Classification of acute pancreatitis
Bollen, T.L.
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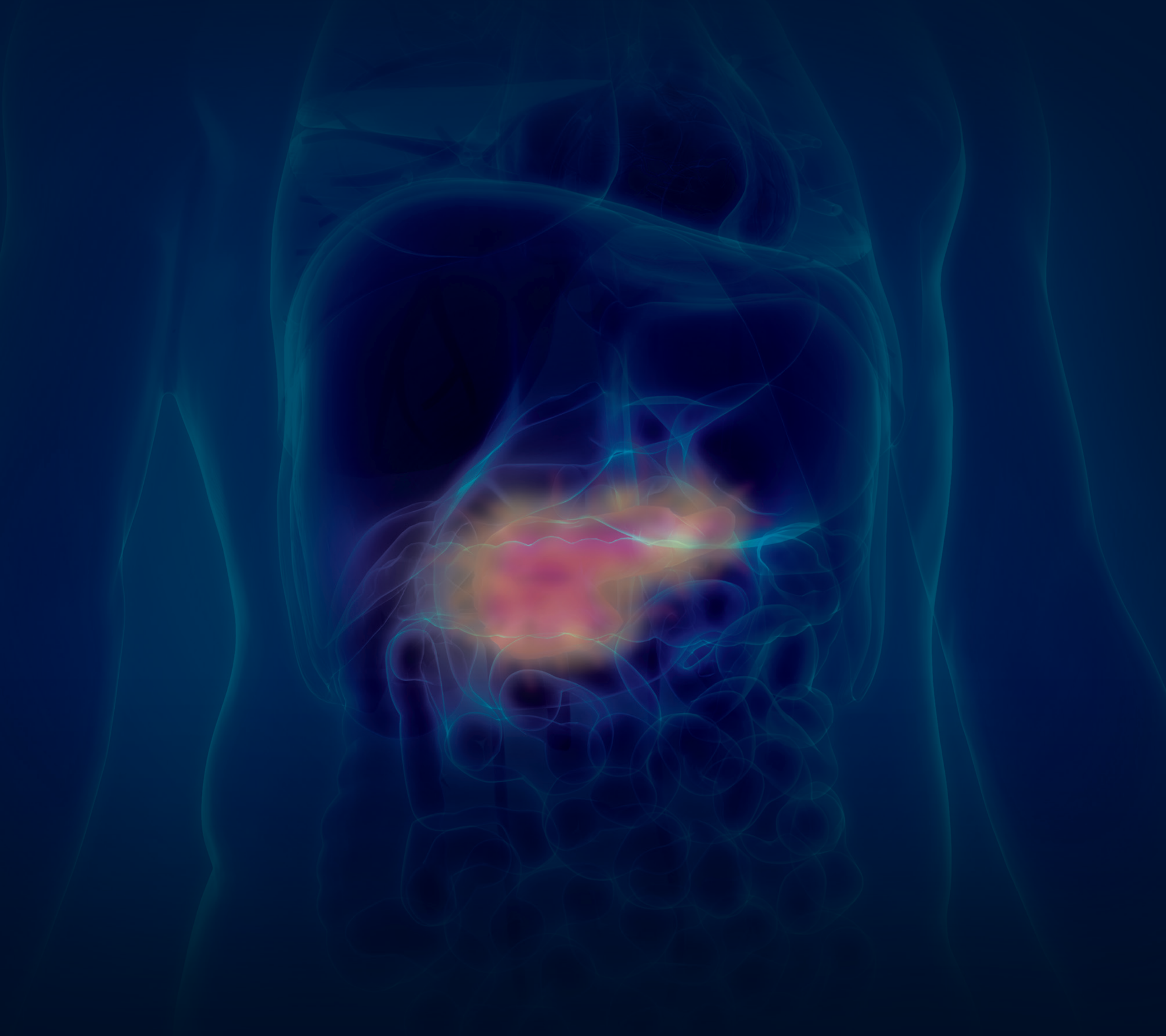
CLASSIFICATION *of* ACUTE PANCREATITIS



THOMAS BOLLEN

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COLOFON

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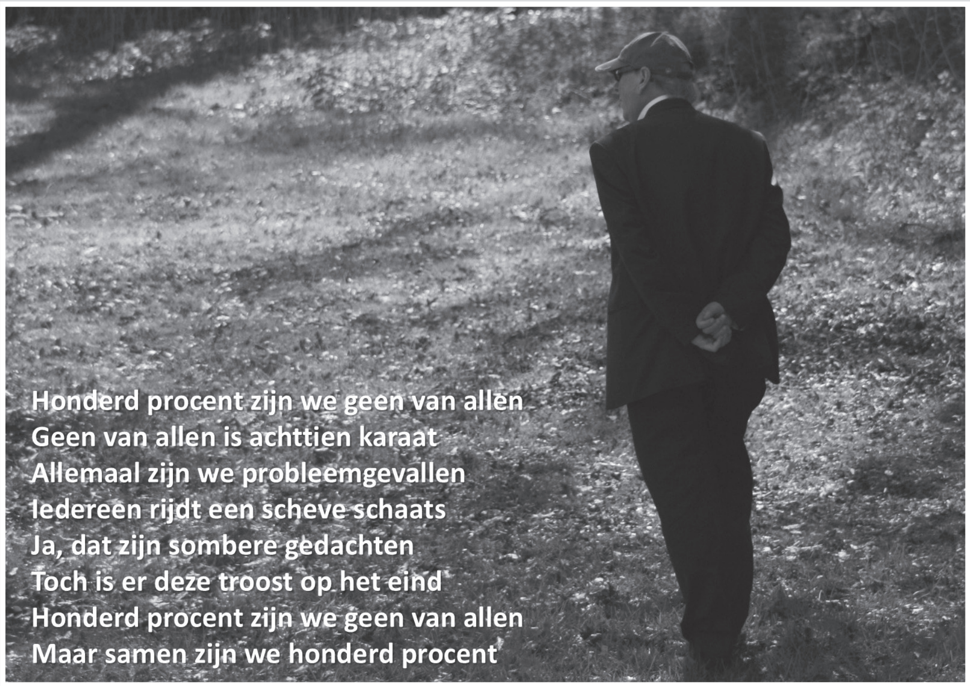

- Frans Halsema & Gerard Cox, 1975

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General Introduction & Outline of this Thesis

GENERAL INTRODUCTION

Pancreas: anatomy and function

The pancreas is an elongated, tapered organ located centrally in the upper abdomen behind the stomach in the retroperitoneum. Traditionally, the pancreas is divided in the head, neck, body, and tail. The pancreatic head is the widest part of the organ and lies along the duodenum. The tapered left side (body and tail) extends slightly upward and ends near the spleen. Unlike other abdominal organs, the pancreas has no well-defined capsule with only a sheet of connective tissue separating the pancreatic parenchyma from surrounding peripancreatic fat. The pancreas has digestive and hormonal functions and is made up of exocrine and endocrine glands. The exocrine gland secretes digestive enzymes (trypsin, amylase, lipase), which help break down carbohydrates, fats, proteins, and acids in the duodenum where they are activated. The exocrine tissue also secretes bicarbonate to neutralize stomach acid in the duodenum. Approximately 1.5 liter of pancreatic juice is produced per day. The endocrine gland, which consists of the islets of Langerhans, secretes hormones into the bloodstream. The main hormones secreted by the endocrine gland in the pancreas are insulin and glucagon, which regulate the level of glucose in the blood, somatostatin, which inhibits insulin and glucose uptake, and pancreatic polypeptide (PP), secreted in response to vagal stimulation and eating. PP modulates pancreatic hormone secretion and affects gastrointestinal secretions (1).

Acute pancreatitis: diagnosis and incidence.

The diagnosis of acute pancreatitis relies on clinical, biochemical and/or radiological criteria and can be made if two of the following three features are present: acute onset of severe abdominal pain often radiating to the back; serum lipase and/or amylase activity at least three times the upper limit of normal; and characteristic acute pancreatitis findings on cross-sectional imaging (2,3). Clinical symptoms of acute pancreatitis are an acute-onset of upper abdominal pain that increases rapidly in severity and persists without spontaneous relief. The intensity of the pain generally results in the patient seeking medical attention. Acute pancreatitis is the leading cause of gastrointestinal-related hospital admissions in the Western world. In the Netherlands, about 4000 patients are admitted with the diagnosis acute pancreatitis annually (4,5). The incidence of acute pancreatitis varies from region to region and is estimated to be 10-50 cases per 100,000 people per year. Worldwide, the incidence of acute pancreatitis is increasing, probably related to the rising incidence of gallstones, obesity, and aging of the population; all are well-known risk factors for acute pancreatitis (6-9).

Acute pancreatitis: causes

There are numerous known causes of acute pancreatitis, all of which precipitate the disease by causing acinar cell injury. Acute pancreatitis can be triggered by mechanical (gallstones, tumor), metabolic (alcohol, hyperlipidemia), vascular (ischemia, vasculitis), or infectious (mumps, ascariasis) events. Up to 10-15% of cases remain idiopathic. Worldwide, gallstone disease and alcohol abuse account for greater than 80% of cases of acute pancreatitis. The incidence of pancreatitis in patients with these conditions is, however, low (5-10%), suggesting that additional co-factors are necessary to precipitate acute pancreatitis (2,3).

Acute pancreatitis: pathophysiology

The common denominator mediating the clinical onset of acute pancreatitis is the premature activation of pancreatic enzymes and their extravasation into the pancreatic interstitium and peripancreatic tissues. It is hypothesized that intraparenchymal and extrapancreatic extravasation of these activated enzymes leads to autodigestion resulting in a variety of pathologic abnormalities ranging from mild edema and reactive inflammatory changes to severe tissue injury, damage to the pancreatic capillary network, hemorrhage and tissue necrosis. The extravasation of pancreatic lipase results in the development of retroperitoneal and subperitoneal fat necrosis, which can undergo secondary infection. Furthermore, these activated enzymes trigger an inflammatory response mediated by cytokines: interleukins and tumor necrosis factor alpha, which is toxic to acinar cells. These cytokines activate and intensify the inflammatory cascade responsible for the development of systematic inflammatory response syndrome (SIRS) that may ultimately culminate in (multiple) organ failure. There are evolving data that the magnitude of the inflammatory response, mediated by the immune system, is responsible for most of the morbidity and mortality in acute pancreatitis rather than the degree and extent of local pancreatic damage (10-13).

Acute pancreatitis: clinical sequelae and morphologic changes

Acute pancreatitis is traditionally categorized in terms of clinical manifestations (mild, moderate severe, and severe dependent on the presence of systemic complications with or without accompanying local complications) or morphologic imaging-based findings (interstitial and necrotizing pancreatitis, dependent on absence or presence of tissue necrosis, respectively) (14,15).

Clinical sequelae

Approximately 80% of patients with acute pancreatitis have a mild illness and recover promptly without significant systemic or local sequelae, whereas 20% have a more serious illness characterized by organ failure, pancreatic necrosis, various infections, and death (2,14). In patients with severe acute pancreatitis, the clinical course is arbitrarily conceptualized as a process evolving in two overlapping phases (early and late phase). During the early phase, the systemic manifestations are linked to the host response to local pancreatic injury caused by activation of the cytokine cascade manifested as the SIRS and/or the compensatory anti-inflammatory syndrome (CARS). SIRS and CARS may occur concurrently in the escalating cascades of cytokine release. Organ failure is likely when SIRS or CARS persists, with dysfunctioning respiratory, renal, or cardiovascular systems. Severity in the early phase depends on the presence and duration of SIRS and organ failure (11,14). The late phase of acute pancreatitis, occurring in those with moderate severe and severe acute pancreatitis, is characterized by ongoing systemic inflammation, complications, and/or organ failure beyond the first week. Organ failure is the main cause of death in severe acute pancreatitis, both in the early and late phase. Organ failure in the early phase is secondary to SIRS, whereas infection and sepsis are the presumed causes of organ dysfunction in the late phase (13,16).

Morphologic changes

Similar to the variability of the clinical presentation of acute pancreatitis, the pattern of pancreatic and extrapancreatic manifestations on imaging in evolving pancreatitis manifests in many ways, including interstitial edema, necrosis of pancreatic parenchyma and peripancreatic tissues, sterile and infected necrosis, and extrapancreatic complications. Morphologically, two types of acute pancreatitis are discriminated: interstitial and necrotizing pancreatitis (14,17).

Interstitial pancreatitis is the most common type (about 80-90%) and usually resolves within a few days. It is characterized by local or diffuse enlargement of the pancreas due to inflammatory edema of the parenchyma and/or peripancreatic tissues, but without recognizable tissue necrosis. On contrast-enhanced computed tomography (CECT), the pancreatic parenchyma is perfused normally with homogeneous or occasionally heterogeneous enhancement (due to edema). The peripancreatic fat may show some inflammatory changes such as haziness or mild stranding (figure 1)(18,19).

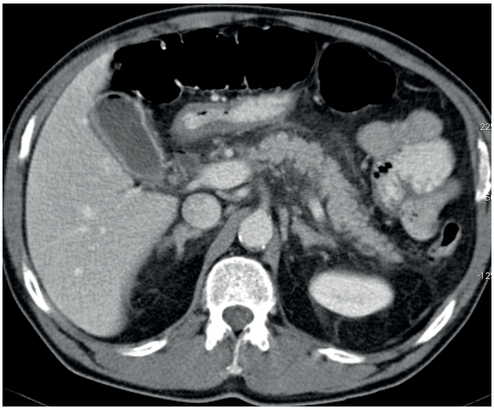

Figure 1 Acute interstitial pancreatitis. Normal enhancement of the pancreas with swelling and little peripancreatic fat stranding.

Necrotizing pancreatitis is less common (about 10-20%). The defining feature of necrotizing pancreatitis is the presence of necrosis within the pancreatic parenchyma or the surrounding tissues. Most commonly, necrosis of both the pancreatic parenchyma and peripancreatic tissues occurs, although either can occur alone. CECT findings of necrosis include non-enhancement of pancreatic parenchyma and inflammatory changes composed of various densities in the surrounding tissues (figure 2). Compromise of pancreatic perfusion and CT signs of peripancreatic necrosis may evolve over days to weeks, respectively. Early CT within 72h after symptom onset may, therefore, underestimate the extent of disease (18,19).

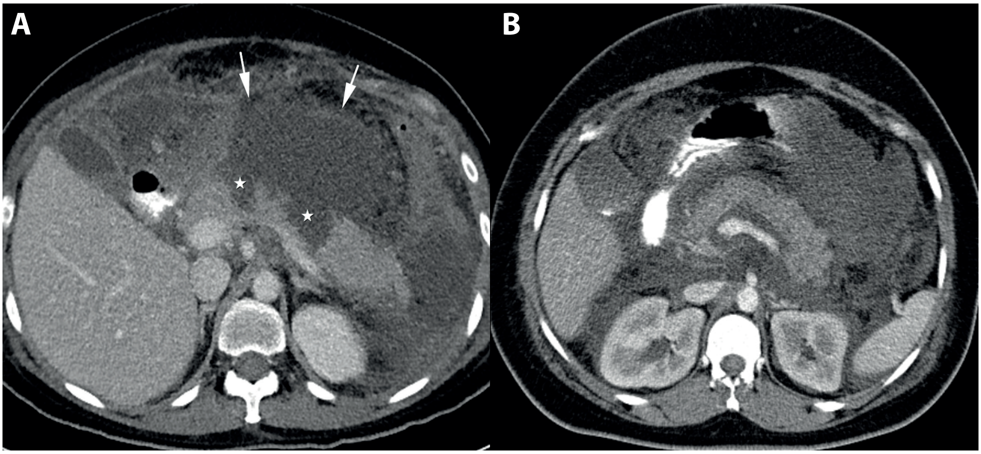

Figure 2A and B Combined necrosis and extrapancreatic necrosis. (**A**) CT shows nonenhancing parts of pancreatic neck and body (asterisks) with surrounding acute necrotic collections (arrows). (**B**) CT depicts a normal enhancing pancreatic parenchyma surrounded by acute necrotic collections. Note, calcified stone in the gallbladder.

The distinction between interstitial and necrotizing pancreatitis is important to physicians in planning appropriate treatment and to the scientist in developing useful protocols for clinical research. Patients with necrotizing pancreatitis have a much higher risk of infection of pancreatic or peripancreatic necrosis, a more severe and prolonged clinical course often with periods of organ failure, and a higher mortality rate than patients with interstitial pancreatitis (16).

Interrelation between clinical sequelae and morphologic changes

In general, the clinical and morphologic changes are interrelated closely; patients with mild acute pancreatitis often have interstitial disease, whereas those with severe acute pancreatitis tend to have necrotizing pancreatitis. Clinical and morphologic severity, however, do not necessarily overlap; thus, patients with clinically mild acute pancreatitis may show severe morphologic manifestations on CT. Conversely, patients may sustain severe disease clinically (i.e. persistent organ failure) whereas CT only shows minimal inflammatory changes. In these patients, clinical severity is often mainly driven by the presence of significant co-morbid disease (20,21).

Acute pancreatitis: imaging

Historically, the pancreas was a difficult organ to evaluate both clinically and by antiquated radiographic methods, including plain radiographs and gastrointestinal contrast studies. These examinations were not very sensitive, were limited to the secondary changes caused by pancreatic complications on the adjacent bowel loops, and thus, were not able to demonstrate the full extent of the disease process adequately. With the development of grey-scale ultrasound in the early 1970s, for the first time it was possible to visualize the pancreas non-invasively, albeit often hindered by overlying, gas-containing bowel loops precluding adequate evaluation of the entire pancreas. The introduction of CT in the late 1970s enabled to visualize the entire pancreas and its diseases, including acute pancreatitis and associated complications, in a relatively fast, reproducible, objective, and non-invasive manner. When CT was first used in acute pancreatitis, scans were non-enhanced and non- or ill-perfused areas of pancreatic necrosis were not demonstrable. Based on the observations by Kivisaari and colleagues in 1983, slow infusion of intravenous contrast medium improved the differentiation of pancreatic parenchymal swelling from peripancreatic edema, albeit necrosis of pancreatic parenchyma was still not identifiable (22). Author groups from Germany and Finland were among the first to combine rapid intravenous contrast bolus with dynamic CT, thereby enabling the identification of areas of reduced pancreatic perfusion corresponding to pancreatic necrosis (23,24). In the last 3 decades, the rapid technological advances of CT and magnetic resonance imaging (MRI) have paralleled the understanding of the pathophysiology and increasing knowledge of the natural clinical course of acute pancreatitis. Particularly, the introduction of contrast-enhanced multidetector high resolution CT imaging has altered the approach to diagnose and evaluate patients suspected of having acute pancreatitis substantially (17,25). Besides complete assessment of acute pancreatitis and its complications, imaging techniques also serve as a platform for innovative minimally invasive interventional therapies.

Acute pancreatitis: role of imaging modalities

In patients with acute pancreatitis, imaging tests are performed to confirm or exclude the clinical diagnosis, establish the cause of pancreatitis, assess severity, detect complications, and provide guidance for patient management (25).

Imaging modalities used commonly include abdominal ultrasound and CT, and occasionally MRI. To elucidate the etiology of acute pancreatitis, abdominal ultrasound is used in the early phase for assessment of biliary stones and biliary obstruction (figure 3). At a later stage, abdominal ultrasound is also helpful for characterization of pancreatic collections, by differentiating fluid from non-liquid material, and for guiding diagnostic or therapeutic interventions. CT is the imaging modality of choice for overall assessment of acute pancreatitis because of its high accuracy, fast acquisition, and wide availability. In the initial phase, CT can provide the diagnosis when in doubt or come up with an alternative diagnosis, help triage patients with different grades of severity, and identify early local complications, such as pancreatic parenchymal necrosis. In the late phase, CT is essential for assessment of evolution of local complications, for guidance of when and how to employ invasive treatment, and for monitoring response to treatment (17,19). MRI is as sensitive as CT for diagnosis and severity assessment, but superior to CT in the characterization of pancreatic collections by identifying accurately non-liquefied material (necrotic tissue or debris) within collections (figure 4) (26,27). MRI also allows for assessment of pancreatic duct integrity. However, availability, longer scanning time leading to motion artefacts, and the need for specialized MRI-compatible monitoring equipment in critically ill patients, and high costs hamper the widespread use of MRI in acute pancreatitis. Therefore, at present, MRI has a complementary role in acute pancreatitis.

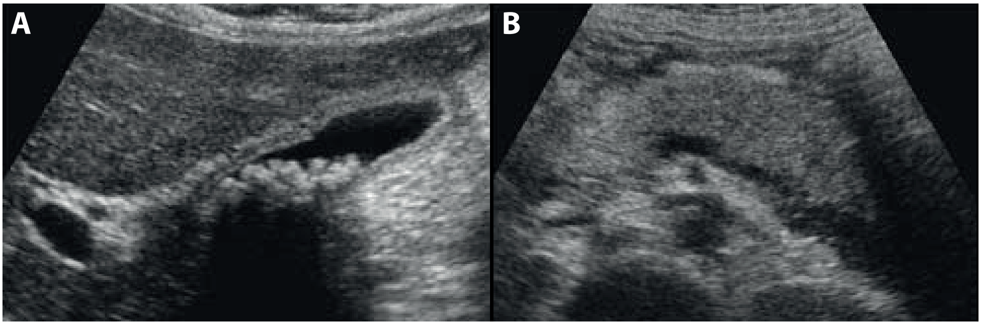

Figure 3A and B Ultrasound of cholelithiasis and biliary pancreatitis. (**A**) Ultrasound depicts multiple tiny stones in a non-distended gallbladder as cause of biliary pancreatitis. (**B**) Ultrasound showing a slightly swollen pancreas with surrounding hypoechoic fluid.

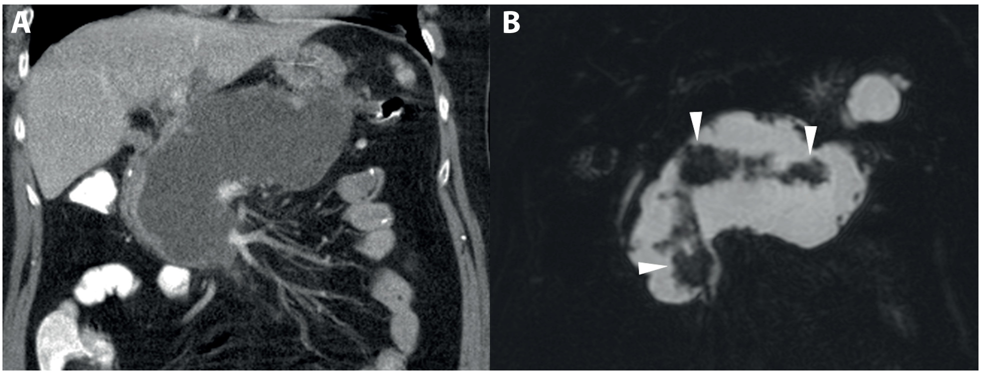

Figure 4A and B CT versus MRI of walled-off necrosis. (**A**) CT shows walled-off necrosis replacing a large part of the pancreatic parenchyma. (**B**) Corresponding T2-weighted MRI accurately depicts necrotic material (arrowheads) within the collection.

Acute pancreatitis: imaging findings

Irrespective of the etiology, morphologic findings of acute pancreatitis can be described in terms of alterations of the pancreatic parenchyma (interstitial edema and necrosis), peripancreatic tissues (fat stranding and collections), and extrapancreatic abnormalities (involvement of parenchymal organs, biliary system, vascular structures, and gastro-intestinal tract). The spectrum of morphologic abnormalities is dictated by the severity of acute pancreatitis. In about 10-20% of all cases, CECT will show normal or near normal findings and the diagnosis of acute pancreatitis hinges on upper abdominal pain and elevated pancreatic enzymes (17,18,28). Typical findings of morphologically mild acute pancreatitis includes focal or diffuse enlargement of the pancreas, parenchymal inhomogeneity due to edema, irregular gland margins with increased attenuation of peripancreatic fat or fat stranding, and/or small fluid collections. In around 20% of cases the inflammation is a focal process, often involving only the head or tail (17,18,28). With increasing severity of the attack, more pronounced abnormalities are observed with development of pancreatic collections and pancreatic necrosis. CT diagnosis of pancreatic necrosis is defined as non-enhancing pancreatic parenchyma. In general, visual comparison between the degree of pancreatic and splenic parenchymal enhancement is deemed adequate for detection of pancreatic necrosis (29). Pancreatic necrosis may be focal or multifocal, limited or extensive, confined to the periphery or full thickness. Pancreatic necrosis develops early in the course of acute pancreatitis (within 24-48h) and is complete within 72-96h after symptom onset (18,28,30). Cross-sectional imaging is performed best after this time period, since early CT may miss or underestimate the presence of pancreatic necrosis (figure 5). When pancreatic necrosis has been established on CECT, the extent of necrosis tends to remain stable during the following disease course as opposed to pancreatic collections. Pancreatic necrosis represents the most severe form of acute pancreatitis and the mediator for most of the systemic and local complications. The presence, and possibly the extent, of pancreatic and peripancreatic necrosis, increases the probability of infection. In turn, when pancreatic necrosis becomes infected, it is associated with a two-to-threefold increase in mortality: about 20-30% for infected necrosis compared with 9-12% for sterile necrosis (6,16).

Acute pancreatitis: classification & prediction

Clinical outcome of patients with mild or severe acute pancreatitis differs considerably. Consequently, classifying and predicting disease severity accurately is crucial, and has resulted in ample attention in the medical literature over the past five decades.

Prediction of disease severity at the onset of the disease is, however, distinctly different from assessing the actual disease severity. Prediction of severity is about identifying factors or parameters that correlate accurately with mild or severe disease, before it actually develops. Assessment of actual disease severity is a method used to grade the severity of acute pancreatitis and, thus, is about classification of severity. In the following sections, this will be discussed in more depth.

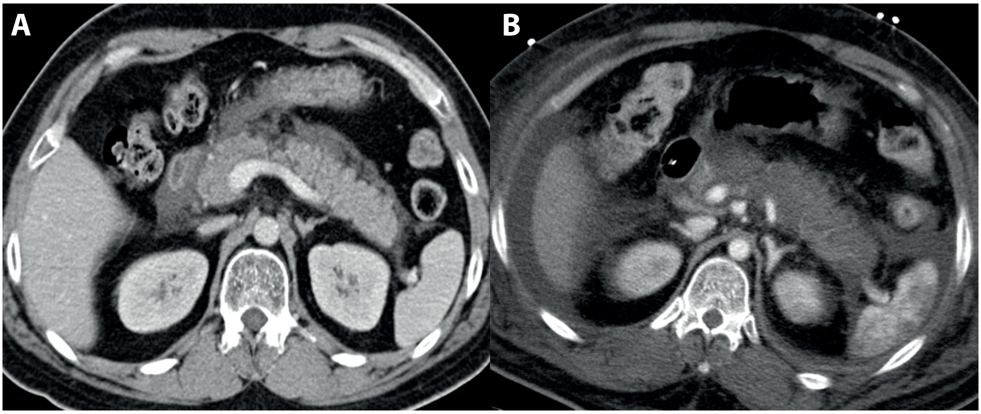

Figure 5A and B False-negative pancreatic necrosis on early CT. (**A**) CT performed on the day of admission shows a normal enhancing pancreatic parenchyma with little surrounding peripancreatic fluid. (**B**) Follow-up CT on day 3 reveals nonenhancement of pancreatic body and tail, indicating pancreatic necrosis.

Classification

Since the first clinical description of acute pancreatitis by Fitz in 1889, several classification systems of pancreatitis have been proposed (31). Terms used initially to describe and classify pancreatitis included 'pancreatic hemorrhage', 'hemorrhagic suppurative, gangrenous pancreatitis', and 'disseminated fat necrosis'. With increasing knowledge and understanding of pancreatitis, modifications to existing classification systems were deemed necessary. Between 1963 and 1992, five interdisciplinary symposia on pancreatitis were convened with the aim to define and classify the spectrum of (acute and chronic) pancreatitis.

In 1963, the first international symposium on pancreatitis was held in Marseille, France. Staging was based on clinical grounds and categorized in acute, relapsing acute, chronic, and relapsing chronic pancreatitis. The spectrum of infectious complications (pancreatic infections), however, was not addressed (32).

In 1983, the second international meeting on classification of pancreatitis was held in Cambridge. At that meeting it was agreed that acute and chronic pancreatitis are essentially distinct entities. For the first time, the 1983 Cambridge Classification acknowledged the varying severity of acute pancreatitis by distinguishing mild and severe disease. Also, infectious complications of acute pancreatitis were addressed and several definitions were proposed: pancreatic phlegmon (inflammatory mass in or around the pancreas) and pancreatic abscess (pus in or around the pancreas) (33).

In 1984, a second Marseille symposium clarified the earlier works and emphasized certain pathologic (calculi, focal necrosis, fibrosis) and physiologic (diabetes, steatorrhea) complications of pancreatitis (34). Both the 1983 Cambridge and 1984 Marseilles Classification acknowledged the variable clinical course of acute pancreatitis and identified various local complications; necrosis, hemorrhage, and pseudocysts.

In 1988, further modifications were added to the 1984 Marseilles Classification at a meeting in Rome, Italy (35,36). These related mainly to clinicopathologic criteria of local pancreatic complications. The 1988 Marseilles-Rome Classification still lacked specific definitions for discriminating the various local complications of acute pancreatitis and nomenclature was often ambiguous. For example, the secondary infections associated with acute pancreatitis were classified as 'pancreatic abscess', 'infected pancreatic necrosis', 'infected pseudocyst', or 'phlegmon'. In research, these entities were used often interchangeable and inappropriate rendering reliable comparison of scientific data impossible (37,38).

In 1992, the final international symposium in the 20th century was held in Atlanta, Georgia, USA (Table 1) (39). This meeting was unique in the sense that it was the first symposium that focused on acute pancreatitis only resulting in a universally applied and accepted classification system depending on both clinical and pathological criteria. The 1992 Atlanta Classification abandoned the terms 'infected pseudocyst', 'phlegmon', 'hemorrhagic pancreatitis', and 'persistent acute pancreatitis'. Definitions were proposed for 'acute pancreatitis', 'mild and severe acute pancreatitis', 'acute fluid collection', 'pancreatic necrosis', 'pseudocyst', and 'pancreatic abscess'.

The 1992 Atlanta Classification initially provided a suitable framework for categorizing and grading acute pancreatitis and proved useful over the following two decades. Over the subsequent years, it became apparent that this classification system became outdated and needed an update, by and large based on studies put forth by the Dutch Pancreatitis Study Group, which forms the basis for this thesis.

Prediction

The early recognition of acute pancreatitis severity enables clinicians to modify their medical management and transfer patients to the appropriate levels of care. The identification of patients most likely to develop organ failure and necrotizing pancreatitis will also facilitate the selection of the most seriously ill group of patients for inclusion in randomized clinical trials (40). Prediction of disease severity can be done using thorough *clinical evaluation* including detailed assessment of established risk factors. Risk factors of severity are patient-related factors or clinical features present at baseline that contribute to a poor outcome. Among these are older age (55 or more years), alcohol, obesity (body mass index: BMI greater than 30 kg/m^2), first or second episode of disease, and presence of co-morbid disease. Based on clinical evaluation alone at the day of admission, however, clinicians fail to predict those with severe acute pancreatitis in up to 30-50% of cases. Other means of determination of the severity include the use of *single prognostic indicators* (e.g. serum blood urea nitrogen, creatinine, hematocrit, levels of C-reactive protein, procalcitonin) and the utilization of *multiple clinical scoring systems*. These predictors of severity can be measured at admission and at various stages thereafter in order to assess response to therapy. Multiple scoring systems incorporate physiologic, laboratory, and

TABLE 1. Summary of the 1992 Atlanta Classification

	Definition
Acute pancreatitis	An acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems Associated with raised pancreatic enzyme levels in blood and/or urine
Severity	
Mild acute pancreatitis	Associated with minimal organ dysfunction and an uneventful recovery; lacks the features of severe acute pancreatitis. Usually normal enhancement of pancreatic parenchyma on contrast-enhanced computed tomography
Severe acute pancreatitis	Associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst
Predicted severity	Ranson score ≥ 3 or APACHE II score ≥ 8
Organ failure and systemic complications	
Shock	Systolic blood pressure < 90 mmHg
Pulmonary insufficiency	PaO_2 ≤ 60 mmHg
Renal failure	Creatinine ≥ 177 μmol/l or ≤ 2 mg/dl after rehydration
Gastrointestinal bleeding	500 ml in 24 h
Disseminated intravascular coagulation	Platelets ≤ 100,000/mm^3, fibrinogen < 1·0 g/l and fibrin-split products > 80 μg/l
Severe metabolic disturbances	Calcium ≤ 1·87 mmol/l or ≤ 7·5mg/dl
Local complications	
Acute fluid collections	Occur early in the course of acute pancreatitis, are located in or near the pancreas and always lack a wall of granulation of fibrous tissue. In about half of patients, spontaneous regression occurs. In the other half, an acute fluid collection develops into a pancreatic abscess or pseudocyst
Pancreatic necrosis	Diffuse or focal area(s) of non-viable pancreatic parenchyma, typically associated with peripancreatic fat necrosis Non-enhanced pancreatic parenchyma > 3 cm or involving more than 30% of the area of the pancreas
Acute pseudocyst	Collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, which arises as a result of acute pancreatitis, pancreatic trauma or chronic pancreatitis, occurring at least 4 weeks after onset of symptoms, is round or ovoid and most often sterile; when pus is present, lesion is termed a 'pancreatic abscess'
Pancreatic abscess	Circumscribed, intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma Often 4 weeks or more after onset Pancreatic abscess and infected pancreatic necrosis differ in clinical expression and extent of associated necrosis

APACHE, Acute Physiology And Chronic Health Evaluation; PaO_2, arterial partial pressure of oxygen.

occasionally CT parameters obtained during the first 48h of hospitalization. For all scoring systems, continuous variables are acquired with incremental increase of scores correlating with clinical outcome parameters, such as organ failure, need for intensive care or intervention, and mortality. Subsequently, these continuous variables are converted into binary values as for each scoring system cutoff scores are derived (e.g. after receiver operating characteristic (ROC)-curve analysis) to differentiate most accurately high-risk from low-risk patients. Among the most studied are the Ranson score, Glasgow score, Imrie score, Systemic Inflammatory Response Syndrome (SIRS), Bedside Index of Severity in Acute Pancreatitis (BISAP), and Acute Physiology and Chronic Health Evaluation (APACHE)-II score (40-43). Finally, since the introduction of CT for diagnosis and assessment of acute pancreatitis some four decades ago, several *imaging-based scoring systems* have been proposed to predict the severity of acute pancreatitis. Determinants of most CT-based scoring systems include pancreatic changes, peripancreatic, and extrapancreatic features.

- Pancreatic changes include the subjective or objective enlargement of the pancreatic gland and presence and extent of parenchymal necrosis.
- Peripancreatic features include fat stranding or edema, (fluid) collection(s) (presence, number, and volume), perirenal edema, mesenteric inflammation and retroperitoneal extension.
- Extrapancreatic features include the presence of ascites, pleural effusion, vascular, gastrointestinal, and/or extrapancreatic parenchymal organ complications.

Over the past four decades, at least 10 different radiographic scoring systems have been developed using incremental numerical scores or grades with higher scores or grades correlating with increasing morbidity and mortality (Table 2) (44-53). Two of these evaluate the presence and extent of parenchymal necrosis (i.e. CT Severity Index (CTSI) and Modified CT Severity Index (MCTSI)) for which the use of intravenous contrast material is indispensable. The remainder of scoring systems can be assessed on unenhanced CT scans.

Among all imaging-based scoring systems available, the CTSI is the most commonly used and studied. The CTSI combines the Balthazar grade (0-4 points) with the extent of pancreatic necrosis (0-6 points) on a 10-point severity scale (Table 3) (47). The calculated CTSI can be subdivided in three categories; CTSI 0-3, 4-6, and 7-10, corresponding to predicted mild, moderate, and severe disease, respectively, with corresponding increase in morbidity and mortality. Main advantage of the CTSI is its intuitive design as it accurately depicts the order of increasing morphologic severity of acute pancreatitis. Interstitial pancreatitis is reflected by CTSI of 0 (normal pancreas), 1 (swelling of the pancreatic gland), and 2 (peripancreatic fat stranding). Extrapancreatic necrosis is potentially reflected by a CTSI of 3 and 4 (1 or more pancreatic collections, respectively). In general, CTSI greater than 4 (5-10) denotes the presence of pancreatic collections and parenchymal necrosis with more points accredited with increasing extent of necrosis (figure 6).

TABLE 2. Radiographic scoring systems in acute pancreatitis

Radiographic scoring system	Year of development	CECT	CT parameters	Advantage(s)	Disadvantage(s)
Extrapancreatic score (EP or Schroeder index, range 0-7)	1985	-	Oedema in part or entire pancreas, ascites, pleural effusion, perirenal fat oedema, mesenteric fat oedema, and bowel paralysis.	Relatively easy to assess	Not validated for early use, presence of ascites and perirenal oedema can be a normal finding
Balthazar Grade (A-E)	1985	-	Pancreatic swelling, peripancreatic fat stranding, presence and number of associated pancreatic collections	Relatively easy to assess	Variable interobserver agreement, counting the number of collections
Pancreatic size index (PSI, cut-off 10 cm^2)	1989	-	Multiplying the maximum anteroposterior measurement of the head and body of the pancreas	Measurement of single parameter	Normal size may vary depending on age and previous attacks
CT Severity Index (CTSI, range 0-10)	1990	+	Balthazar grade + presence and extent of parenchymal necrosis	Most used and studied, depicts the order of morphologic severity in acute pancreatitis	Variable interobserver agreement for counting pancreatic collections and assessing % of necrosis
MOP score (range 0-2)	2003	-	Mesenteric oedema and peritoneal fluid (ascites)	Measurement of two parameters only, simple and easy to assess	Not validated for early use, ascites can be physiologic in female and elderly
MCTSI (range 0-10)	2004	+	Pancreatic swelling or fat stranding, pancreatic collection(s), presence and extent of parenchymal necrosis, extrapancreatic complications including vascular, parenchymal, gastrointestinal organs and pleural effusion and ascites	Inherent simplifications, easier to assess for non-experienced readers	Does not perform better than original CTSI
Retroperitoneal Extension Grade (I-VI)	2006	-			Advanced interpretative skills required, may not be practical for routine clinical practice
EPIC score (range 0-7)	2007	-	Pleural effusion, ascites, retroperitoneal and mesenteric inflammation	Relatively easy to assess	Not extensively studied, original study biased towards severe disease
Renal Rim Grade (A-C)	2010	-		Easy to assess	Not validated for early use, not extensively studied
EXPN Volume (cut-off 100 mL)	2014	-	Volume of extrapancreatic exudate or fluid	Objective	Not validated for early use, additional software required for calculating volume

TABLE 3. Balthazar Grade and CT Severity Index

Characteristics	Balthazar Grade	CTSI
Pancreatic inflammation		
Normal pancreas	A	0
Focal or diffuse enlargement of the pancreas	B	1
Peripancreatic inflammation / fat stranding	C	2
Single acute fluid collection	D	3
Two or more acute fluid collections	E	4
Pancreatic parenchymal necrosis		
None		0
Less than 30%		2
Between 30 and 50%		4
More than 50%		6

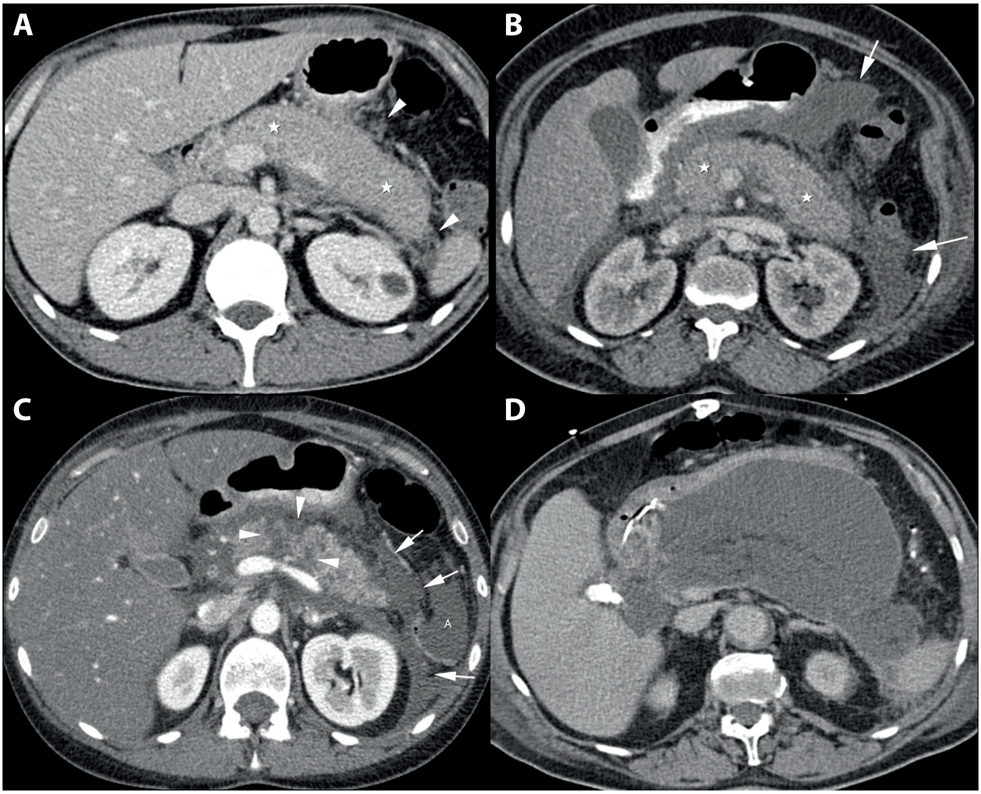

Figure 6A-D CT severity index. (**A**) CTSI of 2: swollen but normal enhancing pancreas (asterisks) with little peripancreatic fat stranding (arrowheads). (**B**) CTSI of 4: normal enhancing pancreatic parenchyma (asterisks) with more than 2 collections (arrows). (**C**) CTSI of 6: less than 30% nonenhancing pancreatic parenchyma at the level of pancreatic body (arrowheads) with associated necrotic collections (arrows); A: ascites in the left paragolic gutter. (**D**) CTSI of 10: extensive necrosis of more than 50% of pancreatic parenchyma with associated necrotic collections. Note, calcified stones in the gallbladder.

