recommended panel includes serum lipase (with or without amylase, depending on institutional practice), electrolytes with calcium, a comprehensive liver panel (ALT, AST, alkaline phosphatase, bilirubin), fasting triglycerides, complete blood count with hematocrit and leukocyte indices, and BUN/creatinine to assess renal perfusion and third spacing [11]. An ALT level ≥150 IU/L early in the disease course, particularly in conjunction with other cholestatic abnormalities, strongly suggests a biliary etiology and warrants urgent right upper quadrant ultrasound. In cases complicated by cholangitis, early ERCP is indicated [4, 37].

Novel biomarkers capturing different biological pathways have shown potential to refine risk stratification. Angiopoietin-2 (Ang-2) correlates with vascular injury and predicts early organ failure [47]. The Endothelial Activation and Stress Index (EASIX), calculated from LDH, platelet count, and creatinine, has been associated with ICU outcomes in retrospective analyses of AP cohorts [48]. Circulating syndecan-1 (SDC-1), reflecting endothelial glycocalyx shedding, rises in severe disease but loses independent prognostic value once adjusted for fluid status and APACHE II scores [49]. Nevertheless, glycocalyx disruption is increasingly recognized as central to microcirculatory dysfunction in AP and may represent a therapeutic target [50].

Biomarkers of cellular stress and innate immune activation are also under investigation. Serum HMGB1, in-

creased expression of NF-κB, and elevated IL-17 have all been linked to poor outcomes in prospective studies [51]. Circulating mitochondrial DNA (mtDNA), quantified by digital PCR, correlates with leukocytosis, CRP, PCT, and overall disease severity [52]. Histones, released during cell death, are highly cytotoxic and have been associated with persistent organ failure and mortality [53].

Pancreatic stone protein (PSP/reg) rises early and has shown good predictive accuracy for severe disease, supporting its potential use in triage [54]. YKL-40 (CHI3L1) and chitotriosidase, both markers of inflammatory activity, are elevated in acute pancreatitis but remain supplementary rather than primary tools [55]. Lower baseline zonulin levels have been linked with complicated trajectories, although the marker is not reliable for initial grading [56]. Intestinal fatty acid–binding protein (I-FABP), reflecting enterocyte damage, has prognostic utility in critical illness and intra-abdominal hypertension, with early data suggesting potential value in pancreatitis [57].

More broadly available tests can also assist in severity assessment. Elevated D-dimer at admission is strongly associated with necrosis, organ failure, and mortality, providing an accessible adjunct marker [58].

Taken together, these emerging biomarkers expand the granularity of early prognostication by capturing distinct biological processes including zymogen activation, vascular dysfunction, immune dysregulation, and cellular injury. While they are not yet recommended for routine clinical use, they represent valuable research tools and may complement established tests in complex cases. International consensus continues to emphasize that lipase, BUN, hematocrit, CRP/IL-6, and PCT remain the foundation of laboratory assessment, with novel markers best applied in conjunction with, rather than in place of, these validated measures [4].

Imaging Modalities

Imaging plays a central role across the entire clinical trajectory of acute pancreatitis, extending beyond diagnosis to include the identification of etiology, grading of severity, detection of local and systemic complications, and guidance of therapeutic interventions. Current international consensus emphasizes that imaging should be selectively employed according to the clinical context and diagnostic objectives, rather than performed routinely or sequentially. The revised Atlanta classification remains the international standard for defining local complications and severity patterns, ensuring consistency across imaging studies and clinical communication [8]. The 2025 IAP guidelines reaffirm this approach, stressing that imaging must be indication-driven and tailored to each disease phase [4].

For etiological evaluation, transabdominal ultrasound is the recommended first-line modality. Its principal role is the detection of gallstones or biliary sludge, which remain among the most common triggers of pancreatitis [59] (Figure 2). When ultrasound results are inconclusive in ruling in or excluding choledocholithiasis, escalation to endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) is preferred over diagnostic ERCP (Figure 3). This algorithm minimizes the risks of unnecessary endoscopic manipulation while maintaining diagnostic accuracy. Comparative studies and meta-analyses indicate that EUS provides slightly greater sensitivity for detecting microlithiasis and very small common bile duct stones, whereas MRCP offers a broader, non-invasive overview of the pancreatobiliary system [60]. The decision between these modalities is influenced by patient suitability, institutional expertise, and whether therapeutic intervention is anticipated [4].

The structured diagnostic pathway recommended by the IAP 2025 consensus is particularly relevant for idiopathic pancreatitis. It advocates repeat ultrasound after discharge to detect microlithiasis missed during initial imaging, followed by EUS for its high sensitivity, and MRCP for anatomical clarification if the etiology remains elusive. In younger patients or those with recurrent idiopathic episodes, genetic testing is advised to investigate possible hereditary predispositions [4]. This tiered strategy underscores the principle that microlithiasis, biliary sludge, and subtle ductal anomalies must be systematically excluded before labeling pancreatitis as truly idiopathic.

While ultrasound and MRCP are fundamental in the initial etiological assessment, contrast-enhanced computed to-

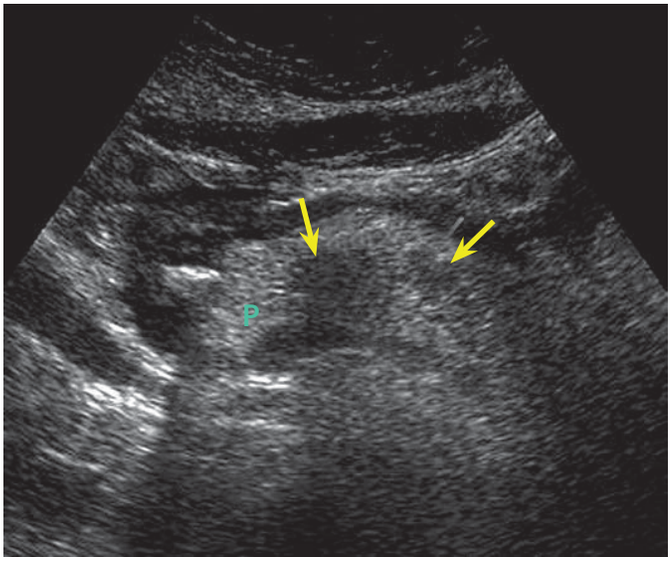

Figure 2.
Interstitial edematous pancreatitis (US) ([59] Reproduced from Türkvatan A, Erden A, Türkoğlu MA, Seçil M, Yener Ö. Imaging of acute pancreatitis and its complications. Part 1: acute pancreatitis. Diagn Interv Imaging. 2015 Feb;96(2):151-160. doi: 10.1016/j.diii.2013.12.017. © Elsevier. Distributed under the Creative Commons Attribution License, CC BY 4.0)

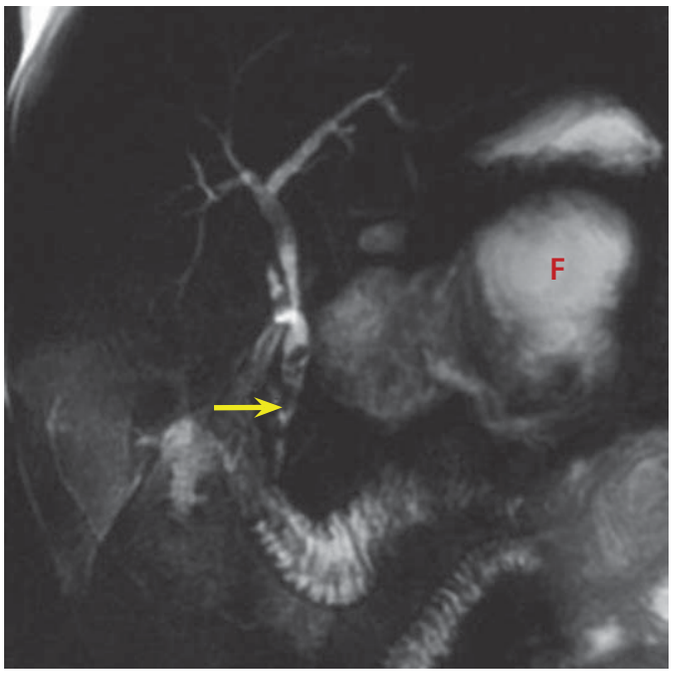

Figure 3.
Acute pancreatitis pancreatitis. MRCP sequence image reveals multiple signal-void stones surrounded by high signal intensity bile in common bile duct (arrow).
A large multiloculated fluid collection (F) is also seen ([59] Reproduced from Türkvatan A, Erden A, Türkoğlu MA, Seçil M, Yener Ö. Imaging of acute pancreatitis and its complications. Part 1: acute pancreatitis. Diagn Interv Imaging. 2015 Feb;96(2):151-160. doi: 10.1016/j.diii.2013.12.017. © Elsevier. Distributed under the Creative Commons Attribution License, CC BY 4.0).

