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Abbreviations:
APACHE II = Acute Physiology and Chronic Health Evaluation
IL = interleukin
TNF = tumor necrosis factor

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Acute Pancreatitis: Assessment of Severity with Clinical and CT Evaluation[1]

Treatment of patients with acute pancreatitis is based on the initial assessment of disease severity. Severe pancreatitis occurs in 20%–30% of all patients with acute pancreatitis and is characterized by a protracted clinical course, multiorgan failure, and pancreatic necrosis. Early staging is based on the presence and degree of systemic failure (cardiovascular, pulmonary, renal) and on the presence and extent of pancreatic necrosis. Individual laboratory indexes (markers of pancreatic injury, markers of inflammatory response), while promising, have not yet gained clinical acceptance. Numeric grading systems with sensitivities of about 70% are commonly used today as indicators of organ failure and disease severity. Contrast material–enhanced computed tomography is used in addition to help evaluate local pancreatic morphology and the presence and extent of pancreatic necrosis. Advantages and limitations of the clinical, laboratory, and imaging prognostic indexes are analyzed and discussed.

Once the diagnosis of acute pancreatitis is established, the treatment of patients is dependent on the early assessment of disease severity. This assessment, based on objective parameters, is crucial for predicting clinical complications and for identifying potentially lethal attacks, which are known to occur in 2%–10% of patients with acute pancreatitis (1–8). Moreover, in the past 10 years it has been established that the increased frequency of death in acute pancreatitis is directly correlated with the development and extent of pancreatic necrosis (1–8). Thus, the early detection of pancreatic necrosis (necrotizing pancreatitis) signifies severe disease and is being used as a grave prognostic indicator in the initial evaluation of these patients.

The purpose of this review is to describe the accepted new concepts in the development of pancreatic necrosis, as well as to survey the most important individual and collective markers that have been proposed to identify patients with severe attacks of pancreatitis. The advantages and limitations of individual prognostic parameters and scoring systems will be outlined. The role of computed tomographic (CT) imaging in the initial staging of acute pancreatitis will be emphasized. This article reflects the progress made in the past decade in the staging of acute pancreatitis and underlines some of the remaining pitfalls in our staging systems.

PATHOPHYSIOLOGY AND CLINICAL FEATURES

Classification

The 1992 Atlanta, Ga, International Symposium on Acute Pancreatitis has classified this entity into mild acute pancreatitis and severe acute pancreatitis (1,9). While this is not a perfect classification system, since intermediate forms of disease do occur, it has provided a more reliable basis for experimental studies and for clinical management of acute pancreatitis. The rationale of previous classifications (10–13) has been based on the extent and degree of pancreatic injury, which could only be assumed at the time of diagnosis and which could sometimes be confirmed later during surgical exploration or postmortem examination. The new classification, for the first time, defines the severity of disease in practical, clinically relevant terms. In essence, the new classification is based on the presence of multiorgan failure (clinical and laboratory parameters) and on the morphology of the pancreatic gland as depicted at CT imaging performed with intravenously administered contrast material (1,2).

The mild clinical variety of pancreatitis, also called edematous or interstitial pancreatitis, occurs in most individuals. It is a self-limiting disease with absent or minimal organ dysfunction, without complications, and with an uneventful recovery. Severe acute pancreatitis, also called necrotizing pancreatitis, occurs in about 20%–30% of all patients with acute pancreatitis, and it is characterized by a protracted clinical course, a high incidence of local complications, and a high mortality rate (1–8). Parenchymal pancreatic injury is the pathologic hallmark of this form of the disease, but the triggering physiologic factors that initiate and sustain this process are not fully resolved.

Pancreatic Injury: Pathophysiology

It has been assumed that the initial triggering event occurs at the cellular level and is based on premature activation of pancreatic enzymes leading to autodigestion of the pancreatic parenchyma and peripancreatic tissues. Unfortunately, the mechanism by which pancreatic enzymes are activated outside the intestinal tract remains obscure. Intraparenchymal and extrapancreatic extravasation of these activated digestive enzymes is responsible for tissue injury and for damage to the pancreatic vascular network. These phenomena explain the development of perilobular and/or panlobular necrosis affecting the acinar cells, islet cells, pancreatic ductal system, and interstitial fatty tissue (14). Furthermore, extravasation of pancreatic lipase results in the development of peripancreatic fat necrosis. A form of primary ischemic necrotizing pancreatitis can be induced by cardiovascular surgery, atheroembolism, hemorrhagic shock, or transplantation of the pancreas, but this etiology is rarely encountered in clinical practice (15–18).

Pathologic examination of severe pancreatitis has shown extensive interstitial fat necrosis, necrotizing vasculitis with occlusions and thrombosis of small feeding arteries and draining veins, areas of hemorrhage, and devitalized pancreatic parenchyma (1,6,8,14). Similar findings are present in variable degrees in extrapancreatic retroperitoneal fatty tissue. Necrosis occurs early, within the first 24–48 hours, and with few exceptions remains stable during a given episode of acute pancreatitis (8,19,20). It can be diffuse or patchy or superficial or deep, and it may affect any part of the pancreatic gland.

Recently, it has been established that during the first 30 minutes of an acute attack of pancreatitis and, dependent on the presence and degree of pancreatic injury, a variety of toxic, biologically active compounds are produced and liberated in the blood stream and ascitic fluid (4,5,7,8,21–25). Increased levels of serum and/or urinary trypsinogen, trypsinogen-activated peptide, phospholipase A2, and polymorphonuclear cell elastase have been detected in patients with severe pancreatitis (21–26). Moreover, a large number of other inflammatory mediators called cytokines are produced in acute pancreatitis and have been isolated in the ascitic fluid (25,27).

Cytokines are a group of low-molecular-weight proteins that are physiologically active in small concentrations and have a diverse range of pharmacologic activities. Some of them, such as interleukin (IL)-1, tumor necrosis factor (TNF), and platelet-activating factor are considered mediators of disease progression. Others, such as IL-2, IL-6, IL-8, IL-10 and other oxygen free radicals are considered mainly to be markers of disease severity. Once cytokines are manufactured and released by several cell types, they stimulate the production of other inflammatory mediators. Furthermore, they trigger and amplify the progression of several postinflammatory cascades, thereby inducing distal organ dysfunction. Experimental models (25,27) have shown that IL-1 and TNF are initially produced in the pancreatic parenchyma. Later, however, with increased cytokines production, IL-1 and TNF are manufactured in large amounts in other organs, such as the lungs, liver, and spleen. Although pancreatitis is not induced by IL-1 or TNF, the liberation of TNF in the pancreatic parenchyma is toxic to acinar cells and is probably responsible for variable amounts of cellular death. Thus, it has been suggested that at least part of pancreatic parenchymal injury and necrosis may be caused by direct TNF cellular toxicity and not exclusively by the autodigestion or ischemic theory previously proposed (25,27). Despite extensive ongoing research, however, it is still obvious that the exact provenance, contributions, and clinical relevance of this diverse group of biologically active toxic substances are still subject to controversy and further investigations.