THESIS OUTLINE

The focus of this thesis is on the classification and severity prediction of acute pancreatitis. Two main topics are addressed:

- Part I: Classification of acute pancreatitis: definitions and terminology.
- Part II: Severity prediction of acute pancreatitis: clinical- versus imaging-based scoring systems and morphologic severity of acute pancreatitis.

Part I – Classification of acute pancreatitis

Severity classification of acute pancreatitis is essential for patient triage and transfer, comparing different methods of therapy, allocation of patients for clinical trials and reporting of scientific data. Regarding the classification of acute pancreatitis, this thesis aimed to explore the validity of the 1992 Atlanta Classification, to offer means of improvement of classifying local pancreatic complications, to present the newly Revised Atlanta Classification, and to investigate the interobserver agreement of the interpretation of CT-based criteria for pancreatic morphologic changes, using the Revised Atlanta Classification.

Although, the 1992 Atlanta Classification represented a *clinical* classification system, some of the Atlanta definitions are used by radiologists to classify morphologic findings of acute pancreatitis on cross-sectional imaging, primarily CT. Hitherto, the interobserver agreement between radiologists using the 1992 Atlanta definitions for describing findings on CT was unknown. Therefore, in **Chapter 2** we performed an interobserver agreement study on categorizing pancreatic collections between five abdominal radiologists using the 1992 Atlanta definitions.

Despite the passage of nearly two decades since the publication of the original 1992 Atlanta Classification, no attempts directed toward objective validation of the Atlanta definitions have been performed. **Chapter 3** provides an overview on the use of the Atlanta definitions in the literature and aimed to assess to what extent the 1992 Atlanta Classification is accepted, including the variation in interpretation of the 1992 Atlanta definitions. In **Chapter 4**, we explored whether the terms abandoned by the 1992 Atlanta Classification (including 'infected pseudocyst' and 'phlegmon') were discarded effectively in the literature and we searched for new terms that emerged after the publication of the 1992 Atlanta Classification to describe manifestations in acute pancreatitis that might not have been addressed adequately.

Based on the results of the interobserver agreement study on the Atlanta definitions (chapter 2) and the two literature reviews (chapters 3 and 4), several deficiencies in the 1992 Atlanta definitions pertaining to complex pancreatic collections were noted. Instead of using subjective interpretative terms (such as the Atlanta definitions), we proposed to use objective descriptive terms to describe morphologic findings of acute pancreatitis on cross-sectional imaging with the aim to improve inter-rater agreement among readers of various specialties. In **Chapter 5**, results of an interobserver agreement study are presented among 17 surgeons, gastroenterologists, and radiologists using a new set of descriptive terms for describing features of acute pancreatitis on CT.

Over the last decade, a number of inconsistencies and ambiguities of the 1992 Atlanta Classification have been identified. This, combined with advances in knowledge of the natural history of acute pancreatitis, improved diagnostic imaging, and the development of minimally invasive treatment options for complicated pancreatitis, necessitated an update of disease severity classification and nomenclature of pancreatic collections. **Chapter 6** presents the 2012 Revised Atlanta Classification which were formulated after an iterative web-based worldwide consultation of specialists involving different disciplines.

The 2012 Revised Atlanta Classification have proposed a new set of terms to classify pancreatic collections depicted by cross-sectional imaging based on their composition and morphology with the aim to facilitate accurate communication between clinicians and radiologists by using a common and unified terminology. **Chapter 7** describes the interobserver agreement regarding CT morphology of acute pancreatitis among abdominal radiologists using the 2012 Revised Atlanta definitions.

Part II – Severity prediction of acute pancreatitis

Given the wide spectrum of clinical manifestations of acute pancreatitis, early identification of those at risk for severe disease, systemic and local complications, and mortality is imperative. Currently, there are a plethora of predictive systems, including single prognostic markers (e.g. serum creatinine, hematocrit, blood urea nitrogen, among others), clinical scoring systems (among them are APACHE-II, BISAP, Glasgow score, and Imrie score), and imaging-based scoring systems.

Pertaining to the actual and predicted severity of acute pancreatitis, this thesis aimed to investigate and compare the accuracy of clinical and imaging-based scoring systems for predicting the ultimate severity of acute pancreatitis, to find out the best means of diagnosing the most severe and lethal local complication of acute pancreatitis (i.e. infected necrosis), and to assess the clinical outcome of the different morphologic types of acute pancreatitis in two different cohort of patients.

Among all imaging-based scores, the CTSI, constructed by Balthazar and colleagues, is the most studied (47). Patients with higher CTSI scores have increased morbidity and mortality. In 2004, a modified CTSI has been proposed, the MCTSI, which adds extrapancreatic findings (pleural effusion, ascites, extrapancreatic complications), reduces the categorization of pancreatic necrosis to none, <30%, and >30%, and simplifies the scoring of peripancreatic changes. In a relatively small study (n=66), the MCTSI compared with CTSI was found to better correlate with patient outcome (54). In **Chapter 8**, we performed a comparative evaluation of the MCTSI and CTSI with the aim to investigate which scoring system performed best in assessing the severity of acute pancreatitis in a large cohort of patients (n=196) using updated definitions for severity.

The challenge for clinicians is to determine quickly and accurately, preferably at admission, those who will progress to organ failure and develop severe acute pancreatitis. Few studies compared the predictive accuracies of imaging-based and clinical scoring systems early in the course of acute pancreatitis. To this end, we compared the accuracy of seven CT scoring systems and two clinical scoring systems for predicting the severity of acute pancreatitis at admission in **Chapter 9**.

In **Chapter 10**, an overview of the role of imaging-based scoring systems in predicting the severity and clinical outcome in patients with acute pancreatitis is addressed, including a review of clinically relevant prognostic CT findings with direct impact on patient management.

Infected necrosis is the most common, most severe, and most lethal of the infectious complications of acute pancreatitis. Diagnosis of infected necrosis can be challenging in patients with severe acute pancreatitis as the disease itself may present with a septic profile (signs of SIRS; fever, leukocytosis, tachycardia, and tachypnea), which may be indistinguishable from infectious extrapancreatic complications or sepsis syndrome. **Chapter 11** addresses this issue and evaluates the role of clinical presentation, cross-sectional imaging, and fine needle aspiration in diagnosing infected necrosis.

Interstitial pancreatitis has been recognized as a distinct clinicopathologic form of acute pancreatitis for almost nine decades. While nearly 85% of patients hospitalized for acute pancreatitis have interstitial pancreatitis, most clinical studies over the past 3 decades have evaluated severity of necrotizing pancreatitis and only a few have focused on the clinical outcome of those with interstitial disease. In **Chapter 12**, we analyzed the severity of interstitial pancreatitis among a cohort of non-transferred consecutive patients and also compared the severity between patients with interstitial pancreatitis and those with extrapancreatic necrosis.

According to the 2012 Revised Atlanta Classification, necrotizing pancreatitis is defined as necrosis of pancreatic parenchyma only, extrapancreatic tissue (EXPN) only, or combined necrosis, which is the most common. Many have reported on clinical outcome of patients with combined necrosis, however, little is known about patients with EXPN alone. In **Chapter 13**, the clinical outcome of patients with EXPN alone was compared with those with combined necrosis in a large multicenter cohort of patients with necrotizing pancreatitis.

It is indisputable that the presence of parenchymal necrosis is associated with increased rates of morbidity and mortality. The relationship between extent of parenchymal necrosis and clinical outcome, however, is contentious. Some have found a clear correlation between extent of parenchymal necrosis versus clinical outcome, whereas others have not. Many studies have reported on the presence and extent of parenchymal necrosis, but few studies have addressed the site of parenchymal necrosis as determining factor for clinical outcome. In **Chapter 14**, we evaluated the clinical significance of the specific location of parenchymal necrosis in a large cohort of patients with necrotizing pancreatitis.

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PART I

Classification of Acute Pancreatitis: definitions and terminology

2

Describing computed tomography findings in acute necrotizing pancreatitis with the Atlanta Classification:

An interobserver agreement study

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PANCREAS. 2006 NOV;33(4):331-5. IMPACT FACTOR: 2.97

ABSTRACT

Objectives: The 1992 Atlanta Classification is a clinically based classification system that defines the severity and complications of acute pancreatitis. A study was undertaken to assess the interobserver agreement of categorizing peripancreatic collections on computed tomography (CT) using the Atlanta Classification.

Methods: Preoperative contrast-enhanced CTs from 70 consecutive patients (49 men; median age, 59 years; range, 29-79 years) operated for acute necrotizing pancreatitis (2000-2003) in 11 hospitals were reviewed. Five abdominal radiologists independently categorized the peripancreatic collections according to the Atlanta Classification. Radiologists were aware of the timing of the CT and the clinical condition of the patient. Interobserver agreement was determined.

Results: Interobserver agreement among the radiologists was poor (κ,0.144; SD, 0.095). In 3 (4%) of 70 cases, the same Atlanta definition was chosen. In 13 (19%) of 70 cases, 4 radiologists agreed, and in 42 (60%) of 70 cases, 3 radiologists agreed on the definition. In 21 cases (30%), 1 or more of the radiologists classified a collection as 'pancreatic abscess' whereas 1 or more radiologist used another Atlanta definition.

Conclusion: The interobserver agreement of the Atlanta Classification for categorizing peripancreatic collections in acute pancreatitis on CT is poor. The Atlanta Classification should not be used to describe complications of acute pancreatitis on CT.

INTRODUCTION

Treatment of acute necrotizing pancreatitis (ANP) is a challenge, and consultation with or referral to specialized institutions is advised on several occasions;[1-3] therefore, adequate communication regarding both the severity and complications of ANP is of utmost importance. In 1992, an international symposium on acute pancreatitis was held in Atlanta to resolve lingering disputes regarding the definitions of various complications in acute pancreatitis. Agreement was reached on a clinically based classification system to define the disease and its complications: the so-called Atlanta Classification.[4]

Contrast-enhanced computed tomography (CECT) is the primary radiological diagnostic modality to assess the various complications of acute pancreatitis.[1-3] The CT severity index (CTSI)[5] was specifically designed to assess the severity of acute pancreatitis. Recently, a 'modified CT severity index' was presented.[6] However, the CTSI and modified CTSI are not designed to characterize peripancreatic collections, and consequently, the Atlanta Classification is frequently used to describe (peri-)pancreatic collections on CT.

To our knowledge, no study has determined the interobserver agreement when using the Atlanta Classification for this purpose. In the current study, to determine the interobserver agreement, 5 abdominal radiologists reevaluated preoperative CECTs from 70 consecutive patients operated for ANP.

MATERIALS AND METHODS

Patient Identification

In 11 hospitals of the Dutch Acute Pancreatitis Study Group, including all 8 Dutch university medical centers, 106 consecutive patients (age, >18 years) who underwent surgical intervention for proven or suspected infection of (peri-)pancreatic necrosis between October 1, 2000, and October 1, 2003, were identified by a hospital computer database search. Surgical outcome of these patients has been described elsewhere.[7] Patients were included in the present study if a preoperative CECT had been performed and was available for analysis.

Data Collection

Date of hospital admission, date of CT, the original CT reports, and the preoperative CTs were retrieved from the participating and referring centers. In the CT reports, the use of the exact terms “pancreatic necrosis,” “pseudocyst,” and “pancreatic abscess” was scored. Terms such as “nonenhancement” or “fluid collection” were not scored, because they are not used in the Atlanta Classification. All preoperative CTs were digitalized by high resolution scanning (Diagnostic Pro; Vidar Systems Corporation, Herndon, Va).

Study Protocol

From the (last) preoperative CT scan, 2 to 3 slices at different anatomic levels were selected; including the slice depicting the maximum diameter of the fluid-containing collection in or around the pancreas. These images were inserted in a computer slide presentation. The individual slides were coded, and the dates of the following events were added: hospital admission, preoperative CT, and surgical intervention. Five experienced abdominal radiologists from 5 different hospitals (TLB, MSVL, JSL, EJVDJ, and SPS) independently reviewed the selected images or the entire CT. The radiologists were aware of the fact that all patients were operated upon for severe acute pancreatitis. The radiologists were, however, blinded for the results of the original report and were blinded for the reports of the other radiologists. If required by a radiologist, the complete digitalized CT was presented. The radiologists were asked to characterize the (peri-)pancreatic collections as acute fluid collection, pseudocyst, pancreatic abscess, or pancreatic necrosis according to the Atlanta Classification, (Table 1). A fifth option 'mixture' was added for cases in which the radiologist felt the morphological changes depicted by CT had features of several definitions and thus did not fit within the confines of the Atlanta Classification. The option 'no collection' was added as it was anticipated that in some cases, no peripancreatic collection was apparent on the CT scan. The radiologists were familiar with the Atlanta Classification, and all read the appropriate definitions before review. The definitions remained available during the entire review process.

TABLE 1. Complications of Acute Pancreatitis as Described by the 1992 Atlanta Classification[6]

Acute fluid collection	Occurs early in the course of acute pancreatitis, are located in or near the pancreas, and always lack a wall of granulation or fibrous tissue.
Acute pseudocyst	A collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue that arises as a consequence of acute pancreatitis or pancreatic trauma or chronic pancreatitis. Formation of a pseudocyst requires 4 or more weeks from the onset of acute pancreatitis.
Pancreatic abscess	A circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis that arises as a consequence of acute pancreatitis or pancreatic trauma.
Pancreatic necrosis	A diffuse or focal area(s) of nonviable pancreatic parenchyma that is typically associated with peripancreatic fat necrosis.

Statistical Analysis

The interobserver agreement was calculated using κ statistics. A κ level of less than 0.00 represents no agreement; 0.00-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0,61-0.80, substantial; 0.81-1.00, almost perfect agreement.[8] Mean κ with SD was calculated for all 10 radiologist pairs within the 5 radiologists. Categorical data were compared using Fisher exact test. Results of continuous data were expressed as median [range]. Comparison of continuous variables was performed using Mann-Whitney *U* test or Kruskal-Wallis test for multiple groups. A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Patients

Of 80 scans available, 10 were non-contrast enhanced and were excluded. Therefore, preoperative CECTs were available for 70 (75%) of 106 patients. The patient baseline characteristics are shown in Table 2. Indications for surgical intervention were persistent sepsis despite maximal conservative therapy (61%), positive fine needle aspiration culture (23%), (peri-)pancreatic air on CT scan (10%), or suspected perforation of the gastrointestinal tract (6%). The diagnosis of infected pancreatic necrosis was confirmed in 63 patients (79%) by means of a positive culture from a peroperative aspirate.

TABLE 2. Patient Characteristics

Male	49	(70)
Age (y)	59	[29-79]
Preoperative intensive care unit admission (d)	38	(54)
Preoperative intensive care unit stay* (d)	7	[1-55]
Preoperative hospital stay	24	[1-140]
Mortality	24	(34)

Values are given as n (%) or median [range]. *Of patients admitted to the intensive care unit.

Original CT Reports

Sixty-four original CT reports (91%) were retrieved. In 48 reports (75%), one of the following terms was used “pancreatic necrosis” (n = 28), “pseudocyst” (n = 6), or “pancreatic abscess” (n = 14).

Interobserver Agreement

Among the 5 abdominal radiologists, there was slight interobserver agreement for categorizing collections according to the Atlanta Classification (ϰ, 0.144; SD, 0.095; Table 3). In 3 (4%) of 70 cases, the radiologists chose the same definition (mixture, n = 2; pancreatic necrosis, n = 1). Four of 5 radiologists agreed in 15 cases (19%), and 3 of 5 agreed in 49 cases (61%). In 24 cases (30%), 1 or more of the radiologists classified a collection as 'pancreatic abscess' whereas 1 or more of the other radiologists classified the collection as 'acute fluid collection,' 'pseudocyst,' or 'pancreatic necrosis.' See Figure 1 for examples.

TABLE 3. Atlanta Classification Used for Defining (Peri-)Pancreatic Collections in 70 Necrotizing Pancreatitis Patients

Radiologist	Acute Fluid Collection	Pancreatic Abscess	Pseudocyst	Pancreatic Necrosis	Mixture	No Collection	Total
1	10 (14)	22 (31)	0 (0)	4 (6)	32 (46)	2 (3)	70 (100)
2	1 (1)	1 (1)	0 (0)	14 (20)	53 (76)	1 (1)	70 (100)
3	8 (11)	4 (6)	0 (0)	7 (10)	51 (73)	0 (0)	70 (100)
4	14 (20)	16 (23)	2 (3)	24 (34)	14 (20)	0 (0)	70 (100)
5	15 (21)	21 (30)	20 (29)	6 (9)	3 (4)	5 (7)	70 (100)
Mean	10 (14)	13 (18)	4 (6)	11 (16)	31 (44)	2 (2)	70 (100)

Values are given as n (%).

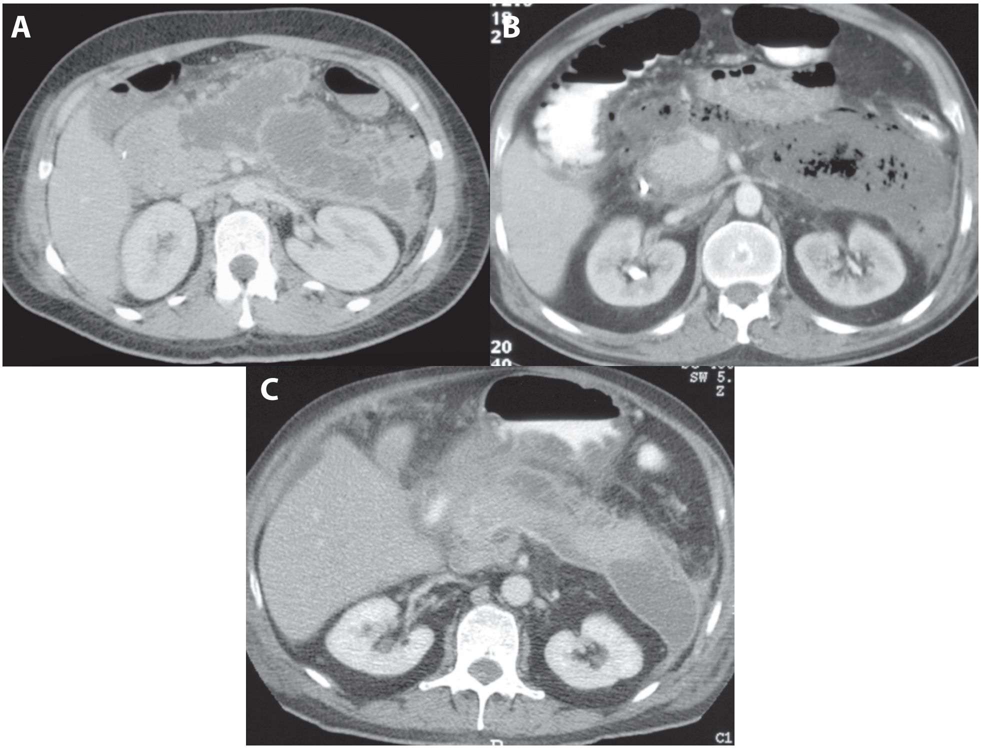

FIGURE 1. The use of the Atlanta Classification on CT in necrotizing pancreatitis. **A**, Computed tomography scan 12 days after onset of disease. The definitions chosen for this collection were "pseudocyst" (n = 1), "pancreatic abscess" (n = 1), "pancreatic necrosis" (n = 1), and "mixture" (n = 2). **B**, Computed tomography scan 27 days after onset of disease. The definitions chosen for this collection were "pancreatic abscess" (n = 3) and "mixture" (n = 2). **C**, Computed tomography scan 31 days after onset of disease. The definitions chosen were "pancreatic necrosis" (n = 1), "pancreatic abscess" (n = 1), "pseudocyst" (n = 1), and "mixture" (n = 2).

DISCUSSION

This study shows that the interobserver agreement for using the Atlanta Classification to categorize (peri-)pancreatic collections on CT is very poor, even when experienced abdominal radiologists are asked to judge CECTs.

Surgeons and gastroenterologists tend to rely heavily on the radiologist's CT report of a patient with ANP to decide upon further treatment. The impact of a report describing a "pseudocyst" is completely different from that of "infected pancreatic necrosis" or a "pancreatic abscess."[1-3] As shown by the original CT reports in this study, radiologists often use the terms of the Atlanta Classification, although it is known that the Atlanta Classification was not designed originally for this specific purpose.

The major finding in this study was that the interobserver agreement for describing (peri-) pancreatic collections on CT scan is very poor even when abdominal radiologists were supplied with the most relevant clinical data in these patients in whom the decision to operate had been made. These findings may be explained partially by the fact that the Atlanta Classification does not describe all manifestations of the disease with respect to (peri-)pancreatic collections.[9] For example, a collection containing both necrosis and fluid does not fit with any of the definitions in the Atlanta Classification (see Table 1). Collections containing both impacted air and necrosis are often called 'pancreatic abscess,' when according to the Atlanta Classification, they are not. This may force the radiologist to decide between 2 definitions, feeling uncomfortable with both. This is a relevant problem as illustrated by the fact that the added option 'mixture' was used by the radiologists in up to 3 quarters of cases. Furthermore, it has been noted that CT is often not capable of detecting solid debris in pancreatic collections, especially when a significant fluid component is present.[10] This leads to problems in the diagnosis of a 'pseudocyst.' It is an extremely common error that collections containing a mixture of necrotic debris and fluid are termed 'pseudocyst.'[9] In 9% of the original scan reports and in a mean of 6% of the 'expert' reports, the term 'pseudocyst' was used, although none of the patients had a pseudocyst, because pancreatic necrosis was detected during surgery in all cases. The recently revised UK guidelines on acute pancreatitis acknowledges this fact because it states that an ultrasound or magnetic resonance should always be performed before the diagnosis of pseudocyst is established. Furthermore, the guideline recommends considering all localized collections after necrotizing pancreatitis to be localized necrosis until proven otherwise.[3]

Most guidelines advice the use of the CTSI developed by Balthazar et al to quantify the extent of morphological changes on CT.[1-3] The CTSI has been reported to have a good interobserver agreement.[11] However, the CTSI is not concordant with the definitions of the Atlanta Classification.

Interobserver agreement studies have never been reported for the Atlanta Classification, so the present study cannot be compared with previous studies. However, our study design is not likely to have introduced much observer bias, as the review was performed in a blinded controlled manner. One might argue that the inclusion of only CT scans of patients operated upon for suspected infected ANP caused selection bias. However, in daily practice, it is in these patients, in whom the decision for intervention is about to be taken, that the characterization of CT findings is most relevant. Different complications require different treatment strategies, ranging from conservative management to invasive percutaneous or surgical intervention. Interobserver variability in characterization of (peri-)pancreatic collections will potentially mislead the clinician in his choice for the appropriate therapy. This fact is illustrated in the present series by the 30% of cases in which the diagnosis of pancreatic abscess (treatment: percutaneous drainage) was used where other radiologists used the definitions pseudocyst (treatment: initially conservative), acute fluid collection (treatment: conservative), or pancreatic necrosis (treatment: surgery when infected).

The poor interobserver agreement of the Atlanta Classification for characterizing (peri-) pancreatic collections on CT has several major implications. It should especially be taken into account in interhospital communication on acute pancreatitis patients, and it may even change our view of previously published clinical studies on intervention strategies in ANP. The Atlanta Classification should not be used to describe complications of acute pancreatitis on CT scan and a new descriptive radiological classification system for acute pancreatitis should be designed. Obviously, both interobserver and clinical studies will have to show the clinical relevance of such a classification. Computed tomography reports should be descriptive and mention the presence or absence of pancreatic necrosis, fluid collections, encapsulation, and/or air. Finally, CT images should be reviewed by the radiologist and the clinician in unison, because this is likely to be the best safeguard against miscommunication and poor interpretation of peripancreatic collections in ANP.

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Toward an update of the Atlanta Classification on acute pancreatitis:

Review of new and abandoned terms

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ABSTRACT

Objectives: The 1992 Atlanta Classification is a clinically based classification system that defines the severity and complications of acute pancreatitis. The purpose of this review was to assess whether the terms abandoned by the Atlanta Classification are really discarded in the literature. The second objective was to review what new terms have appeared in the literature since the Atlanta symposium.

Methods: We followed a Medline search strategy in review and guideline articles after the publication of the Atlanta Classification. This search included the abandoned terms: "phlegmon," "infected pseudocyst," "hemorrhagic pancreatitis," and "persistent pancreatitis."

Results: A total of 239 publications were reviewed, including 10 guideline articles and 42 reviews. The abandoned terms 'hemorrhagic pancreatitis' and 'persistent pancreatitis' are hardly encountered. In contrast, both 'infected pseudocyst' and 'phlegmon' are frequently used, and several authors question their abandonment. New terminology in acute pancreatitis consists of 'organized pancreatic necrosis,' 'necroma,' 'extrapancreatic necrosis,' and 'central gland necrosis.'

Conclusions: This review demonstrates that the Atlanta Classification is still not universally accepted. Several abandoned terms are frequently used, and new terms have emerged that describe manifestations in acute pancreatitis that were not specifically addressed during the Atlanta symposium.

INTRODUCTION

Between 1963 and 1992, 5 interdisciplinary symposia on pancreatitis have been convened to define and classify the spectrum of acute and chronic pancreatitis. The first symposium on pancreatitis was held in Marseille, France, in 1963.[1] Staging was based on clinical grounds and categorized in acute, relapsing acute, chronic, and relapsing chronic pancreatitis. After the introduction of computed tomography (CT), this classification was revised in 1984 and 1988 using morphological criteria to classify the spectrum of pancreatitis.[2-4] This classification system lacked specific definitions for the complications of acute pancreatitis, and the nomenclature of complications was often ambiguous. Secondary infections of the pancreas associated with acute pancreatitis were classified as pancreatic abscess, infected pancreatic necrosis, or phlegmon. Often, no distinction was made between these entities, and many morphological terms were used interchangeably and inappropriately by radiologists and clinicians, including surgeons and gastroenterologists.

The last international symposium on defining acute pancreatitis and its complications was held in Atlanta, Georgia, in 1992.[5] This international meeting was unique in the sense that it was the first symposium that focused on acute pancreatitis only, and this resulted in a universally applied classification system depending on both clinical and pathological criteria.[5] The Atlanta symposium abandoned the terms 'infected pseudocyst,' 'phlegmon,' 'hemorrhagic pancreatitis,' and 'persistent acute pancreatitis.' Definitions were proposed for 'acute pancreatitis,' 'mild/severe acute pancreatitis,' 'acute fluid collection,' 'pancreatic necrosis,' 'pseudocyst,' and 'pancreatic abscess.'[5] As early as 1990, Lumsden[6] and Lumsden and Bradley[7] stressed the importance of using precise terminology and definitions for the various pancreatic complications because each requires a distinct treatment strategy. Not only are unequivocal definitions crucial in the communication between physicians, they are also imperative to compare interinstitutional studies. Fourteen years after the Atlanta symposium, it is unknown whether the abandoned terms according to the Atlanta Classification are universally discarded or not. Therefore, we conducted a literature search to investigate the use of the abandoned terms after the publication of the Atlanta Classification. Furthermore, we searched for new terms that emerged in the literature after 1993 to describe manifestations in acute pancreatitis that were not addressed in the Atlanta symposium.

MATERIALS AND METHODS

The terms abandoned by the Atlanta Classification were systematically explored by a Medline search strategy using the following terms: “phlegmon,” “infected pseudocyst,” “hemorrhagic pancreatitis,” and “persistent pancreatitis.”

To find potential new terms published after the publication of the Atlanta Classification in 1993, we followed a predetermined strategy for a Medline search from 1993 to 2006 including the following terms: “acute pancreatitis; and review or guidelines.” Of 1291 hits, only articles addressing diagnostic and/or management strategies were included.

Bibliographic references from the guidelines and reviews were retrieved and analyzed. All types of publications were included (ie, original work, reviews, guidelines, case reports, editorials, comments). Studies published in a language other than English or German were excluded.

RESULTS

In all guidelines, published after 1993, most of the Atlanta definitions are accepted,[8-17] and in only 1 guideline,[15] we found a term that was abandoned by the Atlanta Classification: in the German guideline on acute pancreatitis, the term 'infected pseudocyst' is used.[15] New and abandoned terms were used primarily in review articles, clinical studies, and case reports. First, the abandoned terms will be discussed, and second, the new terms on acute pancreatitis will be presented.

Abandoned Terms

Phlegmon

The term 'phlegmon' was abandoned by the Atlanta symposium because this condition was described in both edematous and necrotizing pancreatitis, either sterile or infected, resulting in considerable clinical confusion and treatment misadventures. However, several articles, published after the Atlanta symposium, still use the term 'phlegmon.'[18-31] Although most authors accept that this term should be discarded, some openly disagree. Neff[25] defines phlegmon as “…areas of peripancreatic infiltration with borders that are ill defined, having a mixed attenuation (solid and fluid), which cannot clearly be defined as fluid density. It represents inflammatory, edematous changes with infiltration of enzyme-rich pancreatic secretions and incites an inflammatory response.” He acknowledges that the term 'phlegmon' is both criticized and lauded because it is nonspecific. Furthermore, Neff[25] states that “…the term phlegmon is particularly useful because it reflects prognostic uncertainty about a process that may resolve or progress and liquefy.” Mortele et al[32-36] mention 'phlegmon' in several articles as ill-defined peripancreatic collections in grade Balthazar D pancreatitis. VanSonnenberg et al[28] defined 'pancreatic phlegmon' as “…inflammatory, viable pancreatic masses that are enhanced with intravenous contrast media during CT as opposed to pancreatic necrosis, which is defined as dead solid tissue.” A recent randomized controlled trial comparing early ductal decompression with conservative management in patients with acute biliary pancreatitis was terminated early when during interim analysis, a significant difference was observed in the incidence of complications between the experimental group and the study group.[18] In 7 of 8 patients in the experimental group, this complication was designated as a 'pancreatic phlegmon.' The authors included pancreatic phlegmon because they felt that this local complication was not adequately defined by the Atlanta Classification. In their article, they provided typical clinical, imaging, and macroscopic (during surgical exploration) features of pancreatic phlegmon.[18] Clinical features of a phlegmon consisted of severe and persistent epigastric pain and tenderness, nausea, vomiting, and protracted or episodic elevation of amylase and bilirubin levels. Radiological features of phlegmon consisted of normal enhancement of pancreatic parenchyma in conjunction with signs of peripancreatitis. Macroscopic features consisted of a pancreatic inflammatory mass, peripancreatic fluid, and fat necrosis.[18]

Infected Pseudocyst

The abandoning of the term 'infected pseudocyst' has been the least accepted. A large number of articles published since 1993 mention 'infected pseudocyst.'[15,19,28,29,37-71] Many authors disagree with the proposition that 'pancreatic abscess' is a better term for this type of collection. Mithofer et al[50] reported that "…it has become apparent that infected pseudocyst, infected necrosis, and pancreatic abscess are different aspects of secondary pancreatic infection that vary in their associated morbidity and mortality" and "…infected pseudocysts are a different clinical entity, the percutaneous drainage of which is easier, safer, and more likely to be successful." In an article on percutaneous drainage of pancreatic abscesses, vanSonnenberg et al[28] excluded patients with infected pancreatic pseudocysts, and they made the following statement: "…although not necessarily reflecting conventional thinking, the definition of pancreatic abscess included infected pancreatic pseudocysts" and "…inclusion of infected pseudocysts might increase the success rate of pancreatic abscess drainage." De Waele et al[43] reported that "pancreatic abscesses and infected pseudocysts arise later in the course of disease and should be considered as separate entities because of differences in therapy and outcome." Baril et al[19] reported that "…the imprecise definition of pancreatic abscess incorporates infected pseudocysts into this category." Pitchumoni et al[66] reported that "…an infected pseudocyst is a localized collection of infected fluid in the peripancreatic area that is enclosed by fibrous walls. Pancreatic abscesses are collections of pus that contain bacteria with little or no necrosis, in or around the pancreas, and are bound by adjacent tissues and organs. Pancreatic abscess differs from infected pseudocyst by lack of a clear membrane and the presence of an indistinct capsule or pseudocapsule consisting of fibrous tissue." Baron[38] reported that "…pancreatic abscess is not synonymous with infected pancreatic pseudocysts or infected pancreatic necrosis, they probably arise from limited pancreatic necrosis that subsequently liquefies and becomes infected." Rau et al[37] provided a new definition of infected pseudocyst: "…a localized collection of infected fluid in the region of the pancreas encapsulated by a wall. The presence of bacteria or fungi represents contamination and has no clinical significance. Furthermore, there is absence of pus and necrosis in infected pancreatic pseudocyst."

Hemorrhagic Pancreatitis

The term 'hemorrhagic pancreatitis' was only found in several case reports and a few clinical studies and is frequently used in cases of necrotizing pancreatitis or in combination with necrotizing pancreatitis (as in 'hemorrhagic-necrotizing pancreatitis').[18,65,72-80]

Persistent Acute Pancreatitis

Persistent pancreatitis was only encountered in 1 review article,[81] 1 case report,[82] and 1 clinical study.[83] This term is used in patients with persistent abdominal pain, inability to eat, and failure to thrive after recovering from the acute phase of the disease. In the study by Fernandez-del Castillo et al,[83] most of these patients had sterile necrosis (80%) and were operated on because of persistent unwellness.

New Terminology

Organized Pancreatic Necrosis

In 1996, Baron et al[84] introduced the term 'organized pancreatic necrosis' for describing, what they felt, was a new type of collection. Since then, their group and others have used this term in several articles.[38,82,85-90]

Other authors referred to this collection as 'subacute pancreatic necrosis,'[81] 'necroma,'[91] or 'pseudocyst associated with necrosis.'[92] According to Baron et al[84] and Petrakis et al,[81] pancreatic necrosis and acute fluid collections evolve and expand the initial area of pancreatic parenchyma necrosis, often accompanied by major pancreatic disruptions. Over a period of 2 to 3 weeks, these collections become encapsulated (become “organized”) and will contain variable amounts of both fluid and solid necrotic debris due to the liquefaction process of necrotic pancreatic and peripancreatic tissue.[81,84] This kind of collection cannot be specifically defined to any of the current Atlanta definitions. Petrakis et al[81] and Baron et al[84] postulate that this type of collection represents an entity in transition from acute pancreatic necrosis to pancreatic pseudocyst. The same authors described in several articles the CT manifestations of 'organized/subacute pancreatic necrosis.' On contrast-enhanced CT (CECT), organized pancreatic necrosis is manifested by a collection of homogeneous or heterogeneous attenuation (fat, fluid, solid density, no gas bubbles), partially or completely surrounded by a wall, and expressing mass effect on adjacent structures. Furthermore, Baron et al,[84] Petrakis et al,[81] and Morgan et al[89] stated that the heterogeneous attenuation can turn into a homogeneous collection on follow-up CECT scans because of the liquefaction process. In such a homogeneous collection, the solid part may then go unnoticed and may be mischaracterized as a pseudocyst. For management purposes, the distinction between organized pancreatic necrosis and pancreatic pseudocyst is deemed very important: failure of simple drainage may occur when partially liquefied necrotic collections are mistaken for pseudocysts.[38,88] It has been demonstrated by Morgan et al[89] that magnetic resonance imaging (MRI) is superior to CECT in identifying solid debris within necrotic collections. Consequently, Morgan et al[89] advocate the use of MRI before intervention in a subpopulation of patients (those who have symptomatic and persistent collections) for accurate delineation of solid debris in a collection.

Extrapancreatic Necrosis

Sakorafas et al[93] first named this entity as 'extrapancreatic necrosis' or 'EXPN,' whereas other authors also alluded to this type of acute pancreatitis.[94,95] According to Sakorafas et al,[93] EXPN represents a necrotic process of peripancreatic fatty and connective tissue without evidence of necrosis of pancreatic parenchyma. The authors regarded EXPN as a subtype of acute necrotizing pancreatitis, rather than as a new entity. The fatty tissue necrosis is probably caused by the destruction of adipocytes by activated pancreatic enzymes such as lipase.[93] The necrotic process is not only restricted to the retroperitoneal fatty tissue, but can also extend to pelvic viscera and bowel ligaments. Pathologically, EXPN consists of fat necrosis, extravasated pancreatic fluid, and inflammatory and hemorrhagic components.[93] In their study, Sakorafas et al[93] found a strong correlation between the extent and localization of EXPN and morbidity and mortality. This observation was confirmed in a recent study by Malangoni and Martin.[49] Despite extensive EXPN, patients can recover without substantial morbidity, especially in the absence of infectious complications. An important feature of EXPN on CECT is a viable, normally enhancing pancreas surrounded by a homogeneous or heterogeneous collection. The normal fatty peripancreatic tissue is replaced by homogeneous or heterogeneous density (fat, fluid, solid density). The aforementioned definition of EXPN resembles the definition of pancreatic phlegmon, which was described previously.[18,96]

Central Gland Necrosis/Disconnected Duct Syndrome

Central gland necrosis was initially described by Banks et al[97] and regarded as a subtype of necrotizing pancreatitis in a study by Freeny et al.[98] Central gland necrosis represents necrosis between the pancreatic head and tail and is nearly always associated with main pancreatic duct disruption.[98] Because of the duct disruption in conjunction with a viable and secreting pancreatic tail, pancreatic enzymes continue to leak into the central cavity. Hence, organized pancreatic necrosis, fistulas, and pseudocysts can be anticipated when necrosis of the body of the gland is observed in the presence of a viable and secreting tail of the pancreas. Other potential complications are pancreatic ascites and pleural effusion. Fluid collections that communicate with the main pancreatic duct respond poorly to percutaneous drainage alone, and definitive treatment often requires distal pancreatectomy.[98-103] Central gland necrosis is also referred to as 'disconnected gland/duct syndrome'[104-109] or 'isolated pancreatic segment.'[51] If a duct disruption is noted during ERCP, Traverso and Kozarek[110] advocate placement of transpapillary stents in the disrupted duct to prevent uncontrolled leakage of pancreatic juice in the pancreatic and peripancreatic space.

DISCUSSION

Acute pancreatitis is a disease with wide clinical variation, running a complicated course in 20% of cases.[17,111] In these patients, various complications may arise that warrant an accurate description because treatment strategies strongly depend on correct interpretation of these complications.[10,17] Despite the definitions provided by the Atlanta symposium, problems exist in daily practice because imprecise terminology is used in the communication between physicians caring for patients with acute pancreatitis.[91,112] This dispute is also found in the literature because abandoned terms are still frequently used in the literature. In addition, the first interobserver study on the radiological use of the Atlanta definitions recently demonstrated a poor interobserver agreement in classifying collections on CECT.[113] In an editorial, Bradley[114] acknowledged the limitations of the current Atlanta definitions and stated that these definitions need updating and amplification. In the last decade, several authors have expressed the need for revision of the Atlanta Classification, and this overview of abandoned and new terminology in acute pancreatitis supports this statement.[81,86,89,115,116]

This review demonstrates that 'infected pseudocyst' and 'phlegmon' are the least accepted as abandoned terms. 'Hemorrhagic pancreatitis' and 'persistent pancreatitis' are hardly used in the literature and can be considered as effectively discarded. The most important rationale for the use of infected pseudocyst is the disagreement in the pathogenesis of pancreatic abscess and infection of a pseudocyst. Several authors are convinced that pancreatic abscess and infected pseudocyst are different entities with different management strategy and outcome. Data on results from therapy management for pancreatic abscess and infected pseudocyst exist in studies before the Atlanta symposium. These results are very difficult to interpret because of the extremely ambiguous use of pancreatic abscess in the literature before the Atlanta symposium.[6,7,117] After 1993, no articles were found that compared differences in therapy management between pancreatic abscess and infected pseudocyst, and therefore, we believe, that there is a lack of reliable evidence that pancreatic abscess and infected pseudocyst differ in therapy and outcome.

Probably, the main reason for the use of the term 'phlegmon' is the fact that the Atlanta symposium did not address a peripancreatic collection on a CT scan that consists of mixed attenuation (solid, fluid, and fat density) and not primarily fluid density as is seen in acute fluid collections. The problem with reintroducing the term phlegmon in the literature is that no consensus exists on the precise definition of this term. Hence, this may propagate more confusion in the literature.

