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REVIEW

Severe acute pancreatitis: Pathogenetic aspects and prognostic factors

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Abstract

Approximately 20% of patients with acute pancreatitis develop a severe disease associated with complications and high risk of mortality. The purpose of this study is to review pathogenesis and prognostic factors of severe acute pancreatitis (SAP). An extensive medline search was undertaken with focusing on pathogenesis, complications and prognostic evaluation of SAP. Cytokines and other inflammatory markers play a major role in the pathogenesis and course of SAP and can be used as prognostic markers in its early phase. Other markers such as simple prognostic scores have been found to be as effective as multifactorial scoring systems (MFSS) at 48 h with the advantage of simplicity, efficacy, low cost, accuracy and early prediction of SAP. Recently, several laboratory markers including hematocrit, blood urea nitrogen (BUN), creatinine, matrix metalloproteinase-9 (MMP-9) and serum amyloid A (SAA) have been used as early predictors of severity within the first 24 h. The last few years have witnessed a tremendous progress in understanding the pathogenesis and predicting the outcome of SAP. In this review we classified the prognostic markers into predictors of severity, pancreatic necrosis (PN), infected PN (IPN) and mortality.

Key words: Acute pancreatitis; Pathogenesis; Prediction; Severity; Necrosis; Infected necrosis; Mortality

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INTRODUCTION

Acute pancreatitis (AP) remains a serious disease. It is defined as an inflammatory process of the pancreas with possible peripancreatic tissue and multi-organ involvement inducing multi-organ dysfunction syndrome (MODS) with an increased mortality rate[1]. The majority of patients present with a mild disease, however approximately 20% run a severe course and require appropriate management in an intensive care unit. According to the Atlanta classification, severe acute pancreatitis (SAP) is defined as an AP associated with local and/or systemic complications. Atlanta classification is a clinically-based classification defining AP, severity and complications. This classification has been proposed in the international symposium on AP, Atlanta, 1992 by 40 international authorities from 15 countries and six medical disciplines[1]. Development of organ dysfunction within 72 h of symptom onset is defined as early severe acute pancreatitis (ESAP). Early severe acute pancreatitis is characterized by a short course, progressive MODS, early hypoxemia, high computed tomography (CT) score, increased incidence of necrosis infection and abdominal compartment syndrome (ACS)[2,3].

Multi-organ dysfunction syndrome, the extent of pancreatic necrosis, infection and sepsis are the major determinants of mortality in AP[4-6]. Pancreatic necrosis is considered as a potential risk for infection, which represents the primary cause of late mortality. Occurrence of acute respiratory (ARF), cardiovascular (CVF) and renal failures (RF) can predict the fetal outcome in SAP[7]. A wide range of mortality (20%-60%) has been reported in SAP[8,9]. Early diagnosis and prognostic evaluation are extremely important and may reduce the morbidity and mortality associated with SAP.

PATHOGENESIS

Inappropriate intracellular activation of proteolytic enzymes induces pancreatic tissue damage in the presence of intracellular lysozyme enzymes and activation of trypsinogen to trypsin. Trypsin in turn activates a cascade of phospholipases, elastases and other mediators with increased neutrophil migration to the pancreas. Consequently a variety of inflammatory cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), platelets activating factor (PAF) and tumor necrosis factor (TNF) are released[10]. Apparently proinflammatory cytokines play a pivotal role in the pathogenesis of AP and its systemic complications[11]. IL-1 and TNF induce the release of IL-6 and IL-8[12,13] The presence of high C-reactive protein (CRP) and serum amyloid A (SAA) strongly suggests their major role in