mography (CECT) remains the reference imaging modality for evaluating complications and guiding interventions [61, 62] (Figures 4-6). CECT reliably identifies pancreatic and peripancreatic necrosis, acute necrotic collections, walled-off necrosis, vascular complications such as venous thrombosis or pseudoaneurysm, and provides the anatomical detail required for interventional planning. Importantly, performing CT within the first 48 hours of symptom onset is discouraged, as necrotic changes evolve over time and early scans may underestimate disease severity. Consistent with the IAP 2025 recommendations and in alignment with the American College of Radiology (ACR) Appropriateness Criteria and WSES 2019 guidelines, CECT should be reserved for cases with uncertain diagnosis, clinical deterioration, or lack of improvement despite optimal therapy, with optimal staging performed at 72–96 hours after onset [4, 12, 63].

For the assessment of severity, contrast-enhanced CT is frequently interpreted using structured scoring systems. The classical Balthazar CT Severity Index (CTSI) (Figure 7) combines morphological grading of pancreatic and peripancreatic changes with the extent of necrosis, while the Modified CT Severity Index (MCTSI) extends this framework by incorporating extra-pancreatic complications such as pleural effusion and ascites. Comparative studies have consistently shown that MCTSI correlates more strongly with clinical outcomes than the original CTSI [64–66].

Although these indices remain valuable for research purposes and standardized radiological reporting, the IAP 2025 guidelines emphasize that persistent organ failure beyond 48 hours continues to be the single most important determinant of prognosis. Imaging scores should therefore complement, rather than replace, clinical and biochemical as-

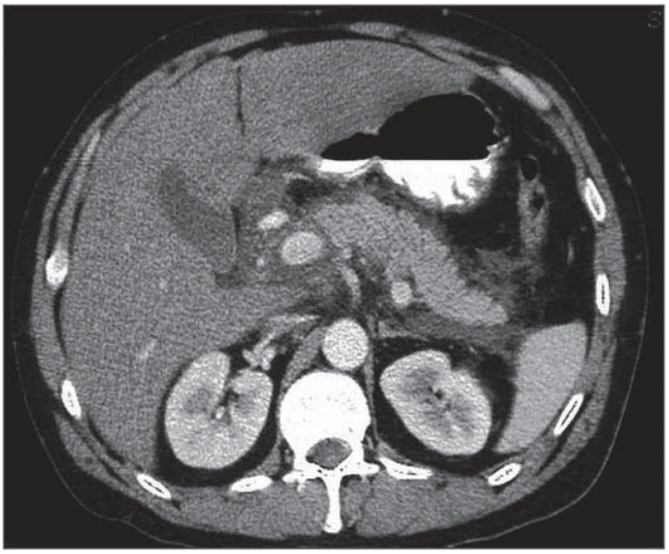

Figure 4.
Contrast-enhanced computed tomography showing interstitial acute pancreatitis ([61] Reproduced from Marino D, Saini J, Tenner S. Management of Acute Pancreatitis. Am J Gastroenterol. 2025 Jan 1;120(1):2-4. doi: 10.14309/ajg.0000000000003180. © Wolters Kluwer Health, Inc. Distributed under the Creative Commons Attribution License, CC BY 4.0)

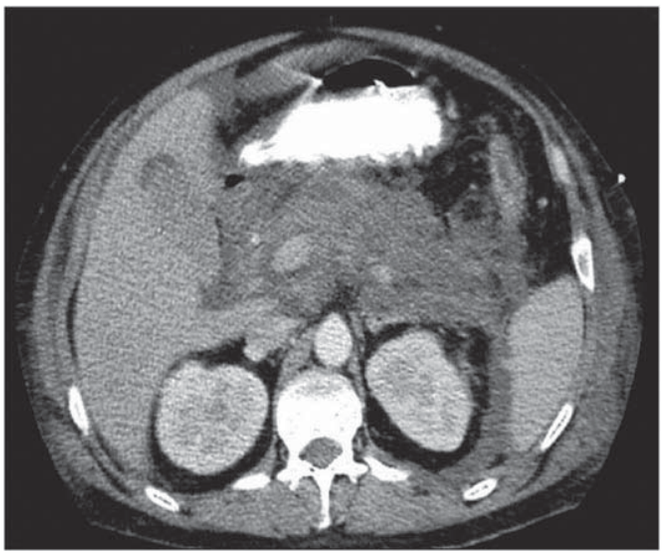

Figure 5.
Contrast-enhanced computed tomography showing pancreatic necrosis ([61] Reproduced from Marino D, Saini J, Tenner S. Management of Acute Pancreatitis. Am J Gastroenterol. 2025 Jan 1;120(1):2-4. doi: 10.14309/ajg.0000000000003180. © Wolters Kluwer Health, Inc. Distributed under the Creative Commons Attribution License, CC BY 4.0)

sessments [4]. Nonetheless, MCTSI is widely employed in both clinical trials and daily practice due to its reproducibility and prognostic accuracy.

Optimization of CT protocols is crucial to ensure diagnostic precision and minimize patient risk. Multidetector CT with thin collimation (≤2 mm) enables high-resolution multiplanar reconstructions, enhancing visualization of both pancreatic and peripancreatic structures. Intravenous contrast is typically administered as 100–150 mL of non-ionic iodinated agent at 3 mL/s, with image acquisition during pancreatic and portal venous phases. This dual-phase approach provides optimal delineation of parenchymal necrosis, peripancreatic extensions, and vascular complications. In the context of follow-up imaging for fluid-predominant collections, however, a single portal venous phase is generally sufficient, thereby reducing cumulative radiation and contrast exposure. Arterial-phase imaging or CT angiography is reserved for suspected vascular complications such as pseudoaneurysm or active hemorrhage [4].

Repeat CT examinations should not be scheduled at fixed intervals but instead guided by clinical evolution. Indications for repeat imaging include unexplained deterioration, persistent or worsening organ dysfunction, rising inflammatory or sepsis markers, or preparation for intervention. This strategy ensures efficient resource utilization while limiting unnecessary radiation and contrast-related nephrotoxicity.

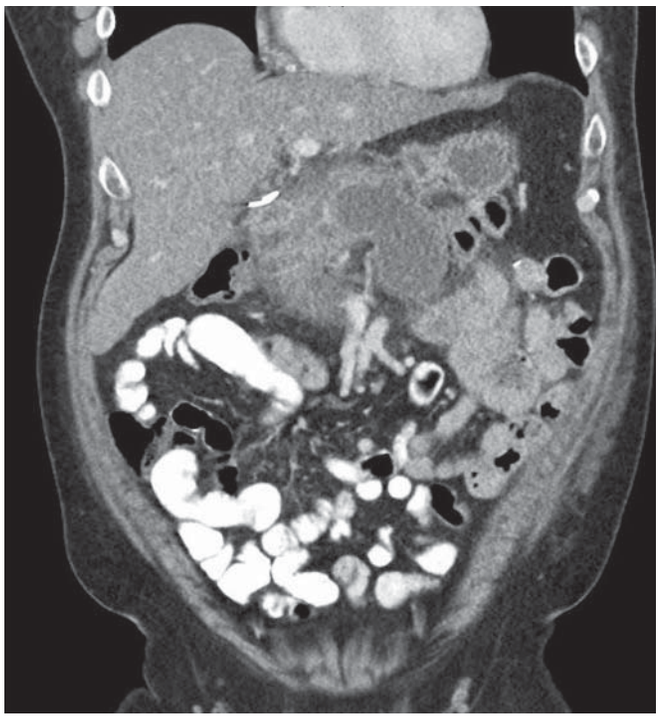

Figure 6.
Pancreatitis with CT showing walled-off necrosis. ([62] Reproduced from Mittal N, Oza VM, Muniraj T, Kothari TH. Diagnosis and Management of Acute Pancreatitis. Diagnostics (Basel). 2025 Jan 23;15(3):258. doi: 10.3390/diagnostics15030258. © MDPI (Basel, Switzerland). Distributed under the Creative Commons Attribution License, CC BY 4.0)