There are several explanations for the appearance of new terms in the literature since the Atlanta symposium. The proposed Atlanta definitions were the result of the knowledge that existed in 1992. Over time, new insights into the pathophysiology of this disease have been acquired. Furthermore, improved diagnostic imaging techniques and new therapeutic strategies for complications of acute pancreatitis are introduced. These new treatment options (ie, minimally invasive surgery, endoscopic necrosectomy, percutaneous drainage) rely on accurate morphological description of complications in acute pancreatitis because the type of intervention is dependent on the contents of a collection. New insights in the pathophysiology of acute pancreatitis have led to the recognition of 2 additional types of acute pancreatitis, with possible important prognostic and management implications. Extensive retroperitoneal peripancreatic necrosis with no recognizable pancreatic parenchymal necrosis (EXPN) can be regarded as a subtype of (necrotizing) pancreatitis that has a better prognosis as compared with patients with gland necrosis. An impediment for introduction of this term may be the difficulty to reliably identify fat necrosis on a CECT because conflicting results are observed in the literature on identification of (peripancreatic) fat necrosis on CECT.[6,95,118-121]

Central gland necrosis can be regarded as a subtype of necrotizing pancreatitis, which is important for the clinician and radiologist to recognize because several complications can be anticipated, such as the formation of organized pancreatic necrosis, pseudocysts, and fistulas. These patients may ultimately require distal pancreatectomy for definitive treatment of refractory collections or pancreatic fistulas.

The problem with the current Atlanta Classification is that it addresses the extremes of the spectrum of complications in acute pancreatitis. Early events in acute severe pancreatitis are the presence of acute fluid collections and pancreatic parenchymal necrosis. Pseudocysts (collection of sterile fluid) and pancreatic abscesses (collection of pus) take at least 4 weeks or more to evolve,[5] and hence, the collections that occur in the meantime are less well defined. Many authors acknowledge the dynamic evolving process of acute pancreatitis and state that overlap of several entities may occur.[50,81,86,122] 'Organized pancreatic necrosis' or 'necroma' is probably the most important new entity that was not recognized at the Atlanta symposium. This kind of collection contains both fluid and necrosis and, therefore, does not fit in any of the current Atlanta definitions. In the current Atlanta Classification, organized pancreatic necrosis may be defined as either pseudocyst or pancreatic necrosis. This entity can easily be misinterpreted as a pseudocyst on a CT if the solid necrotic debris in the collection is not recognized. With the advent of more sophisticated imaging techniques, such as MRI and endoscopic ultrasonography, the necrotic debris can better be delineated and, hence, can direct the type of intervention that is deployed (simple drainage vs endoscopic/surgical necrosectomy).[10]

How can this review help us in designing a new Atlanta Classification? First, we feel that this review points out which terms may truly be abandoned. Second, the current Atlanta definitions should be modified to effectively discourage the use of the abandoned terms by providing strict clinical, pathological, and radiological criteria for every definition. Third, the term 'organized pancreatic necrosis,' representing a collection that contains both fluid and necrotic debris, seems useful for introduction. Fourth, a classification of acute pancreatitis should leave room for introduction of EXPN. In this regard, interstitial or edematous pancreatitis refers to a type of pancreatitis that is characterized by normal pancreatic enhancement on CECT or MRI and absence of peripancreatic (fluid) collections. EXPN is defined as a normal enhancing pancreatic parenchyma on CECT or MRI surrounded by (fluid) collection(s). Necrotizing pancreatitis refers to non-enhancement of pancreatic parenchyma on CECT or MRI with or without peripancreatic (fluid) collections. Finally, central gland necrosis should be regarded as a subtype of necrotizing pancreatitis.

For universal application of any new classification system, we realize that acceptance is only achieved if international consensus is accomplished.

CONCLUSIONS

This review demonstrates that several abandoned terms are still frequently used, and new terms on acute pancreatitis have emerged that describe manifestations in acute pancreatitis that were not specifically addressed during the Atlanta symposium. Therefore, an update of the Atlanta Classification seems prudent, to make comparison of research data more reliable and improve patient management.

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The Atlanta Classification of acute pancreatitis revisited

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ABSTRACT

Background: In a complex disease such as acute pancreatitis, correct terminology and clear definitions are important. The clinically based Atlanta Classification was formulated in 1992, but in recent years it has been increasingly criticized. No formal evaluation of the use of the Atlanta definitions in the literature has ever been performed.

Methods: A Medline literature search sought studies published after 1993. Guidelines, review articles and their cross-references were reviewed to assess whether the Atlanta or alternative definitions were used.

Results: A total of 447 articles was assessed, including 12 guidelines and 82 reviews. Alternative definitions of predicted severity of acute pancreatitis, actual severity and organ failure were used in more than half of the studies. There was a large variation in the interpretation of the Atlanta definitions of local complications, especially relating to the content of peripancreatic collections.

Conclusion: The Atlanta definitions for acute pancreatitis are often used inappropriately, and alternative definitions are frequently applied. Such lack of consensus illustrates the need for a revision of the Atlanta Classification.

INTRODUCTION

Over the past five decades, several classification systems on pancreatitis have emerged from interdisciplinary symposia[1–4]. The most recent international meeting on this topic, the 1992 Atlanta symposium, produced a clinically based classification system[4,5]. Definitions of acute pancreatitis, its severity, organ failure and the local complications 'acute fluid collection', 'pancreatic necrosis', 'pseudocyst' and 'pancreatic abscess' were proposed. The Atlanta Classification attempted to introduce uniformity in the assessment of clinical severity and the various complications of the disease. This is the only widely accepted classification system used by clinicians and radiologists. With increasing knowledge of the pathophysiology of pancreatitis and the development of new means of intervention, several authors have pointed out shortcomings in the Atlanta Classification[6–13]. A recent review demonstrated that terminology abandoned by the Atlanta symposium, for instance 'phlegmon' and 'infected pseudocyst', is still used frequently in the literature, and that various new terms, such as 'organized pancreatic necrosis' and 'necroma', have been introduced since 1993[14]. A critical evaluation of the use of the Atlanta Classification in the literature has never been performed. The present review assesses whether the definitions of the Atlanta Classification are accepted in the literature and evaluates the extent of variation in interpretation of these definitions.

METHODS

A Medline search of literature published between 1993 and 2006 was performed using the following terms: 'acute pancreatitis and review' and 'acute pancreatitis and guidelines'. From the identified guidelines and reviews, cross-references were retrieved. The search included all types of publication (reviews, guidelines, original studies, case reports and editorials), but excluded those not in English and animal experimental studies. One author (T.L.B.) performed the selection and reviewed all full-text papers to assess whether the original Atlanta definitions (*Table 1*) or other definitions were used for the following five components of the Atlanta Classification: diagnosis (cut-off levels of pancreatic enzymes lipase and amylase); predicted severity (predictive scoring systems, cut-off levels of scoring systems); actual severity (distinction between mild and severe pancreatitis, distinction between predicted and actual severity); organ failure (determinants of individual failing organ systems, cut-off levels of determinants, distinction between single-organ failure and multiorgan failure); local complications (pancreatic necrosis and peripancreatic necrosis, infection of necrosis, morphological aspects and distinction of different types of collection).

If different definitions for the components were identified, this was double checked by one of two other authors (H.C.v.S., M.G.B.). All disagreements were resolved by discussion among the authors. In addition, study results leading to new insights that might have influenced the interpretation of the Atlanta Classification were recorded and are discussed. As a large number of references were retrieved, for each component of the Atlanta Classification that was assessed only the three most recent articles are cited here; the remaining references are published in *Appendix 1* (available as supplementary material online at www.bjs.co.uk).

TABLE 1. Summary of the 1992 Atlanta Classification

	Definition
Acute pancreatitis	An acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems Associated with raised pancreatic enzyme levels in blood and/or urine
Severity	
Mild acute pancreatitis	Associated with minimal organ dysfunction and an uneventful recovery; lacks the features of severe acute pancreatitis. Usually normal enhancement of pancreatic parenchyma on contrast-enhanced computed tomography
Severe acute pancreatitis	Associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst
Predicted severity	Ranson score ≥ 3 or APACHE II score ≥ 8
Organ failure and systemic complications	
Shock	Systolic blood pressure < 90 mmHg
Pulmonary insufficiency	PaO_2 ≤ 60 mmHg
Renal failure	Creatinine ≥ 177 µmol/l or ≤ 2 mg/dl after rehydration
Gastrointestinal bleeding	500 ml in 24 h
Disseminated intravascular coagulation	Platelets ≤ 100,000/mm^3, fibrinogen < 1·0 g/l and fibrin-split products > 80 µg/l
Severe metabolic disturbances	Calcium ≤ 1·87 mmol/l or ≤ 7·5mg/dl
Local complications	
Acute fluid collections	Occur early in the course of acute pancreatitis, are located in or near the pancreas and always lack a wall of granulation of fibrous tissue. In about half of patients, spontaneous regression occurs. In the other half, an acute fluid collection develops into a pancreatic abscess or pseudocyst
Pancreatic necrosis	Diffuse or focal area(s) of non-viable pancreatic parenchyma, typically associated with peripancreatic fat necrosis Non-enhanced pancreatic parenchyma > 3 cm or involving more than 30% of the area of the pancreas
Acute pseudocyst	Collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, which arises as a result of acute pancreatitis, pancreatic trauma or chronic pancreatitis, occurring at least 4 weeks after onset of symptoms, is round or ovoid and most often sterile; when pus is present, lesion is termed a 'pancreatic abscess'
Pancreatic abscess	Circumscribed, intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma Often 4 weeks or more after onset Pancreatic abscess and infected pancreatic necrosis differ in clinical expression and extent of associated necrosis

APACHE, Acute Physiology And Chronic Health Evaluation; PaO_2, arterial partial pressure of oxygen.

RESULTS

A total of 447 articles was reviewed, including 12 guidelines and 82 reviews. These articles reported on studies that were not specifically designed to evaluate the Atlanta Classification; they merely mentioned Atlanta definitions (for example a randomized trial comparing two treatment strategies with the outcome 'pseudocyst'). Therefore, an assessment of methodological quality was deemed inappropriate. *Table 2* gives an overview of the papers according to type of article and impact factor of the journals in which they were published. The most important discrepancies for the five components of the Atlanta Classification and discrepancies in the 12 guidelines are discussed in order.

TABLE 2. Characteristics of retrieved articles (1993–2006) specified according to impact factor of journal

		Impact factor		
	Total no. of studies (n = 447)	High (>5·0) (n = 89)	Intermediate (1·5–4·9) (n = 273)	Low (<1·5) (n = 85)
Meta-analyses	3	2	1	0
Randomized controlled trials	34	13	18	3
Prospective series	144	28	99	17
Retrospective series	147	23	95	29
Reviews	82	10	44	28
Guidelines	12	5	5	2
Editorials	5	2	3	0
Other	20	6	8	6

Diagnosis

The Atlanta Classification provides no cut-off value for pancreatic enzyme levels. In 116 studies, the diagnosis of acute pancreatitis was defined as a characteristic clinical history of abdominal pain and an increased level of pancreatic enzymes to three or more times the upper limit of normal. However, 31 studies used different thresholds, ranging from two or more[15–17] to more than four[18–20] and more than five[21–23] times the upper limit of normal.

Predicted severity

A total of 283 articles provided criteria for predicting severity in acute pancreatitis. Some 86 reports used the severity scoring systems proposed by the Atlanta symposium[16,17,23]. However, 197 studies used a different cut-off level for defining severity, or used different or additional scoring systems, such as computed tomography (CT) severity index, Imrie (Glasgow) score, Simplified Acute Physiology score, Sequential Organ Failure Assessment or severity predictors (such as C-reactive protein)[15,24,25]. Cut-off values for severity stratification differed considerably between reports. For the CT severity index, the most established radiological scoring system developed by Balthazar and colleagues[26] in 1990, the cut-off value to differentiate between mild and severe disease ranged from three or more to eight or more points[27–29]. In 32 studies, threshold values for Acute Physiology And Chronic Health Evaluation (APACHE) II score (other than eight or more) varied from five or more to 11 or more, whereas the time for calculating the score varied from day of admission to 24 and 48 h after admission[30–32]. Eleven studies used different threshold values for the Ranson criteria (other than three or more), ranging from more than three to more than five[32–34].

Since the Atlanta symposium in 1992, many studies have identified new predictors of severity and these have been incorporated in several guidelines. Such predictors include age (over 55[6], over 70[35] or over 80[36] years), obesity (body mass index over 30 kg/m^2)[11,24,37], pleural effusion (left or bilateral) on chest radiograph[38–40], raised haematocrit level[6,41,42] and C-reactive protein level greater than 150 mg/dl after 48h[43–45].

Actual severity

Of 297 articles providing definitions for severe acute pancreatitis, 195 defined severe disease according to the Atlanta Classification, although 61 merely stated that the Atlanta criteria were used without specification[46–48]. The remaining 102 articles used definitions of severe disease other than those of the Atlanta Classification. These definitions were based on admission to an intensive care unit, length of intensive care unit or hospital stay, complications requiring medical or operative intervention, mortality or various other, additional or non-specified criteria[17,49,50]. The authors of 45 articles used the absence and presence of pancreatic necrosis broadly synonymously with mild and severe acute pancreatitis respectively[47,51,52]. Some reports, however, pointed out that patients with the morphological diagnosis of interstitial pancreatitis may develop clinically severe disease[44,53,54].

The relationship between the development of organ failure and pancreatic necrosis (the most important determinants of severe acute pancreatitis) is contentious. Several reports noted that only 51– 55 per cent of patients with pancreatic necrosis manifested organ failure[55–57]. In the study by Lankisch and colleagues[53], 15 per cent of patients with acute oedematous pancreatitis developed organ failure. In a recent study, organ failure was the main risk factor for mortality, regardless of the presence or absence of pancreatic necrosis[23]. Conversely, other studies showed a good correlation between organ failure and the extent of pancreatic necrosis[16,58,59].

Finally, in 38 articles, the differentiation between 'predicted severe' acute pancreatitis (Ranson, Imrie or APACHE II score) and 'actual severe' disease (systemic or local complications) was not apparent from the published data[17,28,60]. The difference is important, because in recent studies less than 50 per cent of patients with predicted severe disease eventually turned out to have actual severe disease according to the Atlanta criteria[25,46]. This lack of distinction may account for the variation in incidence of severe acute pancreatitis among institutions.

Organ failure

Criteria for organ failure were found in 149 articles. In 35 reports the exact Atlanta definitions for organ failure were specifically stated and used[23,61,62]. Seven articles restricted organ failure to two of the four Atlanta determinants for organ failure: respiratory and renal insufficiency[63–65]. However, 107 articles used additional criteria for organ failure and systemic complications, such as leucocytosis, temperature, coagulopathy, nervous system failure, hepatic failure, systemic inflammatory response syndrome or sepsis, or used altered thresholds or adjustments for the Atlanta definitions of organ failure[52,66,67]. The remaining articles gave no definition of organ failure, or simply noted that the Atlanta criteria were used, without specification.

In recent years, multiorgan failure has been acknowledged as a major determinant of mortality. However, no uniform definition for multiorgan failure exists: 20 reports defined it as failure of two or more organ systems[31,46,49], and eight as failure of three or more organ systems[23,68,69], although most studies did not define multiorgan failure.

The dynamic process of organ dysfunction is increasingly recognized, and several authors differentiated between transient and persistent organ failure[70–72]. In addition, several studies showed that early and progressive organ failure was associated with high mortality, but most patients with transient organ failure had an uncomplicated course[72–74]. The recent UK guidelines on acute pancreatitis state that organ failure in the first week resolving within 48h should not be considered an indicator of severe disease[43].

Since 1993, several new organ failure grading systems have been developed (Goris score, Marshall or multiple organ dysfunction score, Bernard score, Sequential Organ Failure Assessment and logistic organ dysfunction syndrome score) that take into account the number of organ systems involved and the degree of dysfunction of each individual organ. Some systems also include the need for inotropic or vasopressor agents, mechanical ventilation and dialysis that the Atlanta symposium did not account for. Several studies have shown that dynamic scoring systems (such as the delta APACHE II score) or scoring systems that account for the physiological response to treatment (such as the delta organ failure score or cumulative Marshall score) are better predictors of outcome than static scoring systems[31,32,71].

Local complications

In a recent interobserver agreement study on the Atlanta definitions regarding the various local complications, interobserver agreement was poor: five radiologists agreed on the respective Atlanta definition in only three of 70 collections depicted by contrast-enhanced CT (CECT)[8].

Acute fluid collection

In 64 articles, a definition was given for an 'acute fluid collection'. The following terms were used to describe acute fluid collections: '(peri)pancreatic fluid collections'[75–77], 'peripancreatic effusions'[78], 'extrapancreatic fluid collections'[61,79,80], 'immature pseudocyst'[81,82] and 'exudates'[54]. (Peri)pancreatic fluid collection was also used as an overall descriptive term for all types of collection related to acute pancreatitis[83–85].

In most reports, the differentiation between acute fluid collection and pseudocyst was made after 4 weeks from onset of disease (as proposed by the Atlanta Classification). In eight reports, however, a different time period was used as a criterion for this distinction, varying from 3 weeks[75,86,87] to 6[88,89] and even 8[90] weeks. Moreover, they did not adequately describe whether acute fluid collections consisted of fluid alone or whether they may have contained necrotic debris[85,91,92].

Authors of 17 articles regarded the occurrence of an acute fluid collection to be a local complication and so a sign of 'severe disease'[46,62,93]. However, most others did not include acute fluid collection either in the definition of local complication or in that of severe disease.

Pancreatic necrosis

Of 152 articles that gave a specific definition for 'pancreatic necrosis' or 'necrotizing pancreatitis' (*Fig. 1*), 47 used the Atlanta criterion of more than 30 per cent parenchymal necrosis to define necrotizing pancreatitis[28,61,94]. However, 85 defined necrotizing pancreatitis as any evidence of pancreatic parenchymal necrosis (including less than 30 per cent parenchymal necrosis)[47,95,96]. A third definition of necrotizing pancreatitis, reported in 20 papers, was the appearance of pancreatic necrosis or extrapancreatic necrosis, or both, on CECT (and a serum C-reactive protein value of more than 150 mg/dl)[52,86,97].

In the Atlanta Classification, the definition of pancreatic necrosis requires pancreatic parenchymal non-enhancement on CECT[4]. However, some clinicians questioned whether non-enhancement on CECT meant irreversible damage and necrosis[86,98,99]. For instance, Traverso and Kozarek[86] defined pancreatic necrosis as devitalized tissue found at operation. This was supported by Takeda and colleagues[100–102], who noted that pancreatic parenchymal perfusion was maintained during intra-arterial angiography, while CECT showed pancreatic non-enhancement. In contrast, several studies demonstrated a good correlation between parenchymal non-enhancement on CECT and the presence of pancreatic necrosis (confirmed at operation)[103–105].

Data on the accuracy of CECT in diagnosing extrapancreatic or peripancreatic fat necrosis are conflicting. Although eight groups claimed that fat necrosis could not be determined reliably by CECT[92,106,107], several studies demonstrated a good correlation between extrapancreatic findings on CECT and the presence of fat necrosis at operation or autopsy[104,108,109].

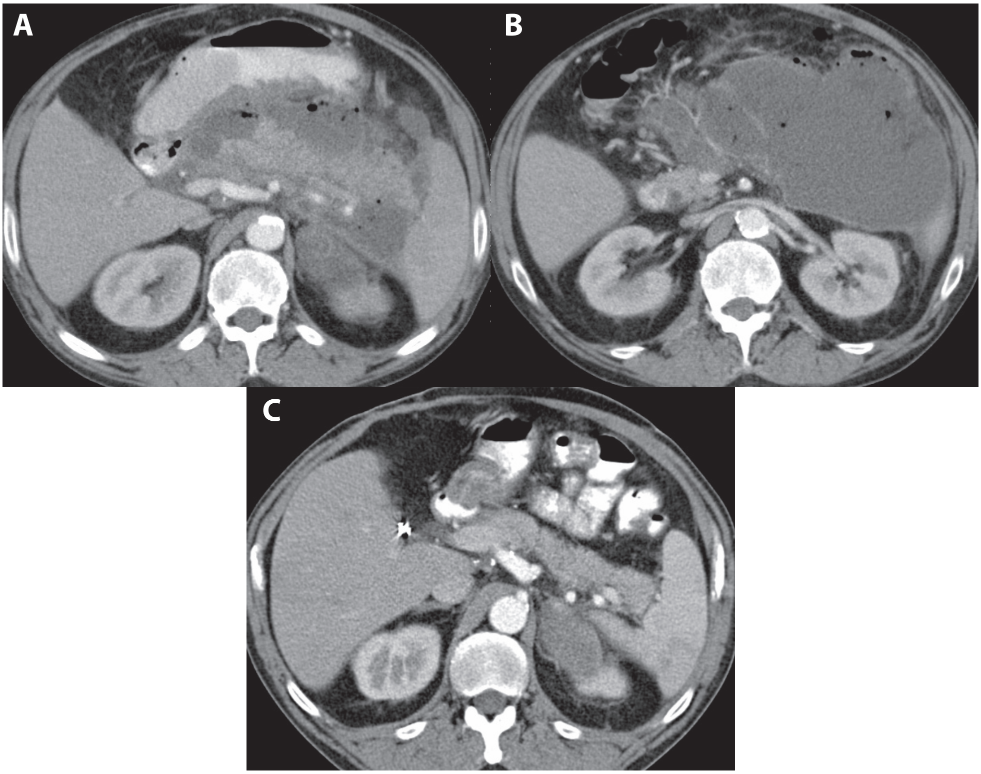

FIG. 1 Contrast-enhanced computed tomography (CT) of a patient with acute pancreatitis 22 days after onset of symptoms, **A** with normal enhancement of the pancreas and **B** surrounded by a large heterogeneous and encapsulated fluid collection with gas bubbles suggesting secondary infection. Some would call this 'necrotizing pancreatitis', but others would call it 'interstitial pancreatitis' because there is no evidence of pancreatic parenchymal necrosis (only peripancreatic necrosis). A large amount of fat necrosis was debrided during operation. **C** Follow-up CT 6 months after operation reveals a normal enhancing pancreatic parenchyma

The Atlanta Classification includes both infected and sterile necrosis within the definition of 'pancreatic necrosis'[4]. Several groups claimed that pancreatic parenchymal necrosis without infection is not a major morbidity risk[110–112] . This was supported by studies showing an uncomplicated course in the presence of necrosis without infection[23,55,56]. Beger and colleagues[81,113] were the first to emphasize that necrosis is a potential nidus for secondary infection occurring in 40 – 70 per cent of patients. Recent studies confirmed this, demonstrating infected necrosis as the primary cause of late mortality[58,114,115]. However, definitions of 'infected necrosis' were also conflicting. Some authors regarded the presence of parenchymal necrosis as a prerequisite for the diagnosis of infected necrosis[116–118], but others defined infected necrosis as infection that could occur in parenchymal necrosis or peripancreatic fat necrosis (in other words, in the absence of parenchymal necrosis), or both[67,76,119].

Pseudocyst

A specific definition for the term 'pseudocyst' was provided in 87 articles, and all were similar to that of the Atlanta Classification. Some controversies, however, remain. Thirty-eight articles included collections containing both fluid and necrotic debris under the heading of pseudocyst (*Fig. 2*)[120–122]. Yet Baron[123] and others[85,124] have stated that pseudocysts should be devoid of solid necrotic debris. Evidence has shown that therapeutic strategy and outcome differed between collections containing fluid alone and those containing necrosis and fluid[84,125,126]. Bradley[127] considered that mischaracterization of (peri)pancreatic fluid collections as pseudocyst by CECT was an extremely common error in contemporary diagnostic radiology. This mischaracterization has two potentially dangerous consequences: first, by instrumentation of a sterile collection containing both fluid and necrosis, infection may be introduced[6,120,128]; second, a delay in appropriate intervention may occur[33,120,129].

The incidence, natural history and options for management differed between acute and chronic pseudocysts. Several authors emphasized that the results of treatment of pancreatic fluid collections in the literature were difficult to interpret, because often no distinction was made between pseudocysts and acute fluid collections, or between pseudocysts that complicated acute and chronic pancreatitis[122,128,130]. Thirty-one original articles on the treatment of pseudocysts were reviewed but only five dealt exclusively with pseudocysts after an episode of acute pancreatitis[89,120,131]. The remaining 26 articles reported results of the treatment of pseudocysts complicating acute and chronic pancreatitis[121,132,133].

Pancreatic abscess

Some 68 articles provided a definition of 'pancreatic abscess', which was generally in line with the original Atlanta definition. Nine original articles after 1993 were identified that reported on the treatment of 'pancreatic abscesses', and the Atlanta definition (collection of pus and virtually no necrotic debris, more than 4 weeks after onset) was strictly applied in three of these[134–136]. The others included collections that contained, in addition to pus, solid necrotic debris[137–139] or that were treated within 4 weeks of onset of disease[140] or after surgery[141,142]. The diagnosis of pancreatic abscess on CECT is also controversial. In ten articles, the 'air bubble' phenomenon was considered 'diagnostic of a pancreatic abscess'[93,143,144]. In 31, however, gas bubbles in a heterogeneous collection on CT were regarded as highly indicative of infected pancreatic necrosis (*Fig. 3*)[61,67,145]. Varying hypotheses exist on the aetiology of pancreatic abscess. Some authors considered 'postacute pseudocysts' and pancreatic abscesses as late consequences of necrotizing pancreatitis[146–148]. In contrast, others maintained that pancreatic abscesses occurred exclusively in interstitial pancreatitis with a normal enhancing pancreas on CECT[117,149,150].

Apart from 'infection of a pseudocyst', several authors hypothesized that pancreatic abscesses evolved from progressive liquefaction of necrotic pancreatic and peripancreatic tissues, in time resulting in complete liquefaction[76,123,151]. According to the Atlanta Classification, most pancreatic abscesses arise at least 4 weeks after onset of symptoms[4], although others diagnose 'pancreatic abscesses' after 1[50,152], 2[153,154] or 3[86,146,147] weeks. Interestingly, when performing operative necrosectomy several months after the onset of severe acute pancreatitis, Morgan and colleagues[10], Howard and Wagner[155] and others[156] observed different degrees of liquefaction of necrotic tissue. Several authors acknowledged this evolving process, and they postulated that a collection may represent a transitional entity from (infected) pancreatic necrosis to an (infected) pseudocyst or pancreatic abscess, as they encountered both pus and necrotic debris in these (infected) collections[7,12,139].

Guidelines

The greatest discrepancies in the 12 guidelines[6,35,36,43,148, 157–165] on acute pancreatitis related to the definitions of organ failure and those of predicted severe disease. These are summarized in *Table 3*.

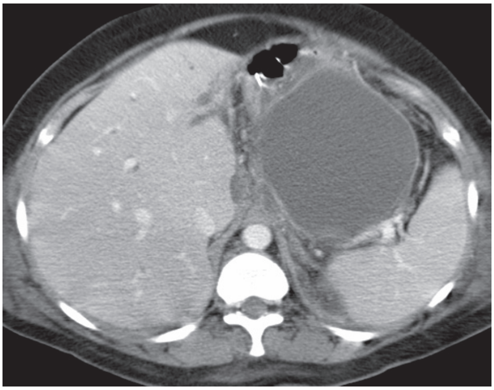

FIG. 2. Contrast-enhanced computed tomography (CT) of a patient with acute pancreatitis 30 days after onset of symptoms. The fluid collection seems to be homogeneous and encapsulated and could be interpreted as a 'pseudocyst' according to the Atlanta Classification. However, at operation the collection was found to contain large amounts of necrotic debris that CT had not shown

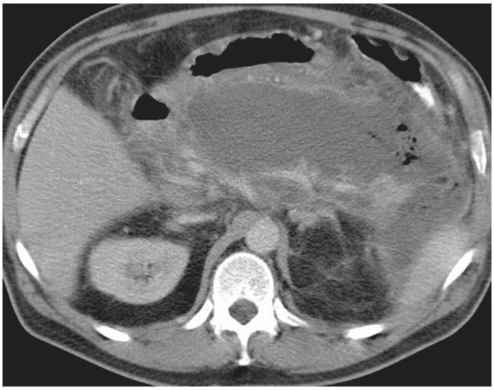

FIG. 3. Contrast-enhanced computed tomography of a patient with acute pancreatitis 36 days after onset of symptoms. The body and tail of the pancreas are largely non-enhancing. Adjacent to the pancreatic bed is a large collection with predominately fluid-like attenuation. Because of the gas bubbles, some would call this a 'pancreatic abscess' but others would call it 'infected pancreatic necrosis'

TABLE 3. Overview of definitions for organ failure and predicted severe acute pancreatitis in guidelines for acute pancreatitis published after 1993

Guideline	Definitions for organ failure	Definitions for predicted severe acute pancreatitis
ACG 1997[157]	Refers to Atlanta Classification 1992	Ranson score ≥3 after 48h APACHE II score >8 after 48h
UK 1998[158]	Refers to Atlanta Classification 1992	Ranson/Glasgow ≥3 CRP >210 mg/l (first 4 days) or >120 mg/l at 1 week APACHE II score ≥9 (severe acute pancreatitis) or ≥6 (includes all severe cases, but PPV of 50%)
SSAT 1998[159]	Not addressed	Not stated
Santorini 1999[160]	Not addressed	BMI >30 kg/m^2 Pleural effusion APACHE II score ≥6 (at 24h) APACHE (obesity) score ≥6 CRP >150 mg/l
French 2000[36]	Renal failure: creatinine >170 µmol/l Shock: systolic BP <90 mmHg despite fluid replacement Pulmonary insufficiency: PaO_2 ≤ 60 mmHg on room air Glasgow Coma Score <13 Platelets <80 g/l	At admission Age >80 years BMI >30 kg/m^2 Chronic renal failure Pre-existing severe illnesses At 24–48h Presence of organ failure by using simple measures or use of scoring system (e.g. SOFA) Ranson/Imrie score >3 CECT: CT severity index ≥4 (48–72h) CRP >150 mg/l *Note: 'The non-specific scores (APACHE II, SAP II, etc) are not recommended by the Jury'*
WCG 2002[35]	SIRS ≥1 vital organ dysfunction ARDS Renal failure: increased serum creatinine >0·5 mg/dl (44 µmol/l) or 50% above baseline or reduction in calculated creatinine clearance >50% or need for dialysis Hypotension: mean arterial pressure <60 mmHg DIC Acute adrenal insufficiency Acute hepatitis Metabolic encephalopathy Ileus	At admission Age >70 years Clinical assessment BMI >30 kg/m^2 Pleural effusion/infiltrates CECT: >30% non-enhancement of the pancreas APACHE II score ≥8 Presence of organ failure At 24–48h Clinical assessment Glasgow score (no cut-off value provided) CRP >150 mg/l Presence of organ failure
IAP 2002[161]	Not addressed	Not stated: surgical guideline
JSAEM 2002[162]	Not addressed	Clinical signs CRP (48h: no cut-off value provided) BMI (no value provided) CECT: necrosis Scoring system, like JMHW, APACHE II at 24h or Ranson/Glasgow at 24–48h: no cut-off values provided Japanese score ≥2

Guideline	Definitions for organ failure	Definitions for predicted severe acute pancreatitis
Nathens 2004[148]	Refers to the guidelines for intensive care unit admission, published in 1999[163]	Elderly (age not specified) BMI >30 kg/m^2 Patients requiring ongoing volume resuscitation CECT: >30% non-enhancement of the pancreas Clinical assessment *Note: 'Disease-specific scoring systems or severity scores are useful adjuncts to identify patients at high risk of a complication, but should not replace serial clinical assessments. In addition, there is a recommendation against the use of markers such as CRP or procalcitonin to guide clinical decision making or predict clinical course of acute pancreatitis or to triage patients'*
UK 2005[43]	Refers to Atlanta Classification 1992	At admission Clinical assessment BMI >30 kg/m^2 Pleural effusion APACHE score >8 At 24–48h Clinical assessment Glasgow score ≥3 APACHE II score >8 Persistent organ failure for 48h (especially if multiple and progressive) CRP >150 mg/l *Note: 'Organ failure present within 1 week, which resolves within 48h, should not be considered an indicator of a severe attack of acute pancreatitis'*
ACG 2006[6]	Refers to Atlanta Classification 1992 *Note: 'Criteria of organ failure will change in the future: gastrointestinal bleeding will undoubtedly be deleted'*	At admission Age >55 years BMI >30 kg/m^2 Presence of organ failure Pleural effusion/infiltrates 24–48h APACHE II score ≥8 Serum haematocrit ≥44% *Note: 'Ranson signs are no longer advocated, due to a comprehensive evaluation of 110 studies that concluded that Ranson signs provided very poor predictive power of severity of acute pancreatitis'*
JSAEM 2006[164,165]	Pulmonary insufficiency: dyspnoea Shock Central nervous system disorders Bleeding tendency Negative base excess failure: rise of blood urea nitrogen level and creatinine level	Japanese score ≥2

ACG, Practice Parameters Committee of the American College of Gastroenterology; APACHE, Acute Physiology And Chronic Health Evaluation; UK, Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, and Association of Upper GI Surgeons of Great Britain and Ireland; CRP, C-reactive protein; PPV, positive predictive value; SSAT, Society for Surgery of the Alimentary Tract; Santorini, Santorini Consensus Conference; BMI, body mass index; French, French Consensus Conference on Acute Pancreatitis; BP, blood pressure; PaO_2, arterial partial pressure of oxygen; SOFA, Sequential Organ Failure Assessment; CECT, contrast-enhanced computed tomography; SAP, Simplified Acute Physiology; WCG, World Congress of Gastroenterology; SIRS, systemic inflammatory response syndrome; ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation; IAP, International Association of Pancreatology; JSAEM, Japanese Society of Emergency Abdominal Medicine; JMHW, Japanese Ministry of Health and Welfare; Nathens, Consensus Statement regarding the management of the critically ill patient with severe acute pancreatitis.

DISCUSSION

The present review has demonstrated that the Atlanta definitions of severity and local complications of acute pancreatitis are being used inconsistently, and that several components of the classification have received considerable criticism. By providing definitions, the result of consensus by over 40 experts based on the data available in 1992, the Atlanta symposium improved the management of acute pancreatitis and clinical research relating to the condition. However, the past 20 years have seen not only new insights in pathophysiology and therapeutic strategies but also improved imaging techniques. Clearly, the time has come to revise the classification of acute pancreatitis.

The various predictive scoring systems have not improved substantially since the Atlanta symposium. They are only moderately accurate in predicting severe disease in an individual patient. As McKay and Imrie[166] have noted, predictive systems were developed initially to allocate patients within clinical trials and not to assess severity in an individual. Defining severity based on the presence or absence of organ failure also has its limitations. It is increasingly recognized that persistent organ failure (for more than 48h) is the most important determinant of morbidity and mortality, which are predominantly related to the number of organ systems failing, the degree of dysfunction of the organs involved and the duration of organ failure.

The definition of necrotizing pancreatitis is controversial because it incorporates both sterile and infected necrosis, and covers both pancreatic parenchymal necrosis and peripancreatic fat necrosis. Interpretations of pseudocyst and pancreatic abscess vary widely because necrotic debris within these collections is often not accounted for. This might be explained by the incapacity of CECT to detect necrotic debris in collections predominantly containing fluid, and its incapacity to discriminate between sterile and infected collections[7,10,12,92,167]. Although magnetic resonance imaging (MRI) and (endoscopic) ultrasonography may be of additional value in classifying these collections[10,168,169], their applicability in severely ill patients has been questioned[92,170].

Although the Atlanta Classification incorporates a pathological and morphological description of different local complications, it does not provide exact radiological criteria for each. The recently demonstrated poor interobserver agreement on the Atlanta Classification of local complications[8] highlights the need for new descriptive morphological terms to describe CECT findings. The existing radiological grading system, the CT severity index, is a numerical scoring system that combines quantification of extrapancreatic changes with the extent of pancreatic necrosis[26]. Although the CT severity index has clear prognostic value with regard to morbidity and mortality[26,171–174], it does not characterize the local complications of acute pancreatitis.

Much of the persisting controversy over the natural course of (peri)pancreatic collections is due to a lack of prospective data from large patient series. The authors of this review, therefore, advocate a collaborative international study to clarify pathophysiology, natural course and optimal management of (peri)pancreatic collections. The present review has aimed to give an overview of the controversies regarding the Atlanta Classification in the literature. There are virtually no studies addressing the validation of the definitions proposed by the Atlanta Classification. Consequently, hardly any original data on this topic are available to analyse. This review, therefore, has merely categorized applications and interpretations of the Atlanta definitions. Correct terminology and standardized definitions are important for adequate communication in clinical practice and for comparing interinstitutional data for clinical research. The continuing failure to use standardized definitions for predicted and actual severe acute pancreatitis, organ failure and the local complications, and the heterogeneity of inclusion criteria of patients in clinical trials, have hampered the progress of evidence-based recommendations. This review has identified many studies that have improved insight into the natural course of the disease. These new insights should be used to design a new classification.

The authors propose the following recommendations for revision of the classification of acute pancreatitis. First, the diagnosis should incorporate two of the following three items: upper abdominal pain, amylase and/or lipase levels at least three times the upper limit of normal (as this cut-off is used most frequently in the literature), and CT or MRI findings compatible with acute pancreatitis. Second, persistent organ failure (for at least 48h) should have an important role in defining severity of acute pancreatitis. Third, it should be decided which predictive scoring system(s), including cut-off value, should be used to define predicted severe acute pancreatitis, based on a systematic review of the available data. Fourth, future studies should always make a clear distinction between predicted severe and actual severe disease, with *a posteriori* validation of the disease severity. Fifth, a systematic review should demonstrate which organ failure scoring system should be used, and definitions for organ failure should take into account the number of organ systems failing, the duration (less or more than 48h) of organ failure, and the need for specific therapy (such as inotropic or vasopressor agents, mechanical ventilation and dialysis). Sixth, peripancreatic fat necrosis without pancreatic parenchymal necrosis should be regarded either as a separate entity or as necrotizing pancreatitis. Seventh, infected necrosis should be regarded as a separate entity. Eighth, a term should be appointed for encapsulated collections containing both fluid and necrotic debris. Ninth, in order to diagnose a collection that contains fluid only (such as pseudocyst), MRI or (endoscopic) ultrasonography should be performed first to exclude necrotic debris in the collection. Tenth a new set of descriptive morphological terms should be designed to describe local complications on CT.

Such a new classification system should be evaluated in high-quality interobserver and prospective clinical studies. Adjustments should be made every few years, based on new data. Most importantly, clinicians and radiologists worldwide should comply with the new classification in clinical practice and research. Progress in the field of acute pancreatitis is hampered greatly when various author groups use their own idiosyncratic definitions. When journal referees are requested to peer-review manuscripts, they should pay special attention to the correct use of definitions as defined by a new classification.

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5

Describing peripancreatic collections in severe acute pancreatitis using morphologic terms:

An international interobserver agreement study

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ABSTRACT

Background/Aims: The current terminology for describing peripancreatic collections in acute pancreatitis (AP) derived from the Atlanta Symposium (e.g. pseudocyst, pancreatic abscess) has shown a very poor interobserver agreement, creating the potential for patient mismanagement. A study was undertaken to determine the interobserver agreement for a new set of morphologic terms to describe peripancreatic collections in AP.

Methods: An international, interobserver agreement study was performed: 7 gastrointestinal surgeons, 2 gastroenterologists and 8 radiologists in 3 US and 5 European tertiary referral hospitals independently evaluated 55 computed tomography (CT) scans of patients with predicted severe AP. The percentage agreement [median, interquartile range (IQR)] for 9 clinically relevant morphologic terms was calculated among all reviewers, and separately among radiologists and clinicians. The percentage agreement was defined as poor (<0.50), moderate (0.51– 0.70), good (0.71–0.90), and excellent (0.91–1.00).

Results: Overall agreement was good to excellent for the terms collection (percentage agreement = 1; IQR 0.68–1), relation with pancreas (1; 0.68–1), content (0.88; 0.87–1), shape (1; 0.78–1), mass effect (0.78; 0.62–1), loculated gas bubbles (1; 1–1), and air-fluid levels (1; 1–1). Overall agreement was moderate for extent of pancreatic nonenhancement (0.60; 0.46–0.88) and encapsulation (0.56; 0.48–0.69). The percentage agreement was greater among radiologists than clinicians for extent of pancreatic nonenhancement (0.75 vs. 0.57, p = 0.008), encapsulation (0.67 vs. 0.46, p = 0.001), and content (1 vs. 0.78, p = 0.008).

Conclusion: Interobserver agreement for the new set of morphologic terms to describe peripancreatic collections in AP is good to excellent. Therefore, we recommend that current clinically based definitions for CT findings in AP (e.g. pancreatic abscess) should no longer be used.