the pathogenesis of AP[14]. Metalloproteinase-9 (MMP-9) may alter the permeability by disruption of the basement membranes of the vascular endothelial barrier[15,16]. Additionally, in experimental pancreatitis activation of mast cells has contributed to the intra and extrapancreatic endothelial barrier dysfunction and may partly contribute to the development of MODS[17]. The endothelial barrier damage in various organs including the pancreas, lungs, kidneys and intestine is associated with an increased permeability and consequent passage of blood constituents to various tissues[18-20]. Lung involvement with development of pleura effusion indicates systemic involvement with an increased mortality risk[21]. In addition, inflammatory mediators may also affect intestinal microcirculation leading to damage of microvilli allowing endotoxine and bacterial translocation (BT) into the systemic circulation and hence increase the risk of pancreatic infection[22,23]. Hyperstimulation of the immune system determines the immunosuppression and the increased mortality risk in the course of acute necrotizing pancreatitis. In the early stage of AP, cytokinemia and the oxidative stress are responsible for the inadequate immune response[24,25]. The inflammatory process is associated with acinar cell damage and an inadequate immune response mediated mainly by monocytes, macrophages, polymorphonuclear cells (PMNs), lymphocytes, mast cells and endothelial cells[26,27]. In SAP the inflammatory process is amplified by the release of cytokines and reactive oxygen species (ROS)[28]. The intensity of oxidative stress correlates well with the severity of AP[24,25]. Antioxidants such as glutathione peroxidase (GPx) play a pivotal role in the process of defense especially, where ROS contribute significantly to the disease etiology[29,30]. Glutathione peroxidase activity is selenium-dependent and is lowered in states associated with selenium deficiency[28]. In the presence of cytokines and ROS, nuclear factor-κB (NF-κB) is activated. It links the inflammatory response and regulates several forms of proinflammatory gene expressions including TNF-α, IL-1, IL-8, chemokines, selectin-E and intracellular adhesion molecule-1 (ICAM-1)[31,32].

During infection, the liver produces large amounts of SAA and other inflammatory markers. Serum amyloid A plays an important role in the activation of PMNs and chemotaxis of PMNs, monocytes and T-lymphocytes and release of proinflammatory mediators such as TNF-α, IL-b and IL-8 from PMNs[33,34]. Neutrophils are also activated by MMP-9, which promotes their endothelial cell adhesion and migration into the inflamed tissue[35]. Proteolytic activity of MMP-9 may further mediate pathological inflammation[36]. TNF-α, IL-1b and IL-8 can stimulate the release of MMP-9, which damage basement membranes and alter permeability[15,16].

Several recent studies have emphasized the role of genetic polymorphism in the predisposition to immune response variations and severe clinical course of AP. This supports the knowledge of genetic and environmental factors as severity modifiers of the disease and helps to provide prophylactic and therapeutic strategies that minimize the morbidity and mortality of SAP. For instance, monocyte chemotactic protein-1 (MCP-1) is increased in the early course of AP and can therefore accurately predict the severity and mortality[37]. Oxidative stress may also contribute to the pathogenesis of SAP. Glutathione-s-transferase (GST) genetic polymorphism also enhances the inflammatory response to pancreatic injury and promotes the progression of mild acute pancreatitis (MAP) to SAP due to the oxidative stress-induced glutathione depletion[38]. In contrast, TNF-α polymorphism has had no relation to severity of pancreatitis, but there has been a strong association with severity of sepsis complicating SAP[39]. However, in another study TNF-α and heat shock protein (HSP-70-2) polymorphism has been associated with risk of SAP[40].

Pancreatic necrosis (PN)

Approximately 20% of patients with AP develop PN. Various factors including ischemia, lysozyme enzymes, vasoactive mediators and ROS are responsible for the development of PN. It is assumed that the lysozomal protease, that activates trypsinogen in the presence of intracinar colocalisation of digestive and lysozyme enzymes, is responsible for the acinar necrosis[41]. Other vasoactive mediators that contribute to the development of PN include endothelin-1[42], phospholipase A2 (PL-A2)[43] and bradykinin inhibition[44]. Phospholipase-A2 also mediates the development of PN and strongly correlates with severity of AP as well as with occurrence of pulmonary and renal complications. Severe AP is associated with microvasculature damage, compromise of the microcirculation and release of ROS from leukocytes and macrophages[45]. Chronic alcohol consumption constitutes a strong risk factor for PN as has been shown in a recent two-arm study[46]. Alcohol, whether acute intake or chronic consumption, increases monocyte response to inflammatory signals and may enhance the inflammatory process in pancreatitis[47]. It is assumed that the most significant determinant prognostic factor of AP is development of PN with subsequent complications[48]. Acute necrotizing pancreatitis consists of an early phase during the first two weeks characterized by a sterile PN and systemic inflammatory response syndrome (SIRS) and a second phase with infection of the PN, septic complications and MODS[49].

