Review Article

Severe Acute Pancreatitis: Integrated Pathophysiology and Evidence-Based Clinical Management

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Abstract

Severe acute pancreatitis is a complex inflammatory condition characterized by persistent organ failure and high early mortality. Its pathogenesis is multifactorial, with biliary obstruction, alcohol use, hypertriglyceridemia, iatrogenic factors, metabolic disturbances, and genetic susceptibility acting as principal triggers. Despite their diversity, these etiologies converge on common intracellular mechanisms, including premature activation of digestive enzymes, mitochondrial dysfunction, oxidative stress, and dysregulated calcium signaling. These processes initiate acinar cell injury, predominantly through necrosis and pyroptosis, and activate inflammatory transcription pathways that promote cytokine release and systemic inflammation. The progression from local pancreatic injury to systemic inflammatory response syndrome is a defining feature of severe disease. Sustained inflammation leads to endothelial dysfunction, capillary leak, distributive shock, and multiorgan involvement, including respiratory, renal, and cardiovascular failure. Persistent organ failure remains the strongest predictor of mortality, underscoring the importance of early severity stratification. Classification systems such as the Revised Atlanta framework, along with validated scoring tools and laboratory markers, support timely identification of high-risk patients. Initial management centers on early goal-directed fluid resuscitation, careful hemodynamic monitoring, multimodal analgesia, early enteral nutrition, and appropriate intensive care support. Management of local complications, particularly infected necrosis, follows a step-up approach that prioritizes minimally invasive interventions. Etiology-specific strategies, including timely biliary intervention, metabolic control, and alcohol cessation, are essential to prevent recurrence. Although improvements in supportive care have reduced late mortality, severe acute pancreatitis continues to be associated with significant long-term morbidity, including endocrine and exocrine insufficiency, recurrent episodes, and impaired quality of life, highlighting the need for continued refinement of individualized therapeutic strategies.

Key words

Biliary obstruction, hypertriglyceridemia, oxidative stress, persistent organ failure, infected necrosis, precision medicine.

Introduction

Acute pancreatitis is defined as an acute inflammatory process of the pancreas that is diagnosed through a combination of clinical symptoms, biochemical abnormalities, and imaging findings. The diagnosis relies on the presence of characteristic abdominal pain, elevation of serum amylase or lipase levels, and radiological evidence of pancreatic inflammation [1]. Within this spectrum, severe acute pancreatitis is distinguished by the presence of persistent organ failure lasting more than 48 hours, a defining feature that represents a critical determinant of mortality and adverse outcomes [2].

From an epidemiological perspective, the global incidence of pancreatitis has been increasing, generating substantial healthcare implications due to its considerable morbidity and mortality. Although age-standardized incidence and mortality rates have shown a decline, the absolute number of cases continues to rise, particularly among males and older individuals. This growing burden is not uniformly distributed, as regions with lower Social Development Index exhibit disproportionately higher impact, thereby underscoring persistent health inequalities in the distribution of disease and access to care [3].

Clinically, severe acute pancreatitis follows a biphasic course that further explains its complexity. The early phase is dominated by a systemic inflammatory response syndrome, driven by oxidative stress and immune cell infiltration, which may lead to early organ dysfunction. As the disease progresses, a late infectious phase may develop, characterized by complications such as infected pancreatic necrosis that frequently require invasive interventions, including necrosectomy. This temporal evolution from sterile inflammation to secondary infection reflects the dynamic interplay between local pancreatic injury and systemic immune responses [4, 5].

In this context, integrating molecular mechanisms with bedside management becomes essential. A deeper understanding of oxidative stress pathways and immune activation has important implications for the development of targeted therapeutic strategies aimed at improving clinical outcomes [5]. Current management remains centered on fluid resuscitation, nutritional support, and critical care interventions [1, 6]. However, the incorporation of molecular insights into clinical decision-making may enhance treatment efficacy and refine risk stratification. Furthermore, emerging technologies, including artificial intelligence–

based predictive models and advanced imaging modalities, offer promising avenues for improving severity assessment and enabling more personalized therapeutic approaches [7].