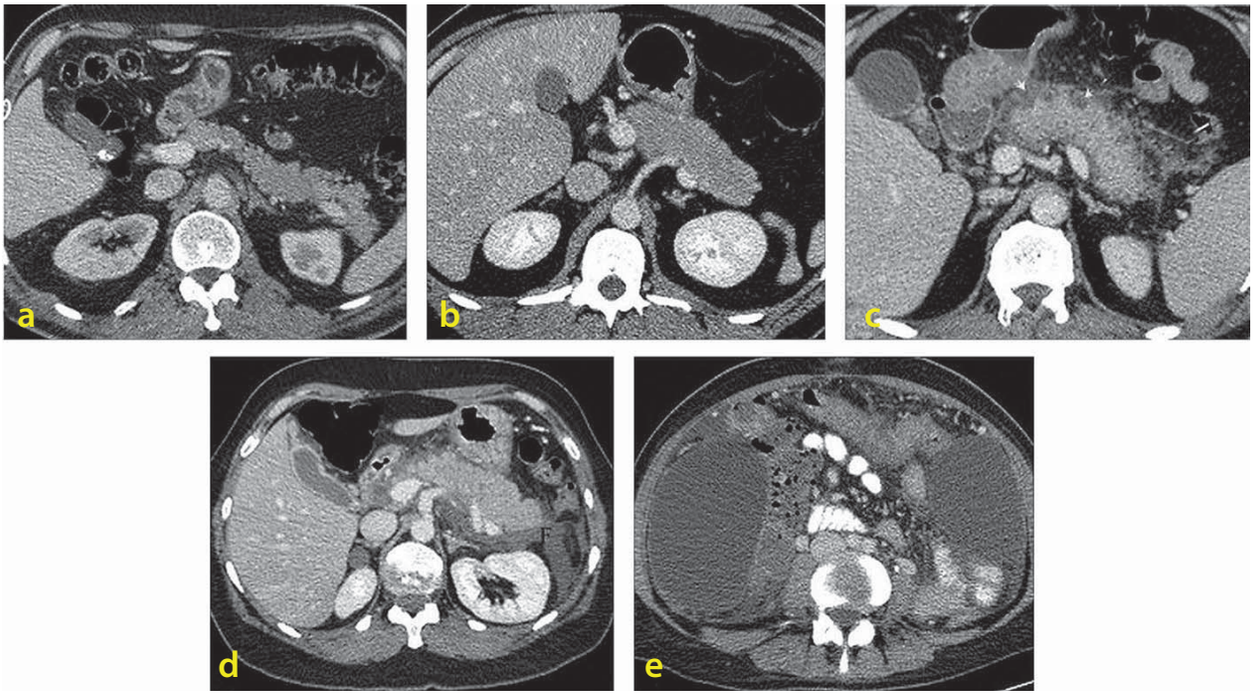

Figure 7.
Balthazar CT scoring system. a: grade A: normal pancreas; b: grade B: pancreatic enlargement; c: grade C: pancreatic and peripancreatic fat inflammation (long arrow) [small superficial necrotic areas (small arrows) are also seen]; d: grade D: single peripancreatic fluid collection (F); e: grade E: two fluid collections (F) ([59]
Reproduced from Türkvatan A, Erden A, Türkoğlu MA, Seçil M, Yener Ö. Imaging of acute pancreatitis and its complications. Part 1: acute pancreatitis. Diagn Interv Imaging. 2015 Feb;96(2):151-160. doi: 10.1016/j.diii.2013.12.017. © Elsevier. Distributed under the Creative Commons Attribution License, CC BY 4.0)

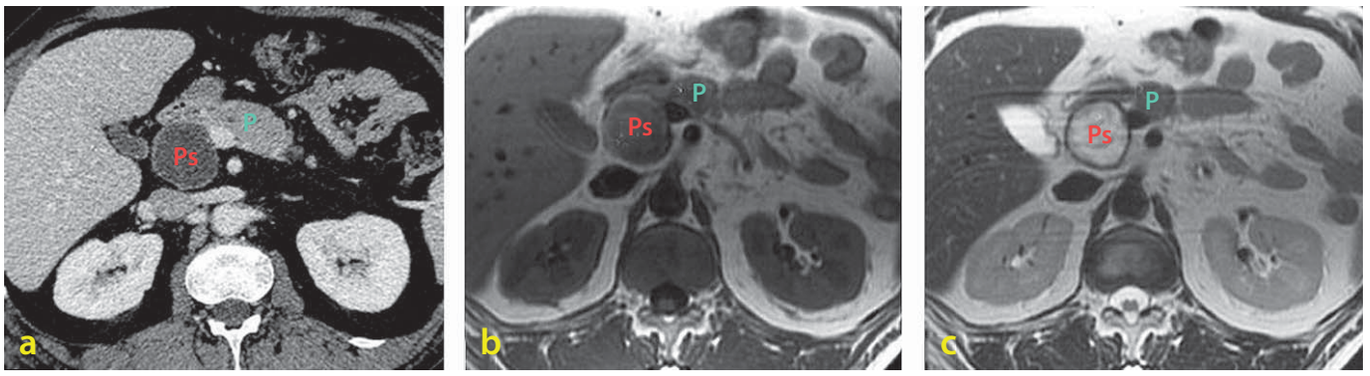

Figure 8.
Pancreatic pseudocyst (Ps) in acute pancreatitis. Axial CT (a), T1-weighted (b) and T2-weighted (c) MR images, obtained 6 weeks after the onset of acute attack, reveals a well defined, homogenous fluid collection (Ps) with a fibrous capsule (P: pancreas) ([59] Reproduced from Türkvatan A, Erden A, Türkoğlu MA, Seçil M, Yener Ö. Imaging of acute pancreatitis and its complications. Part 1: acute pancreatitis. Diagn Interv Imaging. 2015 Feb;96(2):151-160. doi: 10.1016/j.diii.2013.12.017. © Elsevier. Distributed under the Creative Commons Attribution License, CC BY 4.0)

Magnetic resonance imaging (MRI) has emerged as a highly valuable complement to CT in the evaluation of acute pancreatitis (Figure 8). Its superior soft-tissue contrast, radiation-free nature, and ability to characterize fluid collections make it particularly advantageous in patients with renal impairment, iodinated contrast allergy, or younger age. MRI is especially effective in distinguishing pseudocysts from walled-off necrosis and in demonstrating internal debris, information that significantly influences prognosis and intervention planning. Furthermore, MRI is highly sensitive in detecting subtle parenchymal and ductal abnormalities that may be underestimated by CT [4]. Magnetic resonance cholangiopancreatography (MRCP) further extends the diagnostic role of MRI, providing accurate and non-invasive visualization of the pancreatobiliary tree. The IAP 2025 guidelines highlight MRCP as a crucial tool in biliary pancreatitis and in suspected ductal anomalies, with secretin-enhanced MRCP offering additional detail on main pancreatic duct continuity and side branches, essential for evaluating conditions such as disconnected pancreatic duct syndrome or recurrent idiopathic disease [4].

Within a tiered diagnostic strategy, MRI and MRCP serve as critical complements to CT, particularly in cases of idiopathic or recurrent disease where detailed anatomical clarification is required before proceeding to endoscopic or genetic evaluation. In advanced centers, pairing EUS with MRCP ensures both high sensitivity for biliary microlithiasis and comprehensive mapping of ductal anatomy, thereby refining patient selection for therapeutic intervention [4].