INTRODUCTION

Severe acute pancreatitis is associated with a wide spectrum of pathologic changes in the pancreatic and peripancreatic region. Changes can include pancreatic gland necrosis and/or various types of intra-abdominal collections containing fluid and peripancreatic fat necrosis [1]. Secondary infection of necrosis and these collections is often an indication for operative intervention and increases mortality to almost 30% [2]. Contrast-enhanced computed tomography (CT) is the imaging study used most widely to describe these pathologic changes [2–5]. Clear communication and agreement on CT findings is crucial, because the choice of treatment (conservative management, percutaneous catheter drainage and necrosectomy by laparotomy or minimally invasive approach) hinges heavily on how surgeons, gastroenterologists and radiologists interpret CT findings. The decision for operative or radiologic intervention is determined by the characteristics of the collections, such as the contents (fluid or solid) and microbial status (sterile or infected) [2, 3, 5, 6]. Miscommunication can put the patient at risk by initiating an inappropriate treatment algorithm [7].

The need for precise descriptions of the many different types of peripancreatic collections in acute pancreatitis was recognized in the early 1990s, resulting in the widely used Atlanta Classification [8]. While this work represented a very important contribution, over the ensuing 15 years, it has become apparent that the clinically based definitions suggested by this symposium, such as 'pseudocyst' and 'pancreatic abscess', lead to confusion in both daily practice and clinical research. This confusion frequently results in errors in diagnosis and management and misinterpretation of communications [2, 9–14]. Critics state that the Atlanta definitions do not accurately represent collections containing both liquid and solid material (i.e. pancreatic parenchymal necrosis and peripancreatic fat necrosis) [2, 11–15], yet these types of collections comprise the vast majority of collections in severe acute pancreatitis. This concern was substantiated in a recent interobserver study on the use of the Atlanta definitions for describing peripancreatic collections on CT, which demonstrated very poor agreement between 5 expert radiologists [13]. Currently, an international working group is consulting the members of several international pancreatic associations to reach consensus on a revised classification of acute pancreatitis. It has been formally recognized that this classification should incorporate objective, morphologic criteria for describing peripancreatic collections on CT [10, 14].

MATERIALS AND METHODS

An international panel of pancreatic surgeons and radiologists designed a scoring sheet with a set of descriptive, morphologic terms to classify peripancreatic collections on CT in severe acute pancreatitis (fig. 1). Definitions for the descriptive terms were not provided, because the aim was to test the interobserver agreement using only the objective, descriptive terminology.

Study Population

In order to test the proposed descriptive, morphologic terms, contrast-enhanced CTs from patients with predicted severe acute pancreatitis were collected. One experienced radiologist (T.L.B.) reviewed all CTs of 248 patients with predicted severe acute pancreatitis that were included in a Dutch randomized controlled multicenter trial [16]. This study was approved by the independent ethics committees of all 15 participating hospitals and informed consent for participation was obtained from all patients. For each patient, a single radiologist determined the CT severity index (CTSI). The CTSI is an accepted prognostic score quantifying pancreatic and peripancreatic abnormalities [2, 5, 17]. The greater the score (range 0–10 points), the greater the risk of complications and death [17]. All CTs were high quality, contrast-enhanced and obtained during the portal venous phase. From these 248 patients, 55 CTs were included to cover the entire clinical spectrum of acute pancreatitis, with emphasis on severe disease (i.e. with pancreatic and/or peripancreatic collections). In order to rule out selection bias, CT selection occurred according to the following predefined and reproducible criteria: the last CT before percutaneous drainage or discharge in the first 30 consecutive patients that did not have operative therapy (5 patients with a CTSI of 1–2, 5 patients with a CTSI of 3–4, 5 patients with a CTSI of 5–6, and 15 patients with a CTSI of 7–10), and the last preoperative CT of the first 25 consecutive patients who underwent operative therapy for infected necrosis (irrespective of CTSI). Median time [interquartile range (IQR)] between admission and CT was 18 (9–32) days. A total of 33/55 patients had infected necrosis as proven by bacterial culture (requiring operative therapy n = 25, or only percutaneous drainage n = 8). Mortality was 16% (9/55).

Participating Centers

The following 3 US and 5 European tertiary referral hospitals participated:

- Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass., USA
- Mayo Clinic, Rochester, Minn., USA
- University of Washington Medical Center, Seattle, Wash., USA
- University Medical Center Utrecht, The Netherlands
- Academical Medical Center, Amsterdam, The Netherlands
- Erasmus MC University Medical Center Rotterdam, The Netherlands
- University of Heidelberg, Heidelberg, Germany
- Royal Liverpool University Hospital, Liverpool, UK

Seven gastrointestinal surgeons, 2 gastroenterologists and 8 hepato-pancreato-biliary radiologists acted as blinded reviewers, 1 clinician and 1 radiologist in each centre. In 1 center (Mayo Clinic), 2 clinicians participated. All reviewers are considered experts in acute pancreatitis. Four of the 17 reviewers (2 radiologists and 2 surgeons) participated in the generation of the scoring sheet. Conversely, 13 reviewers were naïve to the scoring sheet and did not receive any form of training prior to reviewing the CTs for this study.

Extent of **PA**ncreatic **N**onenhancement:

☐ none
☐ <30%
☐ 30–50%
☐ >50%

Is there a **CO**llection? (= any fluid more than 'fat stranding')

☐ yes
☐ no

If 'yes', please choose one **DE**scription per question:

Relation with pancreas:

☐ intrapancreatic only
☐ intrapancreatic and adjacent to pancreas
☐ only adjacent to pancreas (no parenchymal perfusion defect)
☐ separate

Encapsulation:

☐ complete
☐ partial
☐ none

Content:

☐ homogeneous
☐ heterogeneous (including fat, hemorrhage, loculation and septa)

Mass effect (= displacement of adjacent structures: vessels, organs etc.):

☐ yes
☐ no

Shape:

☐ round or oval
☐ irregular

Loculated gas bubbles:

☐ yes
☐ no

Air-fluid level:

☐ yes
☐ no

FIG. 1. Scoring sheet using the descriptive morphologic terms for this study. (The descriptor headings form the acronym PANCODE: Pancreatic Nonenhancement, Collection Descripition).

Data Collection

Two investigators visited each center and had separate meetings with the clinicians and radiologists. In a single session, each reviewer evaluated individually the 55 digital CTs using DICOM viewer software (version 3.116, Acculite, San Francisco, Calif., USA) and completed the scoring sheet for each CT (fig. 1). The investigators briefly explained the scoring sheet and software to the reviewers but did not coach the reviewers during the review process in any way. The reviewers were blinded to the clinical background and timing of the CT. In the case of multiple collections, the reviewer was asked to describe the most prominent collection. Data from the scoring sheets were entered into a database by 1 investigator and 1 independent data manager, separately. Discrepancies were solved by a third investigator using the original scoring sheets.

Data Analysis

For each item on the scoring sheet, the distribution (i.e. 20 and 80%) of options (i.e. 'yes' and 'no') within the 55 CTs was assessed for each of the reviewers individually. The median distribution of options (IQR) is shown for radiologists and clinicians separately as well as for all reviewers. Subsequently, the percentage agreement for each scored item was determined. The percentage agreement was defined as the number of reviewer combinations (e.g. reviewer 1 vs. reviewer 2, reviewer 1 vs. reviewer 3) in agreement (i.e. choosing the same option, e.g. collection: 'yes') divided by the total number of possible reviewer combinations (n = 153) [18]. The percentage agreement was calculated for each of the 55 CTs individually; the median of the percentage agreement (IQR) is shown for clinicians and radiologists separately and for all reviewers. A percentage agreement of 0.91–1.00 was defined as excellent agreement, 0.71–0.90 as good agreement, 0.51–0.70 as moderate agreement and <0.50 as poor agreement. When the percentage agreement was <0.71, an exploratory analysis was performed to assess whether combinations of options resulted in greater agreement. The percentage agreement was compared between clinicians and radiologists using the Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant.

RESULTS

The distribution of the scored options within the 55 CTs is shown in table 1. According to the reviewers, the vast majority of CTs showed pancreatic nonenhancement (84%) with collections (median 96%) that were intrapancreatic and adjacent (78%) to the pancreas. In most of the CTs, the reviewers concluded that the collections were encapsulated (either partially or completely; 88%), heterogeneous (95%), with mass effect (80%) and were irregularly shaped (89%). Loculated gas bubbles were scored in 24% of CTs, while an air-fluid level was deemed present only in 5% of CTs. One of the CTs that was reviewed is shown in figure 2.

The percentage agreement for the descriptive terms is shown in table 2. Agreement among clinicians was excellent for collection, relation, shape, loculated gas bubbles, and air-fluid level; it was good for content and mass effect, moderate for encapsulation and poor for pancreatic nonenhancement. Among radiologists, agreement was excellent for collection, relation, content, mass effect, shape, loculated gas bubbles, and air-fluid level; it was good for extent of pancreatic nonenhancement and moderate for encapsulation. Agreement among all reviewers taken together was good to excellent for all items, except for extent of pancreatic nonenhancement

TABLE 1. Distribution of the options of the scored descriptive terms for 55 CT scans of patients with predicted severe acute pancreatitis (not interobserver agreement)

Term	Radiologists	Clinicians	All
Extent of pancreatic nonenhancement			
0%	25 (16–29)	12 (7–20)	16 (13–27)
<30%	15 (14–19)	23 (15–25)	18 (14–24)
30–50%	14 (12–15)	16 (9–20)	15 (11–20)
>50%	46 (42–51)	49 (49–53)	49 (44–53)
Presence of collection			
Yes	96 (95–99)	95 (91–96)	96 (95–98)
No	4 (1–5)	5 (4–9)	4 (2–5)
If 'yes' to presence of collection			
Relation with pancreas			
Intrapancreatic only	2 (2–2)	2 (2–2)	2 (2–2)
Intrapancreatic and adjacent	75 (70–80)	82 (76–89)	78 (73–84)
Only adjacent to pancreas	18 (10–24)	13 (4–15)	15 (13–20)
Separate	0 (0–0)	0 (0–2)	0 (0–0)
Encapsulation			
Complete	11 (9–20)	15 (5–31)	11 (7–24)
Partial	47 (40–52)	38 (33–51)	44 (35–51)
None	35 (26–40)	35 (27–42)	35 (27–42)
Content			
Homogeneous	2 (1–4)	2 (0–7)	2 (0–5)
Heterogeneous	95 (92–95)	93 (84–96)	95 (89–96)
Mass effect (on adjacent organs/structures)			
Yes	83 (76–91)	75 (58–84)	80 (69–87)
No	13 (4–17)	18 (13–29)	16 (9–29)
Shape			
Round/oval	9 (5–10)	4 (2–11)	9 (2–11)
Irregular	89 (85–91)	89 (84–96)	89 (84–93)
Loculated gas bubbles			
Yes	24 (23–24)	22 (22–25)	24 (22–24)
No	72 (71–76)	73 (71–75)	73 (71–75)
Air-fluid level			
Yes	8 (5–12)	4 (2–5)	5 (4–7)
No	87 (83–93)	91 (91–93)	91 (84–93)

Values are median percentages with the IQR percentages in parentheses. Percentages may not sum to 100% because values are medians and data are missing when the option 'no collection' was chosen.

and encapsulation, which were only moderate. However, when in the exploratory analysis the extent of pancreatic nonenhancement option 1 (0%) and option 2 (<30%) were combined, the agreement (median percentage agreement; IQR) was good among all reviewers (0.88; 0.52–1), good among clinicians (0.78; 0.44–1) and excellent among radiologists (1; 0.75–1). When encapsulation option 1 (complete) and option 2 (partial) were combined, the percentage agreement was good among all reviewers (0.78; 0.65–0.88) and clinicians (0.71; 0.56–1), and excellent among radiologists (1.0; 0.69–1). For the extent of pancreatic nonenhancement, encapsulation, content, and mass effect, the percentage agreement was greater among radiologists than among clinicians ($p < 0.05$; table 2).

TABLE 2. Percentage agreement among 17 reviewers for scored descriptive terms for 55 CT scans of patients with predicted severe acute pancreatitis (interobserver agreement)

Term	Radiologists	Clinicians	All	p value[1]
Extent of pancreatic nonenhancement	0.75 (0.46–1)	0.57 (0.44–0.78)	0.60 (0.46–0.88)	0.008
Presence of a collection	1 (1–1)	1 (1–1)	1 (1–1)	0.15
Relation with pancreas	1 (0.75–1)	1 (0.62–1)	1 (0.68–1)	0.55
Encapsulation	0.67 (046–0.75)	0.46 (0.36–0.61)	0.56 (0.48–0.69)	0.001
Content	1 (1–1)	0.78 (0.78–1)	0.88 (0.87–1)	<0.0001
Mass effect	1 (0.71–1)	0.78 (0.50–1)	0.78 (0.62–1)	0.01
Shape	1 (0.75–1)	1 (0.78–1)	1 (0.78–1)	0.39
Loculated gas bubbles	1 (1–1)	1 (1–1)	1 (1–1)	0.24
Air-fluid level	1 (1–1)	1 (1–1)	1 (1–1)	0.06

Values are medians with the IQR in parentheses. A percentage agreement of 0.91–1.00 is excellent agreement; 0.71–0.90 good agreement; 0.51–0.70 moderate agreement, and <0.50 poor agreement. Similar outcomes [e.g. 1 (1–1)] may not lead to similar p values since the range represents the IQR.

[1] Wilcoxon signed rank test (radiologists vs. clinicians).

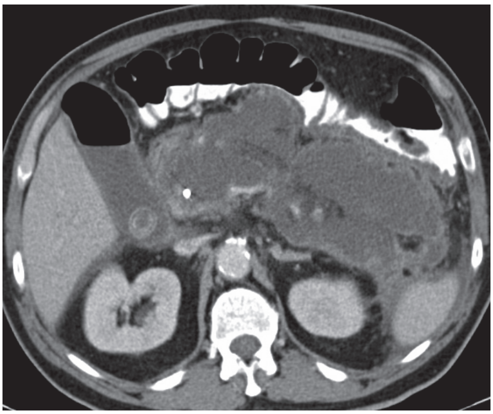

FIG. 2. One of the 55 CT scans reviewed in this interobserver agreement study. The vast majority of reviewers described this CT as >50% pancreatic nonenhancement, with an intrapancreatic and adjacent collection which is encapsulated (either partially or completely), heterogeneous, with mass effect, an irregular shape and without loculated gas bubbles or an air-fluid level.

DISCUSSION

This multidisciplinary, international interobserver study showed good to excellent interobserver agreement when peripancreatic collections in severe acute pancreatitis were described using a new set of descriptive, morphologic terms. This study was a follow-up to a similar interobserver study that showed very poor interobserver agreement for the widely used Atlanta Symposium terminology (e.g. 'pseudocyst', 'pancreatic necrosis', 'pancreatic abscess') [13]. In the prior study, 5 experienced radiologists agreed on the Atlanta definition in only 3 of 70 contrast-enhanced CTs [13]. These inconsistent and incongruent interpretations in large part led to the current study, as well as the interest in developing a more accurate classification of acute pancreatitis [14]. The results of the present study demonstrate that, with the new set of terms, it was much easier to obtain objective agreement among all physicians, in contrast to the Atlanta definitions.

Exploratory analysis led to an even greater interobserver agreement. In this analysis, the combination of the first 2 options of encapsulation (complete and partial) and extent of pancreatic nonenhancement (0 and <30%) is acceptable, because the most important clinical differentiations are between (1) no encapsulation and some encapsulation, and (2) no or little nonenhancement (<30%) and substantial nonenhancement (>30%). Notably, in the Atlanta Symposium, pancreatic nonenhancement <30% was not even considered pancreatic necrosis [8].

Interobserver agreement on several relevant terms was significantly greater among radiologists than surgeons and gastroenterologists. This finding was not unexpected given the noted expertise of radiologists in their field of practice. In contrast, the managing clinicians are best at correlating the radiologic findings with the clinical condition in order to determine the appropriate treatment. The current data, therefore, highlight the need for a true, multidisciplinary team approach to severe acute pancreatitis, both in terms of clinical care and research publications.

Why is this study relevant? Accurate multidisciplinary communication regarding CT findings in severe acute pancreatitis is of considerable importance because decisions on treatment depend on adequate radiologic interpretation of peripancreatic collections [1–7, 19]. The descriptive terms used in this study each have clinical relevance regarding the type and timing of (operative) intervention. For example, the finding of pancreatic necrosis (extent of pancreatic nonenhancement) and collections with peripancreatic fat necrosis (presence of a collection, heterogeneous content, relation with pancreas) would both be treated initially without percutaneous drainage or operative intervention [1–3, 5]. When and if secondary infection occurs (loculated gas bubbles), some form of intervention is generally indicated [1–3, 5, 19]. The content of the peripancreatic collection (homogeneous, air-fluid level) can indicate a collection with a fluid-predominant content, such that percutaneous drainage would be performed initially and, if percutaneous drainage is unsuccessful, followed by operative debridement [2, 3, 5, 19]. The majority of peripancreatic collections, however, tend to resolve without any intervention at all. These include collections referred to by the Atlanta symposium as 'acute fluid collections', i.e. homogenous peripancreatic collections occurring early on in the disease that have not formed any capsule whatsoever and that do not contain gas bubbles or an air-fluid level [8]. Whenever intervention for collections with necrosis does seem necessary, delaying operative intervention until demarcation (encapsulation) is documented allows easier and safer debridement [1, 2, 5, 20], possibly by endoscopic or minimally invasive operative techniques [21, 22–24]. Sterile collections causing gastric or biliary obstruction (mass effect) are treated usually by percutaneous or endoscopic therapy [2, 3, 5, 12, 21].

One might wonder whether the radiologic diagnoses (i.e. the descriptive terms chosen by the reviewers) in this study really reflect the true morphologic features of the peripancreatic collections, because the results of the radiologic decisions were not correlated with clinical findings (e.g. operative findings). We explicitly chose not to do this because the aim of this study was merely to determine the interobserver agreement of the descriptive terms, instead of their clinical relevance. The tested terminology is commonly used in daily practice, and it is obvious that all those caring for patients with acute pancreatitis should 'speak the same language'. Although the clinical relevance of the described terms seems obvious, the exact magnitude of that relevance and, therefore, the impact on treatment decisions will need to be the subject of future large prospective studies. It should be noted, however, that the current terminology from the Atlanta Classification is also mostly based on expert opinion, rather than evidence from clinical studies, and is neither used reliably or accurately [10, 13].

A limitation of this study is that Cohen's kappa statistic could not be used because of the substantial imbalance in distributions for the majority of terms (e.g. presence of collection, yes vs. no: 96% vs. 4%; table 1). In case of a substantial imbalance in the distribution, kappa values will be very low or even negative, while agreement may still, in fact, be good [25]. In such an event, the kappa statistic becomes meaningless [25]. To present only kappa values for the terms without imbalance was considered not possible because there is no generally accepted cut-off value for defining imbalance. Even though the percentage agreement is not a chance-adjusted measure, the interobserver agreement in the present study was good, given the high values of percentage agreement demonstrated.

Because the reviewers in the present study were from centers renowned for their experience in pancreatic disease, one might question how generalizable are the results to the general community of surgeons and radiologists. It should be noted, however, that the previous interobserver study using the Atlanta definitions between a similar group of expert radiologists showed very poor interobserver agreement [13], in contrast to the good to excellent agreement reported in the present study with the new descriptors. Four of the 17 reviewers in the present study were involved in designing the scoring sheet, and one might argue that this introduced bias. However, when these 4 reviewers were excluded from the current analysis the interobserver agreement did not change (data not shown).

Our findings are most likely explained by the fact that the majority of the proposed morphologic, descriptive terms are used already in daily clinical practice by both clinicians and radiologists and are considered intuitive and relatively easy to use. Nevertheless, despite the strength of the current study it is our intent to direct our next prospective study to further validation of the proposed descriptive, morphologic terms and establishing how generalizable they are.

In summary, the overall interobserver agreement using the proposed morphologic terms when describing peripancreatic collections in severe acute pancreatitis, is good to excellent. This study provides another piece of important data in support of using more objective, descriptive, morphologic terms to describe CT findings in acute pancreatitis rather than the subjective Atlanta symposium terms (e.g. 'pseudocyst', 'pancreatic abscess').

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6

Classification of acute pancreatitis-2012:
Revision of the Atlanta Classification and definitions by international consensus

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GUT. 2013 JAN;62(1):102-11. IMPACT FACTOR: 16.66

ABSTRACT

Background and objective: The Atlanta Classification of acute pancreatitis enabled standardised reporting of research and aided communication between clinicians. Deficiencies identified and improved understanding of the disease make a revision necessary.

Methods: A web-based consultation was undertaken in 2007 to ensure wide participation of pancreatologists. After an initial meeting, the Working Group sent a draft document to 11 national and international pancreatic associations. This working draft was forwarded to all members. Revisions were made in response to comments, and the web-based consultation was repeated three times. The final consensus was reviewed, and only statements based on published evidence were retained.

Results: The revised classification of acute pancreatitis identified two phases of the disease: early and late. Severity is classified as mild, moderate or severe. Mild acute pancreatitis, the most common form, has no organ failure, local or systemic complications and usually resolves in the first week. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications or exacerbation of co-morbid disease. Severe acute pancreatitis is defined by persistent organ failure, that is, organ failure >48h. Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected). We present a standardised template for reporting CT images.

Conclusions: This international, web-based consensus provides clear definitions to classify acute pancreatitis using easily identified clinical and radiologic criteria. The wide consultation among pancreatologists to reach this consensus should encourage widespread adoption.

BACKGROUND

The Atlanta Symposium in 1992 attempted to offer a global 'consensus' and a universally applicable classification system for acute pancreatitis.[1] Although the Atlanta Classification has been useful, some of the definitions proved confusing.[2] Better understanding of the pathophysiology of organ failure and necrotising pancreatitis and their outcomes, as well as improved diagnostic imaging, have made it necessary to revise the Atlanta Classification. This revision includes a clinical assessment of severity and provides more objective terms to describe the local complications of acute pancreatitis.

The goal of this report is to present the updated revision of the Atlanta Classification of acute pancreatitis in adults (>18 years). This revision was designed to incorporate modern concepts of the disease, to address areas of confusion, to improve clinical assessment of severity, to enable standardised reporting of data, to assist the objective evaluation of new treatments, and to facilitate communication among treating physicians and between institutions. This consensus classification defines criteria for the diagnosis of acute pancreatitis, differentiates the two types of acute pancreatitis (interstitial oedematous pancreatitis and necrotising pancreatitis), classifies the severity of acute pancreatitis into three categories, and defines the morphology seen on imaging of pancreatic and peripancreatic collections that arise as complications of acute pancreatitis. This revision is not intended to be a management guideline.

METHODS

This classification was generated by an iterative, web-based consultation process led by a working group and incorporating responses from the members of 11 national and international pancreatic societies. All responses were reviewed by the working group, and the process was repeated by a web-based approach until the current fourth draft, which was then finalised for submission. A full description of the methods is shown in online supplementary appendix 1. There are many substantial and important differences in the current document when compared to our preliminary working draft that appeared on the Pancreas Club website[3] and which has been referred to by other authors.[4–8]

Revised definitions and classification of acute pancreatitis

The following definitions and classifications are proposed for use in clinical and research communications.

Definition of diagnosis of acute pancreatitis

The diagnosis of acute pancreatitis requires two of the following three features: (1) *abdominal pain* consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum *lipase activity (or amylase activity) at least three times greater* *than the upper limit of normal*; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography.[9–13]

If abdominal pain suggests strongly that acute pancreatitis is present, but the serum amylase and/or lipase activity is less than three times the upper limit of normal, as may be the case with delayed presentation, imaging will be required to confirm the diagnosis.[13 14] If the diagnosis of acute pancreatitis is established by abdominal pain and by increases in the serum pancreatic enzyme activities, a CECT is not usually required for diagnosis in the emergency room or on admission to the hospital.

Definition of onset of acute pancreatitis

The onset of acute pancreatitis is defined as the time of onset of abdominal pain (not the time of admission to the hospital). The time interval between onset of abdominal pain and first admission to the hospital should be noted. When patients with severe disease are transferred to a tertiary hospital, the intervals between onset of symptoms, first admission and transfer should be noted. Data recorded from a tertiary care hospital should be stratified to allow separate consideration of the outcomes of patients who were admitted directly and those admitted by transfer from another hospital (see online supplementary appendix 2 for suggested recording of data).

Definition of types of acute pancreatitis

Acute pancreatitis can be subdivided into two types: interstitial oedematous pancreatitis and necrotising pancreatitis.

Interstitial pancreatitis

The majority of patients with acute pancreatitis have diffuse (or occasionally localised) enlargement of the pancreas due to inflammatory oedema. On CECT, the pancreatic parenchyma shows relatively homogeneous enhancement, and the peripancreatic fat usually shows some inflammatory changes of haziness or mild stranding. There may also be some peripancreatic fluid (see below, Definition of pancreatic and peripancreatic collections) (figures 1 and 2). The clinical symptoms of interstitial oedematous pancreatitis usually resolve within the first week.[15]

Necrotising pancreatitis

About 5–10% of patients develop necrosis of the pancreatic parenchyma, the peripancreatic tissue or both (see below, Definition of pancreatic and peripancreatic collections) (figures 3, 4, 5). Necrotising pancreatitis most commonly manifests as necrosis involving both the pancreas and peripancreatic tissues and less commonly as necrosis of only the peripancreatic tissue, and rarely of the pancreatic parenchyma alone.

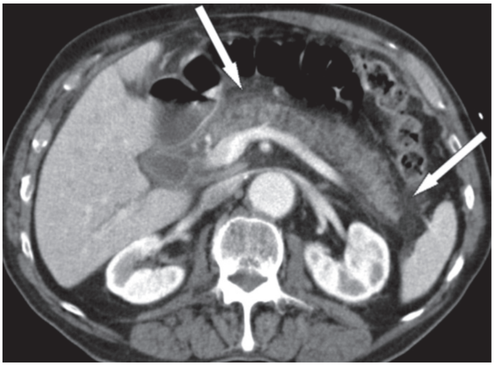

FIGURE 1. A 63-year-old man with acute interstitial oedematous pancreatitis. There is peripancreatic fat stranding (arrows) without an acute peripancreatic fluid collection; the pancreas enhances completely but has a heterogeneous appearance due to oedema.

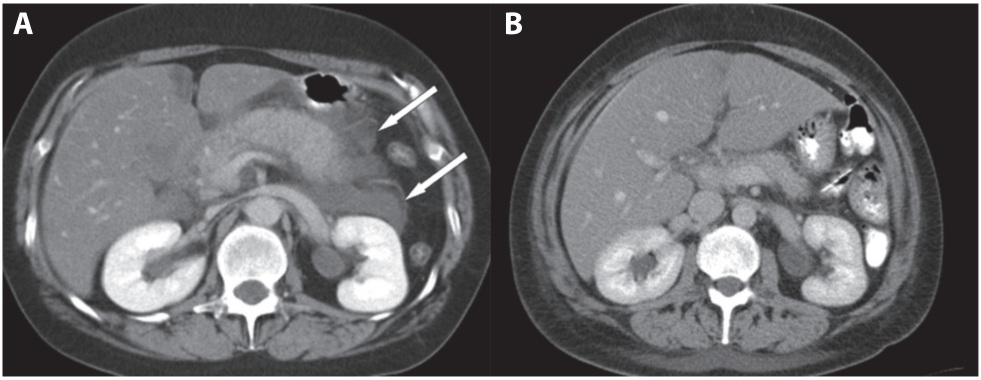

FIGURE 2 (A) A 38-year-old woman with acute interstitial oedematous pancreatitis and acute peripancreatic fluid collection (APFC) in the left anterior pararenal space (white arrows showing the borders of the APFC). The pancreas enhances completely, is thickened, and has a heterogeneous appearance due to oedema. APFC has fluid density without an encapsulating wall. **(B)** A few weeks later, a follow up CT shows complete resolution of the APFC with minimal residual peripancreatic fat stranding.

The impairment of pancreatic perfusion and signs of peripancreatic necrosis evolve over several days,[16–19] which explains why an early CECT may underestimate the eventual extent of pancreatic and peripancreatic necrosis. In the first few days of the illness, the pattern of perfusion of the pancreatic parenchyma as seen on CECT may be patchy, with variable attenuation before the area of impaired enhancement becomes more demarcated and/or confluent. After the first week of the disease, a non-enhancing area of pancreatic parenchyma should be considered to be pancreatic parenchymal necrosis.

In peripancreatic necrosis, the pancreas enhances normally on CECT as it does with interstitial oedematous pancreatitis, but the peripancreatic tissues develop necrosis. Patients with peripancreatic necrosis alone have increased morbidity and intervention rates compared to patients with interstitial oedematous pancreatitis.[15 17 20]

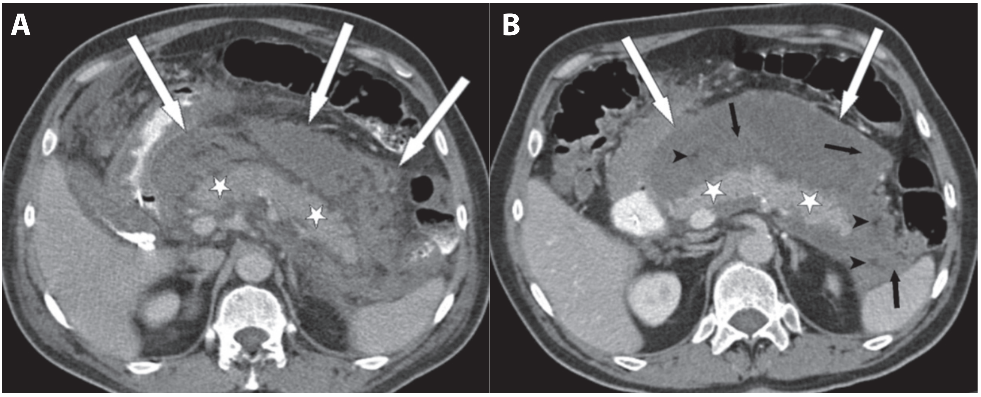

FIGURE 3 (A) Acute necrotic collections (ANC) in a 44-year-old man with acute necrotising pancreatitis involving only the peripancreatic tissues. Note enhancement of the entire pancreatic parenchyma (white stars) and the heterogeneous, non-liquid peripancreatic components in the retroperitoneum (white arrows pointing at the borders of the ANC). **(B)** The ANC in the same patient as (A) but imaged a few weeks later demonstrate a heterogeneous collection with areas of fat (black arrowheads) surrounded by fluid density, and areas which have a slightly greater attenuation (black arrows) than seen in collections without necrosis such as shown in figure 7. This finding is typical for peripancreatic necrosis. White arrows denote border of ANC; white stars denote enhancement of pancreatic parenchyma. The ANC are not yet fully encapsulated.

The natural history of pancreatic and peripancreatic necrosis is variable, because it may remain solid or liquefy, remain sterile or become infected, persist, or disappear over time.

Infected pancreatic necrosis

Pancreatic and peripancreatic necrosis can remain sterile or become infected; most of the evidence suggests no absolute correlation between the extent of necrosis and the risk of infection and duration of symptoms.[21–24] Infected necrosis is rare during the first week.[21 25]

The diagnosis of infected pancreatic necrosis is important because of the need for antibiotic treatment and likely active intervention.[22] The presence of infection can be presumed when there is extraluminal gas in the pancreatic and/or peripancreatic tissues on CECT (figure 6) or when percutaneous, image-guided, fine-needle aspiration (FNA) is positive for bacteria and/or fungi on Gram stain and culture.[26] There may be a varying amount of suppuration (pus) associated with the infected pancreatic necrosis, and this suppuration tends to increase with time with liquefaction. The original Atlanta Classification proposed the term 'pancreatic abscess' to define a 'localised collection of purulent material *without significant necrotic material*'.[1] This finding is extremely uncommon, and because the term is confusing and has not been adopted widely,[27] the term 'pancreatic abscess' is not used in the current classification. The development of secondary infection in pancreatic necrosis is associated with increased morbidity and mortality.[28]

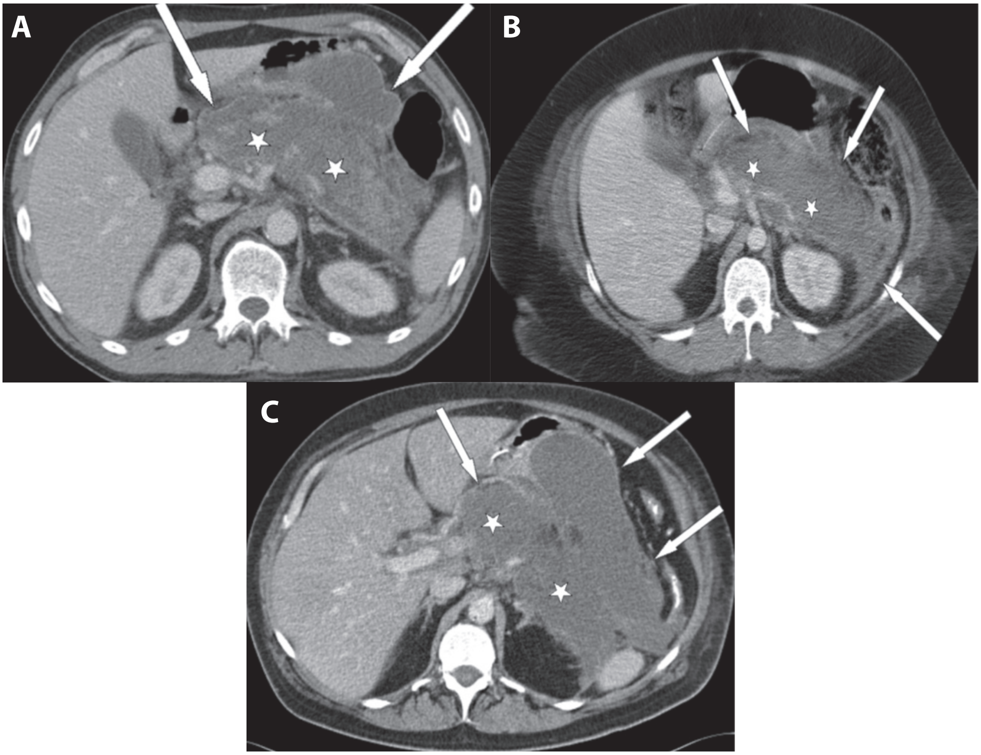

FIGURE 4. Three different patients (**A, B, C)** with acute necrotising pancreatitis and acute necrotic collections (ANC) involving the pancreatic parenchyma and the peripancreatic tissues. In all three patients, there is extensive parenchymal necrosis (white stars) of the body and tail of the pancreas. Heterogeneous collections are seen in the pancreatic and peripancreatic tissues (white arrows pointing at the borders of the ANC) of the left anterior pararenal space (**A, B, C**) and in the lesser sac (**A, C**). These latter collections represent peripancreatic necrosis.

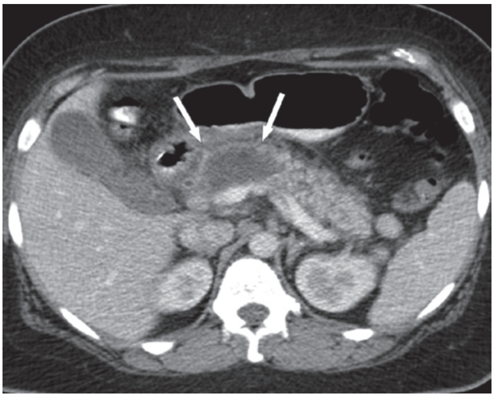

FIGURE 5. Acute necrotic collection (ANC) in a 47-year-old woman with acute necrotising pancreatitis involving the pancreatic parenchyma alone. Thin white arrows denote a newly developed, slightly heterogeneous collection in the region of the neck and body of the pancreas, without extension in the peripancreatic tissues.

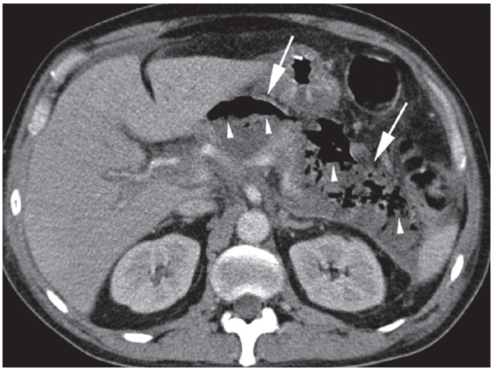

FIGURE 6. A 47-year-old man with acute necrotising pancreatitis complicated by infected pancreatic necrosis. There is a heterogeneous, acute necrotic collection (ANC) in the pancreatic and peripancreatic area (white arrows pointing at the borders of the ANC) with presence of gas bubbles (white arrowheads), usually a pathognomonic sign of infection of the necrosis (infected necrosis).

Complications of acute pancreatitis

Definition of organ failure

Three organ systems should be assessed to define organ failure: respiratory, cardiovascular and renal. Organ failure is defined as a score of 2 or more for one of these three organ systems using the modified Marshall scoring system[29] (table 1). The modified Marshall scoring system has the merit of simplicity, universal applicability across international centres, and the ability to stratify disease severity easily and objectively.[10] The modified Marshall scoring system is preferred to the SOFA scoring system,[30] which is for patients managed in a critical care unit and which takes into account the use of inotropic and respiratory support. Both scoring methods have the advantage of being able to be used on presentation and repeated daily.[30 31] They also allow stratification of the severity of organ failure, although that is not part of the current classification.

Definition of local complications

The original Atlanta Classification[1] distinguished between uncomplicated interstitial pancreatitis and acute pancreatitis associated with 'local complications'. This distinction (local complications being absent or present) is useful. The natural history and clinical consequences of different local complications are now better understood and described. Local complications are acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis. The morphologic features of these local complications are described in detail later in this document (see below, Definition of pancreatic and peripancreatic collections). Other local complications of acute pancreatitis include gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis.

Local complications should be suspected when there is persistence or recurrence of abdominal pain, secondary increases in serum pancreatic enzyme activity, increasing organ dysfunction, and/or the development of clinical signs of sepsis, such as fever and leucocytosis. These developments usually prompt imaging to detect local complications. The morphologic features of acute pancreatitis are well delineated by high resolution, multi-detector CECT and form the basis of the new, more objective definitions for the local complications of acute pancreatitis (box 1).

Pancreatic and peripancreatic collections should be described on the basis of location (pancreatic, peripancreatic, other), the nature of the content (liquid, solid, gas), and the thickness of any wall (thin, thick). The pattern and extent of impaired pancreatic parenchymal perfusion, if present, should also be described.[27] The morphologic description of local complications is necessary for accurate diagnosis. Local complications alone, however, do not define the severity of acute pancreatitis (see below, Definition of severity of acute pancreatitis).[32 33]

Definition of systemic complications

Exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis is defined as a systemic complication. In this document, we distinguish between persistent organ failure (the defining feature of severe acute pancreatitis) and other systemic complications, which are an exacerbation of pre-existing co-morbid disease.

TABLE 1. Modified Marshall scoring system for organ dysfunction

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal*					
(serum creatinine, µmol/l)	≤134	134–169	170–310	311–439	>439
(serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2

For non-ventilated patients, the FiO_2 can be estimated from below:

Supplemental oxygen (l/min)	**FiO_2 (%)**
Room air	21
2	25
4	30
6–8	40
9–10	50

A score of 2 or more in any system defines the presence of organ failure.
*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 µmol/l or ≥1.4 mg/dl.
†Off inotropic support.

Box 1 Revised definitions of morphological features of acute pancreatitis

1. Interstitial oedematous pancreatitis
   Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognisable tissue necrosis
   CECT criteria
   - Pancreatic parenchyma enhancement by intravenous contrast agent
   - No findings of peripancreatic necrosis (see below)
   - See figures 1 and 2
2. Necrotising pancreatitis
   Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
   CECT criteria
   - Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
   - Presence of findings of peripancreatic necrosis (see below—ANC and WON)
   - See figures 3, 4, 5 and 8
3. APFC (acute peripancreatic fluid collection)
   Peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial oedematous pancreatitis and without the features of a pseudocyst.
   CECT criteria
   - Occurs in the setting of interstitial oedematous pancreatitis
   - Homogeneous collection with fluid density
   - Confined by normal peripancreatic fascial planes
   - No definable wall encapsulating the collection
   - Adjacent to pancreas (no intrapancreatic extension)
   - See figure 2
4. Pancreatic pseudocyst
   An encapsulated collection of fluid with a well defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis to mature.
   CECT criteria
   - Well circumscribed, usually round or oval
   - Homogeneous fluid density
   - No non-liquid component
   - Well defined wall; that is, completely encapsulated
   - Maturation usually requires >4 weeks after onset of acute pancreatitis; occurs after interstitial oedematous pancreatitis
   - See figure 7
5. ANC (acute necrotic collection)
   A collection containing variable amounts of both fluid and necrosis associated with necrotising pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
   CECT criteria
   - Occurs only in the setting of acute necrotising pancreatitis
   - Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in their course)
   - No definable wall encapsulating the collection
   - Location—intrapancreatic and/or extrapancreatic
   - See figures 3–5
6. WON (walled-off necrosis)
   A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well defined inflammatory wall. WON usually occurs >4 weeks after onset of necrotising pancreatitis.
   CECT criteria
   - Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous)
   - Well defined wall, that is, completely encapsulated
   - Location—intrapancreatic and/or extrapancreatic
   - Maturation usually requires 4 weeks after onset of acute necrotising pancreatitis
   - See figure 8

Phases of acute pancreatitis

There are two overlapping phases in this dynamic disease process with two peaks of mortality: early and late.[34–37] The early phase, which usually lasts for the first week, is followed by a second later phase which can run a protracted course from weeks to months. It is helpful to consider these two phases separately.