Infected pancreatic necrosis (IPN)

The presence of bacteria in focal or diffuse areas of intra- or extrapancreatic tissue is defined according to the Atlanta definition as IPN[1]. The gut represents the main source of pancreatic contamination and related septic complications[49]. The mechanism of pancreatic infection is not yet fully explored. However, recent investigations have focused on the bacterial translocation (BT) from the intestine. Systemic inflammatory response syndrome associated ischemia, release of ROS and acidification are responsible for the mucosal dysfunction in patients with SAP[50]. Transmural[51], hematogenous[52] and lymphogenous[53] spread are the major pathways of BT. Several factors including altered gut motility, immunosuppression, bacterial overgrowth and damaged mucosal barrier promote BT and hence pancreatic contamination with septic complications and increased mortality rate[54]. Acute pancreatitis by itself

may promote BT with subsequent pancreatic infection and related complications[55]. Experimental studies have suggested BT *via* a damaged intestinal barrier[45] and immunosuppression[56] as the two important key factors of pancreatic contamination.

The incidence of infection in AP usually does not exceed 10%[57], however it approaches 80% in NP with increased morbidity and mortality rates[58,59]. The risk of infection is correlated with the extension of necrosis. It occurs in 30%-40% of patients with ⩾ 30% necrosis. Aggravation of abdominal pain, fever, leukocytosis, although not specific, may indicate infection of pancreatic necrosis. However, a definite diagnosis is established only by US- or CT-guided fine needle aspiration (FNA)[60,61]. Currently, FNA and culture of the aspirate are recommended to confirm IPN in patients with sepsis[62]. The mortality rate in IPN is around 25% compared to 10% in sterile necrosis and no mortality in MAP[63]. Infection and septic complications account for 60%-80% of mortality in AP[64,65].

Multi-organ dysfunction syndrome (MODS)

Several factors are thought to contribute through their injurious effect on the endothelial barrier to the pathogenesis of MODS. These factors include cytokines[66], ROS[67], PL-A2, elastases[68] and calcium flux[69]. In SAP the development of MODS is a result of hemodynamic abnormalities possibly secondary to activation of kinin and other vasoactive peptides[70]. Reactive oxygen species originate from various sources including xanthin oxidases, mitochondrial cytochrome oxidases, arachidonic acid metabolism and PMNs[71,72]. In SAP, the microcirculatory dysfunction is apparently mediated by ROS, leukotriens, PAF, interleukins and other proinflammatory mediators[73]. Proinflammatory cytokines (TNF-α, IL-1b and IL-6) play a significant role in the pathogenesis of AP and may mediate systemic complications[11]. These complications may result from an exaggerated and uncontrollable host response leading to SIRS[74]. Multi-organ dysfunction syndrome is apparently induced by cytokines, and inflammatory mediators released in a state of SIRS[2,75] which occurs in 72%-90% of patients with SAP. Single organ failure (SOF) accounts for 25%-37% and multi-organ failure (MOF) accounts for 35%-66% of MODS. The most commonly encountered SOF has been respiratory, cardiovascular, hepatic and renal failure in 39.1%-63%, 23%-37.7%, 20.7% and 5.8%-13% of patients, respectively[76-78]. In a similar study, 61.7% have had MOF and 26.6 SOF mainly respiratory (35.1%), cardiovascular (22.3%), GI (19.1%), hepatic (15.9%) and renal (14.9%) in origin[7]. Development of MODS is considered a major risk of mortality[11,79].