Pancreatic Necrosis: Clinical Relevance

The importance of early detection of pancreatic necrosis in clinical practice cannot be overemphasized. Reported mortality rates of less than 1% in patients with interstitial pancreatitis show a dramatic increase to 10%–23% in patients with necrotizing pancreatitis (1–8). Moreover, virtually all life-threatening complications occur in patients with necrotizing pancreatitis. Secondary bacterial contamination occurs in 40%–70% of patients with pancreatic necrosis, and it constitutes a major risk of death (28). In the series reported by Beger et al (8), a mortality rate of 67% was found in patients with infectious necrosis of more than 50% of the pancreatic gland. Most patients with acute pancreatitis who develop multiorgan failure have necrotizing pancreatitis, and more than 80% of deaths occur in patients with pancreatic necrosis (8). In the attempt to improve medical care and decrease morbidity and mortality, the attention of clinical investigators in the past decade has been focused on different means of detecting pancreatic necrosis. Patients with pancreatic necrosis are closely monitored in the intensive care unit, and follow-up clinical, laboratory, and CT examinations are routinely performed in this setting.

Pancreatic Necrosis: Detection

Early detection of severe pancreatitis, and thus necrotizing pancreatitis, by noninvasive means such as clinical evaluation, laboratory investigations, or imaging studies have been historically frustrating but have greatly improved in the past 10 years (1–8).

An ideal or desirable detection system should *(a)* have high sensitivity and positive predictive values, *(b)* be able to depict necrosis early (<48 hours), *(c)* be performed rapidly (<4 hours), *(d)* be available in most hospitals, *(e)* be relatively inexpensive, and *(f)* be objective and not observer dependent (2). The extent to which different clinical and/or laboratory detection methods satisfy these requirements vary greatly and show distinct limitations and advantages peculiar to each individual system.

Severe Pancreatitis: Clinical Evaluation

Recognition of severe pancreatic injury by means of clinical examination is unreliable. Clinical parameters such as tachycardia, orthostatic hypotension, shock, respiratory distress, and signs of peritonitis are consistent with a severe attack. They are, however, rarely seen, are not specific, and usually develop late, which limits their clinical usefulness (1,2,7). Old age, hyperlipidemia, and obesity are associated with an increased risk of death (29–31). Individ-

TABLE 1
Signs of Organ Failure in Acute Pancreatitis

Sign	Parameter
Shock	Systolic blood pressure < 90 mm Hg
Pulmonary insufficiency	Pao_2 < 60 mm Hg
Renal failure	Serum creatinine level > 177 μmol/L
Gastrointestinal bleeding	Volume > 500 mL per 24 h

ually, however, these parameters are not reliable prognostic factors and cannot be used as indicators of disease severity. Flank ecchymosis (Grey-Turner sign) or periumbilical ecchymosis (Cullen sign) are more specific and have been associated with a 37% mortality rate (32). These signs are rarely present, however, and they often appear 48–72 hours after the onset of symptoms.

It has been estimated that experienced clinicians can correctly predict a severe attack of pancreatitis in only 34%–39% of patients at the time of admission (33,34). Furthermore, the authors of previous reports (35) have documented that the diagnosis was missed in 30%–40% of patients with fatal necrotizing pancreatitis until the time of autopsy. Thus, individual clinical signs have only limited value for the assessment of the severity of acute pancreatitis. These signs are often absent in patients who develop later complications, lack objective quantification, and are subjective in interpretation.

Severe Pancreatitis: Laboratory Evaluation

Plasma levels of the pancreatic enzymes amylase and lipase, while useful diagnostic indicators, have no role in the assessment of disease severity (1,2). The serum trypsinogen level may be useful as a predictive indicator, but it has not gained clinical acceptance because a useful clinical assay is not currently available (2,36). Detection of urinary trypsinogen-activated peptide levels has recently been shown to be promising in identifying patients with severe pancreatitis (26). The presence of trypsinogen-activated peptide in urine correlates directly with premature activation of trypsinogen. This enzyme is specific to the pancreas, and it is liberated within the first several hours of the disease (26). Its clinical accuracy as an indicator of pancreatic necrosis has yet to be determined.

More specific markers for pancreatic injury are methemalbumin and pancreatic ribonuclease (4,37–39). The presence in serum of methemalbumin indicates hemorrhagic pancreatitis. Moreover, pancreatic ribonuclease is an intracellular enzyme liberated only in conjunction with necrotic tissue. Despite good specificity, the sensitivity of these tests for the detection of necrosis is marginal, and their clinical application has been in doubt (37–39).

Elevated serum levels of TNF may be detected in patients with necrotizing pancreatitis. This enzyme is produced intermittently, however, and its capricious and temporary release in the serum makes it less suitable as a method for reliable detection of a severe attack (40–42).

Among the cytokines produced by activated neutrophils, IL-6 and phospholipase A2 have been shown to reflect a close relationship between serum concentrations and the clinical severity of pancreatitis. Phospholipase A2 has been implicated in the development of pancreatic necrosis and pulmonary failure, and assays for this cytokine have been reported to have an overall accuracy of about 80% for the detection of necrotizing pancreatitis. However, these laboratory test methods are cumbersome and are not currently available in a clinically useful assay (43–45).

The plasma concentration of polymorphonuclear cell elastase has shown great promise in helping identify patients with severe pancreatitis (24,46). The assay for this enzyme has been reported (46) to have a positive predictive value of over 90% in severe pancreatitis and a high accuracy in the initial demonstration of pancreatic necrosis. This potent enzyme can hydrolyze key plasma proteins such as coagulation and fibrinolysis factors, as well as attack and damage normal-functioning cells in other organs. Its pathophysiologic toxic effects explain some of the systemic early complications seen in patients with severe pancreatitis. An improved assay that is clinically tested, inexpensive, and easily performed is needed for this test to gain clinical acceptance (2,46).

The C-reactive protein assay is cheap, widely available, and fast to perform but lacks specificity and can be used as an indicator of a severe attack only 2–3 days after onset (2,23). C-reactive protein is a nonspecific mediator of inflammation produced by hepatocytes in the liver and is induced by cytokine (particularly IL-6) stimulation. It has been reported to be a prognostic indicator of disease severity with a sensitivity and specificity of 80% (2,23,47,48).

Despite remarkable progress, the clinical usefulness of most of these parameters remains to be further tested in clinical trials. Although these parameters are demonstrated in patients with severe pancreatitis, a direct correlation with the presence and, particularly, the extent of pancreatic necrosis has yet to be proved. Furthermore, many of the assays are still cumbersome and not routinely available. Their utility in clinical practice will be based on the development of new, easily performed, and reproducible biochemical assays.