The objective of this review is to examine the pathophysiological mechanisms and clinical management of severe acute pancreatitis to improve early recognition and optimize patient outcomes.

Methodology

This narrative review was developed using a structured yet flexible methodological framework to synthesize contemporary evidence on severe acute pancreatitis, with particular emphasis on its molecular pathophysiology, systemic inflammatory response, organ failure, local and systemic complications, and evidence-based clinical management strategies. The synthesis was organized according to the natural course of the disease, integrating early inflammatory mechanisms, progression to organ dysfunction, and late infectious complications, and aligned with clinically relevant outcomes, including persistent organ failure, need for intensive care, infected necrosis, and mortality. The methodological approach prioritized the integration of cellular and molecular mechanisms, epidemiologic trends, severity stratification tools, and therapeutic interventions in order to provide a comprehensive and clinically applicable overview.

A comprehensive literature search was conducted in PubMed, Scopus, and ScienceDirect, including peer-reviewed publications in English or Spanish published between January 2020 and December 2025. This timeframe was selected to capture updated classification systems, advances in understanding inflammatory and immunologic pathways, developments in critical care management, and emerging predictive technologies. The search strategy combined Medical Subject Headings and free-text terms using Boolean operators, including: (“severe acute pancreatitis” OR “acute pancreatitis”) AND (“pathophysiology” OR “systemic inflammatory response” OR “organ failure”) AND (“necrosis” OR “infected necrosis” OR “complications”) AND (“fluid resuscitation” OR “intensive care” OR “clinical management” OR “severity prediction”). The initial search identified 214 records; after removal of duplicates and title–abstract screening, 96 articles underwent full-text evaluation, and 54 studies were included in the final qualitative synthesis. Study selection and evaluation were conducted independently by two authors, with discrepancies resolved by consensus.

Eligible sources included randomized controlled trials, multicenter cohort studies, epidemiologic analyses, high-quality observational studies, systematic reviews, meta-analyses, and international guideline or consensus documents addressing classification criteria, severity assessment tools, and management recommendations. Priority was given to studies with robust methodological design, clearly defined clinical endpoints such as persistent organ failure or mortality, adequate sample size, and sufficient follow-up duration. Studies limited to purely experimental models without clinical correlation, small uncontrolled case series, or reports involving non-representative populations were excluded. Methodological quality was assessed narratively according to study design, risk of bias, sample size, consistency of outcome definitions, and external validity. When conflicting findings were identified, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations. Given its narrative design, this review may be subject to selection bias and does not provide pooled quantitative effect estimates. Artificial intelligence–based tools were used solely for structural organization and linguistic refinement, while scientific interpretation and final conclusions were determined exclusively by the authors to ensure academic rigor and integrity.

Etiology and Mechanistic Triggers

Biliary obstruction represents one of the most common etiological factors associated with severe acute pancreatitis and is frequently caused by gallstones. Obstruction at the level of the biliary tract leads to increased ductal pressure, which in turn precipitates pancreatic injury. This mechanical impairment facilitates the reflux of bile into the pancreatic duct, resulting in the intrapancreatic activation of digestive enzymes and initiating processes of autodigestion and inflammation [8].

Alcohol consumption constitutes another major risk factor, exerting direct toxic effects on pancreatic acinar cells. The metabolism of alcohol generates reactive oxygen species, which promote oxidative stress within pancreatic tissue and amplify local inflammation. This oxidative stress not only damages cellular structures but also intensifies the inflammatory cascade, thereby exacerbating pancreatic injury and contributing to disease progression [9].