Abdominal compartment syndrome (ACS)

The combination of intra-abdominal hypertension (IAHT) and end-organ dysfunction has been described as ACS. It is determined by measurement of abdominal pressure[80]. The diagnosis of ACS is established when intra-abdominal pressure exceeds 15 mmHg (2 kPa) associated with low cardiac output, progressive oliguria and hypoxia[2]. Abdominal compartment syndrome is associated with a high mortality rate correlated with sepsis and MODS. Recent reports have described the association of ACS with SAP. Approximately 11% of patients with SAP develop ACS with a higher incidence in fulminant AP, higher mortality[81-83] and organ failure rates in the majority of patients[84]. More frequently, IAHT has occurred in association with ESAP. Approximately 78% of patients with ESAP have had IAHT[2]. Abdominal compartment syndrome may develop in association with an aggressive fluid replacement[85] and during the infection and SIRS stages[86]. It is mainly correlated with uncontrolled and sustained IAHT and characterized by a severely distended abdomen and MODS. Anuria and IAHT are the most important determinants of mortality[87].

Mortality

Several authors have reported various rates of mortality varying according to the stage and severity of AP. While MAP has no mortality, the rate amounts to 10% in NP and 25% in IPN[63]. Higher rates ranging from 20%-60%[8,9] and 30%-90% in fulminant pancreatitis[88] have been reported. There are two peaks of mortality in SAP. The early phase mortality, mostly due to SIRS and MODS, occurs within the first few days and the second peak induced by PN, IPN and MODS occurs after the second week[79]. Approximately 23% of the early mortality has occurred within the first 3 d and 53% within the first week[3]. Another study has reported early mortality in 51% within the first two weeks primarily due to MODS and later 49% mainly due to IPN[89]. Sepsis and MODS may complicate pancreatic contamination contributing to > 80% of mortality[65]. Early diagnosis and appropriate management are important to decrease morbidity and mortality. A delay of transfer to ICU > 24 h after admission is associated with a four fold increased mortality risk[90]. Several factors such as etiology, age, gender, race, genetic makeup, severity on admission, the extent and infection of PN have been reported to influence the mortality[77]. On the contrary, other authors have reported a correlation between the mortality and the severity of the attack but no correlation with the cause of AP[88]. The persistence of organ failure is a strong marker of poor outcome and mortality[91]. PN, IPN and MODS are the major determinants of mortality[6,58]. The majority of deaths are due to MODS[6,92]. In a multivariate logistic analysis ARF,CVF and RF have been the independent prognostic factors of mortality[7] and IPN and MODS are the most significant causes of hospital mortality[93,94]. Other authors have reported ARF and RF as the main cause of mortality and no influence of PN on mortality in SAP[95]. Despite improvement in diagnostic and therapeutic modalities, SAP remains associated with a high mortality rate[96] ranging from 15%-20%[88] and may be as high as 40%[97]. While some authors have reported a persistence of the mortality rate for the last decades[96,98], others have reported a significant decline[79,99].

PROGNOSTIC EVALUATION

SAP is associated with a high early mortality rate (30%-50%) mostly as a result of MODS[100,101]; hence early diagnosis and appropriate management are essential. However, identification of severe cases during the first

Table 1 Predictors of severity of acute pancreatitis

Severity predictor	Reference
Multifactorial scoring system	
Ranson, Imrie, APACHE II	[14]
Clinical data	
Age	[108]
Etiology	[108]
Obesity	[63,109]
Simple prognostic scores	
BUN (=/> 25 mg/dL), LDH (=/> 900 IU/L) and PN on CE-CT	[104]
Age, highest serum creatinine (within 72 h), chronic health status and requirement for mechanical ventilation	[119]
Inflammatory markers:	
IL-6, IL-8	[10]
PL-A2, CRP	[64]
PMN-elastase	[122]
TAP	[123]
PCT	[124]
CT-scoring index (CTSI)	[140]

PN: Pancreatic necrosis; CE-CT: Contrast enhanced computed tomography; IL-6: Interleukin-6; IL-8: Interleukin-8; PL-A2: Pancreatic phospholipase A2; TAP: Trypsinogen activation peptide; CRP: C-rective protein; PTC: procalcitonin; PMN: Polymorphonuclear cells; LDH: Lactate dehydrogenase.