Peritoneal Aspiration and Lavage

The presence, volume, and color of aspirated intraperitoneal fluid has been used as an indicator of the severity of an attack of acute pancreatitis (33,35). Aspiration of more than 10 mL (35) or more than 20 mL (49) or lavaged fluid dark in color is often seen in patients with severe pancreatitis. The procedure can be performed rapidly, but it has substantial drawbacks. In a large series (49), aspiration led to a correct diagnosis in only 53% of severe attacks. Peritoneal aspiration is an invasive procedure associated with a small number of complications and is poorly tolerated by patients. The results of this procedure have a high predictive value for depicting cases of fulminant pancreatitis, but they are not specific and have a low sensitivity for staging, particularly in patients with biliary pancreatitis (33,35,49).

Multiple Prognostic Indexes

For many years, it has been recognized that obvious alterations of clinical parameters and some abnormal results of routine laboratory tests are often present in patients with severe pancreatitis. For instance, a low serum calcium level (<7.5 mg/dL [1.88 mmol/L]) detected in the background in cases of an acute attack of pancreatitis is a worrisome sign that is seen mainly in patients with severe disease (1–8). Furthermore, it has been shown that the risk of death is increased in patients in whom the serum glucose level is above 250 mg/dL (13.9 mmol/L) and the serum creatinine level after rehydration is above 2 mg/dL (177 μmol/L) (1–8). Signs of multiorgan failure (5) (Table 1) and some specific abnormal clinical and laboratory findings can help identify patients with a severe, potentially lethal form of disease. The presence

of one or several signs of distal organ failure was associated with a 50% mortality rate in the series of Bank et al (50). None of the individual clinical or laboratory parameters, while useful in clinical practice, are sufficiently sensitive or specific to help identify most patients with necrotizing pancreatitis.

In the attempt to overcome these deficiencies, various scoring systems that combine clinical and laboratory parameters have been devised to help identify patients with severe pancreatitis. These scoring systems use the number of specific abnormalities, called prognostic signs, grave signs, risk factors, or objective indicators, to stage acute pancreatitis. It should be emphasized that these physiologic alterations reflect systemic abnormalities; they do not correlate well with severity and extent of local disease, and they certainly do not have diagnostic specificity, because they can be seen in a variety of other conditions.

The first numeric system, proposed by Ranson et al (51) in 1974 (hereafter, Ranson system, Ranson signs), is still the most widely used in this country. It is based on 11 objective signs: five determined initially, and six within 48 hours (Table 2). With an increased number of risk factors, there is a corresponding increase in the morbidity and mortality rates. In patients with fewer than three positive signs, there is no mortality, while in patients with six or more signs the mortality rate is over 50%. Individuals with more than six grave signs usually have necrotizing pancreatitis. The system is an objective indicator of disease severity and is particularly useful at the two ends of the scale. Pancreatitis is mild when there are two or fewer grave signs, whereas pancreatitis is severe when there are more than six grave signs. The correlation with severity of disease or development of necrosis in patients with three to five grave signs, which is a common occurrence, is deficient (5,6). Moreover the system requires the completion of 11 measurements, which necessitates a total of 48 hours of observation for proper evaluation.

Alternative grading systems, each using different parameters, have since been constructed, with a prognostic capability generally similar to that of the Ranson system. The Glasgow original or modified system, the Simplified Acute Physiology, or SAP, score, and simplified prognostic criteria (52,53) have been used (Table 3). Blamey et al (52) introduced a modification of the Ranson system, which they based on eight prognostic criteria (Table 3). They omitted hematocrit level, base deficit, age, and fluid sequestration but included serum albumin level of less than 32 g/L as an important criterion of severity. Despite modifications and fine tuning, however, the overall sensitivity of the aforementioned numeric systems in the initial staging of an attack of pancreatitis ranges from 57% to 85%, with a specificity of 68%–85% (2,7,52,53).

TABLE 2
Criteria of Ranson et al (51) for Severity of Acute Pancreatitis

Parameter	Value
At admission	
Age	>55 y
WBC count	>16,000/μL (16 × 10^9/L)
Serum glucose level	>11.1 mmol/L
SLDH/ALT	>350 IU/L
AST level	>250 IU/L
During initial 48 h	
Hematocrit	Decrease of more than 0.10
BUN level	Increase of more than 5 mg/dL (1.8 mmol/L)
Calcium	<2 mmol/L
Pao_2	<60 mm Hg
Base deficit	>4 mmol/L
Fluid sequestration	>6 L

Note.—AST = asparate aminotransferase, BUN = blood urea nitrogen, SLDH/ALT = serum lactate dehydrogenase to alanine aminotransferase ratio, WBC = white blood cell.

TABLE 3
Simplified Prognostic Criteria in Acute Pancreatitis

System and Parameter	Criterion
Cardiac	
Blood pressure	<90 mm Hg
Tachycardia	>130 beats per min
Pulmonary	
Po_2	<60 mm Hg
Renal	
Urinary output	<50 mL/h
Metabolic	
Calcium level	<8 mg/dL (2 mmol/L)
Albumin level	<32 g/L

Note.—Assessment performed during initial 48 hours.

TABLE 4
Acute Pancreatitis Graded with CT

Grade	CT Finding
A	Normal pancreas
B	Pancreatic enlargement
C	Pancreatic inflammation and/or peripancreatic fat
D	Single peripancreatic fluid collection
E	Two or more fluid collections and/or retroperitoneal air