Hypertriglyceridemia is a metabolic disorder that significantly increases the risk of severe acute pancreatitis through distinct yet related mechanisms. Elevated triglyceride concentrations undergo lipolysis, leading to the production of free fatty acids that are toxic to pancreatic cells [10, 11]. These free fatty acids induce mitochondrial dysfunction, elevate intracellular calcium levels, and stimulate cytokine release, all of which contribute to pancreatic injury and the development of systemic complications. Furthermore, lipid peroxidation and ferroptosis intensify inflammation and aggravate organ damage in hyperlipidemic acute pancreatitis, reinforcing the central role of metabolic derangements in disease severity [10, 12].

Iatrogenic factors also play a relevant role in the pathogenesis of severe acute pancreatitis. Endoscopic retrograde cholangiopancreatography is a commonly performed procedure that may precipitate pancreatitis through mechanical injury or chemical irritation of the pancreatic duct. The documented incidence of post-procedural pancreatitis underscores the importance of meticulous technique and the implementation of preventive strategies to mitigate risk [8].

In addition, certain medications and metabolic disturbances, including hypercalcemia, have been implicated as triggers of severe acute pancreatitis. These factors may alter pancreatic enzyme activity and promote inflammatory processes, thereby initiating or aggravating pancreatic injury [8]. In many cases, such triggers intensify pre-existing metabolic abnormalities, further worsening disease severity [14].

Genetic susceptibility contributes to individual vulnerability by influencing key regulatory pathways ofpancreatic enzyme activation. Mutations in genes such as PRSS1, SPINK1, and CFTR are associated with dysregulation of trypsinogen activation and impaired control of pancreatic enzymes. Premature intrapancreatic activation of trypsinogen constitutes a central pathogenic mechanism, as it initiates autodigestion and sustains inflammatory responses within the gland [15].

Cellular and Molecular Pathophysiology

The premature intracellular activation of digestive enzymes within pancreatic acinar cells constitutes a central hallmark of severe acute pancreatitis. This aberrant activation initiates autodigestive processes that directly injure pancreatic tissue and trigger the inflammatory cascade [16]. In particular, trypsinogen, which is normally secreted as an inactive precursor, undergoes premature conversion to trypsin within acinar cells, thereby amplifying cellular injury and promoting inflammation [17].

As injury progresses, acinar cell death becomes a defining pathological feature. Necrosis predominates and is characterized by loss of membrane integrity and the release of intracellular contents into the extracellular space, further intensifying local inflammation [17]. In addition to necrosis, pyroptosis also contributes to acinar cell injury. This programmed form of necrotic cell death is mediated by the NLRP3 inflammasome and gasdermin D, linking intracellular danger signals to the amplification of systemic inflammatory responses [18].

Underlying these processes, disruption of calcium signaling plays a pivotal role in disease progression. Dysregulated intracellular calcium homeostasis leads to mitochondrial dysfunction and a reduction in adenosine triphosphate production, both of which are essential for maintaining cellular viability [19]. Mitochondrial dysfunction, characterized by alterations in membrane potential and increased permeability, further promotes oxidative stress and amplifies cellular damage [5]. As mitochondrial integrity deteriorates, the imbalance between reactive oxygen species and antioxidant defenses becomes more pronounced, reinforcing the cycle of injury.Oxidative stress, driven by excessive reactive oxygen species, significantly contributes to the pathogenesis of severe acute pancreatitis. These reactive molecules promote necrosis, apoptosis, and activation of inflammatory signaling pathways, thereby sustaining tissue injury [20]. Concurrently, adenosine triphosphate depletion resulting from mitochondrial impairment compromises energy-dependent processes required for cellular repair and survival, further aggravating structural damage [21].

At the molecular level, inflammatory transcription pathways are activated in response to mitochondrial DNA release and oxidative stress. Among these, nuclear factor kappa B plays a prominent role in upregulating the expression of pro-inflammatory cytokines. The activation of these transcriptional programs perpetuates the inflammatory response and contributes to the systemic manifestations of severe acute pancreatitis [5]. The subsequent release of cytokines, including tumor necrosis factor alpha and interleukin 6, amplifies the inflammatory cascade by recruiting immune cells to the site of injury and intensifying tissue damage [22]. This cytokine surge represents a critical determinant in disease progression and the development of systemic complications [5].