Beyond CT and MRI, contrast-enhanced ultrasound (CEUS) has gained attention as a supportive modality. By allowing real-time visualization of microvascular perfusion, CEUS differentiates viable pancreatic tissue from necrotic areas and provides rapid bedside assessment in critically ill patients when cross-sectional imaging is not immediately available. CEUS may also help detect vascular complications, such as splanchnic vein thrombosis, or distinguish between inflammatory and ischemic changes within pancreatic and peripancreatic tissues [4]. However, its diagnostic value is limited by operator dependence and inconsistent global availability. Consequently, the IAP 2025 guidelines do not recommend CEUS as a substitute for CT or MRI but acknowledge its role as a complementary tool in specialized centers.

Similarly, Doppler ultrasound contributes hemodynamic information in suspected vascular complications such as portal, splenic, or superior mesenteric vein thrombosis. While Doppler can reveal altered flow dynamics and intraluminal thrombi, confirmatory cross-sectional imaging with CT or MRI is typically required for accurate staging and treatment planning. In clinical practice, Doppler serves as a useful screening tool, with positive findings prompting more definitive imaging [4].

The IAP 2025 guidelines highlight the importance of aligning imaging with disease phase. In the early phase (first week), diagnosis should rely primarily on clinical and biochemical findings, supplemented by transabdominal ultrasound for etiological assessment, particularly gallstones or biliary sludge. Routine CT during this period is discouraged, as necrotic changes are not yet fully established and early imaging risks underestimating severity. CECT should therefore be reserved for patients with uncertain diagnosis, unexplained clinical deterioration, or failure to improve despite optimal therapy. If biliary obstruction is suspected without cholangitis, EUS or MRCP should be used to confirm choledocholithiasis before ERCP, thereby reducing unnecessary endoscopic interventions [4].

In the late phase (beyond one week), cross-sectional imaging with CECT or MRI becomes central to defining the extent of necrosis, characterizing collections such as pseudocysts and walled-off necrosis, and planning minimally invasive interventions. CT angiography is indicated when ar-

terial pseudoaneurysm or hemorrhage is suspected, as vascular findings directly determine whether endovascular or surgical management is appropriate. In addition, MRI with secretin-enhanced MRCP is recommended when ductal disruption or disconnected pancreatic duct syndrome is suspected, ensuring precise mapping before drainage procedures are attempted [4].

Repeat imaging should never follow rigid schedules but rather be dictated by clinical necessity. Indications include unexpected clinical deterioration, persistence or worsening of organ dysfunction, rising inflammatory or septic markers, or the need for pre-procedural planning. For patients with fluid-predominant collections who remain otherwise stable, a single portal venous phase CT is often adequate, minimizing radiation and contrast exposure. When additional tissue characterization is needed, MRI offers further advantages by distinguishing pseudocysts from walled-off necrosis and identifying solid debris that influences drainage strategies [63, 67]. This patient-centered, milestone-driven approach ensures that imaging contributes directly to decision-making rather than functioning as a routine checkpoint.

Beyond diagnosis and staging, imaging has become indispensable in guiding therapeutic interventions. Multiphase CECT defines the extent and distribution of necrosis, the maturity of collections, and their anatomical relationship to surrounding structures, thereby providing the roadmap for percutaneous or endoscopic drainage. It is also essential for diagnosing disconnected pancreatic duct syndrome, with CT or secretin-enhanced MRCP delineating ductal continuity before long-term drainage or surgical strategies are implemented [4].

The step-up approach to infected necrosis, endorsed by the IAP 2025 guidelines, illustrates the therapeutic value of imaging. Initial management emphasizes antibiotics and optimized nutritional support, with image-guided drainage as the next step if infection is confirmed or highly suspected. Only when drainage fails to achieve control should minimally invasive necrosectomy be pursued. Imaging determines both the optimal timing – typically after 3–4 weeks, once collections are partially encapsulated – and the route of intervention, whether percutaneous retroperitoneal, endoscopic transluminal with lumen-apposing stents, or less commonly transgastric surgical approaches [4].

Vascular complications are another domain where imaging directly shapes management. CT angiography is crucial for detecting arterial pseudoaneurysms and active hemorrhage, conditions associated with significant mortality risk. Imaging not only confirms the complication but dictates therapy, with endovascular embolization preferred as first-line treatment and surgery reserved for refractory cases. Similarly, CECT provides the standard evaluation for splanchnic venous thrombosis, with findings guiding anticoagulation decisions depending on whether the portal, mesenteric, or splenic veins are involved [64–67].

Additional complications, including gastrointestinal fistulas, are also best evaluated radiologically. While many upper gastrointestinal fistulas can be managed conservatively, persistent sepsis or evidence of contamination may necessitate surgery, and the decision depends heavily on imaging evidence of fistula anatomy and associated collections.

Overall, imaging in acute pancreatitis has shifted from a purely diagnostic adjunct to a therapeutic compass. CT remains the cornerstone for staging and procedural planning, while MRI and MRCP provide unique problem-solving capacity in complex or recurrent cases. The IAP 2025 guidelines highlight three specific clinical scenarios where MRI/MRCP is particularly decisive: confirmation of disconnected pancreatic duct syndrome, investigation of recurrent idiopathic pancreatitis after negative standard work-up, and characterization of heterogeneous collections with significant solid debris that influence drainage modality selection. Across all phases, imaging must be aligned with clinical milestones rather than fixed schedules, serving as an adaptive decision-making tool.

Thus, modern imaging practice in acute pancreatitis integrates diagnostic accuracy with therapeutic planning, ensuring that radiological insights directly inform the step-up approach to necrotizing pancreatitis, vascular risk stratification, and procedural selection. This dynamic, guideline-driven strategy transforms imaging into a cornerstone of precision care in acute pancreatitis, aligning technology with patient-specific trajectories and optimizing outcomes [4].

Thus, imaging in AP has evolved from a purely diagnostic exercise into a therapeutic compass, aligning radiological insights with evidence-based clinical pathways and ensuring that patient care is both timely and targeted (Table 1).

Severity Scoring Systems

Acute pancreatitis presents with striking variability, ranging from self-limited inflammation to fulminant disease with persistent organ failure, infected necrosis, and high mortality. This heterogeneity has long motivated the development of severity scoring systems designed to identify patients at greatest risk of adverse outcomes as early and accurately as possible. The revised Atlanta classification of 2012 remains the global benchmark, dividing the disease into three categories: mild pancreatitis, defined by the absence of organ failure or complications; moderately severe disease, characterized by transient organ failure or the presence of local or systemic complications; and severe disease, defined as persistent organ failure lasting longer than 48 hours [8]. This tripartite scheme continues to underpin both bedside management and the validation of prognostic scores. The most recent IAP 2025 consensus reaffirmed the Atlanta framework but stressed the importance of inte-

grating early scoring with dynamic monitoring of systemic inflammation and organ dysfunction to achieve the most accurate risk stratification [4].

The earliest predictive models included the Ranson criteria, developed in the 1970s, and the Glasgow–Imrie score, widely used in the United Kingdom. Both systems incorporated a mixture of biochemical and clinical variables collected at presentation and again at 48 hours [68, 69]. While historically influential and still frequently cited, their clinical usefulness is limited by the reliance on 48-hour data, which restricts their ability to guide immediate triage and early management decisions.

The APACHE II score, adapted from intensive care medicine, represented an important advance by allowing continuous risk assessment from the time of admission onward. Validation studies confirmed that APACHE II surpassed Ranson and Glasgow in predicting mortality [70, 71]. Its main advantages are real-time recalculation and broad applicability, though it is labor-intensive and not pancreas-specific. Parallel to this, organ dysfunction-based systems such as the Marshall score gained prominence and were later incorporated into the revised Atlanta classification, establishing persistent organ failure as the reference definition of severe pancreatitis [72].

A major step forward in early triage was the development of the Bedside Index for Severity in Acute Pancreatitis (BISAP). This five-point score incorporates blood urea nitrogen above 25 mg/dL, altered mental status, systemic inflammatory response syndrome (SIRS), age greater than 60 years, and the presence of pleural effusion. Risk of death rises progressively with higher scores, reaching over 20% when all five variables are present [38]. Its accuracy has been repeatedly confirmed in prospective cohorts [39], and meta-analyses have validated its predictive value for mortality and severe outcomes [73]. Because of its simplicity, reproducibility, and reliance on readily available admission data, the WSES 2019 guidelines endorsed BISAP as a pragmatic tool for early triage [12].