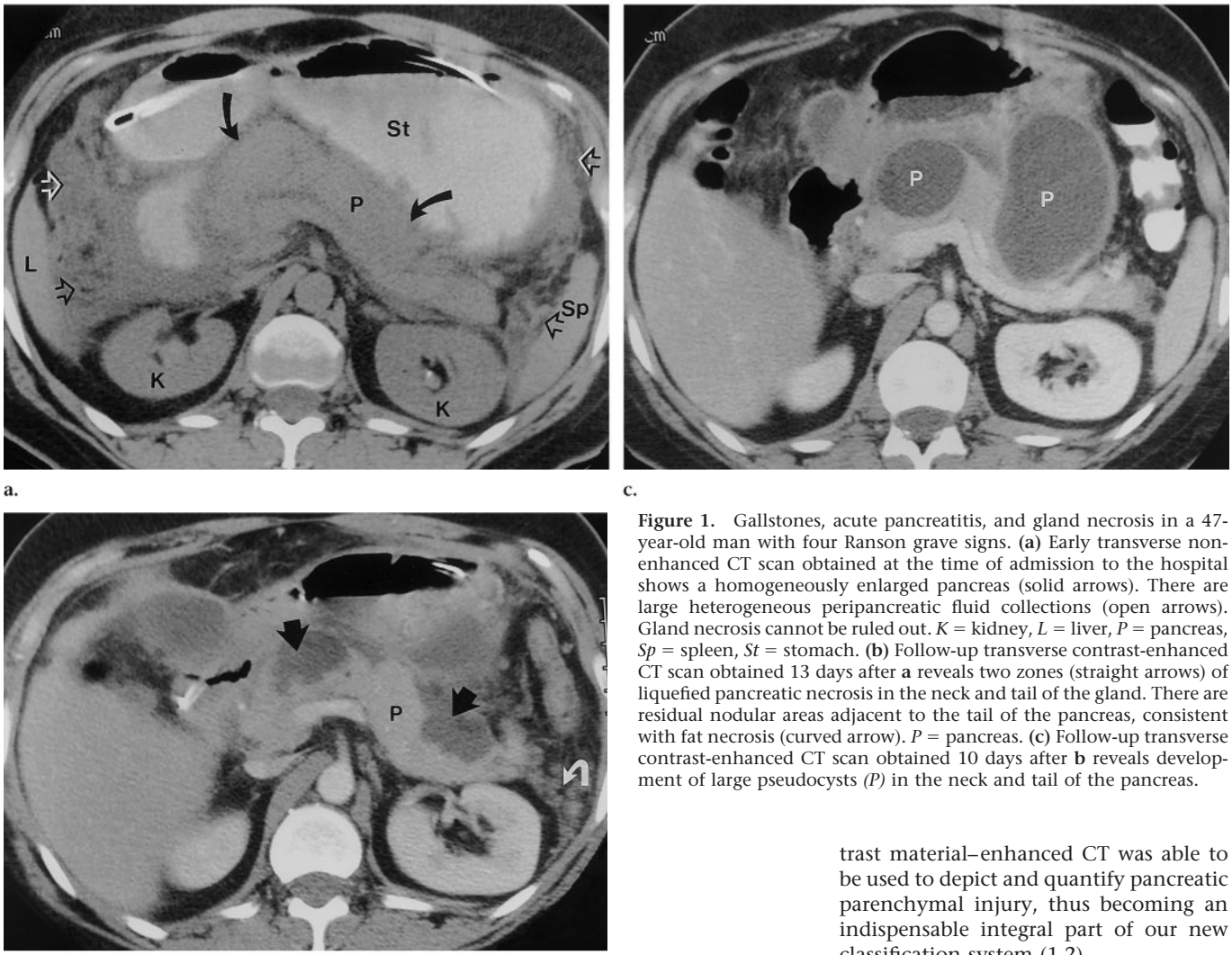
More recently, the Acute Physiology and Chronic Health Evaluation (APACHE II) assessment and monitoring system has become popular, because it is considered to be more reliable (54–56). The system is complex and more difficult to perform, because 12 physiologic measurements are used. The higher the total score, the more severe the pancreatitis, with a corresponding increase in morbidity and mortality. It has been suggested that a cutoff APACHE II score of greater than 8 indicates severe pancreatitis (1,2,5–7). The major advantage of the APACHE II numeric system, as compared with the other systems, is that it can be used throughout the patient's hospital course in monitoring the patient's response to therapy (3,5,6). The accuracy of the APACHE II system at admission for the assessment of the severity of pancreatitis has been about 75%. The test is useful as an early prognostic indicator of disease severity to help identify patients for intensive care unit treatment. After 48 hours, APACHE II scores are comparable with Ranson system scores in distinguishing mild from severe pancreatitis, with an accuracy of about 70%–80% (1,2,5–7).

IMAGING EVALUATION

Conventional abdominal radiographs and barium studies, while occasionally useful in helping diagnose pancreatitis and detect late complications (abscess, strictures, fistulas), have no role in the early evaluation of disease severity. Abnormal chest radiographs however, either alone or in combination with renal function tests (plasma creatinine level), can be useful for the prediction of severity (57–59). The reported (60) incidence of pulmonary findings (infiltrates, effusions) in acute pancreatitis is 15%–55%, seen mainly in patients with severe disease. The predictive value is increased with left-sided or bilateral pleural effusions. An isolated left pleural effusion, however, is seen in only 43% of patients with severe pancreatitis (61).

Ultrasonographic Evaluation

Ultrasonography (US) is indicated early in an acute episode of pancreatitis, to help evaluate for the presence of gallbladder and/or common duct stones. US



a. c.

b.

Figure 1. Gallstones, acute pancreatitis, and gland necrosis in a 47-year-old man with four Ranson grave signs. **(a)** Early transverse nonenhanced CT scan obtained at the time of admission to the hospital shows a homogeneously enlarged pancreas (solid arrows). There are large heterogeneous peripancreatic fluid collections (open arrows). Gland necrosis cannot be ruled out. *K* = kidney, *L* = liver, *P* = pancreas, *Sp* = spleen, *St* = stomach. **(b)** Follow-up transverse contrast-enhanced CT scan obtained 13 days after **a** reveals two zones (straight arrows) of liquefied pancreatic necrosis in the neck and tail of the gland. There are residual nodular areas adjacent to the tail of the pancreas, consistent with fat necrosis (curved arrow). *P* = pancreas. **(c)** Follow-up transverse contrast-enhanced CT scan obtained 10 days after **b** reveals development of large pseudocysts *(P)* in the neck and tail of the pancreas.

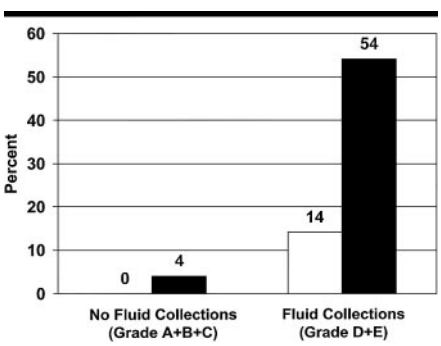


Figure 2. Bar graph shows clinical relevance of CT grading in acute pancreatitis (67). Black bars = complications, white bars = mortality.

however, has limited applications in the early staging of the disease. Visualization of the pancreas is often impaired because of overlying bowel gas, and the detection of intraparenchymal and retroperitoneal fluid collections correlates poorly with pancreatic necrosis. Abnormal US findings are seen in 33%–90% of patients with acute pancreatitis. A diffusely enlarged and hypoechoic gland is consistent with interstitial edema, while extrapancreatic fluid collections (lesser sac, anterior pararenal space) are detected in patients with severe disease (62,63).

CT Evaluation

CT, as used to aid the diagnosis and staging of acute pancreatitis, has greatly improved and has changed the clinical management of this condition. Most of the clinical and laboratory parameters hitherto discussed are used to evaluate the systemic effects of pancreatitis and only indirectly to try to infer the presence and degree of pancreatic damage. For the first time, to our knowledge, contrast material–enhanced CT was able to be used to depict and quantify pancreatic parenchymal injury, thus becoming an indispensable integral part of our new classification system (1,2).

The authors of several early studies (64–66) based on CT images obtained without intravenous contrast material or with slow intravenous infusions and 8–10-mm collimation have described the potential use of CT in assessing acute attacks and complications of acute pancreatitis. In our study, published in 1985 (67), we graded the severity of pancreatitis into five distinct groups, from A to E (Table 4), and attempted to correlate the CT grade with clinical follow-up findings, morbidity, and mortality. We found that most patients with severe pancreatitis exhibit one or several pancreatic fluid collections (grades D and E) on the initial CT study (Fig 1). Patients with grade D or E had a mortality rate of 14% and a morbidity rate of 54%, as compared with no mortality and a morbidity rate of only 4% in patients with grade A, B, or C (Fig 2). Similar observations were later reported by other clinical investigators (68,69).