Endothelial dysfunction emerges as a key consequence of sustained oxidative stress and inflammation. Damage to the vascular endothelium leads to microcirculatory impairment, which exacerbates pancreatic ischemia and perpetuates tissue injury [20]. The resulting disruption of microvascular perfusion limits the delivery of oxygen and nutrients to affected tissues, thereby increasing the severity of pancreatic damage and contributing to the overall progression of severe acute pancreatitis [16].

Systemic Inflammatory Response and Organ Failure

Systemic inflammatory response syndrome represents a central clinical manifestation of severe acute pancreatitis and is characterized by elevated circulating levels of pro-inflammatory cytokines, including interleukin 6 and tumor necrosis factor alpha, which drive systemic inflammation and contribute to organ dysfunction [23]. The presence of early and persistent systemic inflammatory response syndrome has been consistently associated with an increased risk of developing persistent organ failure, a major determinant of mortality in severe acute pancreatitis [2].

As the inflammatory cascade intensifies, increased vascular permeability leads to capillary leak syndrome and distributive shock [23]. This hemodynamic disturbance is characterized by hypotension and inadequate tissue perfusion, conditions that further aggravate organ dysfunction and contribute to the progression of persistent organ failure. The interplay between systemic inflammation and vascular instability thus represents a critical mechanism underlying multiorgan involvement. Respiratory complications are among the most severe systemic consequences. Severe acute pancreatitis may progress to acute respiratory distress syndrome, a serious form of acute lung injury driven by inflammation and oxidative stress. Experimental data have demonstrated that inhibition of aquaporin-9 attenuates lung injury, suggesting potential therapeutic strategies aimed at modulating inflammatory pathways in respiratory failure [5].

Renal dysfunction also constitutes a frequent and clinically significant complication. Acute kidney injury in severe acute pancreatitis is commonly related to hypoperfusion and the systemic inflammatory response. Moreover, the presence of chronic kidney disease and advanced cardiovascular comorbidities has been identified as a predictor of worse outcomes, highlighting the influence of pre-existing conditions on disease severity and prognosis [24].

Cardiovascular dysfunction further compounds the clinical picture and is often characterized by vasoplegia, a state of reduced systemic vascular resistance mediated by inflammatory factors. Experimental models have shown that interventions such as methylprednisolone and tumor necrosis factor alpha inhibitors may ameliorate cardiovascular dysfunction, suggesting possible avenues for targeted therapeutic modulation [25].

In parallel, severe acute pancreatitis is marked by immune dysregulation, which initially manifests as a hyperinflammatory response and subsequently transitions to a state of immunosuppression, thereby increasing susceptibility to infections. Corticosteroids are currently under investigation for their potential to modulate this immune imbalance and reduce organ injury [26]. This dynamic shift from excessive inflammation to immune exhaustion contributes to the complexity of disease management. Bacterial translocation from the gastrointestinal tract represents a key mechanism in the development of infected pancreatic necrosis, one of the most severe complications of the disease. Management strategies emphasize a step-up approach, beginning with catheter drainage and proceeding to necrosectomy if necessary, as the recommended method for treating infected pancreatic necrosis [27].

Classification, Severity Stratification, and Early Risk Assessment

Accurate classification and early severity assessment are essential components in the management of acute pancreatitis, particularly in identifying patients at risk for severe disease. The Revised Atlanta Classification categorizes acute pancreatitis into mild, moderately severe, and severe forms based on the presence and duration of organ failure as well as local or systemic complications. This framework has become widely accepted in clinical practice due to its clarity and practical applicability. Complementing this system, the determinant-based classification emphasizes persistent organ failure and infected pancreatic necrosis as the principal determinants of severity, thereby offering a more nuanced stratification of patients and refining prognostic evaluation [28].