Early phase

During the early phase, systemic disturbances result from the host response to local pancreatic injury. This early phase is usually over by the end of the first week but may extend into the second week. Cytokine cascades are activated by the pancreatic inflammation which manifest clinically as the systemic inflammatory response syndrome (SIRS)[38–40] (box 2). When SIRS is persistent,[41 42] there is an increased risk of developing organ failure (table 1). The determinant of the severity of acute pancreatitis during the early phase is primarily the presence and duration of organ failure. This is described as '*transient* organ failure' if the organ failure resolves within 48h or as '*persistent* organ failure' if organ failure persists for >48h.[39 41 43] If organ failure affects more than one organ system, it is termed multiple organ failure (MOF).

Box 2 Signs of systemic inflammatory response syndrome (SIRS)

SIRS—defined by presence of two or more criteria:

- Heart rate >90 beats/min
- Core temperature <36°C or >38°C
- White blood count <4000 or >12000/mm^3
- Respirations >20/min or PCO_2 <32 mm Hg[13]

Although local complications may be identified during the early phase, they are not the predominant determinants of severity,[32] and it may be unreliable to determine the extent of necrosis during the first few days of disease. In addition, the extent of morphologic changes is not directly proportional to the severity of organ failure.[24] Therefore, the definition of severe or moderately severe acute pancreatitis in the early phase depends on the presence and duration of organ failure (see below, Definition of severity of acute pancreatitis).

Late phase

The late phase is characterised by persistence of systemic signs of inflammation or by the presence of local complications, and so by definition (see below), the late phase occurs only in patients with moderately severe or severe acute pancreatitis. Local complications evolve during the late phase. It is important to distinguish the different morphologic characteristics of the local complications by radiologic imaging, because these local complications may have direct implications for management. Persistent organ failure, however, remains the main determinant of severity, so characterisation of acute pancreatitis in the late phase requires both clinical and morphologic criteria.

The SIRS of the early phase may be followed by a compensatory, anti-inflammatory response syndrome (CARS) that may contribute to an increased risk of infection; however, these events are complex and poorly understood.[44]

Definition of severity of acute pancreatitis

There are important reasons to define and stratify the severity of acute pancreatitis. First, on admission, it is important to identify patients with potentially severe acute pancreatitis who require aggressive early treatment. Second, in a secondary care setting, clinicians need to identify such patients for possible transfer to specialist care. Third, for specialists who receive such referrals, there are advantages to stratifying these patients into subgroups based on the presence of persistent organ failure and local or systemic complications.

This classification defines three degrees of severity: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis.[32 33] Terminology that is important in this classification includes transient organ failure, persistent organ failure, and local or systemic complications (boxes 1 and 3). Transient organ failure is organ failure that is present for <48h. Persistent organ failure is defined as organ failure that persists for >48h. Local complications include peripancreatic fluid collections and acute necrotic collections[13 14 39 41] (box 1), while systemic complications can be related to exacerbations of underlying co-morbidities related to the acute pancreatitis.

Mild acute pancreatitis

Mild acute pancreatitis is characterised by the absence of organ failure and the absence of local or systemic complications. Patients with mild acute pancreatitis will usually be discharged during the early phase. Patients with mild acute pancreatitis usually do not require pancreatic imaging, and mortality is very rare.[15]

Box 3 Grades of severity

- Mild acute pancreatitis
  - No organ failure
  - No local or systemic complications
- Moderately severe acute pancreatitis
  - Organ failure that resolves within 48h (transient organ failure) and/or
  - Local or systemic complications without persistent organ failure
- Severe acute pancreatitis
  - Persistent organ failure (>48h)
    - Single organ failure
    - Multiple organ failure

Moderately severe acute pancreatitis

Moderately severe acute pancreatitis is characterised by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure. An example of a symptomatic local complication is a peripancreatic collection resulting in prolonged abdominal pain, leucocytosis and fever, or that prevents the ability to maintain nutrition orally. An example of a symptomatic systemic complication is exacerbation of coronary artery disease or chronic lung disease precipitated by the acute pancreatitis. Moderately severe acute pancreatitis may resolve without intervention (as in transient organ failure or acute fluid collection) or it may require prolonged specialist care (as in extensive sterile necrosis without organ failure). Mortality of moderately severe acute pancreatitis is far less than that of severe acute pancreatitis.[32]

Severe acute pancreatitis

Severe acute pancreatitis is characterised by persistent organ failure.[39 41] Organ failure that develops during the early phase is set in motion by the activation of cytokine cascades resulting in SIRS[38 39 40] (box 2). When SIRS is present and persistent,[39 41 42] there is an increased risk that the pancreatitis will be complicated by persistent organ failure, and the patient should be treated as if they have severe acute pancreatitis.

Persistent organ failure may be single or multiple organ failure. Patients with persistent organ failure usually have one or more local complications. Patients who develop persistent organ failure within the first few days of the disease are at increased risk of death, with a mortality reported to be as great as 36–50%.[38 39 41] The development of infected necrosis among patients with persistent organ failure is associated with an extremely high mortality.[22 28]

Evolution of severity of acute pancreatitis

At admission, mild pancreatitis is identified by the absence of organ failure. When organ failure is present within the first 24h (and organ failure that occurs during the first week of acute pancreatitis is usually present on admission to hospital), it may be difficult to determine the final grade of severity, because it is not known whether the patient will prove to have transient or persistent organ failure; the patient does not have mild pancreatitis and should be classified and treated initially as potentially having severe acute pancreatitis. If the organ failure resolves within 48h (indicating only transient organ failure), the patient should be classified as having moderately severe acute pancreatitis. If the patient develops persistent organ failure, they should be classified as having severe acute pancreatitis.[39 45] During the early phase, the severity of acute pancreatitis can be reassessed on a daily basis while the pancreatitis is still evolving. Convenient time points to re-evaluate are 24h, 48h and 7 days after admission to hospital.

While local complications may be identified during the early phase, it is generally not necessary to document local complications by imaging during the first week. The reasons for this are as follows. First, the presence and extent of pancreatic and peripancreatic necrosis may not be defined clearly on imaging during the first few days of disease.[16] When necessary, a CECT 5–7 days after admission is more reliable in establishing the presence and extent of pancreatic necrosis. Second, the extent of morphologic changes and necrosis is not directly proportional to the severity of organ failure.[24 46] Third, even if imaging during the first week identifies the presence of peripancreatic fluid collections or pancreatic necrosis, in general no treatments are required for these conditions at that time.

In the late phase of moderately severe or severe acute pancreatitis, local complications evolve more fully, although some patients with persistent organ failure may recover without local complications.[39] The presence of infection within areas of necrosis is a marker of increased risk of death. Infected necrosis without persistent organ failure, however, has a lesser mortality rate than infected necrosis with persistent organ failure. A systematic review[33] found 11 deaths (11%) in 93 patients with infected necrosis without organ failure and led to the suggestion of a four-tier grading of severity.[47] Analysis of two large national studies from the Netherlands[25 48] shows five deaths (6%) in 84 patients with infected necrosis without organ failure.

It is important to distinguish the different morphologic characteristics of the local complications, because these local complications may require a variety of interventions to avoid a fatal outcome.

Patients with moderately severe and severe acute pancreatitis can be described more precisely and stratified for the purpose of clinical studies by the nature and number of morphologic and clinical features (box 1 and 3). The descriptors are local complications (absent, sterile or infected) and persistent organ failure (single or multiple).[28 33] Use of these terms will aid clear communication and will focus attention towards the problems that require management in each case.

Definition of pancreatic and peripancreatic collections

In the present classification, an important distinction is made between collections that are composed of fluid alone versus those that arise from necrosis and contain a solid component (and which may also contain varying amounts of fluid). Below, we define the following terms: *acute peripancreatic fluid collection* (APFC) occurring in interstitial oedematous pancreatitis; *pancreatic pseudocyst* as a delayed (usually >4 weeks) complication of interstitial oedematous pancreatitis; and necrosis, which may be an *acute necrotic collection* (ANC, in the early phase and before demarcation) or *walled-off necrosis* (WON), which is surrounded by a radiologically identifiable capsule (which rarely develops before 4 weeks have elapsed from onset of pancreatitis).

Acute peripancreatic fluid collection

Fluid collections usually develop in the early phase of pancreatitis.[49] On CECT, APFCs do not have a well defined wall, are homogeneous, are confined by normal fascial planes in the retroperitoneum, and may be multiple (figure 2). Most acute fluid collections remain sterile and usually resolve spontaneously without intervention.[19 49] When a localised APFC persists beyond 4 weeks, it is likely to develop into a pancreatic pseudocyst (see below), although this is a rare event in acute pancreatitis. APFCs which resolve or remain asymptomatic do not require treatment and do not by themselves constitute severe acute pancreatitis.

Pancreatic pseudocyst

The term pancreatic pseudocyst refers specifically to a fluid collection in the peripancreatic tissues (occasionally it may be partly or wholly intra-pancreatic). A pancreatic pseudocyst is surrounded by a well defined wall and contains essentially no solid material (figure 7). Diagnosis can be made usually on these morphologic criteria. If aspiration of cyst content is performed, there is usually a markedly increased amylase activity. A pancreatic pseudocyst is thought to arise from disruption of the main pancreatic duct or its intra-pancreatic branches without any recognisable pancreatic parenchymal necrosis; this theory suggests that consequent leakage of pancreatic juice results in a persistent, localised fluid collection, usually after more than 4 weeks. When there is evident solid necrotic material within a largely fluid-filled cavity, the term pseudocyst should not be used. The development of a pancreatic pseudocyst is extremely rare in acute pancreatitis, and thus the term pancreatic pseudocyst in the setting of acute pancreatitis may fall into disuse. In this classification, pseudocyst does not result from an ANC (defined below). Although CECT is the imaging modality used most commonly to describe pseudocysts, MRI or ultrasonography may be required to confirm the absence of solid content in the collection.

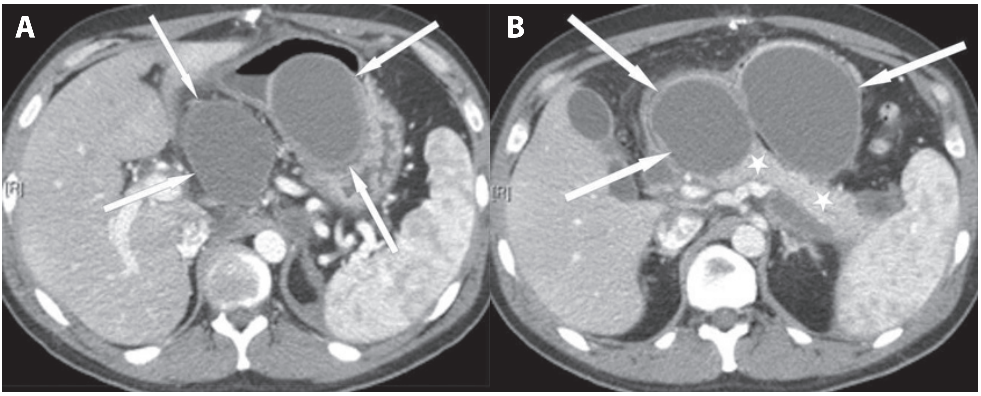

FIGURE 7 A 40-year-old man with two pseudocysts in the lesser sac 6 weeks after an episode of acute interstitial pancreatitis on CT (**A**, **B**). Note the round to oval, low-attenuated, homogeneous fluid collections with a well defined enhancing rim (white arrows pointing at the borders of the pseudocysts), but absence of areas of greater attenuation indicative of non-liquid components. White stars denote normal enhancing pancreas.

A pseudocyst may also arise in the setting of acute necrotising pancreatitis as a result of a 'disconnected duct syndrome', whereby pancreatic parenchymal necrosis of the neck or body of the gland isolates a still viable distal pancreatic remnant.[50] A pseudocyst may be evident many weeks after operative necrosectomy due to localised leakage of the disconnected duct into the necrosectomy cavity. Necrosis is absent because it has been removed by the earlier necrosectomy.

Acute necrotic collection

During the first 4 weeks, a collection containing variable amounts of fluid and necrotic tissue is termed an ANC (figures 3, 4, 5) to distinguish it from an APFC. The necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues. On CECT, acute pancreatic or peripancreatic necrotic collections contain varying amounts of solid necrotic material and fluid, may be multiple, and may appear loculated. An ANC is not an APFC, because an ANC arises from necrotising pancreatitis (necrosis of the pancreatic parenchyma and/or peripancreatic tissues) and contains necrotic tissue. An ANC may be associated with disruption of the main pancreatic duct within the zone of parenchymal necrosis and can become infected.

Sequential imaging may be useful to characterise acute collections. Within the first week of the disease, it may be difficult to differentiate an APFC from an ANC. At this stage, both types of collections may appear as areas with fluid density (figure 3). After the first week, the distinction between these two important types of collections becomes clear, such that at this stage of necrosis, a peripancreatic collection associated with pancreatic parenchymal necrosis can be properly termed an ANC and not an APFC. MRI, transcutaneous ultrasonography or endoscopic ultrasonography may be helpful to confirm the presence of solid content in the collection.

Walled-off necrosis

WON consists of necrotic tissue contained within an enhancing wall of reactive tissue. It is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis and has a well defined inflammatory wall (figure 8); usually this maturation occurs ≥4 weeks after onset of necrotising pancreatitis. Previous suggested nomenclature had designated this entity as organised pancreatic necrosis,[51] necroma,[52] pancreatic sequestration,[53] pseudocyst associated with necrosis,[54] and subacute pancreatic necrosis.[55]

WON derives from necrotic pancreatic parenchyma and/or necrotic peripancreatic tissues and may be infected, may be multiple, and may be present at sites distant from the pancreas. CECT may not readily distinguish solid from liquid content, and, for this reason, pancreatic and peripancreatic necrosis may be misdiagnosed as a pancreatic pseudocyst. For this purpose, MRI, transabdominal ultrasonography or endoscopic ultrasonography may be required for this distinction. Demonstration of the presence or absence of pancreatic ductal communication is not necessary in this classification, although determination of such ductal communication is of potential importance, because it may affect management.

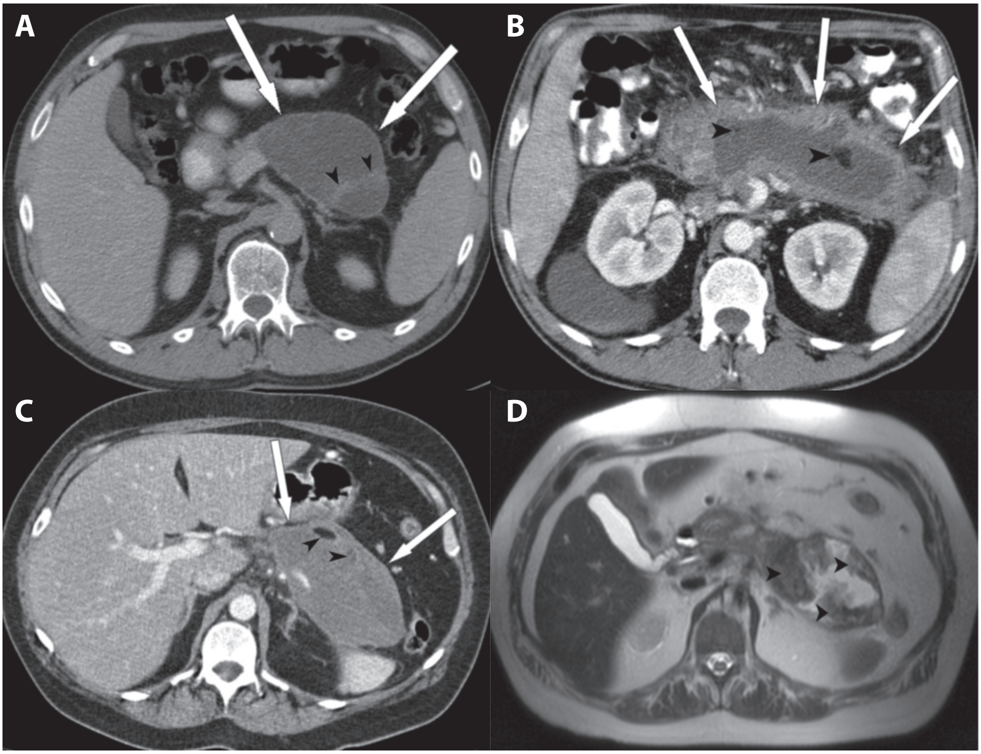

FIGURE 8 (A–C) Three different patients with walled-off necrosis (WON) after an acute attack of necrotising pancreatitis. In all three patients, a heterogeneous, fully encapsulated collection is noted in the pancreatic and peripancreatic area. **(A)** Non-liquid components of high attenuation (black arrowheads) in the collection are noted. The collection has a thin, well defined, and enhancing wall (thick white arrows). **(B, C)** A largely liquefied collection in the bed of the pancreas is observed with non-liquid components representing areas of trapped fat (black arrowheads). **(D)** represents the corresponding T2-weighted MRI to **(C)**, showing the true heterogeneity of the collection. Black arrowheads denote areas of necrotic debris surrounded by fluid (white on T2-weighted image).

Infected necrosis

The diagnosis of infection (infected necrosis) of an ANC or of WON can be suspected by the patient's clinical course or by the presence of gas within the collection seen on CECT (figure 6). This extraluminal gas is present in areas of necrosis and may or may not form a gas/fluid level depending on the amount of liquid content present at that stage of the disease. In cases of doubt, fine needle aspiration for culture may be performed, but some series have shown that the large majority of patients can be managed without FNA, especially if percutaneous drainage is part of the management algorithm.[25]

CONCLUSION

This classification revises and updates the definitions from the Atlanta Classification of acute pancreatitis. An important feature is the recognition that acute pancreatitis is an evolving, dynamic condition and that the severity may change during the course of the disease. Early in the disease, SIRS or organ failure indicate potentially severe disease. If the patient improves rapidly during the early phase without organ failure and without local or systemic complications, the disease is defined as mild acute pancreatitis. If the patient develops local or systemic complications and has no persistent organ failure, the disease is defined as moderately severe acute pancreatitis. If the patient develops persistent organ failure, the disease is defined as severe acute pancreatitis and is associated with very high morbidity and mortality rates.

The accurate description of local complications, including the presence of fluid or necrosis in or around the pancreas, the time course of progression, and the presence or absence of infection, will improve the stratification of patients both for clinical care in specialised centres and for reporting of clinical research.

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7

Significant inter-observer variation in the diagnosis of extrapancreatic necrosis and type of pancreatic collections in acute pancreatitis -

An international multicenter evaluation of the revised Atlanta Classification

Sternby H, Verdonk RC, Aguilar G, Dimova A, Ignatavicius P, Ilzarbe L, Koiva P, Lantto E, Loigom T, Penttilä A, Regnér S, Rosendahl J, Strahinova V, Zackrisson S, Zviniene K, Bollen TL

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ABSTRACT

Background: For consistent reporting and better comparison of data in research the revised Atlanta Classification (RAC) proposes new computed tomography (CT) criteria to describe the morphology of acute pancreatitis (AP). The aim of this study was to analyse the interobserver agreement among radiologists in evaluating CT morphology by using the new RAC criteria in patients with AP.

Methods: Patients with a first episode of AP who obtained a CT were identified and consecutively enrolled at six European centres backwards from January 2013 to January 2012. A local radiologist at each center and a central expert radiologist scored the CTs separately using the RAC criteria. Center dependent and independent interobserver agreement was determined using Kappa statistics.

Results: In total, 285 patients with 388 CTs were included. For most CT criteria, interobserver agreement was moderate to substantial. In four categories, the center independent kappa values were fair: extrapancreatic necrosis (EXPN) (0.326), type of pancreatitis (0.370), characteristics of collections (0.408), and appropriate term of collections (0.356). The fair kappa values relate to discrepancies in the identification of extrapancreatic necrotic material. The local radiologists diagnosed EXPN (33% versus 59% $P < 0.0001$) and non-homogeneous collections (35% versus 66%, $P < 0.0001$) significantly less frequent than the central expert. Cases read by the central expert showed superior correlation with clinical outcome.

Conclusion: Diagnosis of EXPN and recognition of non-homogeneous collections show only fair agreement potentially resulting in inconsistent reporting of morphologic findings.

INTRODUCTION

Acute pancreatitis (AP) is a complex disease with potentially severe and fatal outcome [1,2]. Simple but clear definitions of the disease are crucial in interdisciplinary consultation, communication, and in reporting of clinical research. Such were the incentives to update the 1992 Atlanta Classification on AP [1]. Besides redefining the disease into three levels of clinical severity, the 2012 revised Atlanta Classification (RAC) has put substantial efforts into clarifying the terminology on the morphologic subtypes of AP and associated peripancreatic collections based on computed tomography (CT)-based criteria [1]. Two morphologic types of AP are discriminated: acute interstitial oedematous pancreatitis and acute necrotising pancreatitis. Acute necrotising pancreatitis is subdivided into three forms: pancreatic parenchymal necrosis, extrapancreatic necrosis (EXPN), and combined necrosis. Peripancreatic collections are classified into four types depending on content and maturation. Acute peripancreatic fluid collections and pancreatic pseudocysts are composed of fluid only and occur in interstitial oedematous pancreatitis. On CT, these collections show a homogeneous fluid density with no or incomplete well-defined wall (acute peripancreatic fluid collection) or a complete wall (pseudocyst). Acute necrotic collections and walled-off necrosis are associated with acute necrotising pancreatitis and contain varying amounts of fluid and necrotic material. On CT, these collections have various densities (fat, fluid, solid material) with no or incomplete well-defined wall (acute necrotic collection) or a complete wall (walled-off necrosis) [1,3-5]. The RAC provides approximate time frames for these pancreatic collections. Acute peripancreatic fluid collection and acute necrotic collection pertain to the first four weeks of disease after which they usually turn into a completely encapsulated pseudocyst and walled-off necrosis, respectively.

It is well established that the morphologic types of AP differ in outcomes, therapies, and prognosis. For prognostication, stratification, and comparing of interinstitutional data, accurate assessment of AP morphology in the different stages of disease is imperative [1]. The extent of variation in interpretation of the new CT criteria is, however, unknown [6-8]. The aim of this study was to assess the interobserver agreement among radiologists in the evaluation of CT morphology using the RAC criteria.

METHODS

Patients and study design

Patients >18 years with a first episode of AP were consecutively identified at six European study centres, going backwards from January 2013 to January 2012. Each center included 50 patients in whom at least one contrast-enhanced CT (CECT) was performed. The cases were anonymously enrolled and each patient obtained a code blinded for all investigators except for the referring center. CECTs performed within 3 months from date of admission were recorded and subsequently reviewed and scored by a local radiologist at each center. The time frame of 3 months was chosen because most CTs are performed within this period and controversies in nomenclature and management of pancreatic collections are most evident during this phase. Exclusion criteria were insufficient quality of the CECT, signs of chronic pancreatitis (i.e. pancreatic calcifications) or patients with prior pancreatitis-related invasive intervention, except from endoscopic retrograde cholangiography. Each CECT was performed in the pancreatic and/or in the portal venous phase (see Supplementary file 1 for CT specifications). Severity and CT morphology of AP were defined according to the RAC (see Box 1 for definitions) [1].

Box 1 Morphological features and CECT criteria in AP according to the RAC.

Morphology groups	CECT criteria	Time
Interstitial oedematous pancreatitis (IEP)	Homogenous enhancement of the pancreatic parenchyma, normal or minor inflammatory changes of the peripancreatic tissue (see below - APFC or pancreatic pseudocyst)	-
Necrotising pancreatitis	Heterogeneous enhancement of the pancreatic parenchyma and/or peripancreatic tissue necrosis (see below - ANC or WON)	-
Acute peripancreatic fluid collection (APFC)	Homogeneous fluid density. No complete wall. No necrosis. Associated with IEP. Solely extrapancreatic location.	≤4 weeks
Pancreatic pseudocyst	Homogeneous fluid density. Fully encapsulated. No necrosis. Associated with IEP. Solely extrapancreatic location.	>4 weeks
Acute necrotic collection (ANC)	Heterogeneous and non-liquid density. No complete wall. Associated with necrotising pancreatitis. Intra- or extrapancreatic location	≤4 weeks
Walled-off necrosis (WON)	Heterogeneous and non-liquid density. Fully encapsulated. Associated with necrotising pancreatitis. Intra- or extrapancreatic location	>4 weeks

CECT = contrast enhanced computed tomography.

The following clinical data was collected from review of medical notes: systemic inflammatory response syndrome (SIRS) upon admission, highest level of C-reactive protein (CRP) during hospitalisation, need for invasive intervention, organ failure (persistent and transient, in line with the RAC), and in-hospital mortality. The six participating local radiologists had expertise in the field of abdominal radiology, each with more than five years' experience. A short instruction sheet was provided to local radiologists to assist in interpretation (Supplementary file 2). All individual CECTs were scored according to a protocol based on the parameters stated in the RAC (Supplementary file 3). Subsequently, all CECTs were reviewed and scored (using the same scoring sheet) by a central expert radiologist (T.L.B) using open source DICOM viewer software (32-bit OsiriX version 3.3, Geneva, Switzerland). Local and central reviewers were blinded to any clinical data except for the timing (number of days after onset of symptoms) of each CECT. Formal approval of the local medical ethical committee was requested and obtained at each study center.

Statistical analysis

Sample size calculations for variables with 2, 3, and 4 categories were performed because most of the variables of the revised Atlanta criteria are based on 2, 3, or 4 categories. Kappa values of > 0.40 and > 0.60 were used since they represent at least moderate and substantial agreement [9]. Based on such a calculation, in a test for agreement between two raters, a sample size of 360 CECTs would provide a 95% confidence interval for the κ statistic with a width not greater than 0.20. Assuming that several patients would have more than one CECT performed, a total of 50 patients were included per center. Interobserver agreement was calculated between the local and the central radiologist, using Cohen's kappa test, for each of the categories scored on the radiology sheet. Agreement levels were defined as: κ level 0.00-0.20 slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; and 0.81-1.00 almost perfect. Continuous data analysis was conducted using Mann-Whitney *U* test. Wilcoxon Signed Rank test was used for paired sample analysis. $P < 0.05$ was considered statistically significant. All analysis was performed using IBM SPSS Statistics for Windows, version 21 and 22, Armonk, NY:IBM corp.

RESULTS

Patients

In total, 301 patients were included at six European centres of whom 159 (56%) were male with a median age of 58 years (range 18-92). Sixteen patients were excluded due to reasons stated in the CECT section below. Baseline characteristics of the remaining 285 patients are summarised in Table 1. Etiology of AP differed substantially between the centres. According to the RAC, 37.5% of the patients had mild AP, 51.5% moderately severe AP and 11.0% severe AP [1]. Overall fourteen patients died (4.9%, range 0-14%), whereas mortality within the severe group was 32.3% (range 0-78%). Each center admits 175-250 patients with AP annually, except for center F where the number is approximately 470.

Contrast-enhanced computed tomography

A total of 405 CECTs derived from 301 patients were collected. Seventeen CECT studies were excluded due to insufficient quality of the CECT or signs of chronic pancreatitis, leaving a study cohort of 285 patients with 388 CECTs. Data on CECTs for the separate centres are presented in Table 2. Median time from onset of disease to CECT for all centres was 7 days (range 0-90, interquartile range 3-13).

Interobserver agreement

For specific information concerning all categories evaluated we refer to Supplementary file 2. The kappa values representing the interobserver agreement are shown in Table 3. There was substantial agreement in seven categories: 'Necrosis - Neck' (0.618); 'Necrosis - Body' (0.628); 'Necrosis - Tail' (0.617); presence of 'Collections' (0.756); 'Location of Collections'

TABLE 1. Baseline characteristics of patients in each center and all centres combined.

	All patients n = 285	Center B n = 42	Center C n = 48	Center D n = 50	Center E n = 48	Center F n = 47	Center G n = 50
Male sex	159 (56%)	28 (67%)	24 (50%)	29 (58%)	18 (37%)	32 (68%)	28 (68%)
Age (years)	58 (18-92) IQR (45-71)	46 (22-83) IQR 34 -61	65 (18-88) IQR 52 -76	62 (21-92) IQR 41-76	60 (22-88) IQR 42-73	52 (35-85) IQR 45-68	62 (23-87) IQR 52-73
Etiology (%)							
Biliary	36.6	24.4	56.3	18.0	54.1	19.2	46.0
Alcohol	35.9	43.9	14.5	26.0	41.7	63.8	28.0
Other	27.5	31.7	29.2	56.0	4.2	17.0	26.0
Highest CRP (mg/l)	261 (0-553)	259 (44-493)	208 (3-480)	281 (0-477)	258 (2-444)	278 (9-519)	277 (41-553)
Classification n (%)							
Mild	107 (37.5)	17 (40.5)	26 (54.2)	10 (20.0)	11 (22.9)	19 (40.4)	24 (48.0)
Moderately severe	147 (51.5)	24 (57.1)	18 (37.5)	31 (62.0)	35 (72.9)	20 (42.6)	19 (38.0)
Severe	31 (11.0)	1 (2.4)	4 (8.3)	9 (18.0)	2 (4.2)	8 (17.0)	7 (14.0)
Mortality (%)	4.9	2.0	0.0	14.0	0.0	8.5	4.0

Continuous variables are median. Range and IQR are displayed if applicable.
n = number of patients.
IQR = Inter quartile range.
CRP = C-reactive protein.

TABLE 2. Characteristics of CECTs of each center and all centres combined.

	All CECTs	Center B	Center C	Center D	Center E	Center F	Center G
No of CECTs	388	49	74	59	73	63	69
No of CECTs performed per patient	1.4 (1-5)	1.2 (1-3)	1.5 (1-5)	1.2 (1-3)	1.5 (1-4)	1.3 (1-4)	1.4 (1-4)
Time to CECT	7 (0-90) IQR 3-13	6 (0-26) IQR 3-8	6.5 (0-90) IQR 3-16	9 (1-31) IQR 4-13	6 (0-87) IQR 3-11	12 (1-67) IQR 3-41	4 (1-88) IQR 2-11
Type of pancreatitis and time to CECT							
Oedematous pancreatitis	3 (0-73) IQR 2-7	4 (0-19) IQR 1-7	5.5 (0-73) IQR 3-9	5 (1-9) IQR 2-8	2 (0-57) IQR 1-6	4 (1-65) IQR 3-7	3 (1-50) IQR 2-4
Necrotising pancreatitis	10 (1-90) IQR 5-21	8 (0-26) IQR 6-12	13 (0-90) IQR 6-33	9 (1-32) IQR 5-14	8 (0-87) IQR 4-15	23 (1-67) IQR 11-46	9 (2-89) IQR 5-27
Indeterminate pancreatitis	3 (0-14) IQR 2-5	2 (0-8) IQR 1-8	4 (1-5) IQR 2-4	4 (1-14) IQR 2-5	4 (1-7) IQR 1-6	2 (2-11) IQR 2-10	2 (1-5) IQR 1-4

No=Number.
IQR=Inter quartile range.
Continuous variables are median. Range and IQR are displayed if applicable. Time to CECT=Time from symptom onset to CECT in days.
Type of pancreatitis and time to CECT = Time from symptom onset to CECT in days divided by type of pancreatitis.

(0.633); presence of 'Wall' (0.675); and presence of 'Intraluminal Gas and/or Fluid level' (0.764). Moderate agreement was reached on 'Parenchymal Necrosis' (0.539) and 'Necrosis - Head' (0.516). Finally, there was fair agreement on the categories 'Type of Pancreatitis' (0.370), 'Extrapancreatic Necrosis' (0.326), 'Characteristics of Collection' (0.408), and 'Collection - most appropriate term' (0.356). The center dependent kappa values differed considerably between centres.

TABLE 3. Center independent and dependent kappa values for all categories scored.

Category	All centres	Center B	Center C	Center D	Center E	Center F	Center G
Type of pancreatitis	0.370	0.317	0.342	0.309	0.098[b]	0.838[a]	0.360
Parenchymal Necrosis	0.539	0.380	0.319[b]	0.609	0.731[a]	0.663	0.465
Necrosis - Head	0.516	0.669	0.345	0.323[b]	1.00[a]	0.660	0.646
Necrosis - Neck	0.618	0.922[a]	0.577	0.822	0.660	0.364	0.236[b]
Necrosis - Body	0.628	0.766	0.611	0.687	0.873	0.392[b]	0.570
Necrosis - Tail	0.617	0.451	0.626	0.687	0.409[b]	0.806[a]	0.532
Extrapancreatic Necrosis	0.326	0.321	0.504	0.293	0.120	0.877[a]	0.024[b]
Collections	0.756	0.780	0.750	0.624[b]	0.864[a]	0.827	0.625
Location of Collections	0.633	0.728	0.761[a]	0.508	0.694	0.604	0.439[b]
Characteristics of collections	0.408	0.397	0.485	0.293	0.305	0.744[a]	0.251[b]
Wall	0.675	0.638	0.638	0.588[b]	0.777[a]	0.726	0.632
Intraluminal gas/fluid level	0.764	0.774	0.671[b]	0.764	0.887[a]	0.837	0.675
Collection - most appropriate term	0.356	0.385	0.480	0.136[b]	0.218	0.673[a]	0.261

[a] Highest kappa value for center B to G for each category.
[b] Lowest kappa value for center B to G for each category.

Discrepancies in the identification of EXPN are shown in Table 4. For image samples see Fig. 1a,b and 2a-c. The expert radiologist diagnosed EXPN significantly more often than the local radiologists (59% vs. 33%, $P < 0.0001$). Table 4 shows that this difference in total number of EXPN stems from the subgroup of isolated EXPN. Since the RAC acknowledges that EXPN might be difficult to diagnose within the first week, interobserver agreement was recalculated for the categories with low kappa values excluding CECTs performed within 72h, seven days and two weeks after onset of disease (see Supplementary file 4). In this subanalysis, kappa values did improve only for CECTs performed after two weeks.

TABLE 4. Number of extrapancreatic necrosis (EXPN) scored by the local radiologists and central expert.

	Total number of EXPN		Combined necrosis		Isolated EXPN	
	Local rad	Central exp	Local rad	Central exp	Local rad	Central exp
Yes	126 (33%)	230 (59%)	85 (22%)	92 (24%)	41 (11%)	138 (36%)
No	245 (63%)	110 (28%)	303 (78%)	296 (76%)	347 (89%)	250 (64%)
Indet	17 (4%)	48 (12%)				

Total number of EXPN = diagnosis of EXPN (yes/no) and indeterminate by local radiologists and central expert, respectively.
Combined necrosis = Extrapancreatic necrosis with Parenchymal necrosis in cases where presence of EXPN (yes/no) was determined.
Isolated EXPN = Extrapancreatic necrosis without Parenchymal Necrosis in cases where presence of EXPN (yes/no) was determined.
Local rad = Local radiologists.
Central exp = Central expert radiologist.
Indet = Indeterminate (radiologist was not able to determine the presence of EXPN, yes/no).

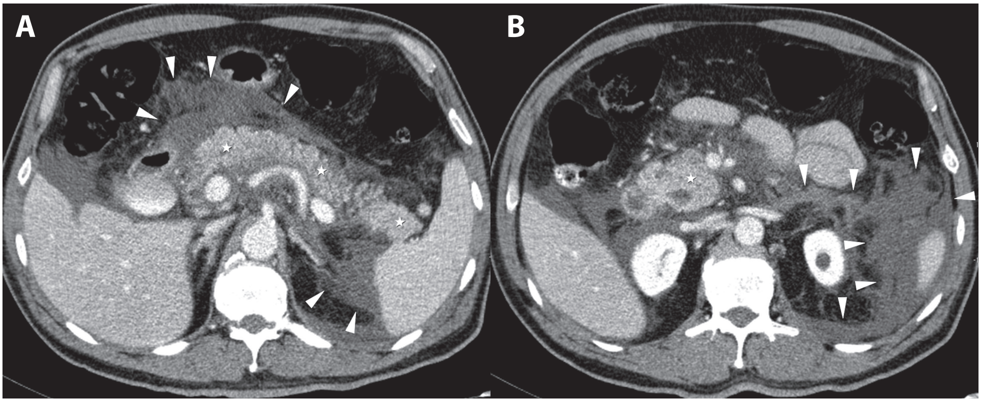

FIG. 1. 70-year-old male with acute pancreatitis **(A, B)**. The pancreas enhances heterogeneously (asterisks) but no apparent necrosis was observed by both reviewers. Peripancreatic collections are present in the retroperitoneal pancreatic compartment and transverse mesocolon (arrowheads pointing at the borders). The local reviewer scored this as interstitial pancreatitis with acute peripancreatic fluid collections; the central reviewer as necrotising pancreatitis, subtype EXPN, with acute necrotic collections.

Morphological findings scored by the central and local radiologists were correlated with clinical outcome parameters (see Table 5). Cases read as interstitial oedematous pancreatitis and isolated EXPN by the central expert correlate significantly better with clinical outcome than scoring by local radiologists. Given the good interobserver agreement for pancreatic parenchymal necrosis, results did not differ significantly between central and local radiologists for this subgroup (Supplementary file 5).

TABLE 5. Correlation of morphologic findings with clinical outcome by central and local radiologists.

		IEP			Isolated EXPN		
	Total (N)	**Local**	**Central**	**P-value**	**Local**	**Central**	**P-value**
All cases	(388)	199	107	0.0001	41	138	0.0001
Organ Failure							
Persistent	(50)	20 (10.0%)	5 (4.7%)	0.0001	4 (9.7%)	24 (17.4%)	0.0001
Transient	(51)	15 (7.5%)	5 (4.7%)	0.002	4 (9.7%)	20 (14.5%)	0.0001
Mortality	(20)	9 (4.5%)	4 (3.7%)	0.025	1 (2.4%)	7 (5.1%)	0.025
Intervention	(79)	11 (5.5%)	6 (5.6%)	ns	12 (29.3%)	26 (18.8%)	0.001
CRP (mg/l)		271	165	0.0001	298	318	ns
SIRS	(104)	41 (20.6%)	12 (11.2%)	0.0001	9 (22.0%)	38 (27.5%)	0.0001

Cases scored as 'indeterminate' are not accounted for. IEP = Interstitial Edematous Pancreatitis.
Isolated EXPN = Extrapancreatic Necrosis without Parenchymal Necrosis. Local = Local radiologists.
Central = Central Expert.
CRP = C-reactive protein, highest value.
SIRS = Systemic Inflammatory Response Syndrome.

DISCUSSION

The RAC proposed a new set of morphologic CT-based criteria to account for alleged shortcomings of the 1992 Atlanta Classification [1,2]. One of the major aims of the RAC was to ease and ensure consistency in the investigation and reporting of data in clinical research [1]. However, the degree of interobserver agreement in the interpretation of CT findings using these new RAC criteria has been questioned [6-8].

Main findings of our study are twofold: on the one hand, the morphologic assessment of the RAC generates overall moderate to good interobserver agreement (range 0.516-0.764) among European radiologists in 9 out of 13 items evaluated. Importantly, agreement among raters was good in evaluating clinically important CT findings in patients with AP, such as the presence of parenchymal necrosis and gas bubbles. On the other hand, only fair agreement (range 0.326-0.408) was obtained for items pertaining to necrosis of extrapancreatic tissues. The central expert diagnosed EXPN significantly more frequent than the local radiologists (59% versus 33%, $P < 0.0001$) with better correlation with patient outcome. Our findings suggest that radiologists are largely unfamiliar with the newly defined entity of EXPN.