This CT grading is easy to perform, is

fast, does not require intravenous administration of contrast material, and can be used to identify a subgroup of individuals (with grade D or E) at risk of death or a high morbidity rate. Its main drawback, however, is the inability to reliably depict pancreatic necrosis and, consequently, further define the risk of complications in patients with retroperitoneal fluid collections at the time of presentation (Fig 1). In our original 1985 study (67), we observed that peripancreatic fluid collections resolved spontaneously in about half (54%) of the patients, while these collections persisted, organized, enlarged, or became infected and developed abscesses or pseudocysts in the other half (46%).

A major improvement in this early grading system was achieved with the introduction of the incremental dynamic bolus CT technique. Investigators in Finland (70) and Germany (71) have shown that the attenuation values of pancreatic parenchyma during an intravenous bolus study can be used as an indicator of pancreatic necrosis and as a predictor of disease severity. Patients with interstitial mild pancreatitis have an intact capillary network with vasodilation and, therefore, should exhibit uniform enhancement of the pancreatic gland (Fig 3). Areas of diminished or no enhancement indicate decreased blood flow and relate to pancreatic zones of ischemia or necrosis (Figs 1, 4). The correlation between CT findings and surgical confirmation of necrosis was investigated by Beger et al (71). CT has shown an overall accuracy of 87% with a sensitivity of 100% for the detection of extended pancreatic necrosis and a sensitivity of 50% if only minor necrotic areas were present at surgery. There were no false-positive CT scans, which yields a specificity of 100% (71,72). These results were subsequently confirmed by Bradley et al (73), and the prognostic importance of CT for detection of pancreatic necrosis was emphasized.

Accepted criteria for the CT diagnosis of pancreatic necrosis have been defined as focal or diffuse zones of nonenhanced pancreatic parenchyma depicted during an examination with intravenous bolus administration of contrast material. The extent of necrosis was further quantified to less than 30%, 30%–50%, and more than 50% of the pancreatic gland (Figs 1, 4).

In our 1990 series (74), an excellent correlation was documented between necrosis (as previously defined), length of hospitalization, development of complications, and death. While patients without necrosis had no mortality and a complication rate of only 6% (Fig 3), patients with CT evidence of necrosis exhibited a 23% mortality rate and an 82% morbidity rate (Fig 5). Furthermore, the extent of necrosis proved to be of major importance. Patients with less than 30% necrosis exhibited no mortality and a 48% morbidity rate (Fig 6), while larger areas of necrosis (30%–50% and >50%) were associated with a morbidity rate of 75%–100% and a mortality rate of 11–25% (Figs 1, 4). The combined morbidity rate in patients with more than 30% necrosis was 94%, and the mortality rate was 29%. Other investigators (75–77) later confirmed the validity of these findings.

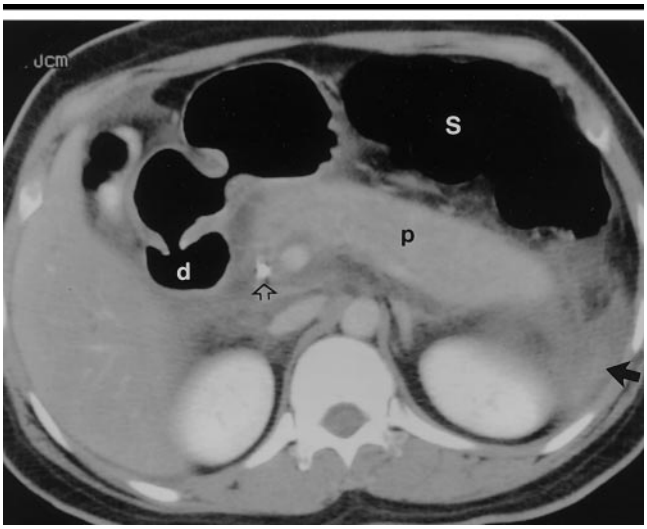


Figure 3. Pancreatitis induced by endoscopic retrograde cholangiopancreatography (ERCP) in a 37-year-old woman. Transverse CT scan obtained with intravenous and oral contrast material shows an enlarged and homogeneously enhancing pancreatic gland *(p)*. Residual contrast material from recent ERCP is seen in the common duct (open arrow). Extravasated fluid (solid arrow) is present around the gland. The patient had an uneventful recovery. *d* = duodenal bulb, *S* = stomach.

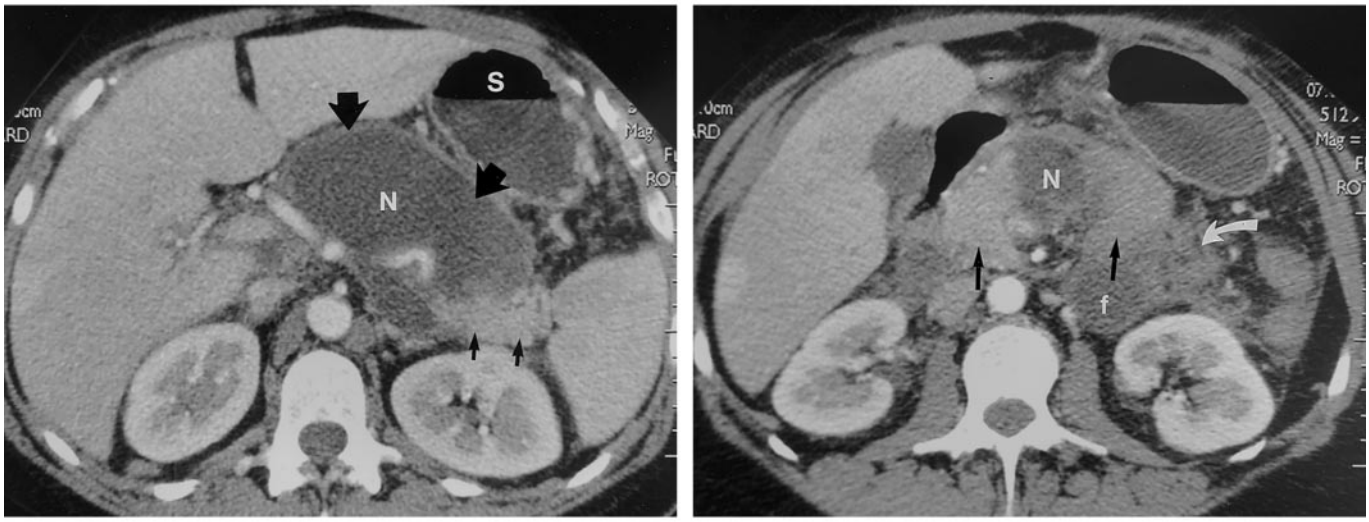
There is general agreement that the development and extent of pancreatic necrosis are the most important indicators of disease severity (1,2,5,6,8,78). It should be emphasized, however, that systemic and local complications may occur during an episode of acute pancreatitis in patients without pancreatic necrosis. In our 1990 series (74), none of the patients with normal enhancing glands died; however, 22% of patients with CT grades of D or E developed complications despite the absence of pancreatic necrosis. Accordingly, a simple scoring system was devised, which combined the original grading system (67) with the degree of pancreatic necrosis (74).