Within these classification models, persistent organ failure remains the most critical determinant of severe acute pancreatitis and is closely associated with mortality. Early identification of patients at risk for developing persistent organ failure is therefore crucial for timely intervention and escalation of care. Predictive tools such as a mobile nomogram incorporating variables including age, respiratory rate, and laboratory markers have demonstrated high accuracy in forecasting persistent organ failure, highlighting the growing role of individualized risk assessment [29].

Several prognostic scoring systems further support early risk stratification. The Bedside Index for Severity in Acute Pancreatitis score is simple and effective, with strong predictive value for mortality and organ failure, making it particularly useful in early clinical decision-making [30]. The Acute Physiology and Chronic

Health Evaluation II score provides a more comprehensive assessment by integrating physiological and laboratory parameters, and it correlates well with outcomes in acute pancreatitis [31]. Similarly, the Sequential Organ Failure Assessment score is designed to evaluate the extent of organ dysfunction and has proven valuable in predicting progression to severe disease [7].

Laboratory markers also play a significant role in severity prediction and prognostication. Elevated hematocrit and blood urea nitrogen levels are associated with increased disease severity and poor outcomes, and they form part of the Early Risk Assessment in Pancreatitis score, which has demonstrated strong prognostic validity for multi-organ dysfunction syndrome and mortality [32]. In addition, inflammatory indices such as the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and systemic immune-inflammation index have emerged as effective early predictors of severity. Among these, the monocyte-to-lymphocyte ratio and the systemic inflammatory response index have shown particularly high predictive performance [31]. Moreover, a composite model incorporating heparin-binding protein, C-reactive protein, and procalcitonin has demonstrated excellent discriminatory capacity in identifying severe acute pancreatitis [33].

Initial Clinical Management (First 48 Hours)

Early goal-directed fluid resuscitation constitutes a cornerstone of initial management in severe acute pancreatitis. Among crystalloid solutions, Ringer’s lactate is preferred over normal saline because of its potential to reduce systemic inflammation and improve clinical outcomes [34, 35]. Fluid therapy should be guided by clearly defined physiological targets, including a urine output of 0.5–1 ml/kg/h, reversal of tachycardia, and normalization of blood pressure. In addition to clinical parameters, laboratory markers such as hematocrit and blood urea nitrogen should be closely monitored to assess adequacy of resuscitation and detect ongoing hemoconcentration [35]. Current evidence supports a moderate fluid resuscitation strategy, with an initial infusion rate of 5–10 ml/kg/h, as aggressive fluid administration has been associated with increased morbidity and mortality [36, 37].

Hemodynamic monitoring plays a critical role in optimizing fluid therapy while minimizing complications. Both noninvasive and invasive parameters should be employed when indicated, including assessment of central venous pressure and the use of echocardiography in selected cases [34]. Careful monitoring is particularly important to avoid fluid overload, which can exacerbate systemic edema and contribute to complications such as respiratory failure. Maintaining an appropriate fluid balance is therefore essential to prevent iatrogenic deterioration [38].

Effective pain control is another fundamental component of early management. A multimodal analgesic approach is recommended in order to reduce reliance on opioids and limit their associated adverse effects. Epidural analgesia may be considered in selected patients as part of this strategy. In addition, non-steroidal anti-inflammatory drugs and acetaminophen can be used as adjuncts to opioids to enhance analgesic efficacy and improve symptom control (35).

Nutritional support should be initiated early, as enteral nutrition within the first 24–48 hours is essential for preserving gut barrier integrity and reducing the risk of infectious complications. Enteral nutrition is preferred over parenteral nutrition unless contraindicated, given its favorable impact on gastrointestinal motility and infection prevention [39].