Table 2 Early predictors of severity

Marker		Period	Reference
Clinical:	Obesity	on admission	[111,112]
Radiological:	Abnormal chest radiograph	within 24 h	[21]
Laboratory:	Serum BUN	within the 1st 24 h	[104]
	Serum creatinine	within the 1st 24 h	[21]
	Hematocrit	on admission	[133]
	Proteinuria	2nd d of admission	[111]
	CRP	24-48 h	[129]
	MMP-9	1-48 h of admission	[132]
	SAA	within the 1st 24 h	[43]
	IL-6, IL-8	within the 1st 24 h	[10]
	IL-18	within the 1st 48 h	[28]
	Trypsinogen-2	on admission	[131]
	Trypsin-2 AAT	on admission	[131]
Factors (in biliary pancreatitis) predicting need for ICU:			
	Heart rate, Glucose, BUN, WBC&CRP	on admission	[136]

CRP: C-reactive protein, MMP-9: Matrix metalloproteinase-9; SAA: Serum amyloid A; IL-6, 8, 18: Interleukins 6, 8 and 18; BUN: Blood urea nitrogen; WBC: White blood cell count, trypsin-2; AAT: Trypsin-2-alpha-1-antitrypsin.

2-3 d of symptoms onset, where MODS takes place, is difficult[102,103]. The best predictors include clinical features, markers of pancreatic injuries and markers of inflammatory response[63].

Currently, several markers are used for prognostic evaluation of different stages in the course of AP and development of complications. They can be classified as markers of severity, early prediction, PN, IPN and mortality (Tables 1-5).

Markers of severity

Multifactorial scoring systems (MFSS): All MFSS such as Ranson, Glascow, Imrie, APATCHE Ⅱ and clinicobiochemical systems have a similar accuracy after 48 h of admission[14]. They are good predictors of severity and PN[104]; however they have insignificant value for prediction of infection in patients with SIRS[105,106]. MFSS are complex, consist of several criteria[104] and are less accurate than the calcitonin precursor in the prediction of infection in patients with SIRS[107] and consume 48 h.

Table 3 Predictors of pancreatic necrosis

Marker	Reference
1 C-reactive protein (CRP)	[48,148]
2 Serum lactate dehydrogenase (LDH)	[153]
3 Procalcitonin (PCT)	[151]
4 Serum amyloid A (SAA)	[14]
5 Serum macrophage migration inhibitory factor (MIF)	[152]
6 Contrast enhanced CT (CE-CT)	[153]

Table 4 Markers of infected pancreatic necrosis

Marker	Reference
1 C-reactive protein (CRP)	[64]
2 Procalcitonin (PCT)	[64,124]
3 Serum amyloid A (SAA)	[14]
4 Interleukin-6, 8 (IL-6, IL-8)	[64]
5 Soluble intracellular adhesion molecule (sICAM-1)	[58]
6 Reactive nitrogen intermediates (RNIs)	[155]
7 US- or CT-guided FNA	[14,60,61]

Table 5 Markers of mortality

Marker	Reference
1 Obesity	[111,112]
2 Serum creatinine > 2 mg/dL	[21]
3 Pleura effusion on chest radiograph	[21]
4 Early nonenhanced CT	[157]
5 Multiorgan dysfunction syndrome (MODS)	[6,92]
6 Pancreatic necrosis (PN)	[6,92]
7 Infected pancreatic necrosis (IPN)	[6,92]
8 Interleukin-6 (IL-6)	[90]
9 Reactive nitrogen intermediates (RNIs)	[58,156]

Clinical data: Some recent reports have discussed the predictive value of clinical data such as age, etiology[108] and obesity[63,109]. Obese individuals have had a worse prognostic score on admission and have developed significantly more complications compared to non-obese patients. For instance, respiratory failure has occurred more frequently in obese subjects[109]. Also the rates of infective complications such as IPN, sepsis and pancreatic abscess have been higher in obese patients[109,110]. Generally, obesity is more frequently associated with SAP, local and systemic complications and mortality; hence it should be used routinely in the initial assessment of severity[111,112]. Obesity increases the risk for SAP by enhancing the immune response to pancreatic injury[113]. Body mass index (BMI) > 30 kg/m^2 is a reliable predictor of severity[63,114]. However, another study has found no effect of BMI on pro- or anti-inflammatory cytokines levels in early pancreatitis[115].