CT Severity Index

The CT severity index is an attempt to improve the early prognostic value of CT in cases of acute pancreatitis (74,78). Patients with grade A–E pancreatitis are assigned zero to four points plus two points for necrosis of up to 30%, four points for necrosis of 30%–50%, and six points for necrosis of more than 50% (Table 5). For instance, a patient with CT grade D is assigned three points; if, in addition, the patient has more than 50% necrosis, an additional six points are assigned, for a total index score of 9 (Table 5). There was a statistically significant correlation, with a continuous increasing incidence of morbidity and mortality in patients stratified according to CT severity index groups. Patients who had a severity index of 0 or 1 exhibited a 0% mortality rate and no morbidity, while patients with severity index of 2 had no mortality and a 4% morbidity rate. In contrast, a severity index of 7–10 yielded a 17% mortality rate and a 92% complication rate (74).

CT Enhancement Values and Pitfalls

The accuracy of CT for assessing the presence and extent of pancreatic parenchymal injury depends on several factors but most importantly on the quality of the study. Intravenous administration of contrast material is essential, particularly in patients with severe pancreatitis, to enable visualization of the pancreas and differentiation of the gland from adjacent heterogenous collections of fluid



a. b.

Figure 4. Pancreatic necrosis in a 50-year-old woman after an episode of acute pancreatitis. **(a, b)** Transverse CT scans obtained with intravenous and oral contrast material reveal an encapsulated fluid collection associated with liquefied necrosis (large straight arrows in **a**) in the body of the pancreas. The head, part of the body, and the tail of the pancreas are still enhancing (small straight arrows in **a**, straight arrows in **b**). Residual fluid collections and areas of soft-tissue attenuation (curved arrow) consistent with fat necrosis are seen adjacent to the pancreas. *f* = fluid, *N* = liquefied gland necrosis, *S* = stomach.

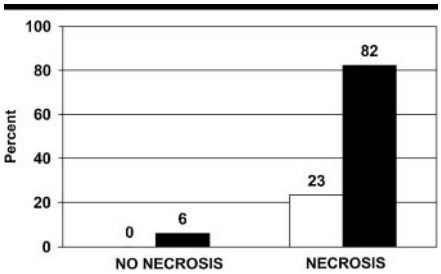


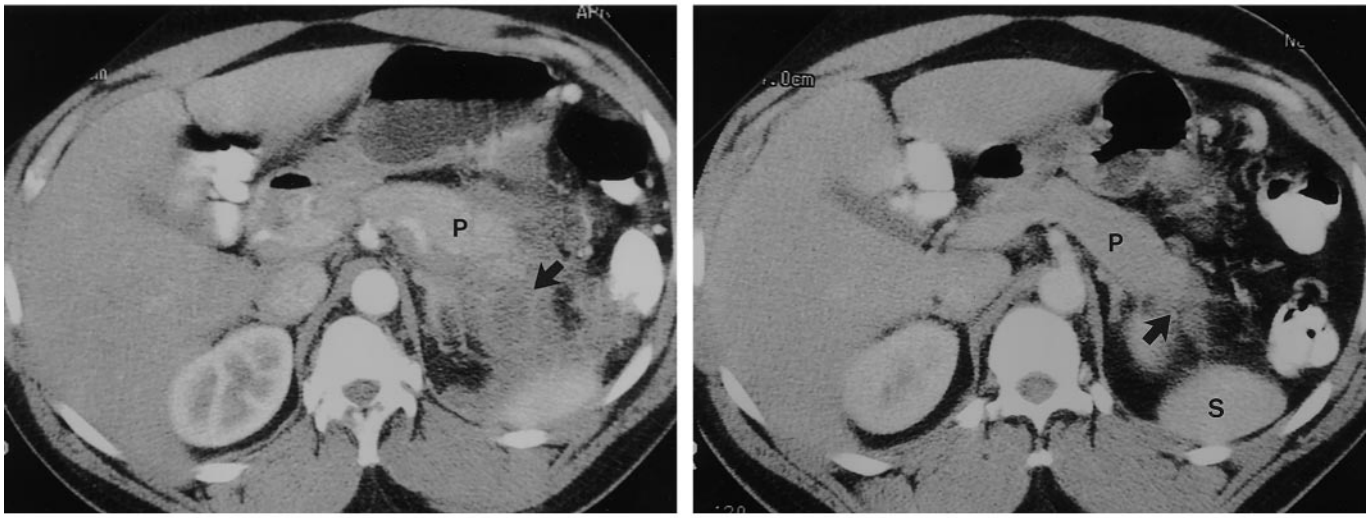
Figure 5. Bar graph shows clinical relevance of CT for detection of pancreatic necrosis in acute pancreatitis (74). Black bars = complications, white bars = mortality.

and peripancreatic inflammatory tissue (Fig 1). With helical or multidetector scanning with rapid acquisition of sequential images and collimation of less than 5 mm, images can be obtained in the early portal venous phase (60–70 seconds after intravenous administration of 150 mL of iodinated contrast material at a rate of 3 mL/sec). We still use a monophasic protocol, starting at the top of the diaphragm and covering the entire abdomen and pelvis. Since unenhanced images are not obtained, the detection of parenchymal injury is based solely on the degree and homogeneity of pancreatic enhancement. Basic pancreatic CT numbers of 40–50 HU seen on unenhanced CT images are expected to increase to 100–150 HU throughout the entire normal gland during contrast material administration, depending on the size of the bolus, the speed of the injection, and the time of image acquisition (Fig 3). Lack of contrast enhancement or minimal contrast enhancement of less than 30 HU of a portion of the pancreas or of the entire pancreas indicates decreased blood perfusion (ischemia) and correlates with the development of necrosis (Figs 1, 4, 6). In this regard, however, several factors and potential pitfalls should be kept in mind.

First, enhancement values of the pancreas during examination with a bolus of contrast material can be substantially decreased in healthy patients with fatty infiltration of the pancreas (Fig 7), as well as in patients with interstitial pancreatitis, due to parenchymal edema (Fig 8). Furthermore, a slight variation in the enhancement values of the head, body, and tail of the pancreas (usually <30 HU) is sometimes seen in healthy individuals. Pancreatic necrosis should not be diagnosed in these cases unless a localized or diffuse change in the texture of the gland is recognized (Figs 1, 4, 6). Whether presumed pancreatic ischemia manifesting as areas of decreased attenuation on the initial CT study is a reversible or inconsequential phenomenon is not known but is subject to speculation (Fig 9). Additionally, small intrapancreatic fluid collections sometimes seen in acute pancreatitis should not be confused with small areas of parenchymal necrosis. The distinction is difficult and sometimes impossible to make unless previous or follow-up CT images are available for review.