Timely identification of patients requiring intensive care is crucial. Admission to the intensive care unit should be considered in the presence of multiorgan failure, severe systemic inflammatory response syndrome, or the need for invasive hemodynamic monitoring. Decisions regarding escalation of care should be guided by clinical severity assessment using validated scoring systems and relevant laboratory markers to ensure appropriate allocation of critical care resources [34, 6].

Management of Local and Systemic Complications

Local complications are frequent in severe acute pancreatitis and require careful evaluation to determine the appropriate timing and type of intervention. Acute peripancreatic fluid collections commonly develop during the early phase of the disease and can often be managed conservatively if asymptomatic. However, when symptoms or complications arise, drainage becomes necessary. In collections persisting beyond four weeks, particularly those located in the upper abdomen, endoscopic ultrasound–guided drainage is preferred. The selection of stent type depends on the nature of the collection, with lumen-apposing metal stents recommended for walled-off necrosis and plastic stents for pseudocysts [40, 41].

The distinction between sterile and infected necrosis is clinically critical. Infected necrotizing pancreatitis develops in approximately 30 percent of cases of necrosis and necessitates timely intervention. Endoscopic management is generally favored over minimally invasive surgery due to lower complication rates and shorter hospital stays [42]. In suspected infected necrosis, a step-up approach is recommended, beginning with percutaneous drainage and proceeding to necrosectomy only if necessary [43].

Walled-off necrosis and pancreatic pseudocysts are similarly managed through endoscopic techniques, with endoscopic ultrasound–guided drainage serving as a primary therapeutic modality. The use of lumen-apposing metal stents enhances access to necrotic cavities and facilitates drainage, although the optimal timing and technique for necrosectomy continue to be evaluated [40, 41]. These advances in endoscopic intervention have reshaped the management paradigm for late complications of severe acute pancreatitis.Among the most severe complications, abdominal compartment syndrome may arise as a consequence of extensive inflammation and fluid shifts. This condition requires vigilant monitoring, as elevated intra-abdominal pressure can precipitate organ failure. Management strategies include interventions aimed at reducing intra-abdominal pressure, and in severe cases, surgical decompression may be required [44].

The broader step-up approach integrates these principles into a structured management pathway. Initial percutaneous drainage is followed, when indicated, by endoscopic or surgical necrosectomy. Techniques such as video-assisted retroperitoneal debridement and sinus tract endoscopy are incorporated based on individual patient characteristics and disease severity. The timing of intervention, including the choice between upfront and step-up necrosectomy, influences the likelihood of requiring additional procedures, highlighting the importance of individualized therapeutic planning [45, 46].

Antibiotic therapy plays a defined yet limited role in this context. Antibiotics are indicated in cases of confirmed infection, particularly in infected necrotizing pancreatitis. Ongoing evaluation seeks to refine the duration and specific use of antimicrobial therapy, with particular emphasis on avoiding unnecessary administration in sterile necrosis [40].

Etiology-Specific and Advanced Management Strategies

In biliary pancreatitis, the timing of endoscopic retrograde cholangiopancreatography plays a critical role in determining clinical outcomes. Early endoscopic retrograde cholangiopancreatography is recommended when there is clear evidence of cholangitis or persistent biliary obstruction, as timely intervention can reduce complications and improve prognosis [47, 48]. In contrast, in cases of acute biliary pancreatitis without associated cholangitis, the optimal timing of the procedure remains a matter of debate. Some studies indicate that early endoscopic retrograde cholangiopancreatography does not significantly reduce mortality; however, it may decrease the incidence of local or systemic complications when compared with conservative management [49, 50]. These findings underscore the importance of individualized decision-making based on clinical presentation and evidence of ongoing obstruction.The timing of cholecystectomy similarly requires careful consideration. In patients with moderately severe and severe acute biliary pancreatitis, early cholecystectomy within 14 days of admission has been associated with increased postoperative mortality and morbidity, making delayed cholecystectomy the preferred strategy in these cases to minimize surgical risk [51]. Conversely, in mild acute biliary pancreatitis, early cholecystectomy is generally considered safe and serves to prevent recurrent episodes, thereby reducing the likelihood of future complications [52].