Several explanations exist for the fair agreement in diagnosing EXPN and for characterisation of pancreatic collections on CT. The RAC regards CT as the first-line imaging modality in AP, albeit acknowledging the fact that necrotic material within pancreatic collections is often overlooked [1]. It is well-established that ultrasound and magnetic resonance imaging are better capable of delineating the exact composition of pancreatic collections, especially for

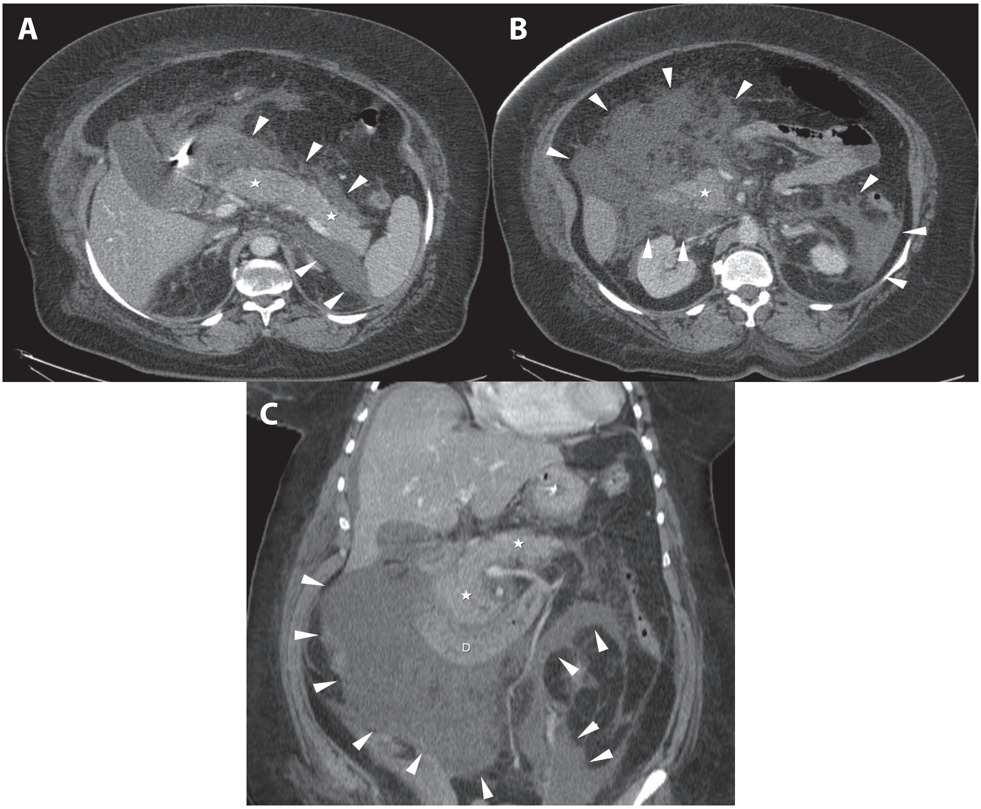

FIG. 2. 55-year-old female with acute pancreatitis **(A-C)**. Normal enhancement of pancreatic parenchyma was noted by both reviewers (asterisks). Extensive peripancreatic collections are present in the retroperitoneum bilaterally and transverse mesocolon (arrowheads pointing at the borders). These represented 'acute peripancreatic fluid collections' and 'acute necrotic collections' according to the local and central reviewer, respectively. Coronal reformatted image **(C)** depicts the magnitude of collections.

depicting necrotic material [10,11]. Furthermore, the CT diagnosis of EXPN and associated necrotic collections relies primarily on subjective secondary findings, such as 'heterogeneity' or the detection of various densities (liquid and non-liquid) within collections, rather than using the more objective and reproducible criteria of perfusion characteristics, which is used for detecting pancreatic parenchymal necrosis. Perfusion characteristics, however, cannot be used to diagnose EXPN because normal extrapancreatic fat does not enhance. In addition, the RAC acknowledges that EXPN is difficult to diagnose initially but becomes easier when the disease process evolves over time [1]. This is in line with our results with improved kappa values for EXPN diagnosis two weeks after symptom onset. Finally, reader expertise and familiarity seem equally important for diagnosing EXPN exemplified by the excellent interobserver agreement between the central expert and the local radiologist affiliated with center F that admits the highest number of patients with AP annually.

In a previous study on CT assessment of morphologic features of AP, good to excellent interobserver agreement was found in 55 cases of AP [12]. However, this study used selected cases biased towards severe disease (likely associated with more established peripancreatic collections) reviewed by tertiary experts. Although imaging is rarely required for mild AP, most patients who undergo CT for evaluation of AP turn out to have interstitial pancreatitis. Our study more closely resembles clinical practice in different European countries by enrolling patients with AP consecutively and evaluating unselected CECTs encompassing the full spectrum of morphologic abnormalities in AP, including mild and equivocal cases.

Previous studies show considerable differences in clinical outcome, treatment strategies, and prognoses between the various morphological types of AP [13-17]. Clinical outcome of EXPN is worse compared with acute interstitial pancreatitis, but better than pancreatic necrosis [13,15,17]. Patients with EXPN stay in hospital considerable longer, develop more often organ failure, and undergo interventional therapy significantly more frequent than those with interstitial pancreatitis. Moreover, when infection ensues of necrotic collections in EXPN patients, outcome, therapy, and prognosis are similar to those with infected pancreatic necrosis [15]. In our study, the interpretation by the central expert more closely corroborated with actual clinical outcome. As such, accurate differentiation between the types of AP is important both from a clinical perspective as for consistent reporting of research and reliable comparison of inter-institutional data.

This study has some limitations. First, a single central expert radiologist served as standard of reference, potentially introducing bias. We considered this a limited risk because of his extensive experience in pancreatic imaging, his involvement in the development of the RAC, the superior correlation with patient outcome, and the excellent agreement with a local radiologist with similar expertise. Second, given the retrospective design of this study, we did not investigate to what extent the inconsistencies observed eventually affected clinical decision-making. Future studies should focus on this interesting topic. Finally, we merely studied the interobserver agreement of morphological abnormalities in AP and did not correlate imaging findings with histopathology.

Results of this study have revealed areas of controversy when using the RAC criteria for CT assessment, especially pertaining to distinguishing interstitial pancreatitis from EXPN only. There are several options for improving consistent reporting in AP. Both radiologists and clinicians need to become better familiar with imaging features of EXPN (i.e. by education or training). Second, the definition of EXPN should preferably be redefined such that stronger interrater agreement will be achieved, even among readers with varying expertise. For example, by adding a time interval of 2 weeks before its diagnosis or by using an alternative imaging (MRI or US) modality as these are better capable of detecting necrotic material within collections [10]. Third, a greater role should be attributed to MRI for overall evaluation of AP. Finally, as has been alluded to in previous reports, a three-degree morphologic classification system ('interstitial pancreatitis' refers to normal enhancing parenchyma without collections, 'EXPN' refers to normal perfused pancreatic parenchyma with pancreatic collections, and 'necrotising pancreatitis' refers to parenchymal necrosis with or without associated collections) could potentially lead to less interobserver variability as the differentiation between the various types of pancreatic collections becomes less of an issue [18,19]. Additionally, Such a system would likely be more in concordance with clinical grades of severity [13-17,20].

In conclusion, this study found only moderate interrater agreement for identification of EXPN. For correctly identifying EXPN and necrotic collections on CT, a diligent search for heterogeneity within pancreatic collections is crucial for accurate and consistent reporting of imaging findings (see Figs. 1 and 2).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at:
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PART II

Severity Prediction of Acute Pancreatitis: clinical- versus imaging-based scoring systems and morphologic severity of acute pancreatitis

8

Comparative evaluation of the modified CT severity index and CT severity index in assessing severity of acute pancreatitis

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AJR AM J ROENTGENOL. 2011 AUG;197(2):386-92. IMPACT FACTOR: 2.78

ABSTRACT

Objective: The purpose of this study was to compare the modified CT severity index (MCTSI) with the CT severity index (CTSI) regarding assessment of severity parameters in acute pancreatitis (AP). Both CT indexes were also compared with the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) index.

Materials and methods: Of 397 consecutive cases of AP, 196 (49%) patients underwent contrast-enhanced CT ($n = 175$) or MRI ($n = 21$) within 1 week of onset of symptoms. Two radiologists independently scored both CT indexes. Severity parameters included mortality, organ failure, pancreatic infection, admission to and length of ICU stay, length of hospital stay, need for intervention, and clinical severity of pancreatitis. Discrimination analysis and kappa statistics were performed.

Results: Although for both CT indexes a significant relationship was observed between the score and each severity parameter ($p < 0.0001$), no significant differences were seen between the CT indexes. Compared with the APACHE II index, both CT indexes more accurately correlated with the need for intervention (CTSI, $p = 0.006$; MCTSI, $p = 0.01$) and pancreatic infection (CTSI, $p = 0.04$; MCTSI, $p = 0.06$) and more accurately diagnosed clinically severe disease (area under the curve, 0.87; 95% CI, 0.82–0.92). Interobserver agreement was excellent for both indexes: for CTSI, 0.85 (95% CI, 0.80–0.90) and for MCTSI, 0.90 (95% CI, 0.85–0.95).

Conclusion: No significant differences were noted between the CTSI and the MCTSI in evaluating the severity of AP. Compared with APACHE II, both CT indexes more accurately diagnose clinically severe disease and better correlate with the need for intervention and pancreatic infection.

INTRODUCTION

Acute pancreatitis (AP) is a common and typically mild, self-limiting disease with only minimal or transient systemic manifestations. However, approximately 15–20% of patients develop clinically severe AP with local and systemic complications [1]. A number of clinical and laboratory prognostic scoring systems have been designed for the early identification of patients at greatest risk of developing clinically severe AP. Overall, these scoring systems have an accuracy varying between 70% and 80% [2]. Imaging by CT or MRI in the assessment of AP is useful not only for diagnosis but also for detecting local pancreatic complications and guiding interventional procedures.

Moreover, in the past two decades, several radiologic prognostic scoring systems have been developed. Among them, the CT severity index (CTSI), designed by Balthazar et al. [3] in 1990, is the most widely adopted for clinical and research settings. The CTSI is a numeric scoring system that combines a quantification of pancreatic and extrapancreatic inflammation with the extent of pancreatic necrosis. In 2004, a modified CTSI (MCTSI) was designed to account for several potential limitations of the CTSI [4]. In contrast to the CTSI, the MCTSI incorporates extrapancreatic complications in the assessment and simplifies the evaluation of the extent of pancreatic parenchymal necrosis (none, ≤ 30%, or > 30%) and peripancreatic inflammation (presence or absence of peripancreatic fluid). In the initial study of 66 patients, the MCTSI, when compared with the CTSI, better correlated with patient outcome, in particular, with regard to the length of hospital stay and, more important, the development of organ failure [4], which has been shown to be the primary determinant of outcome in the early phase of AP [5].

To our knowledge, no validation of the MCTSI in a larger cohort has been performed. Furthermore, in the initial study of the MCTSI, no detailed evaluation was provided with regard to the specific prevalence of each of the extrapancreatic complications. Finally, no comparison has been performed between both radiologic scoring systems and the existing clinical prognostic scoring system that is commonly used for research purposes (Acute Physiology, Age, and Chronic Health Evaluation, [APACHE II] score) [6]. Therefore, the primary aim of our study was to compare the MCTSI with the CTSI with regard to the ability to assess clinical severity among a consecutive cohort of patients with AP. The secondary aim was to compare both radiologic scoring systems with APACHE II with regard to clinical severity parameters.

MATERIALS AND METHODS

Subjects

A retrospective analysis of a prospectively collected database was performed. The demographic, clinical, and laboratory data of 397 consecutive cases of AP in patients admitted or transferred to our institution between June 2005 and December 2007 were reviewed for this study.

Institutional review board approval and written informed consent of each patient were obtained. AP was defined as two or more of the following: characteristic abdominal pain (i.e., severe upper abdominal pain), serum amylase or lipase levels three or more times the upper limit of normal (i.e., > 210 U/L and > 180 U/L, respectively), and changes consistent with AP on cross-sectional imaging [7]. Of the 397 cases of AP, there were 196 (49%) cases in 179 patients (107 men, 89 women; mean age, 53 years; age range, 21–94 years) who underwent contrast-enhanced CT (n = 175) or MRI (n = 21) that was performed within 1 week of onset of symptoms. Median interval between onset of symptoms and CT or MRI was 2 days (range, 0–7 days). Of the remainder of cases, 167 were excluded because no contrast-enhanced imaging study was done, 20 cases were excluded because they were admitted with acute or chronic pancreatitis, nine cases were excluded because imaging was done more than 1 week after onset of symptoms, and five cases were excluded because they had undergone previous pancreatic surgery or surgery for pancreatitis.

In our final study cohort of 196 cases, the causes of AP were biliary stones in 66 (34%) cases, alcohol abuse in 43 (22%) cases, miscellaneous (e.g., hypertriglyceridemia, hereditary) in 31 (16%) cases, idiopathic in 26 (13%) cases, postendoscopic retrograde pancreatography in 16 (8%) cases, and drug-induced in 14 (7%) cases. Appropriate clinical and laboratory data were recorded prospectively by two of the authors (who were unaware of the radiologic data) to permit calculation of APACHE II scores at the day of CT or MRI [6].

Imaging Technique

In 140 cases, CT examinations were performed on a 4-MDCT scanner (Volume Zoom, Siemens Healthcare). Contrast-enhanced CT scans (collimation, 4 × 2.5 mm; reconstruction section thickness, 5 mm; reconstruction intervals, 5 mm) were obtained 40–50 seconds after IV injection of 100 mL of iopromide (Ultravist 300, Bayer HealthCare), injected at a rate of 3.0 mL/s, using a mechanical power injector. In 35 cases, contrast-enhanced CT studies using a variety of parameters were retrieved from the referring hospitals; these studies were deemed of good quality (i.e., at least one contrast-enhanced CT scan in the pancreatic or portal venous phase).

In 21 cases, contrast-enhanced MRI was performed within 1 week of onset of symptoms. MRI was performed with a 1.5-T magnet (Signa EchoSpeed Plus, GE Healthcare) using a phased-array torso coil. Axial T2-weighted fast recovery fast spin-echo, axial and coronal heavily T2-weighted single-shot fast spin-echo, axial T1-weighted dual-echo gradient-recalled echo images, and axial fat-suppressed T1-weighted 3D gradient-echo images were obtained. Contrast-enhanced T1-weighted gradient-recalled echo images were obtained 25, 60, and 180 seconds after IV administration of 20 mL of gadopentetate dimeglumine (Magnevist, Bayer HealthCare).

Image Analysis

The first available contrast-enhanced imaging study was used for this study. All 35 digital CT studies from outside hospitals were retrieved and retrospectively reviewed using DICOM viewer software (DicomWorks, version 1.3.5, freeware). The remainder of in-house CT and MRI studies were retrospectively reviewed on a PACS workstation (Centricity, GE Healthcare). Two experienced radiologists separately and independently reviewed all imaging studies and recorded all pancreatic, peripancreatic, and extrapancreatic findings and complications, each blinded to patient outcome. Pancreatic findings included pancreatic enlargement and presence and extent of areas lacking enhancement. Peripancreatic findings included peripancreatic fat stranding and number of fluid collections. Extrapancreatic complications included ascites, pleural effusion, pericardial effusion, vascular complications (venous thrombosis, hemorrhage, and arterial pseudoaneurysm formation), gastrointestinal complications (ileus [adynamic ileus or mechanical obstruction], signs of ischemia, marked bowel-wall thickening, perforation, and intramural fluid collection), and extrapancreatic parenchymal complications (infarction, hemorrhage, and subcapsular fluid collection). In all cases, the morphologic severity of pancreatitis was assessed using the CTSI, developed by Balthazar et al. [3], and the MCTSI, more recently developed by Mortele et al. [4] (Table 1). For the CTSI, the morphologic severity of pancreatitis was categorized as mild (0–3 points), moderate (4–6 points), or severe (7–10 points). For the MCTSI, the morphologic severity of disease was categorized as mild (0–2 points), moderate (4–6 points), or severe (8–10 points) (Fig. 1). Both indexes were scored during the same interpretation session.

TABLE 1: CT Severity Index (CTSI) and Modified CTSI (MCTSI)

Characteristics	CTSI (0–10)	MCTSI (0–10)
Pancreatic inflammation		
Normal pancreas	0	0
Focal or diffuse enlargement of pancreas	1	2
Peripancreatic inflammation	2	2
Single acute fluid collection	3	4
Two or more acute fluid collections	4	4
Pancreatic parenchymal necrosis		
None	0	0
Less than 30%	2	2
Between 30% and 50%	4	4
More than 50%	6	4
Extrapancreatic complications[a]	0	2

[a] One or more of pleural effusion, ascites, vascular complications, parenchymal complications, or gastrointestinal tract involvement.

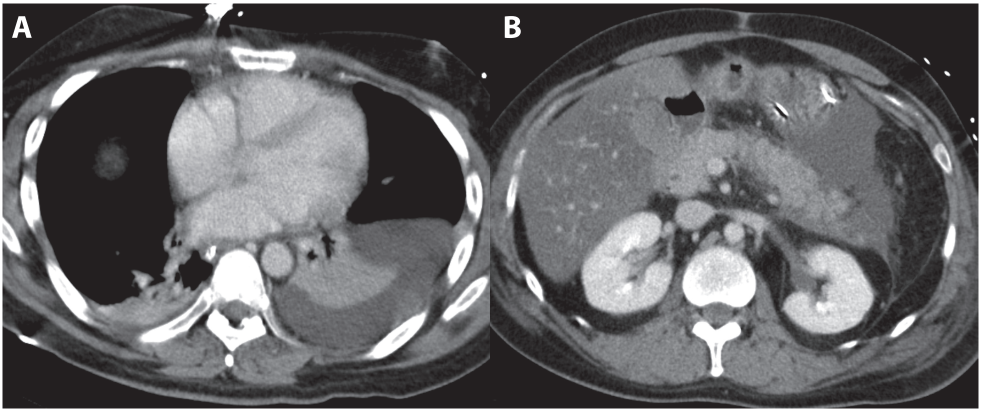

FIG. 1. 46-year-old woman with acute pancreatitis. **A,** Axial contrast-enhanced CT scan shows presence of bilateral pleural effusions with atelectasis of lower lobes. **B,** Axial contrast-enhanced CT scan shows one peripancreatic fluid collection and slightly heterogeneous enhancing pancreatic parenchyma without apparent areas of nonenhancement. Score was 3 (morphologic mild pancreatitis) on CT severity index and 6 (morphologic moderate severe acute pancreatitis) on modified CT severity index. Patient survived but experienced persistent organ failure and, thus, was diagnosed with clinically severe acute pancreatitis.

Definitions and Severity Parameters

Severity parameters for all patients were collected during the course of each patient's hospitalization, including in-hospital mortality, length of hospital stay, admission to and length of ICU stay, presence and duration of organ failure (transient, ≤ 48 hours; persistent, > 48 hours), pancreatic infection (infection of pancreatic or peripancreatic necrosis or collections documented on the basis of percutaneous aspiration), need for intervention (endoscopic or percutaneous drainage or surgical necrosectomy), and clinical severity of pancreatitis. AP was defined as clinically severe if the patient died, had organ failure persisting more than 48 hours, had local pancreatic complications that required intervention (endoscopic or radiologic drainage or surgical necrosectomy), or had prolonged hospitalization (such as need for enteral feeding or parenteral antibiotics). This new definition of clinically severe AP is in accordance with the most updated version of the revised Atlanta Classification [8]. Organ failure was defined as a score of 2 or more in one or more of the three (respiratory, renal, and cardiovascular) organ systems of the modified Marshall score [8, 9].

Data Analysis

The interobserver agreement for correlating the morphologic severity of AP (mild, moderate, or severe) determined by both the CTSI and the MCTSI was assessed using the kappa statistic. An independent radiologist reviewed interobserver discrepancies and agreement was obtained by consensus. Descriptive statistics were used for baseline characteristics, outcomes of interest, and extrapancreatic findings. Chi-square or Fisher's exact tests were used to assess relationships between categoric outcomes and morphologic severity of CTSI and MCTSI. Analysis of variance or Kruskal-Wallis tests were used to assess relationships between numeric outcome variables and morphologic severity of CTSI and MCTSI. The area under curve (AUC) with standard error and 95% CI was calculated for each scoring system. The receiver-operating characteristic (ROC) curve was examined for an optimal cutoff value for both CT scoring systems that most closely correlated with clinical severity of disease. To rule out potential bias introduced by incorporating transferred patients, discriminative analysis was also performed in the nontransferred group. A reduced p value of < 0.01 was considered statistically significant because of multiple testing. All statistical analyses were performed using SAS version 9.1 (SAS Institute), SPSS version 15.0 (SPSS), and MedCalc version 10.4.3.0 (MedCalc).

RESULTS

Morphologic Severity of Pancreatitis

For the CTSI, the observers graded the morphologic severity of pancreatitis as mild in 136 (69%), moderate in 41 (21%), and severe in 19 (10%) cases. Interobserver agreement between the two observers was 0.85 (95% CI, 0.80–0.90), indicating excellent agreement. For the MCTSI, the morphologic severity of pancreatitis was graded as mild in 86 (44%), moderate in 75 (38%), and severe in 35 (18%) cases, with interobserver agreement of 0.90 (95% CI, 0.85–0.95), also indicating excellent agreement.

Patient Outcome

Among the 196 cases, 162 (83%) cases involved clinically mild AP and 34 (17%) were diagnosed clinically as severe AP (Table 2). On imaging, 35 patients had acute necrotizing pancreatitis, of whom 24 (69%) developed clinically severe AP. Nineteen patients (10%) needed intervention for local complications: 12 underwent surgical débridement (5 after prior percutaneous drainage) and 7 underwent percutaneous drainage only. Organ failure occurred in 38 (19%) patients, of whom 20 (53%) experienced persistent organ failure. Infection of pancreatic or extrapancreatic necrosis occurred in seven (4%) cases. Eleven (6%) patients died.

Extrapancreatic Findings

Table 3 outlines the descriptive statistics for the extrapancreatic findings that were observed on imaging studies. In 110 (56%) cases, 2 points were credited for extrapancreatic complications using the MCTSI. Of these, 85 (77%) cases had either a pleural effusion or ascites without vascular, gastrointestinal, or extrapancreatic parenchymal complications. Pleural effusion or ascites with the presence of vascular, gastrointestinal, or extrapancreatic parenchymal complications were found in 23 (21%) cases. Therefore, only two (2%) cases had vascular, gastrointestinal, or extrapancreatic parenchymal complications without the presence of pleural effusion or ascites.

TABLE 2: Severity Outcomes for Full Case Cohort ($n = 196$)

Outcome	Frequency (%)	Median (Q1, Q3)
Length of hospital stay (d)	6, range 0–113	3, 12
ICU stay	42 (21)	
Length of ICU stay (d)	8.5, range 0–113	3, 12
Need for intervention	19 (10)	
Percutaneous catheter drainage	12[a]	
Surgical necrosectomy (débridement)	12	
Organ failure		
Transient	18 (9.2)	
Persistent	20 (10.2)	
None	158 (80.6)	
Pancreatic infection	7 (4)	
Clinically severe acute pancreatitis	34 (17)	
Death	11 (6)	

[a] Seven cases were treated with percutaneous drainage only, and five cases needed subsequent surgical necrosectomy.

TABLE 3: Descriptive Statistics for Extrapancreatic Findings in Modified CT Severity Index

Extrapancreatic Findings	Present (%)
Ascites	80 (41)
Pleural effusion	69 (35)
Gastrointestinal tract involvement	10 (5)
Vascular complications	16 (8)
Parenchymal complications	3 (2)

Correlation of CT Scoring Indexes With Severity Parameters

Table 4 outlines the relationship between severity parameters and both CTSIs. Table 5 shows the comparisons of ROC curves for all severity parameters. For both CT indexes, a significant relationship was observed between the score obtained and the severity parameters studied ($p < 0.0001$). The MCTSI had the higher AUC for the severity parameters of death and ICU stay, whereas the CTSI had higher AUCs for persistent organ failure, need for intervention, and pancreatic infection. However, for all severity parameters studied, no statistically significant difference was observed between the CTSI and MCTSI. The optimal cutoff score for assessing clinically severe disease from the ROC curves was > 4 for CTSI and > 6 for MCTSI. By using these cutoff scores, both MCTSI and CTSI showed similar diagnostic accuracy with regard to clinical severity of disease (sensitivity, 71% [95% CI, 53–85%]; specificity, 93% [95% CI, 88–97%]; negative predictive value, 94% [95% CI, 89–97%]; and positive predictive value, 69%

TABLE 4: Relationship Between Severity Parameters and Morphologic Severity of CT Severity Index (CTSI) and Modified CT Severity Index (MCTSI)

	CTSI				MCTSI			
Severity Parameter	**Mild (0–3, n = 136)**	**Moderate (4–6, n = 41)**	**Severe (7–10, n = 19)**	***p***	**Mild (0–2, n = 86)**	**Moderate (4–6, n = 75)**	**Severe (8–10, n = 35)**	***p***
Length of hospital stay (d)	5 [3, 8]	12 [6, 20]	16 [10, 22]	< 0.0001	4 [2, 6]	8 [5, 15]	18 [11,34]	< 0.0001
ICU stay (d)	15 (11)	11 (27)	16 (84)	< 0.0001	3 (3)	16 (21)	23 (66)	< 0.0001
Need for intervention	0 (0)	10 (24)	9 (47)	< 0.0001	0 (0)	2 (3)	17 (49)	< 0.0001
Organ failure								
Transient	7 (5)	7 (17)	4 (21)	< 0.0001	1 (1)	9 (12)	8 (23)	< 0.0001
Persistent	4 (3)	5 (12)	11 (58)	< 0.0001	2 (2)	4 (5)	14 (40)	< 0.0001
None	125 (92)	29 (71)	4 (21)		83 (97)	62 (83)	13 (37)	
Pancreatic infection	0 (0)	3 (7)	4 (21)	< 0.0001	0 (0)	1 (1)	6 (17)	< 0.0001
Clinically severe acute pancreatitis	6 (4)	14 (34)	14 (74)	< 0.0001	2 (2)	8 (11)	24 (69)	< 0.0001

Note—Data are expressed as number with percentage in parentheses or median.

[95% CI, 51–83%]). In addition, post hoc analysis showed that when points for extrapancreatic complications were restricted to only the presence of a pleural effusion or ascites, the discriminative power of the simplified MCTSI was similar to the MCTSI incorporating all extrapancreatic complications (data not shown).

TABLE 5: Area Under Curve for CT Severity Index (CTSI), Modified CT Severity Index (MCTSI), and Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) for Severity Parameters

Severity Parameter	CTSI	MCTSI	APACHE II
ICU stay	0.81 (0.75–0.87)	0.84 (0.79–0.89)	0.84 (0.78–0.88)
Need for intervention	0.94 (0.90–0.97)	0.92 (0.88–0.96)	0.74 (0.67–0.80)
Persistent organ failure	0.85 (0.79–0.90)	0.85 (0.79–0.90)	0.90 (0.85–0.94)
Pancreatic infection	0.92 (0.87–0.95)	0.91 (0.86–0.95)	0.67 (0.59–0.73)
Clinically severe acute pancreatitis	0.87 (0.82–0.92)	0.87 (0.82–0.92)	0.82 (0.76–0.87)
Death	0.78 (0.72–0.84)	0.79 (0.73–0.84)	0.89 (0.84–0.93)

Note—Data are presented with 95% CI in parentheses.

Correlation of All Scoring Indexes With Severity Parameters

When comparing the CT scoring indexes and APACHE II, no statistically significant differences were found for mortality, ICU stay, persistent organ failure, and clinical severity of AP. Both CT scoring indexes more accurately correlated with pancreatic infection compared with APACHE II, albeit without reaching statistical significance (for CTSI: $p = 0.04$, for MCTSI: $p = 0.06$) (Fig. 2).

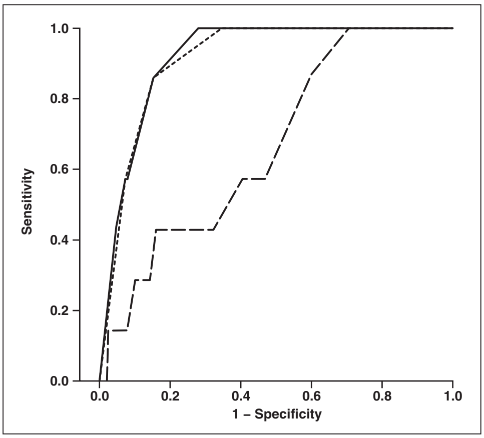

FIG. 2. Graph shows receiver operating characteristic curve for pancreatic infection. Solid line indicates CT severity index (CTSI), dotted line indicates modified CTSI, and dashed line indicates Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) index.

Compared with APACHE II, the CTSI significantly better correlated with the need for intervention ($p = 0.006$), whereas the MCTSI did not reach statistical significance ($p = 0.01$) (Fig. 3). No major changes in results were observed when excluding the transferred patients, except that statistical significance was reached for both CT scoring systems compared with APACHE II for the need for intervention (data not shown).

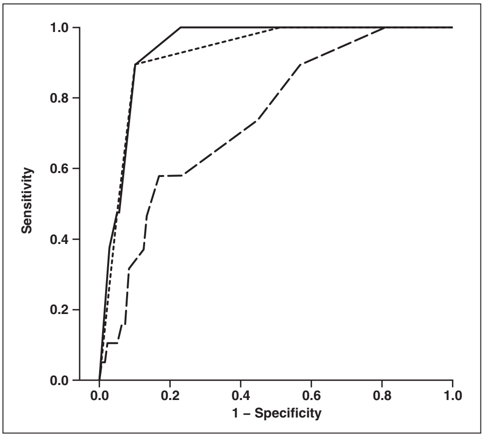

FIG. 3. Graph shows receiver operating characteristic curve for need for intervention. Solid line indicates CT severity index (CTSI), dotted line indicates modified CTSI, and dashed line indicates Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) index.

DISCUSSION

In this study on the comparative evaluation of MCTSI versus CTSI, we did not detect any statistically significant differences between the two CT scoring systems with regard to all the studied severity parameters. Both the MCTSI and CTSI were significantly associated with all severity parameters evaluated and showed excellent interobserver agreement. Furthermore, compared with APACHE II, both CT scoring systems more accurately correlated with pancreatic infection and the need for intervention and showed higher accuracy for diagnosing clinically severe disease.

In the initial study by Mortele et al. [4], a better correlation was observed between the MCTSI and the development of organ failure and length of hospital stay in comparison with the CTSI. Our present study did not reproduce these prior results. The differences observed may be due to differences in criteria for organ failure and clinically severe AP (the current study used criteria in accordance with the most updated revised Atlanta Classification). Also, the current study evaluated a larger number of patients, including larger proportion of patients with clinically severe AP, and used discrimination analysis, which is regarded as more accurate for comparing and assessing the diagnostic accuracy of prognostic scoring systems [10].

Both CT scoring systems yielded excellent interobserver agreement among two experienced readers. The MCTSI could potentially be further improved by using a simplified MCTSI in which extrapancreatic complications can be restricted to only the presence of pleural effusion or ascites with similar prognostic value in our post hoc analysis. This is supported by the fact that only two cases received points for extrapancreatic complications in the absence of pleural effusion or ascites. However, further prospective studies are needed to validate this observation. In light of the results of this study, there is no obvious reason to use one CT scoring system over the other. However, the MCTSI (especially by using the simplified MCTSI) may have better interobserver agreement among less-experienced readers. Future studies should be performed to elucidate this hypothesis.

In 1990, Balthazar et al. [3] introduced the CT severity index for assessment of AP, which correlated well with morbidity, mortality, and length of hospital stay. Although several studies reported a strong correlation between the CTSI and the clinical severity of AP [11–15], other studies have not corroborated these findings [16–19]. A few studies have noted a significant relationship between CTSI and mortality [11, 14, 20], whereas De Waele and colleagues [16] did not observe a similar relationship. Leung et al. [11] and Chatzicostas et al. [13] noted a strong association between CTSI and development of systemic complications, including organ failure; however, other investigators did not reach the same conclusions [19, 21, 22]. The strong relationship between the development of local complications and the CTSI score has been confirmed in many studies [11–14, 19–21], except for one study [22]. The current study again corroborates this association. In fact, compared with APACHE II, the two CT scoring systems correlated better with pancreatic infection and the need for intervention. Previous studies compared the CTSI and APACHE II in assessing the clinical severity of AP [11–13, 19, 21]. In line with the results of the current study, prior studies also reported a better performance of the APACHE II for assessing systemic complications and organ failure [13, 19, 21]. This is to be expected because the APACHE II scoring system gauges the physiologic response of the patient to the inflammatory cascade in AP, which drives systemic complications, whereas CT assesses the morphologic changes that can result in local complications. However, the APACHE II score contains many variables, limiting its use in clinical practice. The observed discrepancies between prior studies may relate to the absence of an accurate distinction between predicted severe disease (i.e., predictive scoring systems) and actual clinical severity of pancreatitis (i.e., clinical endpoints, such as mortality or persistent organ failure) as well as variation in the definitions of severe AP, systemic complications, and organ failure. Furthermore, differences in treatment regimes and health care practices among institutions could account for the difference in length of hospitalization and ICU stay. Uniformity in definitions in a complex disease, such as AP, is essential for comparing interinstitutional data [1, 23]. Therefore, the current study used definitions from the recently revised Atlanta Classification [8]. By using these updated definitions, the current study confirmed the earlier observations by Balthazar et al. [3] and Mortele et al. [4] and showed a significant association between the CT scoring systems and clinical severity of disease and all severity parameters.

Similar to the original studies from Balthazar et al. [3] and Mortele et al. [4], who designed the scoring systems studied, we used a 7-day interval for correlating imaging scores to clinical severity parameters. This study was not designed to predict clinical outcome parameters because some outcome parameters are often present at the time of examination (i.e., organ failure, which is the most important determinant of outcome in AP and is often present in the first few days of hospitalization in patients with clinically severe AP). We included contrast-enhanced MRI in our study because recent studies have shown that MRI has comparable diagnostic accuracy in assessing morphologic severity of AP [24, 25]. Patients who underwent unenhanced MRI, however, were not included because pancreatic parenchymal necrosis, which is part of both the CTSI and MCTSI, cannot reliably be assessed without the administration of gadolinium.

This study has one important limitation that is shared by many radiologic studies of AP. Although the data of all patients were prospectively gathered, not all patients who were diagnosed with AP underwent contrast-enhanced CT or MRI within 1 week of the onset of symptoms. Apparently, a proportion of patients with AP have either mild symptoms, obviating imaging, or are unable to undergo imaging studies because of their condition. For this reason, our study may appear biased toward more severe AP. However, all studies will contend with this topic because patients with very mild symptoms do not require cross-sectional imaging for diagnosis or management of their condition.

In conclusion, our study did not detect any significant differences between the CTSI and MCTSI in evaluating the severity of AP. Furthermore, this study showed that clinical scoring systems do not obviate cross-sectional imaging in the evaluation of AP. Clinical scoring systems accurately correlate with systemic complications and mortality, but radiologic scoring systems more accurately diagnose clinically severe disease and better correlate with pancreatic infection and the need for intervention.

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9

A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis

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ABSTRACT

Objectives: The early identification of clinically severe acute pancreatitis (AP) is critical for the triage and treatment of patients. The aim of this study was to compare the accuracy of computed tomography (CT) and clinical scoring systems for predicting the severity of AP on admission.

Methods: Demographic, clinical, and laboratory data of all consecutive patients with a primary diagnosis of AP during a two-and-half-year period was prospectively collected for this study. A retrospective analysis of the abdominal CT data was performed. Seven CT scoring systems (CT severity index (CTSI), modified CT severity index (MCTSI), pancreatic size index (PSI), extrapancreatic score (EP), 'extrapancreatic inflammation on CT' score (EPIC), 'mesenteric oedema and peritoneal fluid' score (MOP), and Balthazar grade) as well as two clinical scoring systems: Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II and Bedside Index for Severity in AP (BISAP) were comparatively evaluated with regard to their ability to predict the severity of AP on admission (first 24h of hospitalization).

Clinically severe AP was defined as one or more of the following: mortality, persistent organ failure and/or the presence of local pancreatic complications that require intervention. All CT scans were reviewed in consensus by two radiologists, each blinded to patient outcome. The accuracy of each imaging and clinical scoring system for predicting the severity of AP was assessed using receiver operating curve analysis.

Results: Of 346 consecutive episodes of AP, there were 159 (46%) episodes in 150 patients (84 men, 66 women; mean age, 54 years; age range, 21–91 years) who were evaluated with a contrast-enhanced CT scan (n = 131 episodes) or an unenhanced CT scan (n = 28 episodes) on the first day of admission. Clinically severe AP was diagnosed in 29/159 (18%) episodes; 9 (6%) patients died. Overall, the Balthazar grading system (any CT technique) and CTSI (contrast-enhanced CT only) demonstrated the highest accuracy among the CT scoring systems for predicting severity, but this was not statistically significant. There were no statistically significant differences between the predictive accuracies of CT and clinical scoring systems.

Conclusions: The predictive accuracy of CT scoring systems for severity of AP is similar to clinical scoring systems. Hence, a CT on admission solely for severity assessment in AP is not recommended.

INTRODUCTION

Acute pancreatitis (AP) is a complex disease characterized by a variable clinical course. AP can vary from a mild self-limited disease with only minimal or transient systemic manifestations in approximately 80–90% of patients, to a clinically severe form in 10–20% with local and systemic complications (1). The identification of patients with clinically severe AP is important for several reasons: first, these patients may benefit from transfer to an intermediate or intensive care unit, where they can receive aggressive fluid resuscitation and be closely monitored for the development of organ failure. Second, these patients may benefit from targeted therapy, i.e., enteral feeding, endoscopic sphincterotomy, or antibiotics (1,2). Finally, severity stratification is important when reporting and evaluating the results of clinical trials in AP. The characterization of high-risk groups of patients is critical for the appropriate comparison of management strategies between institutions (1,3).

There are several clinical and laboratory prognostic systems currently used to assess and predict the severity of AP with variable accuracy (3,4). Besides assessment of relevant clinical and biochemical parameters in AP, in many centers, it is standard practice to obtain a computed tomography (CT) scan on admission (i.e., within 24h of hospitalization), not only for diagnostic purposes but also for assessing the severity of disease. The severity of AP by CT imaging can be evaluated using unenhanced or contrast-enhanced CT studies. Unenhanced CT scoring systems evaluate the extent of pancreatic and peripancreatic inflammatory changes (Balthazar grade (5) and 'pancreatic size index' or PSI (6)) or evaluate both peripancreatic inflammatory changes and extrapancreatic complications ('mesenteric oedema and peritoneal fluid' or MOP score (7), 'extrapancreatic' or EP score (8), and the more recently developed 'extrapancreatic inflammation on CT' or EPIC score (9)). In addition, there are two CT scoring systems that require the use of intravenous contrast agents to determine the presence and extent of pancreatic parenchymal necrosis. The 'CT severity index' or CTSI is a numerical scoring system combining the quantification of extrapancreatic inflammation with the extent of pancreatic necrosis (10). Mortele *et al.* (11) proposed a 'modified CTSI' or MCTSI, which, in addition to the CTSI, assigns points for extrapancreatic complications (vascular, gastrointestinal and extrapancreatic parenchymal complications as well as the presence of pleural effusion and/ or ascites).

Although many studies have demonstrated a correlation between morphologic severity according to CT scoring systems and clinical disease severity, only five utilized data from "early" CT scans, defined as those obtained within 24h of admission to the hospital (8,9,12–14). In addition to methodological shortcomings, limitations of these prior studies are that no comparison of the accuracy of the existing CT scoring systems was performed and no comparative assessment was done between the CT scoring systems and clinical scoring systems such as the Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II (15) and the recently developed and validated Bedside Index for Severity in AP (BISAP) (16–18).

The aim of this study is to compare the accuracy of seven different existing CT scoring systems in predicting the severity of AP on the first day of admission. The secondary aim is to assess whether these CT scoring systems are superior to two commonly employed clinical scoring systems.

METHODS

The demographic, clinical, and laboratory data of all consecutive patients with a primary diagnosis of AP admitted or transferred to our institution during a 2.5-year period was prospectively collected for this study. A retrospective analysis of this prospectively collected clinical database was performed. Institutional review board approval was obtained for this study, and written informed consent for collecting data during hospitalization was obtained from all patients. AP was defined as two or more of the following: characteristic abdominal pain; serum amylase and/or lipase levels three or more times the upper limit of normal (i.e., >210 and 180 U/l, respectively); and/or an imaging study (CT or magnetic resonance imaging) demonstrating changes consistent with AP (19). The day of admission was defined as the first 24h of hospitalization in our institution or in the referring hospital.

For all episodes, appropriate clinical data were recorded prospectively by two authors (V.K.S. and K.R.), who were unaware of the CT scores, to permit calculation of the APACHE-II, BISAP, and Charlson Comorbidity Index scores. The decision to obtain a CT scan was based on the clinical discretion of the evaluating physician (**Figure 1**). All CT scans from outside hospitals were retrieved and reviewed soft copy using DICOM viewer software (DicomWorks, version 1.3.5, Lyon, France). The remainder of CT scans, performed at our institution, was reviewed on PACS workstations (Centricity GE, Milwaukee, WI). Two radiologists retrospectively reviewed all CT studies and were unaware of patient outcomes. **Table 1** details the CT parameters that were evaluated for the study cohort.

The following parameters were collected for each episode of AP: in-hospital mortality, length of hospital stay, admission to and length of intensive care unit stay, presence and duration of organ failure (transient; < 48h and persistent; > 48h), pancreatic infection (infection of pancreatic and/or peripancreatic necrosis), and need for intervention (endoscopic, percutaneous drainage, and/or surgical necrosectomy). Clinically severe AP was defined as one or more of the following: mortality, persistent organ failure and/or the presence of local pancreatic complications that require intervention (endoscopic or radiologic drainage or surgical necrosectomy). This definition is in accordance with the most updated revised Atlanta Classification (20). The principle distinction between the new and former definition of clinical severity is that the mere presence of pancreatic parenchymal necrosis, peripancreatic collections, or organ failure is not regarded as clinically severe disease, unless organ failure exceeds 48h in duration or complications of pancreatic necrosis or peripancreatic collections occur, which require active intervention. Organ failure was defined as a score of ≥2 in one or more of the three (respiratory, renal, and cardiovascular) organ systems of the modified Marshall score (20,21).

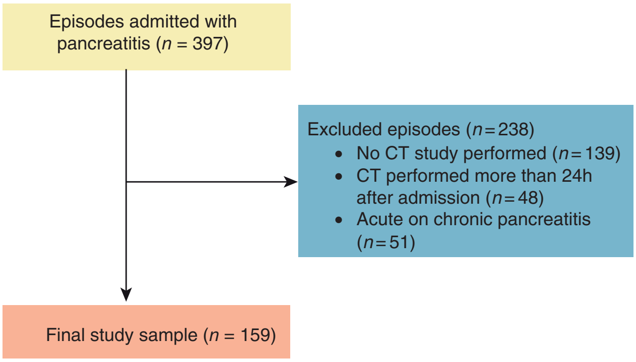

FIGURE 1 . Flowchart outlines the selection of episodes with pancreatitis. Data in parentheses are numbers of episodes.