While some studies have not found a correlation between etiology on one hand, course and outcome of AP on the other hand[88,116], others have reported the highest mortality rate in patients with idiopathic pancreatitis[117,118].

Laboratory markers: Current prognostic markers of severity are valuable, but immediate evaluation is difficult to establish[109]. However, Simple prognostic score (SPS), consisting of blood urea nitrogen (BUN) ⩾ 25 g/dL, serum lactate dehydrogenase (LDH) ⩾ 900 U/L and presence of PN on contrast enhanced-CT (CE-CT), is comparable with MFSS with the advantage of simple prediction of SAP on admission[104]. Another SPS constituting four variables including age, highest serum creatinine within three days of primary admission, chronic health status and mechanical ventilation requirement have had a similar predictive performance as APACHE Ⅱ[119].

Inflammatory markers: Cytokines have a central role in the pathogenesis of SAP. The proinflammatory cytokine response is reflected by an increased IL-6 level and release of anti-inflammatory mediators. Elevated levels of pro- and anti-inflammatory cytokines occur early, persist for several days in systemic circulation and are independent of sepsis. By univariate analysis an IL-6 level > 1000 pg/mL is associated with an increased risk of mortality at day one[90]. Inflammatory markers such as IL-6, TNF-α, PL-A2 and CRP are good predictors of severity, however, their role in identifying those at risk to develop IPN is not determined yet[64]. Significantly higher levels of IL-6, IL-8 and TNF-α differentiate independently MAP from SAP. TNF-α is difficult to measure compared to IL-6 and IL-8[10]. IL-ra and IL-15 are useful predictors of complications, especially MODS[120,121] and mortality[121].

Other markers such as PMN-elastase[122], trypsinogen activation peptide (TAP)[123] and procalcitonin (PCT)[124] are elevated in SAP and can be used for severity assessment. They are able to predict the severity, but they are not widely available. Currently, CRP is the only marker applied routinely in clinical use[125]. It is considered as the standard severity and prognostic serum marker in SAP[126]. The levels of CRP in SAP have differed from control and MAP after 48 h of symptom onset. In contrast, SAA plasma level has differed significantly ($P < 0.001$) in SAP from MAP and control and can predict severity earlier and better than CRP[14]. In SAP CRP and SAA levels are significantly higher than other acute phase proteins[127].

Early markers for prediction of severity

Various markers including IL-6, IL-8[119,128], TNF-α, PMN-elastase[129], TAP[130], PLA-2[43] can be used as early predictors of SAP, however they need to be made clinically applicable[63]. CRP is the widely used and clinically applied marker of severity 48 h after the onset of symptoms[129]. Other early predictors of severity include a marked decrease of GPx and selenium serum concentration, which reflect the significance of oxidative stress, are associated with a marked increase of IL-18 during the first two days of admission in patients with SAP. Hence, GPx and IL-18 may be used as predictors of severity[28]. Trypsinogen-2 and trypsin-2-alpha-1-antitrypsin (trypsin-2 AAT) have been reported as early accurate markers of severity already at admission, therefore, they are considered as useful markers for clinical use[131].

In addition, MMP-9, a Zn^{2+} containing enzyme[132] has been reported as a valuable early predictor of severity. It significantly degrades the basement membrane components in the inflammatory process and is involved in the deterioration of SAP. In comparison to normal subjects and those with MAP, it increases significantly one hour after admission, decreases after 48 h and is able to differentiate SAP from MAP already one hour after admission. It also correlates well with CRP and TNF-α levels and APACHE Ⅱ in patients with SAP[98].