Second, it has been determined that pancreatic necrosis develops early, within the first 24–48 hours after the onset of clinical symptoms (8,19). CT performed during the initial 12 hours may show only equivocal findings, with a slight heterogeneous decrease in attenuation of the pancreas (ischemia) but a normal parenchymal texture (Fig 9). When pancreatic necrosis develops, zones of tissue liquefaction become better defined and more easily recognized 2–3 days after the initial onset (Figs 1, 4, 9). Thus CT scans obtained 3 days after clinical onset yield higher accuracy in the depiction of necrotizing pancreatitis and in the discrimination of normal variants or equivocal zones of ischemia from pancreatic necrosis. This phenomenon is probably responsible for the few reported cases of late development of necrosis (74) or enlarging areas of pancreatic necrosis on follow-up CT scans (77). When the clinical diagnosis of pancreatitis is in doubt, an initial early CT study is used to confirm the clinical suspicion or to help detect alternative acute abdominal conditions that mimic acute pancreatitis. For staging purposes, however, more reliable results are obtained with the use of bolus contrast-enhanced CT performed 48–72 hours after the onset of an acute attack of pancreatitis.

Third, extravasation of activated pancreatic enzymes induces the development of retroperitoneal fat necrosis, a



a. b.

Figure 6. Alcoholism-related pancreatitis in a 32-year-old man with necrosis of the tail of the pancreas. *P* = pancreas. **(a)** Initial transverse CT scan obtained with intravenous and oral contrast material shows fluid collections (arrow) adjacent to the body and tail of the pancreas. There is lack of enhancement of the tail of the pancreas. **(b)** Follow-up transverse CT scan obtained 6 months later reveals scarring with atrophy of the tail of the pancreas (arrow). *S* = spleen.

common phenomenon that occurs in patients with or without parenchymal necrosis (8,14). The retroperitoneal chemical injury results in multiple areas of fat necrosis, which interfere with fluid absorption and favor secondary bacterial contamination. This phenomenon probably explains the 22% incidence of local complications in patients without pancreatic necrosis but with peripancreatic fluid collections (74). CT cannot be used to help reliably diagnose, nor can it help accurately quantify, retroperitoneal fat necrosis. It has been suggested (2), therefore, that in clinical practice all heterogeneous peripancreatic collections should be considered areas of fat necrosis until proven otherwise (Figs 1, 4, 6). Necrotic fatty tissue can manifest as small heterogeneous collections on follow-up CT scans. Infection cannot be excluded in these patchy areas of fat necrosis.

TABLE 5
CT Severity Index

CT Grade	Points	Necrosis: Percentage	Necrosis: Additional Points	Severity Index*
A	0	0	0	0
B	1	0	0	1
C	2	<30	2	4
D	3	30–50	4	7
E	4	>50	6	10

* CT grade points are added to points assigned for percentage of necrosis.

CT Correlation with Numeric Systems

There is a wide variation in the relationship of prognostic signs (Ranson, APACHE II) and early CT findings in acute pancreatitis. Patients with a CT grade of A or B may exhibit between zero and five Ranson grave signs, while patients with a CT grade of D or E grades may have one to eight grave signs at 48 hours (Figs 1, 9). All patients with more than five Ranson prognostic signs were assigned a CT grade of E in our original survey (67). The mortality rate was significantly higher in patients

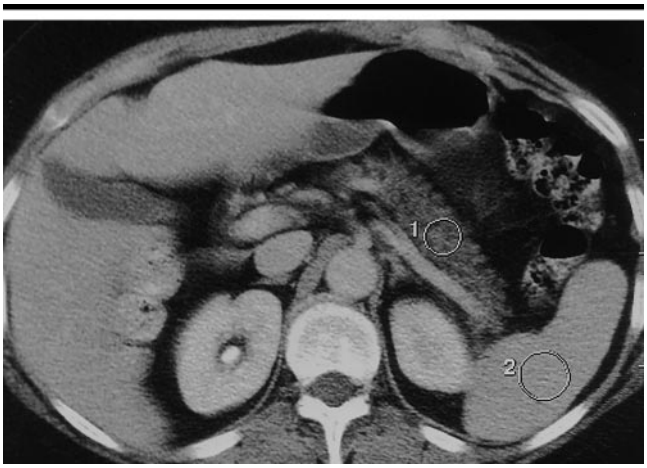
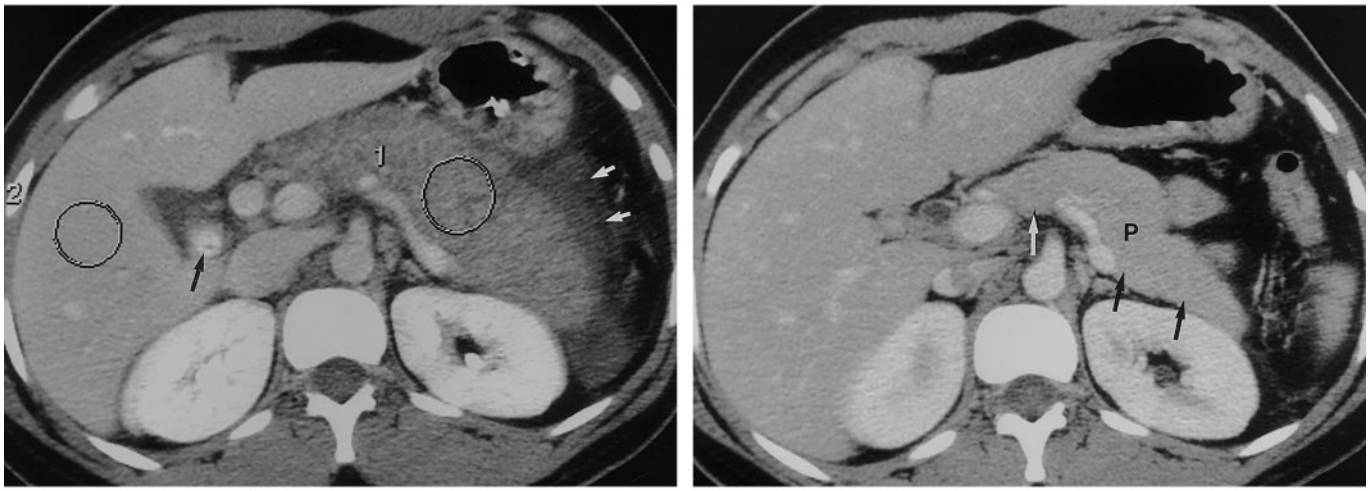
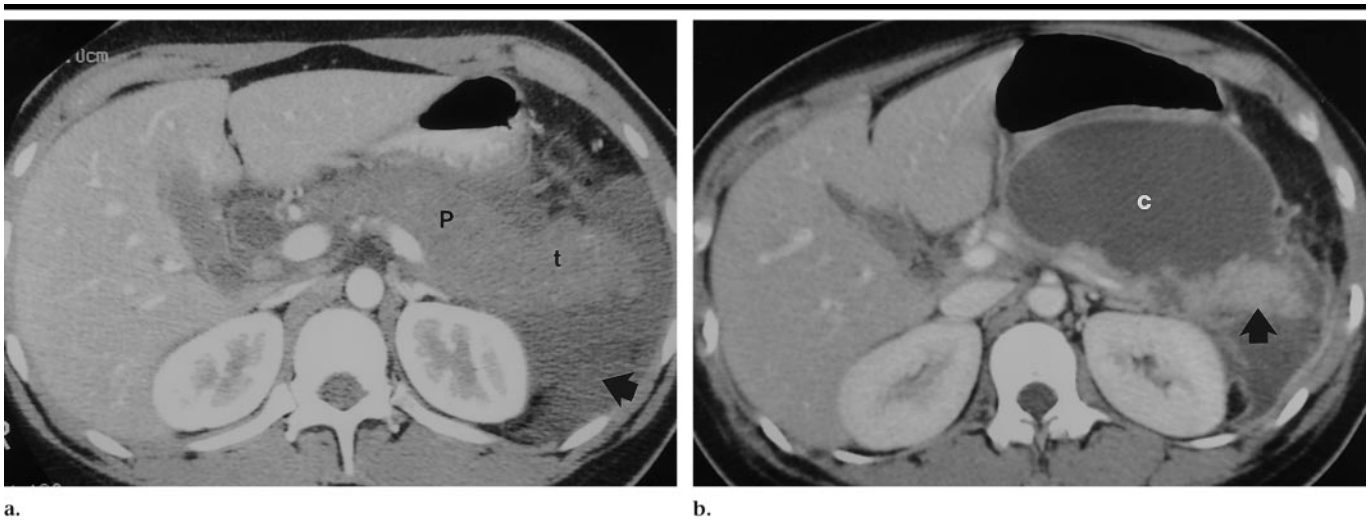