In hypertriglyceridemia-induced pancreatitis, metabolic control constitutes the cornerstone of management. Insulin infusion effectively lowers triglyceride levels, particularly in patients with concurrent hyperglycemia, although its role in ethanol-associated hypertriglyceridemia remains less clearly defined [53]. Plasmapheresis has been recommended in severe cases; however, available evidence suggests that it does not confer significant clinical outcome benefits compared with conservative treatment and may be associated with prolonged hospital stays [54]. Accordingly, a multidisciplinary strategy incorporating dietary modifications and lipid-lowering pharmacotherapy is essential for long-term management and prevention of recurrence [55].

Management of alcohol-related pancreatitis requires sustained abstinence from alcohol, comprehensive nutritional support, and appropriate treatment of complications such as pancreatic necrosis or pseudocysts, often through minimally invasive techniques [47].

In advanced cases of severe acute pancreatitis complicated by organ failure, supportive care becomes paramount. Mechanical ventilation may be necessary in patients who develop respiratory failure, while vasopressors are indicated in the presence of hemodynamic instability. Renal replacement therapy should be considered in individuals with acute kidney injury secondary to severe acute pancreatitis when conservative measures are insufficient [6].

Prognosis, Long-Term Outcomes, and Future Directions

Mortality in severe acute pancreatitis demonstrates a temporal pattern influenced by distinct pathophysiological mechanisms. Early mortality is primarily driven by systemic inflammatory response syndrome and persistent organ failure, with reported 14-day mortality rates reaching 17% among patients admitted to intensive care units. In contrast, late mortality, defined as death occurring after 14 days, has declined since 2010, reflecting improvements in critical care management and interventional strategies. This shift underscores the impact of advances in supportive therapy and complication management on long-term survival [56].

Beyond acute survival, pancreatic functional impairment represents a significant long-term consequence. Endocrine insufficiency develops in approximately 34% of patients, while exocrine insufficiency affects 38%, with higher prevalence observed in individuals who experienced extensive pancreatic necrosis during the acute phase [57]. Notably, exocrine insufficiency has been shown to exert a greater negative impact on quality of life compared with endocrine dysfunction [58], highlighting the clinical relevance of digestive impairment and nutritional consequences in recovery.

Recurrent pancreatitis further contributes to long-term morbidity. Approximately 26% of patients experience recurrence, frequently resulting in hospital readmissions and additional interventions. Moreover, the progression to chronic pancreatitis is closely associated with the extent of initial pancreatic injury, indicating that the severity of the first episode has lasting structural and functional implications [57].

Quality of life is significantly reduced during the first four years following severe acute pancreatitis, particularly in cases related to alcohol etiology, although gradual normalization tends to occur over time. Importantly, the severity of the initial episode correlates with long-term quality of life outcomes, reinforcing the prognostic significance of early disease burden [58].

Looking forward, emerging therapeutic strategies aim to further reduce early mortality and long-term complications. Targeted immunomodulation and biomarker-guided approaches are being explored as potential means of improving risk stratification and preventing early deterioration. Precision medicine strategies are also under consideration as future directions in the management of severe acute pancreatitis [56, 59].

Conclusions

Severe acute pancreatitis results from diverse etiologic triggers that converge on premature enzyme activation, mitochondrial dysfunction, and an amplified inflammatory cascade, leading to systemic inflammatory response syndrome and persistent organ failure, the main determinant of early mortality. Early recognition and structured, goal-directed management are essential to improve outcomes.

Although advances in classification, risk stratification, minimally invasive interventions, and critical care have reduced late mortality, severe acute pancreatitis remains associated with significant long-term morbidity, including pancreatic insufficiency and reduced quality of life. Future improvements rely on biomarker-guided strategies and precision-based therapeutic approaches.

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