In contrast, the Harmless Acute Pancreatitis Score (HAPS) was designed to identify patients at minimal risk of complications. It requires only three admission variables: absence of peritonism, normal hematocrit, and preserved renal function. When all criteria are met, patients are very unlikely to develop severe disease, making the score especially useful in emergency or resource-limited settings [74]. The IAP 2025 guidelines recommend BISAP as the preferred admission tool for early risk stratification and HAPS as a reliable method for ruling out severe disease, highlighting their complementary value within the first 24 hours [4].

Radiology-based systems offer another perspective on severity, particularly for local complications. The original CT Severity Index (CTSI), introduced by Balthazar, combined radiological grades of pancreatic inflammation with the extent of necrosis seen on contrast-enhanced CT [64]. Mortelé and colleagues later refined this system into the modified CTSI (mCTSI), simplifying necrosis assessment and incorporating extra-pancreatic complications such as ascites and pleural effusion. Comparative studies demonstrated that the mCTSI correlates more strongly with morbidity, intensive care requirements, and length of hospitalization than the original score [65, 66].

A 2019 meta-analysis confirmed that CT-based indices are effective in predicting local complications but are less reliable in forecasting mortality compared with clinical scores [75]. Reflecting this evidence, the IAP 2025 guidelines recommend delaying CT-based scoring until at least 72 hours after onset, limiting its use to characterizing necrosis and informing interventional planning, rather than as a tool for early triage [4].

Recognition of systemic inflammation as a central driver of disease severity has placed particular emphasis on the role of SIRS. When systemic inflammatory response persists for more than 48 hours, the risk of organ failure and mortality rises substantially [76]. This concept directly informed the construction of the BISAP score and the incorporation of the modified Marshall organ dysfunction score into the revised Atlanta classification, reinforcing their role as essential tools for severity assessment.

An additional step in refinement was the determinant-based classification, proposed by an international multidisciplinary panel [77]. This model identified two critical factors that determine prognosis: persistent organ failure and infected pancreatic necrosis. The coexistence of both defines so-called “critical” pancreatitis, the subgroup associated with the highest mortality. The IAP 2025 guidelines incorporate this determinant-based perspective into their framework, while reaffirming persistent organ failure as the single strongest predictor of outcome [4].

In modern practice, no scoring system is universally superior across all clinical endpoints. Historical systems such as Ranson and Glasgow remain of educational importance but are rarely used in daily management. APACHE II allows continuous monitoring but is resource-intensive and not specific to pancreatitis. BISAP has emerged as the most practical and widely recommended early risk stratification tool, while HAPS remains useful as a rapid exclusion tool in low-risk patients. CT-based indices provide valuable information on necrosis and complications but are inappropriate for early prognostication. SIRS and Marshall scores remain fundamental, forming the backbone of both the Atlanta and determinant-based classifications. The IAP 2025 consensus recommends applying BISAP or APACHE II at admission, monitoring organ dysfunction dynamically with Marshall-based scoring, and reserving CT indices for lat-

Characteristics of visualization methods in GP

Method	Advantages	Limitations	Typical clinical role
Transabdominal ultrasound	Widely available, inexpensive, can be performed at the patient's bedside First-line method for detecting gallstones, biliary sludge, and gallbladder wall changes	Dependence on the physician Limitations due to intestinal gas and obesity Low sensitivity to small stones in the common bile duct	Initial etiological examination Screening for gallstone disease/sludge in all patients
EUS	Highest sensitivity to microlithiasis and small stones (<5 mm) in the common bile duct Allows direct transition to therapeutic ERCP High resolution for the periampulary region	Invasive, requires sedation Limited availability Dependence on the physician	Confirmation of choledocholithiasis in case of uncertainty Stage prior to diagnosis of "idiopathic" GP
MRCP	Non-invasive, no radiation Excellent mapping of bile and pancreatic ducts Secretin-enhanced MRCP improves visualization of ducts	Less sensitive to microlithiasis than EUS Requires patient cooperation, time-consuming Limited applicability in unstable patients	Supplement to EUS when biliary/idiopathic HP is suspected Assessment of strictures, split PZ, disconnected pancreatic duct syndrome
Contrast-enhanced CT	Gold standard for detecting complications: necrosis, collections, false aneurysms, venous thrombosis Guides the planning of interventions (percutaneous/endoscopic) Widely available, quick to perform	Radiation exposure Risk of contrast nephrotoxicity Early (less than 48 hours) scans underestimate severity	Reserved for patients with diagnostic uncertainty, worsening condition, or no improvement Staging and intervention planning 72–96 hours after onset
MRI	Excellent soft tissue contrast Distinguishes between pseudocysts and encapsulated necrosis Detects internal debris and ductal abnormalities No radiation exposure	Long-term, limited availability Not ideal for unstable patients and those with claustrophobia Contraindicated for certain implants	Alternative to CT in cases of contrast allergy, renal dysfunction, young age Interpretation problems in cases of complications or recurrence
Contrast-enhanced ultrasound	Real-time perfusion assessment Distinguishes between viable and necrotic tissue Can be performed at the patient's bedside, without radiation exposure	Dependence on the physician Limited global availability Not standardized in guidelines	Additional method in specialized centers Rapid bedside assessment of perfusion/vascular complications
Doppler ultrasound	Assesses blood flow in the portal hepatic, splenic, and superior mesenteric veins Non-invasive, possible at the patient's bedside	Lower sensitivity than CT/MRI. Confirmatory imaging required	Screening for venous thrombosis Initial vascular assessment in HP

er stages when local complications need to be defined [4].

Emerging strategies focus on the integration of machine learning and artificial intelligence to refine prediction of outcomes. By leveraging longitudinal laboratory values, electronic health records, and imaging data, AI-based models have shown improved sensitivity and predictive accuracy compared with conventional scoring systems. A recent systematic review and meta-analysis confirmed that such models consistently outperform traditional tools in forecasting severe disease [78]. While these approaches remain largely confined to research settings, the IAP 2025 guidelines acknowledge their potential but emphasize the need for robust external validation and incorporation into clinical workflows before routine adoption [4].

In summary, severity assessment in acute pancreatitis has progressed from delayed, laboratory-heavy models toward streamlined bedside scores combined with continuous monitoring of systemic inflammation and organ function. Current consensus favors BISAP or APACHE II at admission, Marshall-based scoring for dynamic organ failure assessment, and CT indices for later evaluation of necrosis and complications. Looking forward, AI-driven tools may even-

tually redefine early risk prediction, but for now a pragmatic, guideline-aligned approach integrating early scoring, dynamic monitoring, and selective imaging remains the most reliable framework for prognostication and management.

Future Directions

The management of AP is moving toward a new era shaped by advances in translational research, biomarker discovery, and patient-centered care. Although diagnostic frameworks and severity stratification have improved considerably, AP remains a condition with unpredictable outcomes and a lack of targeted therapies. Future work must therefore focus on mechanistic insights, early risk prediction, therapeutic innovation, and long-term surveillance strategies. Recent discoveries emphasize the central role of mitochondrial dysfunction, calcium overload, and impaired autophagy in acinar cell injury, while novel forms of regulated cell death – including pyroptosis, ferroptosis, and defective mitophagy – have emerged as critical determinants of disease progression [22, 28, 29]. These insights suggest that future therapeutic strategies must combine inhibition of harmful inflammatory cascades – such as inflammasome activation and oxidative stress–with reinforcement of resolution programs through macrophage reprogramming and specialized pro-resolving mediators [30].

Biomarker development is another key area. While CRP and BUN remain established severity markers, they lack precision for early prediction. Novel candidates such as interleukin-6, procalcitonin, mitochondrial DNA, circulating histones, angiopoietin-2, and syndecan-1 show potential for refining triage and guiding therapy [47, 51, 52]. Incorporating such biomarker panels into clinical algorithms could transform early risk assessment and enable more precise, individualized care.

Diagnostic imaging is also evolving. While transabdominal ultrasound remains the cornerstone for detecting gallstones and biliary pathology, stepwise protocols using EUS and MRCP are increasingly recommended for idiopathic cases [4]. The integration of artificial intelligence into radiology may soon enable radiomics-based risk stratification, providing predictive information beyond what current indices can achieve. The combination of AI-assisted imaging, clinical scoring, and biomarker profiling could yield a comprehensive precision medicine framework for AP.