Figure 7. Fatty infiltration of the pancreas in an asymptomatic 42-year-old patient. Transverse CT scan obtained with intravenous and oral contrast material reveals a low-attenuating (7-HU) pancreas *(1),* which maintains its normal acinar texture. *2* = spleen (95 HU).



a. b.

Figure 8. Gallstone-induced pancreatitis in a 27-year-old woman. **(a)** Transverse CT scan obtained with intravenous and oral contrast material reveals a large, edematous, homogeneously attenuating (73-HU) pancreas *(1)* and peripancreatic inflammatory changes (white arrows). Although the attenuation values are low, there is no pancreatic necrosis. Calcified gallstones are seen in gallbladder (black arrow). *2* = liver (140 HU). **(b)** Follow-up transverse CT scan obtained 7 days later reveals total resolution, with a normal pancreas (*P,* arrows) with CT number of 104 HU.



a. b.

Figure 9. Acute pancreatitis in an 18-year-old woman with three Ranson grave signs. **(a)** Initial early transverse CT scan obtained with intravenous and oral contrast material reveals an enlarged low-attenuating (50–70-HU) pancreas *(P),* consistent with pancreatic ischemia and necrosis. Degree of necrosis is difficult to ascertain. A large fluid collection (arrow) is seen around the pancreatic body and tail *(t).* **(b)** Follow-up transverse CT scan obtained 14 days later reveals a fluid collection associated with liquified necrosis of most of the body of the pancreas, with the development of a pseudocyst *(c).* Note that the tail of the pancreas (arrow) is enhancing normally at this time.

with grade E and more than five Ranson prognostic signs.

The utility of the Ranson analytic criteria compared with that of the Balthazar CT criteria for detection of severe pancreatitis was recently analyzed in 100 consecutive patients (79), and CT evaluation results were found to be better prognostic indicators, owing to greater sensitivity and specificity. A similar comparison study between the Balthazar CT severity index and the Simplified Acute Physiology score in predicting outcome was recently published (80). Both systems were similar in facilitating the identification of patients with severe outcome, but the Balthazar score and CT severity index were found to be superior to the Simplified Acute Physiology score for prediction of a favorable outcome.

The relationship between the APACHE II numeric system and the CT severity index was recently surveyed (81). APACHE II scores of higher than 8 were present in 22 of 80 patients with interstitial pancreatitis (CT severity index, 0–4), as compared with 13 of 23 patients with necrotizing pancreatitis (CT severity index, 5–10). It was concluded that the APACHE II score cannot be used to reliably differentiate interstitial from necrotizing pancreatitis, owing to a sensitivity and specificity of 56% and 72%, respectively. A high APACHE II score, however, correlated well with the need for intensive care treatment and monitoring (81).

Magnetic Resonance Imaging

The development of high-field-strength magnetic resonance (MR) imaging, rapid gradient-echo breath-hold techniques, and fat-suppression techniques has made MR

imaging an excellent alternative noninvasive modality to help evaluate patients and stage acute pancreatitis (82–85). MR imaging is particularly useful in patients who cannot receive iodinated contrast material due to allergic reactions or renal insufficiency. Gadolinium-enhanced T1-weighted gradient-echo MR images can depict pancreatic necrosis as areas of nonenhanced parenchyma. Fat-suppression images are also helpful for defining subtle, diffuse, or focal parenchymal abnormalities. T2-weighted images can accurately depict fluid collections, pseudocysts, and areas of hemorrhage. Compared with CT images obtained with intravenous contrast material and collimation less than 5 mm, similar results should be expected by using MR imaging. MR imaging is an acceptable ancillary modality that can be used to stage acute pancreatitis or better characterize equivocal CT abnormalities.

CONCLUSIONS

An objective assessment of the severity of acute pancreatitis is based on clinical and laboratory evaluation (mainly numeric systems) and contrast-enhanced CT imaging. Numeric systems (APACHE II, Ranson) are commonly used today to help detect organ failure, and the acquired data are used as indirect evidence of disease severity, with a sensitivity of about 70%. Use of individual risk factors determined with laboratory tests (markers of pancreatic injury and markers of inflammatory response) has been proposed to help predict clinical outcome. While very promising, most of the individual markers have been studied mainly in a research setting, and their relative clinical usefulness remains to be determined.

Contrast-enhanced CT is the imaging modality of choice to help stage the severity of inflammatory processes, detect pancreatic necrosis, and depict local complications. CT has been shown to yield an early overall detection rate of 90% with close to 100% sensitivity after 4 days for pancreatic gland necrosis. The CT severity index has shown an excellent correlation with the development of local complications and the incidence of death in this population.

At this time, a single unified scoring system to help identify disease severity is not available. Future comprehensive clinical studies in which CT findings (CT severity index) are combined with a numeric system or with one or several laboratory markers may be useful to better quantify the severity of disease in patients with acute pancreatitis.

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