BUN, a marker of hypovolemia and catabolism has been suggested as the most useful prognostic predictor in the first 24 h of SAP onset[104]. In addition, serum creatinine level exceeding 2 mg/dL (> 176.8 μmol/L) and the presence of pleura effusion or parenchymal densification on chest radiography identify within 24 h of admission those with a severe or adverse clinical course[21]. The presence of pleural effusion particularly, left-sided or bilateral, has an excellent predictive value[99]. Furthermore, patients with SAP commonly develop proteinuria, which can discriminate on the second day of admission SAP from MAP[111].

Hematocrit (Hct) has also been reported as an early, reliable, easily obtainable and cheap marker. Its prognostic value on admission is comparable to MFSS after 48 h of admission. It limits the requirement of CE-CT to those who do not improve[133]. On the contrary, other authors have not found a significant difference in the decrease of the 24 h Hct concentration in MAP and SAP[134] and hemoconcentration has recently been reported as a poor predictor of PN[135]. In patients with biliary pancreatitis serum glucose, BUN, WBC, tachycardia and APACHE Ⅱ scores independently predict patients requiring intensive care management[136].

Early localization of PN by CE-CT can predict the outcome in SAP. Necrosis of the head or the entire pancreas is associated with high risk complications compared to the distal part[137]. The accuracy is enhanced by additional use of Hong-Kong simple biochemical criteria (BUN and glucose)[138]. Additionally the presence of extrapancreatic collection and non-visualization of portal and splenic veins on CT predicts complicated outcome in SAP[139]. Balthazar CT-severity index (CTSI) ⩾ 5 is an accurate tool for assessing the severity and outcome of AP. It has been superior to Ranson's criteria and APACHE Ⅱ in predicting outcome of AP[140].

Lipid peroxidation products, which suggest a pivotal role of oxidative burst, may help to predict the prognosis in SAP[141]. Also plasma alph2-macroglobulin proteolysis, which induces local and distant tissue injuries and has been associated with increased MMP-2, MMP-9 and serine proteinase plasma levels can be used as a prognostic marker of severity in SAP[142]. Further, recently reported prognostic markers include SAA and neopterin. Serum amyloid A is a sensitive marker of inflammation and tissue injury. It predicts early severity and it has been superior to CRP within the first 24 h of symptom onset[43]. Neopterin, a marker of macrophage activation along with IL-6 serum

levels reflect pancreatitis severity and therefore it may act as a predictor of severity within the first week of AP onset[143]. While PCT has been reported to be of limited additional clinical value in the early assessment of AP[144], it has been found to be an early predictor of severity and can be used to monitor the clinical prognosis[145]. In addition, a more recent prospective international multicenter study has reported PCT as an early and reliable marker of clinically relevant pancreatic infections and the overall prognosis in SAP[146]. The initial data of a recent study has also suggested serum proteomic profile as a predictor of severity that differentiates SAP from MAP[147].

Markers of PN

PN usually develops within the first three days of SAP onset. Several markers are implicated in the prognostic evaluation of PN. These include IL-6[78], TNF[134], CRP, PMN-elastase[148], TAP[149] and SAA[14]. Among these markers CRP is the only available marker in clinical laboratories[59]. CRP is produced in the liver cells under stimulation by IL-1 and IL-6. Although the peak serum concentration is reached after 72 h[150], it is able to differentiate SAP from interstitial pancreatitis within 24 h. CRP with a cut-off level of 110 mg/L has a highest sensitivity and negative predictive value for PN[48]. Its predictive value for PN has been higher than those of PCT and IL-8. The area under the curve (AUC) of ROC has been 0.92, 0.79 and 0.52 respectively[151]. CRP concentration rises significantly in early stages of PN with a high sensitivity and negative predictive value (NPV) of approximately 95%. In a multivariate analysis serum macrophage migration inhibitory factor (MIF) has recently been reported to be an independent predictor of PN[152]. CE-CT is a valuable diagnostic modality for PN with almost 100% sensitivity between 4 and 10 d. It is the gold standard method that confirms the diagnosis of PN; however CRP and LDH, a marker of tissue damage, are routinely utilized as markers of PN[153].