Equally important is the patient perspective. The inclusion of patient voices in the 2025 IAP guidelines reflects a shift toward patient-centered decision-making, with emphasis on non-invasive diagnostics, transparency in communication, and psychosocial considerations such as the financial implications of genetic testing [4]. Building on this, future studies should systematically evaluate patient-reported outcomes, quality of life, and socioeconomic burden as integral endpoints. Long-term management models must also incorporate structured surveillance for PPDM, EPI, and pancreatic cancer [5, 14].

Finally, translational and preventive research holds great promise. Genetic studies implicating PRSS1, SPINK1, and CFTR variants offer opportunities for individualized prevention [21]. In parallel, microbiome research has revealed how gut–pancreas interactions influence inflammation and systemic complications, suggesting that microbiota modulation may emerge as a novel therapeutic and preventive approach [79]. These frontiers underscore the importance of moving beyond acute management to holistic, personalized strategies that combine mechanistic, diagnostic, therapeutic, and preventive innovations.

Conclusions

Acute pancreatitis remains a highly heterogeneous disease with a clinical spectrum ranging from mild, self-limiting inflammation to severe, life-threatening organ dysfunction. Despite advances in diagnostic frameworks and supportive care, the burden of morbidity, mortality, and long-term complications remains considerable. The recent international consensus has emphasized not only the need for accurate early diagnosis and reliable risk stratification but also the importance of patient-centered approaches and structured long-term follow-up.

Future progress will depend on the integration of mechanistic insights, novel biomarkers, advanced imaging technologies, and translational discoveries into clinical practice. At the same time, personalized and patient-focused strategies must become central to the management of AP, ensuring that both the acute episode and the chronic sequelae are effectively addressed. By combining innovation with patient perspectives, the field is poised to transition from reactive treatment to proactive, preventive, and comprehensive care, ultimately improving survival, quality of life, and long-term outcomes for patients worldwide.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

These authors contributed equally to this work and share first authorship.

Funding

The authors declare that no financial support was received for the research and/or publication of this article.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Patient consent statement

Informed consent was not required as this study does not involve human participants.

References

1. Peery AF, Crockett SD, Murphy CC, Jensen ET, Kim HP, Egberg MD, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2021. Gastroenterology. 2022 Feb;162(2):621-44. doi: 10.1053/j.gastro.2021.10.017. Epub 2021 Oct 19. PMID: 34678215.
2. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. Lancet. 2020 Sep 5;396(10252):726-34. doi: 10.1016/S0140-6736(20)31310-6. PMID: 32891214.
3. Hart PA, Bradley D, Conwell DL, Dungan K, Krishna SG, Wyne K, et al. Diabetes following acute pancreatitis. Lancet Gastroenterol Hepatol. 2021 Aug;6(8):668-75. doi: 10.1016/S2468-1253(21)00019-4. Epub 2021 Jun 3. PMID: 34089654.
4. IAP/APA/EPC/IPC/JPS Working Group. International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society. Pancreatology. 2025 Sep 22;25(6):770-814. doi:10.1016/j.pan.2025.04.020. PMID: 40651900.
5. Xu D, Liu C, Zhou J. Long-term quality of life after acute pancreatitis: a systematic review and meta-analysis. BMC Gastroenterol. 2025 Jul 7;25(1):502. doi: 10.1186/s12876-025-04095-4. PMID: 40624607.
6. Kirkegård J, Cronin-Fenton D, Heide-Jørgensen U, Mortensen FV. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. Gastroenterology. 2018 May;154(6):1729-36. doi: 10.1053/j.gastro.2018.02.011. Epub 2018 Feb 9. PMID: 29432727.
7. Lee PJ, Papachristou GI. New insights into acute pancreatitis. Nat Rev Gastroenterol Hepatol. 2019 Aug;16(8):479-96. doi: 10.1038/s41575-019-0158-2. PMID: 31138897.
8. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779. Epub 2012 Oct 25. PMID: 23100216.
9. Pandol SJ, Gottlieb RA. Calcium, mitochondria and the initiation of acute pancreatitis. Pancreatology. 2022 Nov;22(7):838-45. doi: 10.1016/j.pan.2022.07.011. Epub 2022 Aug 3. PMID: 35941013.
10. Zaman S, Gorelick F. Acute pancreatitis: pathogenesis and emerging therapies. J Pancreatol. 2024 Mar;7(1):10-20. doi: 10.1097/JP9.0000000000000168. Epub 2024 Jan 2. PMID: 38524855.
11. Trikudanathan G, Yazici C, Evans Phillips A, Forsmark CE. Diagnosis and Management of Acute Pancreatitis. Gastroenterology. 2024 Sep;167(4):673-88. doi: 10.1053/j.gastro.2024.02.052. Epub 2024 May 15. PMID: 38759844.
12. Tenner S, Vege SS, Sheth SG, Sauer B, Yang A, Conwell DL, et al. American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. Am J Gastroenterol. 2024 Mar 1;119(3):419-37. doi: 10.14309/ajg.0000000000002645. Epub 2023 Nov 7. PMID: 38857482.
13. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019 Jun 13;14:27. doi: 10.1186/s13017-019-0247-0. eCollection 2019. PMID: 31210778.
14. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut. 2019;68(6):1044-51. doi:10.1136/gutjnl-2017-314657. Epub 2018 Jun 27. PMID: 29950344
15. He W, Wang G, Yu B, Xia L, Zhu Y, Liu P, et al. Elevated hypertriglyceridemia and decreased gallstones in the etiological composition ratio of acute pancreatitis as affected by seasons and festivals: A two-center real-world study from China. Front Cell Infect Microbiol. 2022;12:976816. doi:10.3389/fcimb.2022.976816. eCollection 2022. PMID: 36506025.
16. Wang CF, Tariq A, Chandra S. Acute Pancreatitis. 2025 Aug 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 29494075.
17. Gao L, Li W. Hypertriglyceridemia and acute pancreatitis: clinical and basic research – a narrative review. J Pancreatol. 2024;7(1):53-60. doi:10.1097/JP9.0000000000000153.
18. Saini J, Marino D, Badalov N, Vugelman M, Tenner S. Drug-Induced Acute Pancreatitis: An Evidence-Based Classification (Revised). Clin Transl Gastroenterol. 2023 Aug 1;14(8):e00621. doi: 10.14309/ctg.0000000000000621. PMID: 37440319.
19. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013 Jun;144(6):1252-61. doi: 10.1053/j.gastro.2013.01.068. PMID: 23622135.
20. Dumonceau JM, Kapral C, Aabakken L, Papanikolaou IS, Tringali A, Vanbiervliet G, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2020 Feb;52(2):127-49. doi: 10.1055/a-1075-4080. Epub 2019 Dec 20. PMID: 31863440.
21. Whitcomb DC, LaRusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet. 2012 Dec;44(12):1349-54. doi: 10.1038/ng.2466. Epub 2012 Nov 11. PMID: 23143602.
22. Tsomidis I, Voumvouraki A, Kouroumalis E. The Pathogenesis of Pancreatitis and the Role of Autophagy. Gastroenterology Insights. 2024; 15(2):303-41. doi: 10.3390/gastroent15020022.
23. Chen F, Xu K, Han Y, Ding J, Ren J, Wang Y, et al. Mitochondrial dysfunction in pancreatic acinar cells: mechanisms and therapeutic strategies in acute pancreatitis. Front Immunol. 2024 Dec 24;15:1503087. doi: 10.3389/fimmu.2024.1503087. eCollection 2024. PMID: 39776917.
24. Luo M, Jin T, Fang Y, Chen F, Zhu L, Bai J, et al. Signaling Pathways Involved in Acute Pancreatitis. J Inflamm Res. 2025 Feb 17;18:2287-303. doi: 10.2147/JIR.S485804. eCollection 2025. PMID: 40230438.
25. Zheng Z, Ding YX, Qu YX, Cao F, Li F. A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management. Ann Transl Med. 2021 Jan;9(1):69. doi: 10.21037/atm-20-4802. PMID: 33553362.