TABLE 1. Computed tomography parameters evaluated

Pancreatic features
Subjective pancreatic enlargement (no, yes)
Pancreatic size index[a]
Pancreatic parenchymal necrosis (no, < 30%, 30–50%, > 50%, not applicable)
Peripancreatic features
Peripancreatic fat stranding (no, partial, entire)
Peripancreatic fluid collection (no, one location, two or more locations)
Perirenal edema (no, yes)
Mesenteric inflammation (no, yes)
Extrapancreatic features
Pleural effusion (no, unilateral, bilateral)
Ascites (no, one location, two or more locations)[b]
Vascular complications (no, yes, not applicable)
(Venous thrombosis, hemorrhage, arterial pseudoaneurysm)
Extrapancreatic parenchymal complications (no, yes, not applicable)
(Infarction, hemorrhage, subcapsular fluid collection)
Gastrointestinal complications (no, yes)
(Ileus, signs of ischemia, perforation, marked bowel wall thickening, intramural fluid collection)

[a] Pancreatic size index defined as multiplication of maximum anteroposterior measurement of the pancreatic head and body. A score of < 10 cm^2 is regarded as predicted mild pancreatitis and ≥10 cm^2 is regarded as predicted severe pancreatitis (6).
[b] Ascites in either one of these locations: perihepatic, perisplenic, interloop, or in pelvis (9).

Statistical analysis

Descriptive statistics were used for baseline characteristics, outcomes, and CT parameters. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for individual scoring systems. Also, for APACHE-II we analyzed these values using an accepted and standard cutoff value of 8 or more. The diagnostic accuracy of each scoring system for mortality and clinical severity were assessed using the area under the receiver operating characteristic curve (AUC) with standard error and 95% confidence intervals (CIs). Pairwise comparisons of AUCs were assessed using difference between areas, 95% CI and *P* values. The comparisons of the AUCs were performed using an approach described by Hanley and McNeil (22). To rule out potential bias introduced by the inclusion of transferred patients, receiver operating characteristic curve (ROC) analysis was also performed in the non-transferred group. All statistical analysis was performed using SAS v.9.1 (SAS, Cary, NC), SPSS v15.0 (SPSS, Chicago, IL), and MedCalc v.10.4.3.0 (MedCalc, Mariakerke, Belgium).

RESULTS

Patient characteristics

During the study period there were 346 episodes of AP in 307 patients and 51 episodes of acute on chronic pancreatitis (the latter were excluded from analysis). Among 346 episodes of AP, there were 159 (46%) episodes in 150 patients in whom a CT (contrast-enhanced CT in 131 episodes, unenhanced CT in 28 episodes) was performed on admission; in 30 (19%) episodes, the CT scan was performed for confirmation of the diagnosis, while in 129 (81%) episodes for assessing severity of AP. The 159 episodes of AP in which an early CT scan was performed constitute our study cohort. The additional 187 episodes in which no (n = 139) or delayed (n = 48) CT imaging was performed, were excluded from the study. In 131 episodes, a contrast-enhanced CT was performed permitting the assessment of all seven CT scoring systems; Balthazar grade, CTSI, MCTSI, EP score, EPIC score, MOP score, and PSI. In 28 episodes, only an unenhanced CT scan was performed, allowing the assessment of only five of the seven CT scoring systems.

The median age of patients was 54 years (range 21–91) with 84 men and 66 women. Etiologies of AP included gallstones in 48 (30%) episodes, miscellaneous (e.g., hypertriglyceridemia, hereditary, and post-endoscopic retrograde cholangiopancreatography) in 38 (24%) episodes, alcohol in 34 (21%) episodes, idiopathic in 27 (17%) episodes, and drug-induced in 12 (8%) episodes. One hundred and thirty episodes (82%) were labeled as mild AP and 29 episodes (18%) as clinically severe AP (**Table 2**). In 16 episodes, the lack of enhancement of pancreatic parenchyma was noted on contrast-enhanced CT on the day of admission, indicating acute necrotizing pancreatitis (four of whom were categorized as having clinically mild disease). On follow-up imaging, 13 more episodes were identified, in whom necrotizing pancreatitis was detected (three of them had an unenhanced CT on admission). The lack of enhancement on follow-up imaging was not used for data analysis. In all episodes, early CT did not reveal an alternative diagnosis or local complication that changed clinical management. A total of 14 (9%) episodes required intervention for local complications: 8 underwent surgical debridement (three with prior percutaneous catheter drainage), and percutaneous catheter drainage was performed as the only treatment in 6. Persistent organ failure occurred in 21 (13%) episodes. Infection of pancreatic and/or extrapancreatic necrosis occurred in five (3%) episodes. A total of 9 out of 150 patients (6%) died during hospitalization. One patient with predicted mild CT scores died due to the presence of significant co-morbid diseases (history of lymphoma and graft versus host disease).

TABLE 2. Severity outcomes for the study cohort (n = 159 episodes)

Outcome	*N* = 159
Death	9 (6)
Length of hospital stay	5 [3, 11] range 0 –74
ICU admission	37 (23)
Length of ICU stay (in days)	6 [2, 16] range 0 –32
Need for intervention	14 (9)
PCD	9
Surgical necrosectomy	8
Organ failure	
Transient	23 (14.5)
Persistent	21 (13.2)
No	115 (72.3)
Pancreatic infection	5 (3)
Clinically severe acute pancreatitis	29 (18)
Charlson Comorbidity Index[a]	2 [0, 4] range 0 – 11
APACHE-II	8 [5, 13] range 0 – 33

APACHE-II, Acute Physiology, Age, and Chronic Health Evaluation-II; ICU, intensive care unit; PCD, percutaneous catheter drainage.
[a] Age adjusted.
Frequency (%), median [Q1, Q3].

Comparison of scoring indices in predicting clinical severity

On the basis of highest sensitivity and specificity values generated from the ROC curves, the following cutoffs were selected for predicting clinically severe disease: CTSI ≥4, MCTSI ≥6, Balthazar grade ≥5, EPIC score ≥3, EP score ≥3, MOP score ≥2, PSI ≥1, APACHE-II ≥10, and BISAP ≥3.

Figure 2 and **Table 3** show the comparisons of ROC curves for clinically severe AP among all scoring systems in all episodes who underwent a CT scan (*n* = 159) and in episodes who underwent only a contrast-enhanced CT scan (*n* = 131). Although the CTSI demonstrated the highest accuracy for predicting clinically severe AP among the 131 cases who underwent contrast-enhanced CT (AUC 0.88; 95% CI: 0.82–0.93), no statistically significant pairwise differences were observed between the CTSI and the other CT scoring systems, except for PSI (*P* = 0.014). Balthazar grade demonstrated the highest accuracy for clinically severe AP for all 159 episodes (AUC 0.79; 95% CI: 0.72–0.85). However, no statistically significant differences were observed between the Balthazar grade and the other CT scoring systems. Also, no statistically significant differences were found between the CT and clinical scoring systems with highest AUC for clinical severity. No significant changes in results were observed when excluding the transferred patients (data not shown).

Comparison of scoring indices in predicting mortality

On the basis of highest sensitivity and specificity values generated from the ROC curves, the following cutoffs were selected for predicting mortality: CTSI ≥4, MCTSI ≥4, Balthazar grade ≥5, EPIC score ≥3, EP score ≥3, MOP score ≥1, PSI ≥1, APACHE-II ≥17, and BISAP ≥3. **Table 4** shows the comparisons of ROC curves for mortality among all scoring systems in all episodes in which a CT scan was performed and in those episodes that only a contrast-enhanced CT was performed. Among the CT indices, Balthazar grade had the highest AUC for mortality in both groups (AUC 0.81; 95% CI: 0.74–0.88 and AUC 0.79; 95% CI: 0.72–0.85, respectively). In the study cohort, the APACHE-II score performed best among all studied indices in both groups of patients (AUC 0.91; 95% CI: 0.85–0.95 and AUC 0.91; 95% CI: 0.86–0.95, respectively). No statistically significant differences were observed between Balthazar grade and the other CT scoring systems and between Balthazar grade and the clinical scoring system with the highest accuracy for predicting mortality (APACHE-II). Again, no significant changes in results were observed when excluding the transferred patients (data not shown). The sensitivity, specificity, positive predictive value, and negative predictive value of different scoring systems in predicting clinical severity and mortality are shown in **Table 5**. When using a fixed cutoff value for APACHE-II for predicting clinically severe disease and mortality (i.e., the universally accepted value of 8 or more) there was an increase of the sensitivity and negative predictive value and concomitant decrease in specificity and positive predictive value compared with the optimal cutoffs derived from the ROC curves (**Table 5**). The AUC value of APACHE-II for both cutoff values was the same and, again, no significant changes were seen between CT scoring system and APACHE-II.

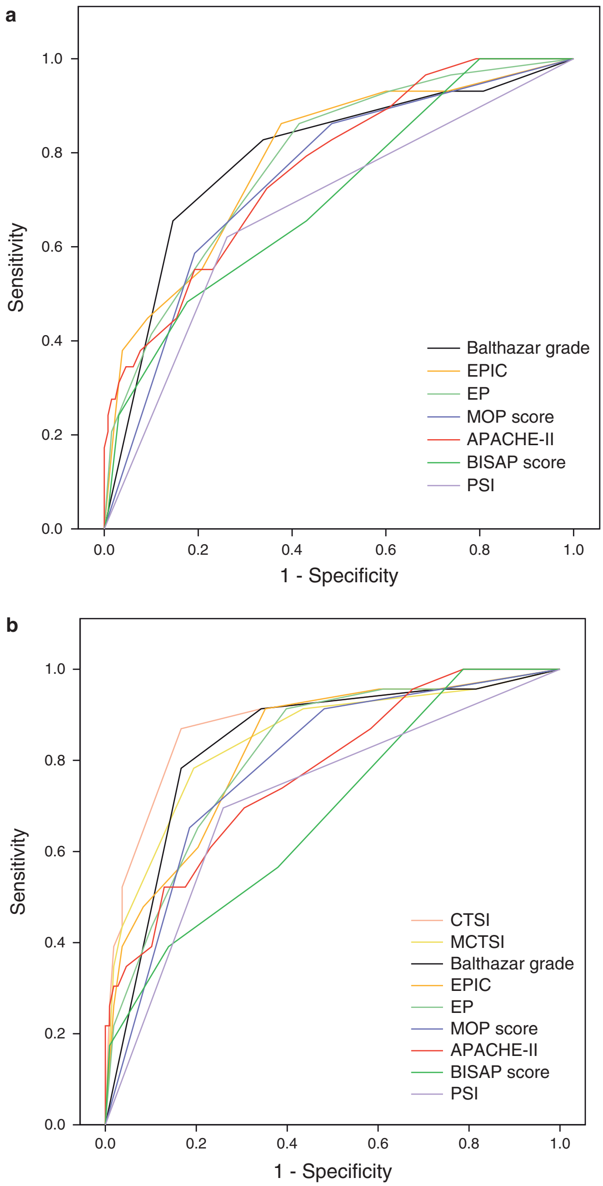

FIGURE 2. AUC comparison of computed tomography (CT) and clinical scoring systems for predicting clinical severity. **(A)** Area under the receiver operating curve (AUC) comparison of all scoring systems in 159 episodes with either contrast-enhanced CT (CECT) or unenhanced CT (UECT) in predicting severe acute pancreatitis (SAP). No significant differences between the CT and clinical scoring systems are noted. **(B)** AUC comparison of all scoring systems in 131 episodes with only CECT in predicting SAP. No significant differences between the CT and clinical scoring systems are noted. APACHE-II, Acute Physiology, Age, and Chronic Health Evaluation-II; BISAP, Bedside Index for Severity in Acute Pancreatitis; CTSI, CT severity index; EP, extrapancreatic score; EPIC, extrapancreatic inflammation on CT score; MCTSI, modified CT severity index; MOP, mesenteric oedema and peritoneal fluid score; PSI, pancreatic size index.

TABLE 3. AUC of different scoring systems in predicting clinical severity

Scoring system	CECT (*n* = 131)	CECT and UECT (*n* = 159)
Clinically severe AP	***N* = 23 AUC (95% CI)**	***N* = 29 AUC (95% CI)**
MCTSI	0.85 (0.77 – 0.90)	
CTSI	0.88 (0.82 – 0.93)	
Balthazar	0.84 (0.76 – 0.90)	0.79 (0.72 – 0.85)
EPIC score	0.83 (0.75 – 0.89)	0.79 (0.71 – 0.84)
EP score	0.81 (0.74 – 0.88)	0.78 (0.71 – 0.85)
MOP score	0.79 (0.71 – 0.86)	0.75 (0.67 – 0.81)
PSI	0.72 (0.63 – 0.79)	0.68 (0.60 – 0.75)
APACHE-II	0.77 (0.69 – 0.84)	0.77 (0.70 – 0.83)
BISAP	0.68 (0.60 – 0.76)	0.71 (0.63 – 0.78)

AP, acute pancreatitis; APACHE–II, Acute Physiology, Age, and Chronic Health Evaluation-II; AUC, area under curve; BISAP, Bedside Index for Severity in Acute Pancreatitis; CECT, contrast-enhanced CT; CI, confidence interval; CTSI, CT severity index; EP, extrapancreatic score; EPIC, extrapancreatic inflammation on CT score; MCTSI, modified CT severity index; MOP, mesenteric oedema and peritoneal fluid score; PSI, pancreatic size index; UECT, unenhanced CT.

TABLE 4. AUC of different scoring systems in predicting mortality

Scoring system	CECT (*n* = 131)	CECT and UECT (*n* = 159)
Mortality	***N* = 7 AUC (95% CI)**	***N* = 9 AUC (95% CI)**
MCTSI	0.72 (0.64 – 0.80)	
CTSI	0.80 (0.72 – 0.86)	
Balthazar	0.81 (0.74 – 0.88)	0.79 (0.72 – 0.85)
EPIC score	0.79 (0.71 – 0.86)	0.77 (0.70 – 0.83)
EP score	0.75 (0.66 – 0.82)	0.73 (0.65 – 0.80)
MOP score	0.72 (0.63 – 0.79)	0.68 (0.60 – 0.76)
PSI	0.70 (0.61 – 0.78)	0.74 (0.66 – 0.81)
APACHE-II	0.91 (0.85 – 0.95)	0.91 (0.86 – 0.95)
BISAP	0.88 (0.81 – 0.93)	0.88 (0.81 – 0.92)

APACHE –II, Acute Physiology, Age, and Chronic Health Evaluation-II; AUC, area under curve; BISAP, Bedside Index for Severity in Acute Pancreatitis; CECT, contrast-enhanced CT; CI, confidence interval; CTSI, CT severity index; EP, extrapancreatic score; EPIC, extrapancreatic inflammation on CT score; MCTSI, modified CT severity index; MOP, mesenteric oedema and peritoneal fluid score; PSI, pancreatic size index; UECT, unenhanced CT.

TABLE 5. Sensitivity, specificity, PPV, NPV of different scoring systems in predicting clinical severity and mortality

%	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Clinical severity				
CTSI	87 (66 – 97)	83 (75 – 90)	53 (36 – 69)	97 (91 – 99)
MCTSI	78 (56 – 93)	81 (72 – 88)	46 (30 – 63)	95 (88 – 98)
Balthazar	66 (46 – 82)	85 (78 – 91)	50 (33 – 67)	92 (85 – 96)
EPIC score	86 (68 – 91)	62 (53 – 71)	34 (23 – 46)	95 (88 – 99)
EP score	86 (68 – 96)	58 (49 – 67)	32 (22 – 43)	95 (88 – 99)
MOP score	59 (39 – 76)	81 (73 – 87)	40 (26 – 57)	90 (83 – 95)
PSI	62 (42 – 79)	74 (65 – 81)	35 (22 – 49)	90 (82 – 95)
APACHE-II	72 (53 – 87)	65 (57 – 74)	32 (21 – 44)	91 (84 – 96)
APACHE-II[a]	83 (64 – 94)	52 (43 – 60)	28 (19 – 38)	93 (85 – 98)
BISAP	48 (29 – 67)	82 (75 – 88)	38 (22 – 55)	88 (81 – 93)
Mortality				
CTSI	86 (42 – 100)	74 (66 – 82)	16 (6 – 31)	99 (94 – 100)
MCTSI	86 (42 – 100)	50 (41 – 59)	9 (3 – 18)	98 (91 – 100)
Balthazar	78 (40 – 97)	79 (72 – 86)	18 (8 – 34)	98 (94 – 100)
EPIC score	89 (52 – 100)	56 (48 – 64)	11 (5 – 20)	99 (94 – 100)
EP score	89 (52 – 100)	53 (44 – 61)	10 (4 – 19)	99 (93 – 100)
MOP score	89 (52 – 100)	47 (38 – 55)	9 (4 – 17)	99 (92 – 100)
PSI	78 (40 – 97)	70 (62 – 77)	13 (6 – 26)	98 (93 – 100)
APACHE-II	78 (40 – 97)	94 (89 – 97)	44 (20 – 70)	99 (95 – 100)
APACHE-II[a]	100 (66 – 100)	48 (40 – 56)	10 (5 – 19)	100 (95 – 100)
BISAP	89 (52 – 100)	81 (73 – 87)	22 (10 – 38)	99 (96 – 100)

APACHE –II, Acute Physiology, Age, and Chronic Health Evaluation-II; AUC, area under curve; BISAP, Bedside Index for Severity in Acute Pancreatitis; CECT, contrast- enhanced CT; CI, confidence interval; CTSI, CT severity index; EP, extrapancreatic score; EPIC, extrapancreatic inflammation on CT score; MCTSI, modified CT severity index; MOP, mesenteric oedema and peritoneal fluid score; NPV, negative predictive value; PPV, positive predictive value; PSI, pancreatic size index; UECT, unenhanced CT.

[a] Sensitivity, specificity, PPV, and NPV when using a universal accepted cutoff value of APACHE-II 8 or more.

DISCUSSION

Since the 1970s, a continuous effort has been made to develop a simple, accurate, and widely available prognostic scoring system in AP to predict which patients are at highest risk of developing clinically severe AP and may require intensive therapy (3). Balthazar *et al.* (5) were among the first who devised a radiologic scoring system for AP in 1985. Since then, several other groups of investigators have also developed CT scoring systems. Although all these scoring systems have been shown to correlate with morbidity and mortality, it remains difficult to accurately identify individual patients who develop clinically severe disease on admission or early in the course of their hospitalization (3,4). Results from this study corroborate this observation. This study did not detect any significant differences between the studied CT scoring systems. There was no advantage of performing a CT on admission as an independent predictor over the more easily obtainable clinical scoring systems in terms of accuracy in predicting clinically severe AP and mortality.

There are several potential explanations for the observed moderate accuracy for clinical severity and mortality using CT scoring systems. First, the anatomic extent of pancreatic inflammation and the size and volume of peripancreatic fluid collections are not included in any of the studied scoring systems; both peripancreatic fat stranding and fluid collections can range from discrete to extensive in magnitude, but are accorded equal points in the studied scoring systems. Second, some patients initially predicted to have mild AP may, nonetheless, progress to clinically severe AP over the initial 48h of hospitalization along with worsening morphologic changes on imaging. Third, pancreatic parenchymal necrosis may be unrecognized on an early CT performed within 24h of admission (38% in the present study). Pancreatic parenchymal necrosis has been shown to correlate with the development of organ failure and local complications (primarily infection of necrosis) that require intervention (23–25). Finally, CT depicts morphologic changes, which are not always clinically relevant and do not always correlate with clinical severity of disease. Predicted mild AP on early CT (i.e., low CT scores) does not imply that the patient will not develop clinically severe AP, especially when significant baseline co-morbidity is present. This limitation is demonstrated in our study as one patient died with predicted mild scores who had significant co-morbid disease that was not accounted for in any CT scoring system. In this patient, it is conceivable that the mild local pancreatic inflammation acted as a trigger for further dysfunction of already impaired organ systems culminating in an adverse outcome. Conversely, patients with severe morphologic findings on CT may run a clinically mild course. A substantial number of patients with pancreatic necrosis established on admission CT (25% in the present study and 38% in a study by Casas *et al.* (12)) did not develop clinically severe disease. It remains poorly understood why different clinical courses are observed in patients with significant pancreatic parenchymal necrosis. In both groups of patients, CT scoring systems will either under- or overestimate the clinical severity of pancreatitis. The overall limitation of CT and clinical prognostic scoring systems is the fact that they were devised to identify groups of high-risk patients and not individual patients (3).

In addition, scoring systems work best at the extremes of the spectrum (i.e., high negative or positive predictive value in patients with very low or high scores), whereas the performance of these scoring systems is only moderate in intermediate scores. This explains the overall moderate accuracy for predictive scoring systems, limiting their use in predicting a severe attack in any single patient.

In five previous studies, the predictive value of early CT was evaluated on admission, all showing a moderate positive correlation between CT score and mortality and morbidity (8,9,12–14). These studies either evaluated small study populations (8,9,13), focused on selective subgroups of patients (e.g., only alcohol-induced pancreatitis) (8), evaluated only one CT scoring system (12) or one single CT parameter (i.e., extent of pancreatic necrosis (13) or presence of peripancreatic fluid collections (14)), and/ or included a high incidence of clinically severe disease (9,13). A comparison of our results with those of previously published studies is difficult for several more reasons. First, no clear definition of clinical severity of disease has been consistently applied, whereas the present study used the most updated definition of clinical severity as proposed in the revised Atlanta Classification. Hitherto, this has been recognized as a major limitation for comparison of results between institutions (1,26). Second, different threshold values, as opposed to ROC curve analysis, were used to predict clinical severity. It is generally acknowledged that the overall performance of a test and comparison of prognostic scoring systems is best performed using ROC curve analysis (27), which was only performed in the study by De Waele *et al.* (9). Third, only one of these studies performed comparative analysis between the CT scoring systems (9) and no studies compared the radiologic systems with clinical scoring systems.

The timing of CT imaging in AP remains an important issue and has engendered significant debate. Many groups of investigators advocate that CT should be avoided in mild disease and should be reserved for those with a more complicated clinical course (28–30), whereas others advocate early CT for prognostication (31,32), or to assist with clinical decision making with regard to the initiation of antibiotic prophylaxis or other interventional procedures, such as continuous regional arterial infusion (2). In recent reports (33,34), however, the use of antibiotic prophylaxis in AP is no longer recommended and there is very limited evidence for early intervention by means of regional intra-arterial infusion and, therefore, generally not accepted as primary therapy in the initial management of AP (1,19).

Although this study highlights the prognostic accuracy of CT, we feel that a more judicious use of CT in AP is warranted for several reasons; AP is a costly disease with annual expenses exceeding 2 billion per year in the United States (35). In addition, CT is associated with significant radiation exposure (36,37) and several studies have shown the lack of correlation between imaging utilization and outcome (38,39). Finally, this study showed that early CT did not reveal any other diagnosis, did not reveal any local pancreatic complication, and underestimated the presence of parenchymal necrosis in a substantial number of patients. Hence, we recommend that CT studies should be reserved only for those patients with predicted severe AP by clinical assessment, for those who fail to improve clinically with conservative management or those in whom the diagnosis is unclear or a severe complication is suspected (such as bleeding, bowel ischemia, or perforation).

Our study had two limitations. First, not all patients admitted or transferred to our hospital underwent a CT on the day of admission. Instead, CT was performed based on the discretion of treating physician (primarily for severity assessment) and, therefore, our methodology reflects, in some respects, current clinical practice. Moreover, it would be difficult to justify performing a CT in all patients hospitalized with AP given the aforementioned high costs and radiation issues. Second, there were a relatively small number of severe cases. However, this study was the largest so far to compare the use of different CT and clinical prognostic scoring systems on the day of admission. In addition, the prevalence of mild and severe cases in our study (82% and 18%, respectively) is similar to the prevalence of clinical severity of AP commonly stated in the literature (1).

In conclusion, our study did not detect significant differences between any of the seven studied CT scoring systems in predicting mortality and clinical severity of AP. Moreover, CT scoring systems were not superior to the studied clinical scoring systems. There appears to be no advantage of performing a CT on admission for prognostic purposes compared with the simpler and more easily obtained clinical scoring systems and, therefore, obtaining a CT for assessment of severity on the day of admission is not recommended. Instead, from a resource utilization perspective and as a way of reducing radiation exposure in AP, when the diagnosis has been made on clinical grounds (abdominal pain and elevated serum amylase and/or lipase), severity and prognosis can initially be assessed by clinical scoring systems with imaging reserved in cases where the diagnosis is equivocal, in patients who have predicted severe AP by clinical assessment or who fail to improve clinically despite conservative therapy or when a life-threatening complication is suspected.

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Imaging Predictors

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ABSTRACT

Acute pancreatitis is a highly variable disease that varies in severity from mild interstitial or edematous pancreatitis to severe forms with considerable local and systemic complications that are associated with significant morbidity, mortality, and public health care impact. For more than four decades, several multifactorial scoring systems have been used to assess disease severity and predict the outcome and prognosis of acute pancreatitis. Early disease stratification is deemed important to identify patients at risk for severe acute pancreatitis early in the disease process, to guide patient triage and management, and to improve patient outcome. Scoring systems related to CT are the most studied imaging tests in acute pancreatitis. Since the introduction of CT for diagnosis and severity assessment of acute pancreatitis, many imaging-based systems have been developed. This chapter will review existing radiologic prognostic systems with their respective advantages and limitations and address key findings on cross-sectional imaging of acute pancreatitis, with an emphasis on the prognostic significance of specific findings that impact patient management.

INTRODUCTION

Acute pancreatitis is a common cause for hospitalization in the Western world. Fortunately, most patients with acute pancreatitis follow a mild clinical course without significant complications [1, 2]. Imaging in these patients is rarely necessary aside from establishing the cause of pancreatitis, i.e., an ultrasound on admission is often requested for assessment of biliary stones. However, about one-quarter of patients develop clinically severe acute pancreatitis accompanied by prolonged hospitalization with high morbidity and mortality rates [1–3]. These patients are responsible for most of the healthcare expenses in acute pancreatitis that include the need for repeated imaging. Despite increased knowledge of the pathophysiology and natural course of acute pancreatitis and notwithstanding the improvements in imaging techniques and critical care, mortality rates in severe acute pancreatitis have been unchanged. Given these differences in length of hospitalization and intensive care stay, the differences in morbidity and mortality and in healthcare costs, a continuous effort for more than four decades has been made to develop a prognostic multifactorial scoring system (based on clinical, biochemical, and/or imaging parameters) for accurate severity stratification, preferably during the first days of admission.

Early severity stratification is deemed important for several reasons. Identification of patients with the highest morbidity and mortality is critical because these patients may benefit most from timely transfer to the intensive care unit or tertiary referral centers for supportive treatment or for targeted therapy (i.e., endoscopic intervention or enteral feeding). In addition, stratification is essential for reliable interinstitutional comparison of new methods of therapy and for inclusion of patients in randomized trials [2, 4].

This chapter will review existing radiologic prognostic systems with their respective advantages and limitations and addresses imaging features of acute pancreatitis with an emphasis on the prognostic significance of specific findings that impacts patient management.

Overview of Imaging Modalities

Multidetector computed tomography (MDCT) is the most widely available imaging modality and is the standard for the evaluation of acute pancreatitis [2, 5]. Other imaging modalities that are used for evaluation of acute pancreatitis include endoscopic and transabdominal ultrasound and magnetic resonance imaging (MRI). Imaging in acute pancreatitis is performed for several reasons that include confirmation of the diagnosis, detection of gallstones or biliary obstruction, assessment of severity of disease, and evaluation of complications related to acute pancreatitis [5–7].

Ultrasound

Ultrasound has only limited value in the assessment of acute pancreatitis and its severity, because overlying bowel gas often obscures portions of the pancreas. However, ultrasound has a high sensitivity for detecting gallstones and is useful for follow-up of established pancreatic fluid collections [8].

Magnetic Resonance Imaging

The use of MRI in the assessment of acute pancreatitis and its complications is gaining increasing acceptance. Indeed, MRI offers similar diagnostic capabilities compared with CT with better depiction of stones in gallbladder or common bile duct and better evaluation of the pancreatico-biliary ductal system [8, 9]. Additionally, MRI is more accurate than CT in characterizing the content of peripancreatic collections that may aid in allowing appropriate drainage techniques to be used [10]. Disadvantages of MRI are its limited availability in an acute setting and that acquisition times are significantly longer than with MDCT.

Computed Tomography

MDCT is the primary imaging modality used in the evaluation of patients with acute pancreatitis. Morphologic changes of the pancreas and peripancreatic region are easily depicted on CT that allows for confirmation of the diagnosis, for assessment of disease severity, and for evaluation of local pancreatic and extrapancreatic complications [11]. A monophasic CT protocol after intravenous contrast administration is usually adequate for assessment of acute pancreatitis [12, 13]. Typically, scans are performed during the pancreatic phase (delay of 40–50 s) or portal venous phase (delay 60–70 s). Multi-phase studies are recommended in case of hemorrhage, ischemia, or suspicion of an arterial pseudoaneurysm [12, 13]. Major disadvantages of CECT remain the radiation exposure and the limited capability of differentiating fluid from necrotic material in peripancreatic collections [10].

Radiologic Scoring Systems

Scoring systems related to CT are the most studied imaging test in acute pancreatitis [14]. Since the introduction of CT for diagnosis and severity assessment of acute pancreatitis in the 1980s, many imaging-based systems have been developed. In this section, the most relevant scoring systems will be reviewed in order of year of development. Determinants of most radiologic scoring systems include pancreatic changes, peripancreatic features, and extrapancreatic features (Table 1). Severity assessment of acute pancreatitis by CT can be done using unenhanced (Schröder index, Balthazar grade, Pancreatic size index (PSI), MOP score, retroperitoneal extension grade, and EPIC score) or contrast-enhanced CT studies (CT severity index and Modified CT severity index).

TABLE 1 CT determinants that constitute radiologic scoring systems

Pancreatic features
Subjective pancreatic enlargement
Pancreatic size index (PSI)[a]
Pancreatic parenchymal necrosis (presence and extent)
Peripancreatic features
Peripancreatic fat stranding
Peripancreatic fluid collection (presence and number)
Perirenal edema
Mesenteric inflammation
Retroperitoneal extension
Extrapancreatic features
Pleural effusion (presence, uni-, bilateral)
Ascites (presence and number of locations)[b]
Vascular complications (venous thrombosis, hemorrhage, arterial pseudoaneurysm)
Extrapancreatic parenchymal complications (infarction, hemorrhage, subcapsular fluid collection)
Gastrointestinal complications (ileus, signs of ischemia, perforation, marked bowel wall thickening, intramural fluid collection)

[a] PSI defined as multiplication of maximum anteroposterior measurement of the pancreatic head and body. A score of <10 cm^2 is regarded as predicted mild pancreatitis and ≥ 10 cm^2 is regarded as predicted severe pancreatitis

[b] Ascites in either one of these locations: perihepatic, perisplenic, interloop, or in pelvis [41]

Schröder Index

In 1985, Kivisaari and Schröder were among the first to develop a CT scoring system for severity stratification in acute pancreatitis based on pancreatic and extrapancreatic findings [15]. The pancreatic CT findings include edema in part of the pancreas and edema of the entire pancreas. Extrapancreatic findings include peritoneal fluid, perirenal fat edema, mesenteric fat edema, pleural effusion, and bowel paralysis. Each of these findings was assigned one point with a maximum score of 7. A total score of <4 correlates with predicted mild acute pancreatitis, and a score of 4 or more with predicted severe acute pancreatitis. This scoring system is relatively easy to apply and practical even among patients with renal failure when no intravenous contrast medium agents can be administered. Limitations are that the presence of peritoneal fluid (especially in female patients) and perirenal fat edema can be a normal finding (especially in the elderly).

Balthazar Grade

In 1985, Balthazar and colleagues developed a CT grading system based on the presence of pancreatic and peripancreatic changes into five grades of severity, ranging from Grade A (normal pancreas) to Grade E (inflamed pancreas with two or more fluid collections) (Fig. 1) [16, 17]. In their original report, Grade A and B correlated with mild uncomplicated clinical course with no mortality, whereas Grade D and E signified severe disease with 54 % morbidity and 14 % mortality [16, 17]. These results have been confirmed in subsequent studies by different groups of investigators [18–20]. The advantages of the Balthazar grading system are that it can be applied at any point during the patient's hospitalization and requires no iodinated contrast medium. Limitations are the subjective assessment of pancreatic enlargement (corresponding to Grade B), the arbitrarily chosen distinction between peripancreatic inflammatory changes ("fat stranding") and a peripancreatic collection (Grade C and D, respectively), and the need for counting peripancreatic collections (differentiating Grade D from Grade E), all of which are associated with moderate interobserver agreement. Some authors maintain that Balthazar grading system simplifies the retroperitoneal compartment rather than acknowledging the different components that constitute the retroperitoneum [21]. Another shortcoming (put forth by Balthazar himself) is that peripancreatic fluid collections (Grade D and E) have a variable natural history; in their study 54 % resolved spontaneously, whereas 46 % became infected necessitating intervention [16, 22].

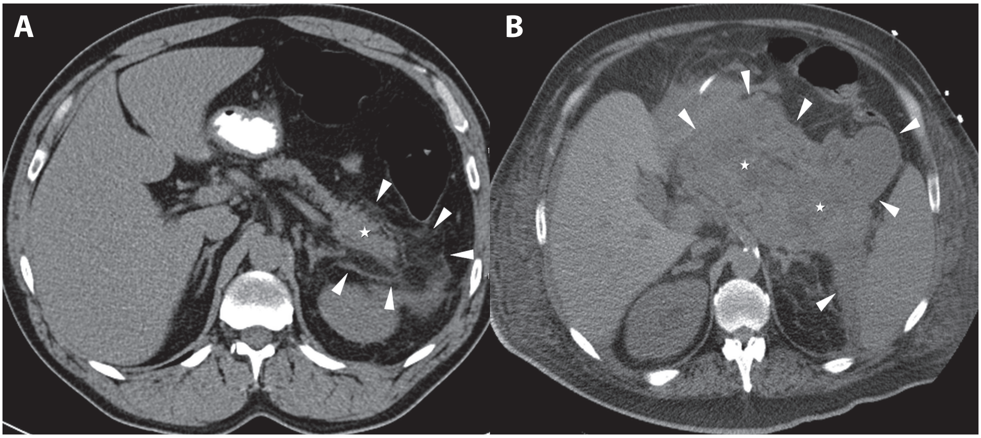

FIGURE 1 (A) A 35-year-old man with acute pancreatitis (Balthazar Grade C). Unenhanced CT shows a swollen pancreatic tail (white star) with peripancreatic fat stranding (arrowheads). **(B)** A 56-year-old man with acute pancreatitis (Balthazar Grade E). Unenhanced CT shows a heterogeneous pancreas (white stars) surrounded by multiple peripancreatic collections (arrowheads)

Pancreatic Size Index

The PSI was first introduced in 1989 by London and colleagues [23]. The PSI (in cm^2) is calculated by multiplying the maximum anteroposterior measurement of the head and body of the pancreas resulting in an objective assessment of pancreatic enlargement (as opposed to subjective assessment in other CT scoring systems, such as Schröder index, CT severity index [CTSI], and modified CT severity index [MCTSI]). By using a cut-off of 10 cm^2 the authors found a sensitivity of 71 % and specificity of 77 % for clinically severe attacks [23]. In several other studies these results were confirmed [24, 25]. The underlying theory behind the PSI is that with increasing degree of pancreatic insult, the resultant swelling of the pancreas releases more toxic cytokines and pancreatic enzymes in the systemic circulation and peripancreatic area, respectively. Advantage of the PSI is the evaluation of only one parameter. Like other CT scoring systems, PSI measurement does not require the administration of intravenous contrast medium. Main limitation is that normal values of pancreatic size may vary considerably according to age and previous attacks.

CT Severity Index

The advent of incremental dynamic bolus CT technique and faster scanning equipment in the early 1990s resulted in considerable improvement of imaging assessment of acute pancreatitis; the use of intravenous contrast medium enabled to differentiate interstitial pancreatitis (with intact capillary network and homogeneous enhancement) from necrotizing pancreatitis (with portions of pancreas failing to enhance) [22]. In 1990, Balthazar made his CT grading system more sophisticated by incorporating the presence and extent of parenchymal nonenhancement (corresponding to parenchymal necrosis) by using intravenous iodinated contrast medium [22]. The resulting CT scoring system (CT severity index or CTSI) combines the Balthazar grade (0–4 points) with the extent of pancreatic necrosis (0–6 points) on a 10-point severity scale (Table 2). The calculated CTSI can then be subdivided in three categories (CTSI 0–3, 4–6, and 7–10; corresponding to predicted mild, moderate, and severe disease, respectively) that have subsequent increases in morbidity and mortality (Fig. 6.2). In the original study, patients with predicted mild disease (CTSI 0–3) had 8 % morbidity and 3 % mortality (of note, no mortality occurred in patients with CTSI 0–2), patients with predicted moderate severe pancreatitis had 35 % morbidity and 6 % mortality, and patients with predicted severe disease (CTSI 7–10) had 92 % morbidity and 17 % mortality [22]. CTSI, of all radiologic scoring systems, is the most studied system, and many reports from different groups of investigators confirmed the utility of using CTSI in assessing patient outcomes [26–29]. However, some have found only a modest correlation between presence and extent of pancreatic necrosis and organ failure [30–32], between pancreatic necrosis and extrapancreatic parenchymal and vascular complications [33, 34], and between extent of parenchymal necrosis and clinical outcome (i.e., no significant differences in patient outcome are observed in patients with 30–50 % necrosis versus those with >50 % necrosis) [35]. Other limitations are the moderate interobserver agreement due to the specific categorization of the evaluation of pancreatic inflammation and necrosis and the need for intravenous contrast agent.

MOP Score

In 2003, King and co-authors tested a simple CT scoring system based on two CT features (mesenteric edema [MO] and peritoneal [P] fluid; resulting in the MOP score) in a cohort of patients [36]. MOP score correlated well with disease severity, especially when both features were present. This scoring system is appealing because it is simple and easy to evaluate even for non-radiologists, requiring no intravenous contrast medium. However, in the original study, patients were included of whom CT was performed up to 10 days after admission, limiting the predictive power of this scoring system.

TABLE 2 CT severity index

Characteristics	Points
Pancreatic inflammation	
Normal pancreas	0
Focal or diffuse enlargement of the pancreas	1
Peripancreatic inflammation	2
Single acute fluid collection	3
Two or more acute fluid collections	4
Pancreatic parenchymal necrosis	
None	0
Less than 30 %	2
Between 30 and 50 %	4
More than 50 %	6

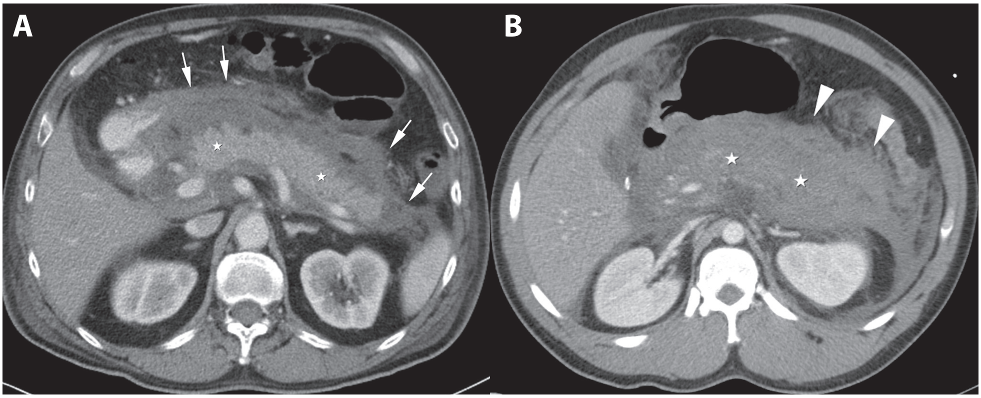

FIGURE 2 (A) A 41-year-old man with acute pancreatitis (CTSI 4). Contrast-enhanced CT shows a normal enhancing pancreatic parenchyma (white stars) with more than two peripancreatic collections (arrows). **(B)** A 32-year-old man with acute necrotizing pancreatitis (CTSI 10). Contrast-enhanced CT shows extensive pancreatic nonenhancement (white stars), representing pancreatic necrosis. More than 50 % of the pancreatic volume is involved in the necrotic process. Peripancreatic collections (acute necrotic collections) are present (arrowheads).

Modified CT Severity Index

In 2004, Mortele and colleagues modified the existing CTSI accounting for the presumed shortcomings of this scoring system by incorporating extrapancreatic complications in the assessment and by simplification of the evaluation of peripancreatic collections and extent of parenchymal necrosis (Fig. 3) [26]. In the original study including 66 patients, the MCTSI, compared with CTSI, more closely correlated with patient outcome (length of hospital stay, need for intervention, and organ failure) with similar interobserver agreement [26]. In a larger cohort, these promising results could not be reproduced (no significant differences were observed between both CT scoring systems for the clinical parameters evaluated; intensive care stay, need for intervention, persistent organ failure, infected necrosis, severity of disease, and mortality) [37]. Possibly, because of the simplifications, the MCTSI may be easier to assess by less experienced readers.