Markers of IPN

The incidence of IPN is influenced by the extent of necrosis and is associated with a prolonged hospital stay and increased rates of morbidity[154] and mortality[155]. In the early stages of the disease there has been no significant difference in the median CRP concentration between IPN and sterile pancreatic necrosis (SPN). Univariate and multivariate regression analysis have shown a correlation between CRP concentration and secondary pancreatic contamination and therefore it has been suggested as a marker to differentiate preoperatively IPN from SPN[64]. Procalcitonin serum level is markedly higher in IPN compared to SPN during the first week. Compared to CRP and IL-6, PCT at a cut-off value of 1.8 ng/mL is closely correlated with the presence and intensity of necrosis infection. On the other hand, a combination of PCT < 2 ng/L and IL-6 < 400 pg/L has been the best to identify patients not at risk of secondary pancreatic contamination. PCT is suggested as a potential and accurate new marker for prediction of IPN[64]. It is a nonspecific marker of infection and sepsis, posses the same diagnostic accuracy of FNA and it correlates well with the presence and severity of infection[64,124].

IL-6 is increased for several days in both infected as well as sterile necrosis, however with significantly higher levels in IPN. Also IL-8 is elevated for a few days in both types of necrosis with markedly higher levels in IPN[64].

IL-8, a potent PMN activating cytokine, is a good indicator of septic MODS in patients with SAP. Other inflammatory cytokine levels for instance, sICAM[58] and nitric oxide in the form of reactive nitrogen intermediates (RNIs)[155] are elevated in both sterile and infected necrosis. Higher levels of NO are associated with an increased risk of sepsis and mortality[156].The gold standard for an accurate and early diagnosis of IPN is the US- or CT-guided FNA with an approximately 90% sensitivity and specifity[14].

Predictors of mortality

Recently, nonenhanced CT has been found to be a valuable predictor of mortality[157]. A novel model for prediction of mortality consisting of four variables: age, highest serum creatinine level within 60-72 h from primary admission, requirement for mechanical ventilation and chronic health status with at least a similar predictive performance of APACHE Ⅱ can predict fetal outcome in the early stage of SAP[119]. ARF, CVF and RF predict mortality in patients with SAP[7]. Systemic complications especially ARF and RF are the main causes of mortality in SAP[95]. Also the presence of chronic renal failure (CRF) worsens the prognosis of AP and is associated with high morbidity and mortality[158]. In a univariate analysis, an IL-6 concentration > 1000 pg/mL has been associated with an increased risk of the first 24 h mortality[90]. Also IL-ra and IL-15 are useful predictors of mortality[120,121].

The mortality risk is correlated with higher serum NO concentration[58]. A serum creatinine level > 2 mg/dL and an abnormal chest radiograph together and isolated are significantly associated with a high mortality risk at 90% sensitivity and 76% specifity[21].

The persistence of organ failure is a strong marker of poor outcome and mortality[91]. PN, IPN and MODS are the major determinants of mortality[6,92].

CONCLUSION

The intracellular presence of inappropriately activated proteolytic enzymes is responsible for the damage of pancreatic tissue. Trypsin in turn activates a cascade of inflammatory markers, which are together with ROS responsible for the development of acute pancreatitis and its complications. Early diagnosis and prognostic evaluation may reduce morbidity and mortality. Prognostic predictors of severity, PN, IPN and mortality are summarized: (1) early severity predictors: obesity, abnormal chest radiograph, serum BUN, creatinine, proteinuria, hematocrit, CRP, MMP-9, SAA, IL-6, IL-8, and IL-18, trypsinogen-2 and trypsinogen-2 AAT, (2) prognostic predictors of necrosis include CE-CT, LDH, CRP, PCT, IL-6, SAA and MIF, (3) prognostic predictors of IPN: CRP, PCT and ultrasound or CT-guided FNA, (4) prognostic predictors of mortality: obesity, pleural effusion on chest radiograph, IL-6, RNIs, PN, IPN, and MODS.

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