26. Jiang Z, Lhamo G, Ma M, Ye X, Chen J, He Y, et al. Quercetin as a therapeutic agent for acute pancreatitis: a comprehensive review. Front Pharmacol. 2025 Apr 28;16:1587314. doi: 10.3389/fphar.2025.1587314. eCollection 2025. PMID: 40356955.
27. Papantoniou K, Aggeletopoulou I, Michailides C, Pastras P, Triantos C. Understanding the Role of NLRP3 Inflammasome in Acute Pancreatitis. Biology (Basel). 2024 Nov 18;13(11):945. doi: 10.3390/biology13110945. PMID: 39596901.
28. Gu X, Huang Z, Ying X, Liu X, Ruan K, Hua S, et al. Ferroptosis exacerbates hyperlipidemic acute pancreatitis. Cell Death Discov. 2024 May 21;10(1):242. doi: 10.1038/s41420-024-02007-1. PMID: 38773098.
29. Li H, Wu D, Zhang H, Liu S, Zhen J, Yan Y, et al. Autophagy-mediated ferroptosis is involved in severe acute pancreatitis. BMC Gastroenterol. 2024 Aug 1;24(1):245. doi: 10.1186/s12876-024-03345-1. PMID: 39090535.
30. Mititelu A, Grama A, Colceriu MC, Pop TL. Overview of the cellular and immune mechanisms involved in acute pancreatitis. Expert Rev Mol Med. 2025 Jan 6;27:e9. doi: 10.1017/erm.2024.40. PMID: 39757373.
31. Li H, Wu D, Zhang H, Li P. New insights into regulatory cell death and acute pancreatitis. Heliyon. 2023 Jul 7;9(7):e18036. doi: 10.1016/j.heliyon.2023.e18036. eCollection 2023 Jul. PMID: 37519748.
32. Rosales-Muñoz GJ, Souza-Arroyo V, Bucio-Ortiz L, Miranda-Labra RU, Gomez-Quiroz LE, Gutiérrez-Ruiz MC. Acute pancreatitis experimental models, advantages and disadvantages. J Physiol Biochem. 2025 Aug;81(3):539-56. doi: 10.1007/s13105-025-01091-w. Epub 2025 May 17. PMID: 40380027.
33. Oppenlander KE, Chadwick C, Carman K. Acute Pancreatitis: Rapid Evidence Review. Am Fam Physician. 2022 Jul;106(1):44-50. PMID: 35839366.
34. Wright WF. Cullen Sign and Grey Turner Sign Revisited. J Am Osteopath Assoc. 2016 Jun 1;116(6):398-401. doi: 10.7556/jaoa.2016.081. PMID: 27214777.
35. Zeng T, An J, Wu Y, Hu X, An N, Gao L, et al. Incidence and prognostic role of pleural effusion in patients with acute pancreatitis: a meta-analysis. Ann Med. 2023;55(2):2285909. doi: 10.1080/07853890.2023.2285909. Epub 2023 Nov 27. PMID: 38010411.
36. Yan G, Li H, Bhetuwal A, McClure MA, Li Y, Yang G, et al. Pleural effusion volume in patients with acute pancreatitis: a retrospective study from three acute pancreatitis centers. Ann Med. 2021 Dec;53(1):2003-18. doi: 10.1080/07853890.2021.1998594. PMID: 34727802.
37. McDermott J, Kao LS, Keeley JA, Nahmias J, de Virgilio C. Management of Gallstone Pancreatitis: A Review. JAMA Surg. 2024 Jul 1;159(7):818-25. doi: 10.1001/jamasurg.2023.8111. PMID: 38691369.
38. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008 Dec;57(12):1698-703. doi: 10.1136/gut.2008.152702. Epub 2008 Jun 2. PMID: 18519429.
39. Singh VK, Wu BU, Bollen TL, Repas K, Maurer R, Johannes RS, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. Am J Gastroenterol. 2009 Apr;104(4):966-71. doi: 10.1038/ajg.2009.28. Epub 2009 Mar 17. PMID: 19293787.
40. Cho IR, Do MY, Han SY, Jang SI, Cho JH. Comparison of Interleukin-6, C-Reactive Protein, Procalcitonin, and the Computed Tomography Severity Index for Early Prediction of Severity of Acute Pancreatitis. Gut Liver. 2023 Jul 15;17(4):629-37. doi: 10.5009/gnl220356. Epub 2023 Feb 15. PMID: 36789576.
41. Li J, Chen Z, Li L, Lai T, Peng H, Gui L, He W. Interleukin-6 is better than C-reactive protein for the prediction of infected pancreatic necrosis and mortality in patients with acute pancreatitis. Front Cell Infect Microbiol. 2022 Nov 18;12:933221. doi: 10.3389/fcimb.2022.933221. eCollection 2022. PMID: 36467730.
42. Siriwardena AK, Jegatheeswaran S, Mason JM; PROCAP investigators. A procalcitonin-based algorithm to guide antibiotic use in patients with acute pancreatitis (PROCAP): a single-centre, patient-blinded, randomised controlled trial. Lancet Gastroenterol Hepatol. 2022 Oct;7(10):913-21. doi: 10.1016/S2468-1253(22)00212-6. Epub 2022 Jul 19. PMID: 35863358.
43. Vincent A, Shashirekha AS. Predicting severity of acute pancreatitis—evaluation of neutrophil-to-lymphocyte count ratio as emerging biomarker: a retrospective analytical study. Cureus. 2024 Nov 30;16(11):e74881. doi: 10.7759/cureus.74881. eCollection 2024 Nov. PMID: 39741615.
44. Li X, Zhang Y, Wang W, Meng Y, Chen H, Chu G, et al. An inflammation-based model for identifying severe acute pancreatitis: a single-center retrospective study. BMC Gastroenterol. 2024 Feb 5;24(1):63. doi: 10.1186/s12876-024-03148-4. PMID: 38317108.
45. Sáez J, Martínez J, Trigo C, Sánchez-Payá J, Compañy L, Laveda R, et al. Clinical value of rapid urine trypsinogen-2 test strip, urinary trypsinogen activation peptide, and serum and urinary activation peptide of carboxypeptidase B in acute pancreatitis. World J Gastroenterol. 2005 Dec 14;11(46):7261-5. doi: 10.3748/wjg.v11.i46.7261. PMID: 16437625.
46. Neoptolemos JP, Kemppainen EA, Mayer JM, Fitzpatrick JM, Raraty MG, Slavin J, et al. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. Lancet. 2000 Jun 3;355(9219):1955-60. doi: 10.1016/s0140-6736(00)02327-8. PMID: 10859041.
47. Lv Y, Yao Y, Liu Q, Lei J. Accuracy of angiopoietin-2 for predicting organ failure in patients with acute pancreatitis: a systematic review and meta-analysis. J Int Med Res. 2021 Feb;49(2):300060520986708. doi: 10.1177/0300060520986708. PMID: 33527867.
48. Wang J, Chen X, Qin C, Zeng X, Du X, Wang D. The endothelial activation and stress index is a potential prognostic indicator for patients with acute pancreatitis managed in the intensive care unit: a retrospective study. Front Med (Lausanne). 2024 Dec 11;11:1498148. doi: 10.3389/fmed.2024.1498148. eCollection 2024. PMID: 39722816.
49. Turunen A, Kuuliala K, Kuuliala A, Puolakkainen P, Kylänpää L, Hästbacka J, et al. Syndecan-1 Levels and Early Positive Fluid Balance Are Associated With Disease Severity in Acute Pancreatitis. Pancreas. 2024 Oct 1;53(9):e739-e747. doi: 10.1097/MPA.0000000000002366. Epub 2024 Apr 30. PMID: 38696459.
50. Li H, Wen H, Liu J, Luo X, Pei B, Ge P, et al. The glycocalyx: a key target for treatment of severe acute pancreatitis-associated multiple

organ dysfunction syndrome. Hum Cell. 2025 May 24;38(4):107. doi: 10.1007/s13577-025-01227-6. PMID: 40411704.
51. Pantelić M, Cvetković D, Jovankić J, Soldatović I, Pantelić M, Dujović M, et al. Predictive Value of Serum HMGB1, NF-κB, and IL-17 Gene Expression in Acute Pancreatitis Outcomes. Diagnostics (Basel). 2025 Aug 26;15(17):2160. doi: 10.3390/diagnostics15172160. PMID: 40941648.
52. Zhang D, Li J, Zhao L, Yang Z, Wu C, Liu Y, et al. Mitochondrial DNA Leakage Promotes Persistent Pancreatic Acinar Cell Injury in Acute Pancreatitis via the cGAS-STING-NF-κB Pathway. Inflammation. 2025 Jun;48(3):1420-37. doi: 10.1007/s10753-024-02132-0. Epub 2024 Aug 24. PMID: 39180578.
53. Liu T, Huang W, Szatmary P, Abrams ST, Alhamdi Y, Lin Z, et al. Accuracy of circulating histones in predicting persistent organ failure and mortality in patients with acute pancreatitis. Br J Surg. 2017 Aug;104(9):1215-25. doi: 10.1002/bjs.10538. Epub 2017 Apr 24. PMID: 28436602.
54. Rodríguez Rojas C, García de Guadiana-Romualdo L, Morán Sánchez S, Prazak J, Algara Soriano V, Que YA, et al. Role of Pancreatic Stone Protein as an Early Biomarker for Risk Stratification of Acute Pancreatitis. Dig Dis Sci. 2022 Jul;67(7):3275-83. doi: 10.1007/s10620-021-07152-6. Epub 2021 Jul 15. PMID: 34268662.
55. Ünal Çetin E, Kamiş F, Çetin AU, Beyazit Y, Kekilli M. Serum chitotriosidase and YKL-40 in acute pancreatitis: Reliability as prognostic marker for disease severity and correlation with inflammatory markers. Turk J Med Sci. 2021 Dec 13;51(6):3038-46. doi: 10.3906/sag-2106-59.PMID: 34579512.
56. Avcıoğlu U, Eruzun H. Serum zonulin levels as an early biomarker in predicting the severity and complications of acute pancreatitis. Eurasian J Med. 2023 Feb;55(1):78-82. doi: 10.5152/eurasianjmed.2022.0272. PMID: 36861872.
57. Strang SG, Habes QLM, Van der Hoven B, Tuinebreijer WE, Verhofstad MHJ, Pickkers P, et al. Intestinal fatty acid binding protein as a predictor for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; a prospective cohort study (I-Fabulous study). J Crit Care. 2021 Jun;63:211-17. doi: 10.1016/j.jcrc.2020.08.023. Epub 2020 Sep 10. PMID: 32980233.
58. Newton MV. D-dimer as a Marker of Severity and Prognosis in Acute Pancreatitis. Int J Appl Basic Med Res. 2024 Apr-Jun;14(2):101-7. doi: 10.4103/ijabmr.ijabmr_483_23. Epub 2024 May 24. PMID: 38912365.
59. Türkvatan A, Erden A, Türkoğlu MA, Seçil M, Yener Ö. Imaging of acute pancreatitis and its complications. Part 1: acute pancreatitis. Diagn Interv Imaging. 2015 Feb;96(2):151-60. doi: 10.1016/j.diii.2013.12.017. Epub 2014 Feb 8. PMID: 24512896.
60. Afzalpurkar S, Giri S, Kasturi S, Ingawale S, Sundaram S. Magnetic resonance cholangiopancreatography versus endoscopic ultrasound for diagnosis of choledocholithiasis: an updated systematic review and meta-analysis. Surg Endosc. 2023 Apr;37(4):2566-73. doi: 10.1007/s00464-022-09744-3. Epub 2022 Nov 7. PMID: 36344899.
61. Marino D, Saini J, Tenner S. Management of Acute Pancreatitis. Am J Gastroenterol. 2025 Jan 1;120(1):2-4. doi: 10.14309/ajg.0000000000003180. Epub 2024 Nov 5. PMID: 39498972.
62. Mittal N, Oza VM, Muniraj T, Kothari TH. Diagnosis and Management of Acute Pancreatitis. Diagnostics (Basel). 2025 Jan 23;15(3):258. doi: 10.3390/diagnostics15030258. PMID: 39941188.
63. Expert Panel on Gastrointestinal Imaging; Porter KK, Zaheer A, Kamel IR, Horowitz JM, Arif-Tiwari H, et al. ACR Appropriateness Criteria® Acute Pancreatitis. J Am Coll Radiol. 2023 Nov;20(11S):S302-S314. doi: 10.1016/j.jacr.2023.08.023. PMID: 38040457.
64. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990 Feb;174(2):331-6. doi: 10.1148/radiology.174.2.2296641. PMID: 2296641
65. Mortele KJ, Wiesner W, Intriere L, Shankar S, Zou KH, Kalantari BN, et al. A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. AJR Am J Roentgenol. 2004 Nov;183(5):1261-65. doi: 10.2214/ajr.183.5.1831261. PMID: 15505289.
66. Bollen TL, Singh VK, Maurer R, Repas K, van Es HW, Banks PA, et al. Comparative evaluation of the modified CT severity index and CT severity index in assessing severity of acute pancreatitis. AJR Am J Roentgenol. 2011 Aug;197(2):386-92. doi: 10.2214/AJR.09.4025. PMID: 21785084.
67. Willis J, vanSonnenberg E. Updated Review of Radiologic Imaging and Intervention for Acute Pancreatitis and Its Complications. J Intensive Care Med. 2025 Jun;40(6):588-97. doi: 10.1177/08850666241234596. Epub 2024 Feb 28. PMID: 38414385
68. Ranson JH, Rifkind KM, Turner JW. Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. Surg Gynecol Obstet. 1976 Aug;143(2):209-19. PMID: 941075.
69. Imrie CW. Prognostic indicators in acute pancreatitis. Can J Gastroenterol. 2003 May;17(5):325-8. doi: 10.1155/2003/250815. PMID: 12772007.
70. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818–29. PMID: 3928249.
71. Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet. 1989 Jul 22;2(8656):201–5. doi:10.1016/s0140-6736(89)90381-4. PMID: 2568529.
72. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995 Oct;23(10):1638–52. doi:10.1097/00003246-199510000-00007. PMID: 7587228.
73. Gao W, Yang HX, Ma CE. The Value of BISAP Score for Predicting Mortality and Severity in Acute Pancreatitis: A Systematic Review and Meta-Analysis. PLoS One. 2015 Jun 19;10(6):e0130412. doi:10.1371/journal.pone.0130412. PMID: 26091293.
74. Lankisch PG, Weber-Dany B, Hebel K, Maisonneuve P, Lowenfels AB. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. Clin Gastroenterol Hepatol. 2009 Jun;7(6):702-5; quiz 607. doi:10.1016/j.cgh.2009.02.020. PMID: 19245846.
75. Mikó A, Vigh É, Mátrai P, Soós A, Garami A, Balaskó M, et al. Computed Tomography Severity Index vs. Other Indices in the Prediction of Severity and Mortality in Acute Pancreatitis: A Predictive Accuracy Meta-analysis. Front Physiol. 2019 Aug 27;10:1002. doi:10.3389/fphys.2019.01002. PMID: 31507427.
76. Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis.

Br J Surg. 2006 Jun;93(6):738-44. doi:10.1002/bjs.5290. PMID: 16671062.

77. Dellinger EP, Forsmark CE, Layer P, Lévy P, Maraví-Poma E, Petrov MS, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg. 2012 Dec;256(6):875-80. doi: 10.1097/SLA.0b013e318256f778. PMID: 22735715.
78. Qian R, Zhuang J, Xie J, Cheng H, Ou H, Lu X, et al. Predictive value of machine learning for the severity of acute pancreatitis: A systematic review and meta-analysis. Heliyon. 2024 Apr 15;10(8):e29603. doi:10.1016/j.heliyon.2024.e29603. PMID: 38655348.
79. Zhang Z, Tanaka I, Pan Z, Ernst PB, Kiyono H, Kurashima Y. Intestinal homeostasis and inflammation: Gut microbiota at the crossroads of pancreas-intestinal barrier axis. Eur J Immunol. 2022 Jul;52(7):1035-46. doi: 10.1002/eji.202149532. Epub 2022 May 15. PMID: 35476255.

Received 23.09.2025