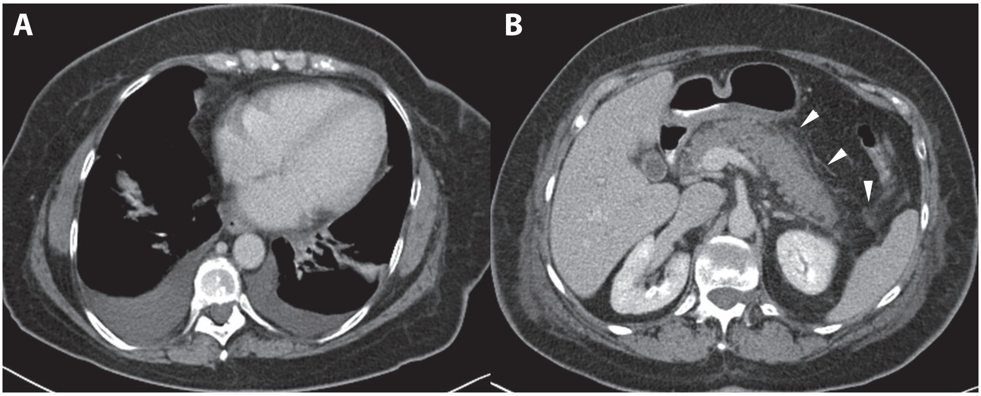

FIGURE 3 A 65-year-old woman with acute interstitial pancreatitis (MCTSI 4). (a) Contrast-enhanced CT of the lung bases shows bilateral pleural effusion. (b) CT at the level of the pancreas shows a normal enhancing pancreatic parenchyma with little peripancreatic fat stranding (arrowheads). The CT severity index is 2 (predicted mild pancreatitis), while the modified CT severity index credits two extra points for pleural effusion (MCTSI 4, representing predicted moderate severe pancreatitis).

Retroperitoneal Extension Grade

Traditionally, it was assumed that the retroperitoneum consisted of three compartments (anterior pararenal space, perirenal space, and posterior pararenal space) demarcated by three well-defined fascia (anterior renal fascia, posterior renal fascia, and lateroconal fascia). New anatomical insights are that each retroperitoneal fascia is composed of multiple layers (i.e., fused leaves of embryonic mesentery), creating potential spaces (the retroperitoneal interfascial planes) that may serve both as a reservoir for decompression of rapidly accumulating fluid collections (as in acute pancreatitis) and as a pathway for spread of an infiltrating neoplasm or inflammatory process [38–40]. In 2006, Ishikawa and collaborators used this new anatomic concept to design a CT grading system based on retroperitoneal extension of pancreatic fluid along the retroperitoneal interfascial planes on a 5-grade severity scale [21]. In their study, patients with Grade I–III (extension of pancreatic fluid from anterior pararenal space to the combined interfascial plane at the lower end of the perirenal space) had 22 % morbidity and 0 % mortality, whereas patients with Grade IV–V (pancreatic fluid extending from the subfascial plane, located between the posterior pararenal space and the transverse fascia, into the posterior pararenal space) had 92 % morbidity and 39 % mortality (Fig. 4) [21]. This grading system can be assessed on unenhanced CT studies, but requires advanced radiologic interpretative skills and may not be easy to use for routine clinical practice.

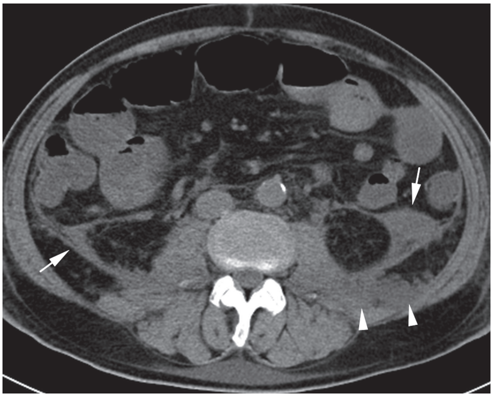

FIGURE 4 A 49-year-old woman with acute pancreatitis (retroperitoneal extension grade V). Unenhanced CT shows extensive bilateral retroperitoneal inflammatory changes due to acute pancreatitis (arrows) with extension to the left posterior pararenal space (arrowheads), representing the highest grade of retroperitoneal extension (Grade V).

EPIC Score

The latest CT scoring system is the ExtraPancreatic Inflammation on CT (EPIC score), developed in 2007, which measures exclusively extrapancreatic inflammatory changes hypothetically regarded as CT signs of systemic inflammation (presence of pleural effusion, ascites, and retroperitoneal and mesenteric inflammation on a 7-point severity scale) [41]. The EPIC score was validated in a small single-center study composed of 40 patients who received an abdominal CT within 24h after admission and proved useful with an area under the receiver operating characteristics (AUC) curve for predicting severe disease and mortality of 0.91 (95 % confidence interval, 0.83–0.99) and 0.85 (95 % confidence interval, 0.71–0.99), respectively [41]. However, this study was biased towards inclusion of a high incidence of severe disease and high need for surgical intervention.

VALUE OF RADIOLOGIC SCORING SYSTEMS FOR SEVERITY PREDICTION

Since over four decades, an exhaustive search for the ideal scoring system has been undertaken to identify patients at risk for severe acute pancreatitis early in the disease process to guide patient triage and management, and to improve patient outcome. An ideal prognostic scoring system should be simple and easy to use in clinical practice, widely available, objective, reproducible, sufficiently accurate in differentiating mild from severe disease and applicable early in the disease process, preferably on day of admission, such that patients at risk for severe acute pancreatitis are more closely monitored or empirically treated (i.e., with tailored fluid resuscitation). Many clinical, biochemical, and imaging-based scoring systems have been developed but none fulfills all of the abovementioned criteria. Several shortcomings are shared by all staging systems. The available staging systems were devised to identify groups of patients at risk of developing organ failure or clinically severe disease rather than identifying individual patients. Furthermore, about one fifth of patients with potentially fatal severe pancreatitis are inappropriately identified using the traditional scoring systems [42]. Indeed, scoring systems perform best at the extremes of the prediction range, while the discriminatory power is moderate at best in the middle prediction range (i.e., the range where the clinician needs most assistance). Also, the variable timing of patient presentation to the hospital affects the clinical, laboratory, and imaging parameters explaining the variability in scores obtained. Finally, scoring systems (radiologic and biochemical systems alike) do not correlate with the risk of particular extrapancreatic complications (e.g., abdominal compartment syndrome (ACS), bowel ischemia, or perforation or arterial pseudoaneurysm) and, therefore, fail to provide detailed information that impacts patient management on an individual basis.

Imaging-based systems have their specific shortcomings compared with clinical and biochemical scoring systems. It is commonly known that severe acute pancreatitis may run a highly variable clinical course; it may manifest early with SIRS, organ failure, and death in the first week or late with local complications demanding intervention [1, 2]. Biochemical scoring systems, compared with imaging-based systems, better correlate with early systemic effects of pancreatic injury (i.e., organ failure; the main determinant for severity of disease in the revised Atlanta Classification) and, thus, are better in predicting clinical severity early in the disease course. Conversely, radiologic scoring systems are best in predicting late local complications (infected necrosis, need for intervention) [37, 42]. Second, radiologic scoring systems are based on visual estimation and, therefore, are subject to variable interpretation, whereas most biochemical scoring systems are derived from objective parameters. Third, radiologic scoring systems do not account for patients preexisting clinical status; such as age, comorbid disease, and obesity which are well-known prognostic factors for morbidity and mortality. Institution of preventative measures requires early identification of patients with severe disease before the development of a complication. However, the timing of the CT scan in reports on the predictive power of radiologic scoring systems has varied from at admission to 10 days after admission [14]. Conversely, clinicobiochemical scoring systems are mostly tested early in the clinical course (within the first 24–48h), i.e., in a timeframe where severity stratification is most useful. Finally, studies on imaging-based systems are biased toward more severe disease because patients with mild or minimal symptoms do not need cross-sectional imaging for clinical management while biochemical scoring systems are tested and applicable in all patients presenting with acute pancreatitis.

Reports on the discriminatory power of radiologic scoring systems all show a positive correlation between the scoring system studied and patient outcome. However, because of the profound lack of homogeneity in study design, differences in methodology used and the wide diversity in definitions for severe acute pancreatitis and clinical end points (e.g., variation in defining organ failure and systemic complications) comparison of these studies is rendered difficult [14]. A recent study comparing seven of the eight abovementioned CT prognostic scoring systems on the day of admission accounted for these shortcomings by using definitions put forth by the working group on revising the Atlanta Classification [43]. This study did not detect significant differences between the studied CT scoring systems in predicting clinical severity or mortality (AUC ranging between 0.72–0.88 and 0.70–0.81, respectively). Moreover, CT scoring systems did not perform better than commonly used clinical scoring systems [43].

The use of early imaging for prognostication is limited by several factors: (1) In most imaging-based systems, the rating of peripancreatic inflammation and fluid is determined based on their presence rather than extent; the latter may vary considerably among patients appreciated with similar grades (Fig. 5). (2) Morphologic signs of severe disease are a time-dependent phenomenon. CT only takes a snapshot of a moment in time, while acute pancreatitis is a continuously evolving disease process. Consequently, patients may progress from mild to severe grades of CT severity. (3) Parenchymal necrosis may not be evident until after 24–48 h and, thus, may be underrated on early imaging (Fig. 6). (4) On the other hand, the presence and extent of parenchymal necrosis do not invariably correlate with organ failure and clinical severity, and (5) the evolution of CT findings does not always parallel the clinical course; CT may show little morphologic signs of severe disease early in the disease process (i.e., on day of admission) in patients who already have organ failure as sign of a severe attack. Conversely, imaging studies late in the disease process may show major morphologic changes (like extensive parenchymal necrosis and retroperitoneal collections) in patients who have only mild clinical discomfort (Fig. 7).

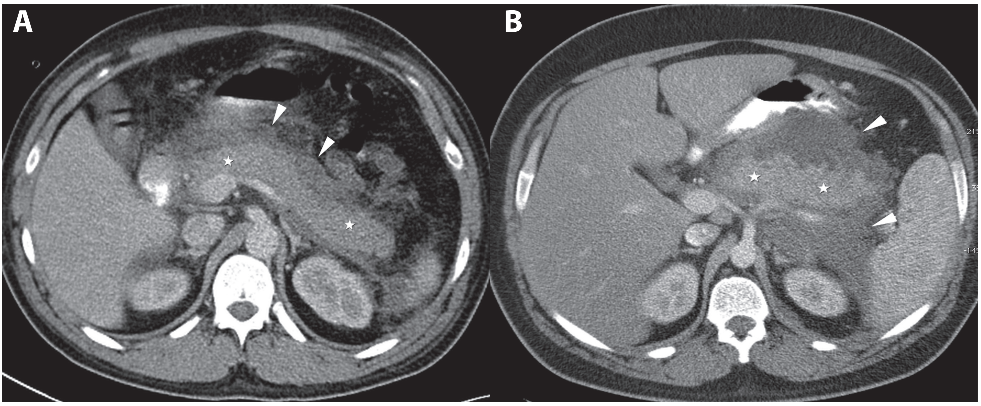

FIGURE 5 Two different patients (A, B) with similar grades of severity but marked difference in magnitude of peripancreatic collections. **(A)** A 44-year-old man with limited peripancreatic collections (arrowheads). **(B)** A 37-year-old man with extensive peripancreatic collections (arrowheads). Both patients are appreciated with similar grades according to all radiologic scoring systems. White stars denote a normal enhancing pancreas in both patients.

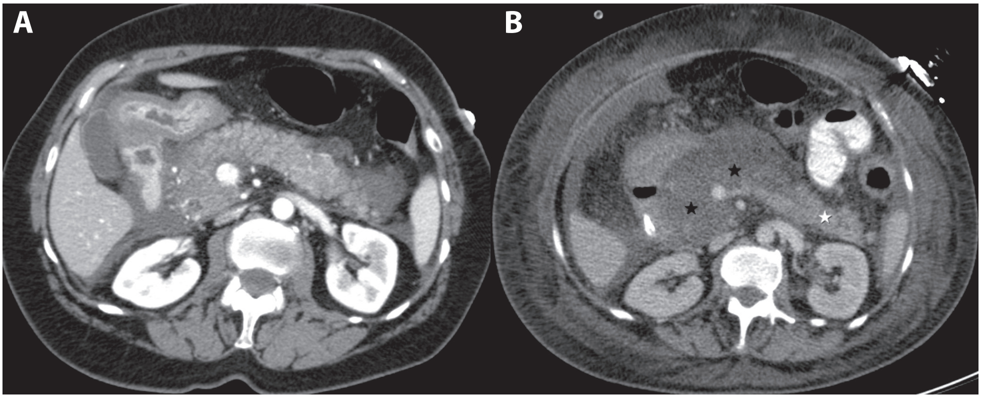

FIGURE 6 A 47-year-old woman with false negative parenchymal necrosis on early CT. **(A)** Contrast-enhanced CT on day 1 shows a heterogeneous enhancing pancreatic parenchyma, but no apparent areas of nonenhancement. **(B)** Repeat CT was performed on day 4 showing clear nonenhancement of pancreatic head, neck and part of body (black stars), while the tail shows preserved enhancement (white star).

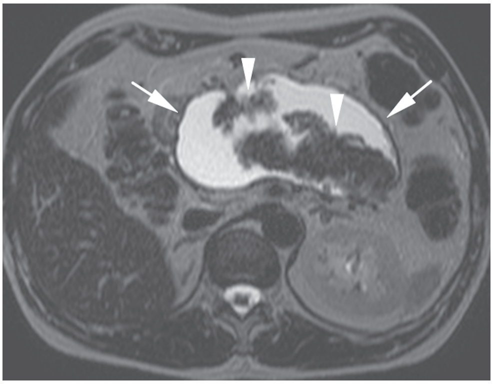

FIGURE 7 A 50-year-old man with extensive necrosis and mild clinical symptoms. MRI was performed for continuing mild discomfort 6 weeks after an episode of acute pancreatitis. T2-weighted sequence shows a fully encapsulated collection (walled-off necrosis) in the pancreatic area (arrows) with dark material (arrowheads), representing necrotic pancreatic and peripancreatic tissue.

In summary, current evidence suggests that there is no role for radiologic scoring systems for prediction purposes. Additionally, given the high costs associated with acute pancreatitis [44], the radiation burden of (serial) CT [45, 46], and the lack of correlation between imaging utilization and patient outcome [46, 47], initial evaluation of a patient presenting with acute pancreatitis is best performed based on clinical assessment and biochemical scoring systems that better correlate with organ failure and systemic complications dominating the clinical picture in the first weeks after the initial attack. Performing a CT on admission (or within the first days after admission) is unlikely to affect patient management, unless a severe complication (like hemorrhage or bowel ischemia) is suspected or in case of a diagnostic dilemma. The decision about when to perform MDCT depends, therefore, on the overall clinical presentation. Unquestionably, the impact of CT is greater in the later phase of the disease process in patients who have predicted severe acute pancreatitis by clinical assessment or who fail to improve clinically despite conservative therapy when local complications (most commonly infection of parenchymal and peripancreatic tissues) predominantly dictate clinical management.

Prognostic Value of Specific Computed Tomography Findings

Morphologic findings of acute pancreatitis include necrosis of pancreatic parenchyma, peripancreatic inflammation with or without fluid and extrapancreatic retroperitoneal or subperitoneal fatty tissue necrosis, subsequent infection of pancreatic or extrapancreatic necrosis, vascular compromise of adjacent veins and arteries, extrapancreatic parenchyma complications, biliary complications, and gastrointestinal complications. Some of these findings or complications are detected on cross-sectional imaging only but nonetheless may harbor significant prognostic importance (Table 3). Given the aforementioned limitations of radiologic scoring systems, this section will review the key findings on cross-sectional imaging associated with prognostic significance, which may directly influence patient management.

TABLE 3 CT findings of complications in acute pancreatitis with clinical implications

CT findings	Clinical implications
Necrosis of pancreatic parenchyma: • Extended necrosis (>30 %) • Central gland necrosis	Increased risk for developing organ failure, infected necrosis, and higher need for intervention
Infected necrosis (gas bubbles in necrotic collections)	Institution of (empiric) antibiotics and/or intervention
Peripancreatic collections exerting mass effect on surrounding structures: • Biliary dilation • Obstructive hydronephrosis	If symptomatic, stent placement
Deep vein thrombosis of iliofemoral veins or pulmonary emboli/infarction	Initiation of anticoagulant therapy
Hemorrhage/arterial pseudoaneurysm	Angiographic coiling/embolization or surgical clipping
Cholecystitis or gallbladder perforation	Percutaneous drainage or surgical cholecystectomy
Bowel ischemia or perforation	Surgical resection
CT signs of abdominal compartment syndrome (ACS)	Percutaneous drainage of ascites (if present) or surgical decompression
Pulmonary complications: • Pleural empyema • Pulmonary infiltrate(s) • Pneumothorax	Initiation of antibiotics (empyema, pneumonia) or drain placement (empyema, pneumothorax)

PANCREATIC FINDINGS

Pancreatic Necrosis

Necrosis of pancreatic tissue signifies the most severe morphologic form of acute pancreatitis and represents the basis for most of the local complications [48]. Necrosis of pancreatic parenchyma results from severe disturbances in the pancreatic microcirculation and occurs early in the disease process [5, 22]. Generally, it is fully established by 72–96h and tends to remain stable across time [5, 22, 49]. CECT is considered the noninvasive reference standard for diagnosing pancreatic necrosis. CECT is highly accurate in assessing parenchymal necrosis when performed after 72–96h after symptom onset and when more than 30 % of pancreatic parenchyma is involved [5, 22]. Early CECT within 72h of disease may miss the presence and extent of necrosis in about 30–40 % of cases [43]. Also, accuracy of pancreatic necrosis detection drops to about 50 % when small areas of pancreatic tissues are affected [5, 50]. Mortality rates in cases of pancreatic necrosis are about 20 %, as opposed to less than 5 % in patients without pancreatic necrosis [3]. Extended pancreatic necrosis (i.e., more than 30 %) is associated with SIRS, organ failure, and development of late local complications such as infection of necrosis [35]. Furthermore, patients with significant necrosis are prone to develop other infections (urinary, respiratory, and systemic infections) during both the early and late phases [51]. These infections complicate the clinical course of acute pancreatitis and prolong hospitalization. Some studies have shown that transparenchymal necrosis concerning the central area (pancreatic neck and/or body) or central gland necrosis also heralds prognostic significance because of the possible involvement of the pancreatic duct, resulting in the pancreatic duct disruption syndrome (Fig. 8) [52, 53]. In central gland necrosis, a viable pancreatic tail causes the ongoing secretion and extravasation of pancreatic fluid in the necrotic collection and peripancreatic area associated with increased need for percutaneous, endoscopic, or surgical intervention [53].

Infection of Necrosis

Necrosis of pancreatic parenchyma and peripancreatic fatty tissue serves as a nidus for bacterial superinfection, resulting in the most severe local complication in acute pancreatitis. Mortality rate in sterile necrosis is around 5–10 % and increases considerably when the necrosis becomes infected [3]. Indeed, infection of necrosis is a major prognostic risk factor in severe acute pancreatitis and sepsis-related multiple organ failure is the main life-threatening complication with a mortality rate up to 20–50 % [3]. On CECT, the presence of gas bubbles in an area of pancreatic and/or peripancreatic fatty tissue necrosis is virtually pathognomonic for the diagnosis of infected necrosis, especially in patients with clinical signs of infection (spiking fever, leukocytosis, elevated C-reactive protein, and/or (new onset) organ failure) (Fig. 9) [54]. In rare instances, gas bubbles can be seen in sterile collections associated with an enteric fistula. However, these patients often lack clinical signs of infection. Unfortunately, gas bubbles on CECT as sign of infected necrosis is only present in about 40 % of cases [54].

Peripancreatic Collections

In the more severe forms of acute pancreatitis peripancreatic (fluid) collections arise most commonly in the lesser sac, the retroperitoneum, and subperitoneal spaces of the mesenteries. According to the revised Atlanta Classification 2012, these are termed an acute peripancreatic fluid collection or pseudocyst in interstitial pancreatitis (collections contain fluid only) or acute necrotic collection or walled-off necrosis in necrotizing pancreatitis (collections contain a mixture of necrotic material and variable amounts of fluid) [48]. The natural history of these collections is highly unpredictable, ranging from spontaneous resolution in over half of cases, to persisting and increasing in size and giving rise to complications like secondary infection (in necrotizing pancreatitis, this is termed infected necrosis), mass effect on neighboring structures (e.g., biliary system resulting in biliary dilation, urogenital system resulting in hydronephrosis, venous system resulting in left-sided portal hypertension, splenomegaly and extensive collateral venous network when the portomesenteric and splenic veins are involved, and gastric outlet obstruction), or rupture into the peritoneal cavity with development of acute peritonitis (Fig. 10) [5, 55, 56].

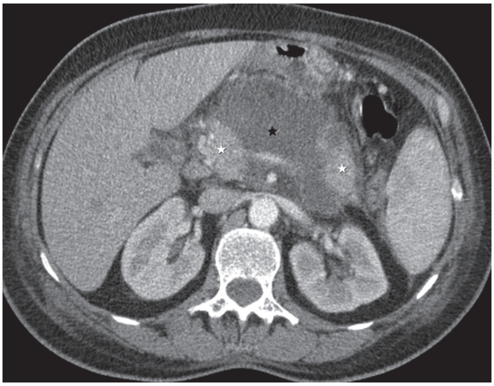

FIGURE 8 A 42-year-old woman with central gland necrosis. Contrast-enhanced CT depicts necrosis of the neck and body of the pancreas (black star) among the viable pancreatic head and tail (white stars). This patient is at risk for having a pancreatic duct disruption with increased need for intervention.

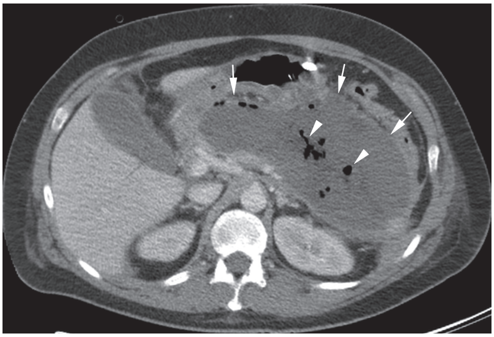

FIGURE 9 A 51-year-old woman with infected necrosis. Contrast-enhanced CT performed on day 26 after symptom onset shows a nearly completely encapsulated necrotic collection (arrows) with impacted gas bubbles (arrowheads), virtually diagnostic for infection of necrosis.

EXTRAPANCREATIC FINDINGS

Vascular Complications

Vascular complications are common in patients with moderate severe and severe acute pancreatitis and include portomesenteric venous thrombosis, arterial pseudoaneurysm, and hemorrhage due to vessel erosion of arteries, veins, or small capillaries either through pancreatic enzymes or, iatrogenically, by surgical, endoscopic, or radiological drains.

Recent studies on splanchnic vein thrombosis report an incidence of about 50 % in patients with parenchymal necrosis, most frequently in the splenic vein, followed by portal and superior mesenteric vein (Fig. 11) [57, 58]. Most are asymptomatic, and spontaneous recanalization occurs in about one third of patients irrespective of the use of systemic anticoagulation. Reported complications include gastrointestinal bleeding and splenomegaly but are rare [59]. Current practice suggests that there is no need for initiation of anticoagulation unless there is propagation of thrombosis on serial CT scans [58]. In the literature, there is lack of data about the true incidence of deep vein thrombosis or pulmonary embolism on abdominal CT

FIGURE 10 A 49-year-old woman with large collection compressing the stomach. Coronal reformatted contrast-enhanced CT shows a large encapsulated necrotic collection (white star) exerting mass effect on the stomach (arrows), which is displaced medially and cranially.

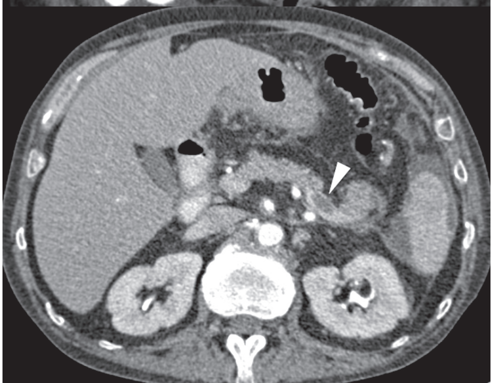

FIGURE 11 A 56-year-old man with thrombus in the splenic vein. Contrast-enhanced CT depicts an intraluminal filling defect in the splenic vein (arrowhead), compatible with a thrombus. Usually, this is not an indication for initiation of anticoagulant therapy.

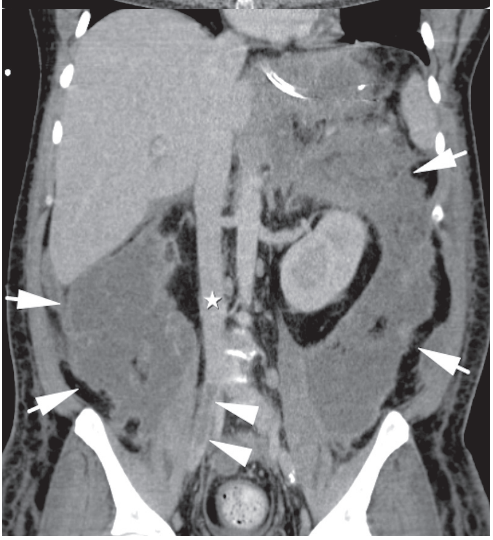

FIGURE 12 A 43-year-old woman with thrombus in the right iliac vein during the course of acute necrotizing pancreatitis. Coronal reformatted contrast-enhanced CT depicts a large filling defect in the right iliac vein (arrowheads), diagnostic for deep vein thrombosis in a patient with necrotizing pancreatitis and extensive retroperitoneal collections (arrows). White star denotes the inferior vena cava. To prevent pulmonary embolism anticoagulant therapy is mandatory.

scans in acute pancreatitis. In the author's experience, this is rare and primarily seen in patients with severe necrotizing acute pancreatitis and prolonged hospitalization. However, opposed to portomesenteric vein thrombosis, the observation of intraluminal clots in the iliac or femoral vein necessitates the initiation of systemic anticoagulation to prevent a fatal outcome (Fig. 6.12).

Another vascular complication is the occurrence of an arterial pseudoaneurysm, which is often a late complication in acute pancreatitis, although rare (estimated incidence of less than 2 %) (Fig. 13) [60]. In order of frequency, the following arteries are involved: splenic artery, gastroduodenal artery, pancreaticoduodenal artery, gastric artery, hepatic artery, and others (superior mesenteric artery, jejunal or ileocolic artery) [60]. Generally, there is an indication for angiographic embolization or coiling. Uncontrollable bleeding from a ruptured arterial pseudoaneurysm requires emergency surgical intervention.

Hemorrhage from erosion of a vascular wall may be a life-threatening complication if an artery is involved or may be an incidental finding in case of damage of small capillaries or veins. The vast majority of vascular complications are readily detectable on routine abdominal CT scans but some (e.g., small arterial pseudoaneurysms or insignificant hemorrhage) require a multiphasic scan protocol (including an unenhanced and arterial phase) for accurate detection [12].

Extrapancreatic Parenchymal Complications

Acute pancreatitis is capable of inflicting damage to adjacent parenchymal organs, like the spleen, liver, and kidneys, due to the central location of the pancreas in the upper abdomen and destructive nature of extravasated pancreatic enzymes. Splenic involvement in acute pancreatitis include hematoma, infarction, and perisplenic inflammatory fluid collections (sterile or infected) attributable to pancreatic secretions that dissect into the splenic hilum as the splenic capsule is continuous with the peritoneum covering the anterior surface of the pancreas (Fig. 14) [61, 62]. Similar complications may occur in the liver [63]. Renal involvement in acute pancreatitis includes perirenal fluid collections and parenchymal abnormalities (e.g., renal infarction) [33, 64]. Renal complications are most often an incidental finding and seem unrelated to the severity of pancreatitis. One renal complication with clinical impact is obstructive hydronephrosis as a result of eccentric compression of the proximal ureter by retroperitoneal pancreatic collections (Fig. 15) [65]. Most of the aforementioned complications lack any specific symptomatology, but are easily identifiable on CECT underlining the importance of CT for their diagnosis.

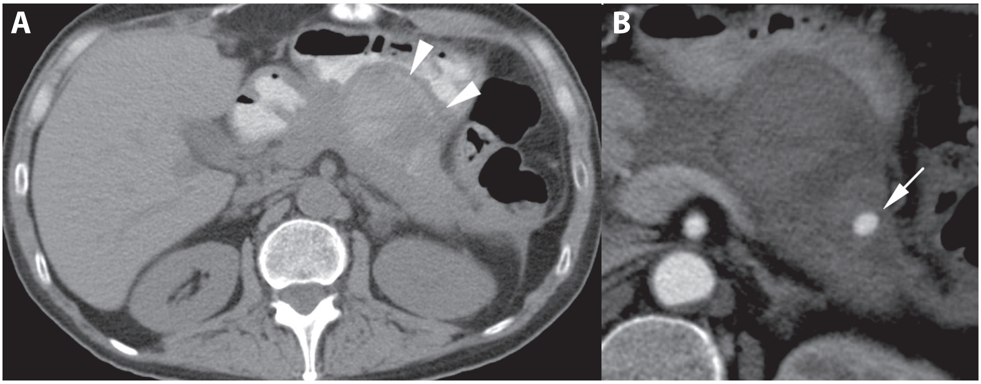

FIGURE 13 A 40-year-old man with an arterial pseudoaneurysm after an episode of necrotizing pancreatitis. **(A)** Unenhanced CT shows a cotllection (arrowheads) with high density, suggestive of hemorrhage. **(B)** Contrast-enhanced CT in the arterial phase depicts a small arterial pseudoaneurysm (arrow) originating from the prepancreatic arcade. Pseudoaneurysm was successfully treated by embolization with platinum coils (not shown).

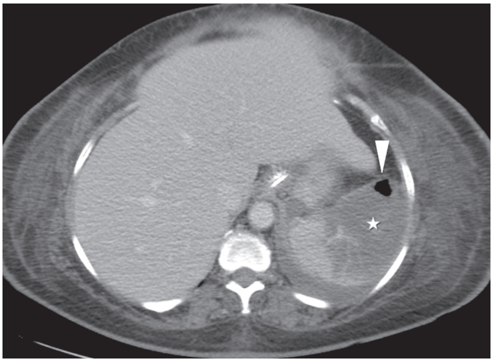

FIGURE 14 A 61-year-old woman with splenic infarction and signs of infection (abscess) complicating acute pancreatitis. Contrast-enhanced CT shows an area of splenic infarction (white star) with a gas bubble (arrowhead) as a sign of a splenic abscess.

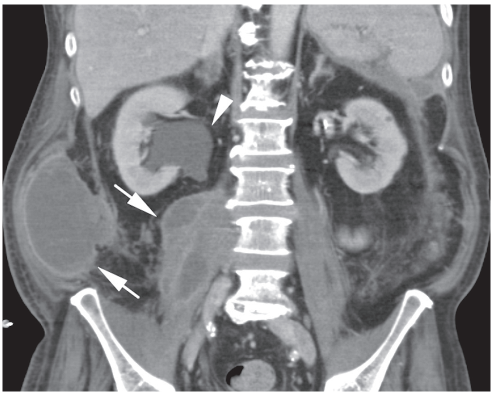

FIGURE 15 A 72-year-old man with obstructive hydronephrosis of the right kidney due to extensive retroperitoneal collections. Coronal reformatted contrast-enhanced CT depicts a newly developed dilatation of the pyelocaliceal system of the right kidney (arrowhead), compatible with hydronephrosis due to obstruction by large retroperitoneal necrotic collections (arrows).

Biliary Complications

Concomitant acute cholecystitis and acute pancreatitis is a rare event [66] but development of acute cholecystitis during the course of acute biliary pancreatitis is not uncommon and is one of the reasons to perform a cholecystectomy shortly after an attack of acute biliary pancreatitis [67, 68]. Performing a cholecystectomy may be a surgical challenge, particularly in the presence of necrotic collections [69]. In these cases, percutaneous cholecystostomy may be an alternative treatment strategy. Assessment of gallbladder pathology can be difficult in the course of acute pancreatitis and findings on CECT may be helpful in the diagnosis and, thus, may directly influence patient management.

Direct extension of the inflammatory process to the duodenal wall and ampulla of Vater may result in transient inflammatory narrowing of the intrapancreatic segment of the common bile duct causing jaundice. Persistence of or development of jaundice a few weeks after the acute onset of pancreatitis, however, may indicate a more significant complication such as a chronic obstruction due to a ductal stricture or compression of the common bile duct by peripancreatic collections (i.e., indication for endoscopic stent placement) [70]. CECT easily depicts biliary dilatation up to the level of obstruction (Fig. 16).

Another severe, but extremely rare complication is perforation of the gallbladder leading to biliary peritonitis [66]. CECT may diagnose this complication by depicting an interruption of the gallbladder wall with adjacent inflammatory fluid. Finally, erosion of the common bile duct wall by the inflammatory process may lead to a pancreaticobiliary fistula [71]. On CECT, the simultaneous presence of gas bubbles in the biliary tract and intrapancreatic collection is highly suggestive of a pancreatic choledochal fistula. Adequate drainage of the pancreatic/peripancreatic collection and bile duct is generally effective.

Gastrointestinal Complications

Involvement of gastrointestinal structures in acute pancreatitis is multifactorial and occurs primarily in necrotizing pancreatitis. Extravasated pancreatic enzymes may directly damage the gastrointestinal tract or may produce vascular thrombosis resulting in ischemic splanchnic injury. Also, early in the course of severe acute pancreatitis, hypovolemic shock with a splanchnic low flow state may occur because of inadequate fluid therapy and third-space loss responsible for further vascular compromise [72–74]. Rare but severe complications are perforation of the stomach (mainly the posterior wall of the stomach) and erosion of the medial wall of the duodenum in patients with pancreatic necrosis [75, 76]. A small but significant number of patients with necrotizing pancreatitis sustain ongoing abdominal pain, nausea, and inability to eat owing to centrally located pancreatic collections that displace and compress the stomach anteriorly giving rise to gastric outlet obstruction [77]. In these patients, endoscopic drainage may be indicated. The most severe small bowel and colonic complication in acute pancreatitis is ischemia and subsequent necrosis and perforation because of thrombosis of feeding or draining

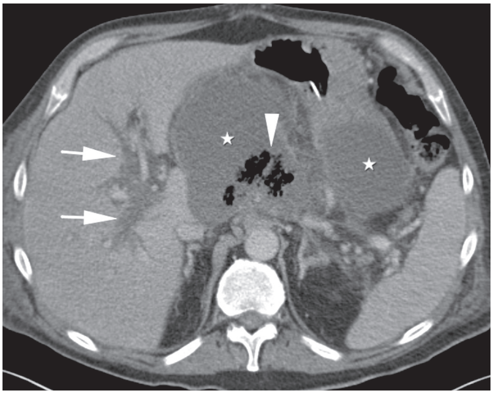

FIGURE 16 A 76-year-old woman with infected necrotizing pancreatitis and biliary dilatation. Contrast-enhanced CT shows large necrotic collections (white stars) and impacted gas bubbles (arrowhead), indicative for infected necrosis. Also, dilatation of the intrahepatic bile ducts (arrows) is noted due to extrinsic compression of the common bile duct.

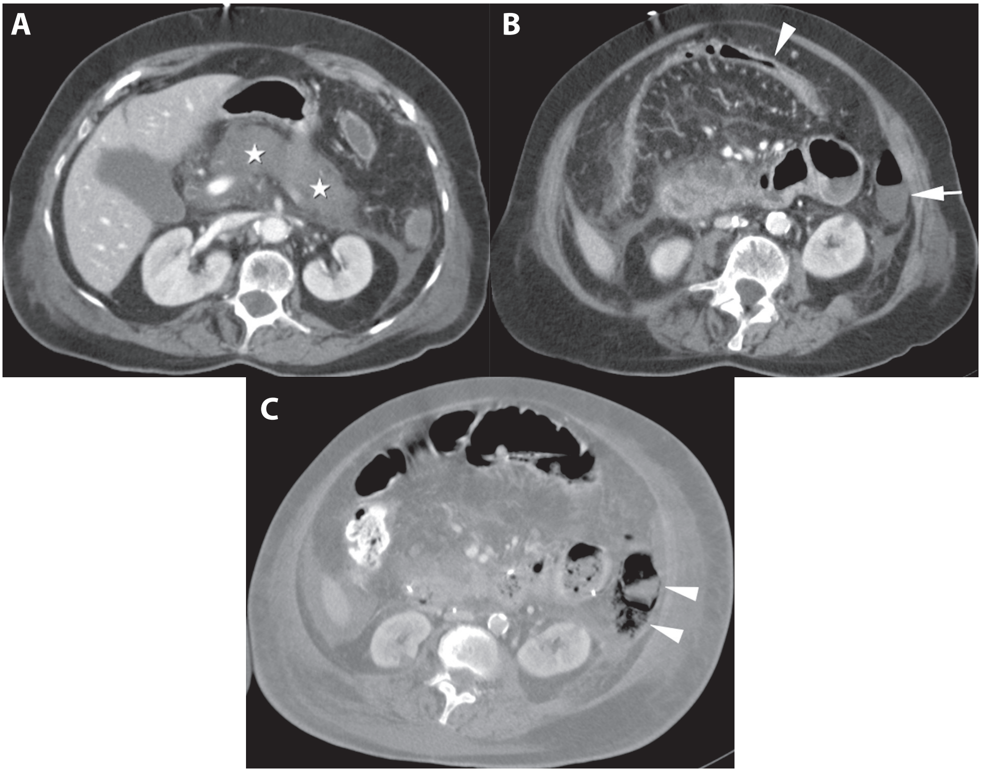

FIGURE 17 A 58-year-old woman with bowel ischemia of descending colon complicating acute necrotizing pancreatitis. **(A)** Contrast-enhanced CT performed on day 2 after symptom onset shows extensive necrosis of pancreatic body and tail (white stars). **(B)** Same CT at a lower level shows normal enhancement of the bowel wall of the transverse colon (arrowhead), while the descending colon shows absent bowel wall enhancement indicative for ischemia, which was overlooked by the radiologist. **(C)** Repeat contrast-enhanced CT 24h later for continuing severe sepsis depicts the development of gas in the bowel wall of the descending colon (pneumatosis intestinalis) and adjacent mesocolon (arrowheads) suggestive for bowel necrosis. Emergency laparotomy was performed which confirmed the CT findings.

vessels in the mesentery (Fig. 17) [72, 73]. The usual sites of involvement of the colon are the transverse colon and the splenic flexure, because of their proximity to the pancreas, and the poor collateral flow [74]. These patients may present with prolonged ileus, gastrointestinal bleeding, and peritonitis along with features of necrotizing pancreatitis. Findings on CECT that are suggestive for bowel necrosis are the presence of pneumatosis intestinalis, gas in the portomesenteric veins, diminished or absent bowel wall enhancement, clots or occlusion of feeding arteries, and free intraperitoneal gas (pneumoperitoneum; virtually diagnostic for a perforated hollow viscus). Identification of these CT signs is critical because intestinal ischemia has a very high mortality if not treated expediently. Other colonic complications with less clinical impact are ileus and fistula formation.

Abdominal Compartment Syndrome

ACS is caused by pathological elevation of intra-abdominal pressure in response to various diseases (including severe acute pancreatitis) leading to multiple organ dysfunction [78]. ACS is increasingly recognized in acute pancreatitis and since the condition is associated with high mortality, early diagnosis is imperative [79]. Usually, the diagnosis of ACS is straightforward by clinical assessment and intravesical pressure measurements; however, diagnosis may be delayed by interfering symptoms from the underlying illness. Abdominal CT scan may reveal subtle findings that include narrowing or collapse of the inferior vena cava, direct renal compression or displacement, bowel wall thickening with increased enhancement, bilateral inguinal herniation, elevated hemidiaphragm, and a rounded appearance of the abdomen (so-called "round-belly sign") [80, 81]. The "round-belly sign" is defined as abdominal distension with an increased ratio of anteroposterior-to-transverse abdominal diameter (ratio > 0.80). Especially, an increasing girth observed on serial CT scans performed at short intervals is worrisome (Fig. 18) [81]. Individually, these CT findings are neither specific nor sensitive, but when present in combination, radiologists should raise the possibility of this life-threatening complication and, in the proper clinical setting, should communicate the presence and significance of these CT findings to the referring clinician.

Miscellaneous Complications

Routine abdominal CT for acute pancreatitis can reveal some complications that may not always be clinically apparent. Among these are abdominal wall extension of infected collections (amenable for percutaneous drainage) and pulmonary complications such as pneumothorax, focal consolidations indicative for pulmonary infiltrates, pleural empyema, features of the adult respiratory distress syndrome, and pulmonary embolus or infarction (Fig. 19) [82].

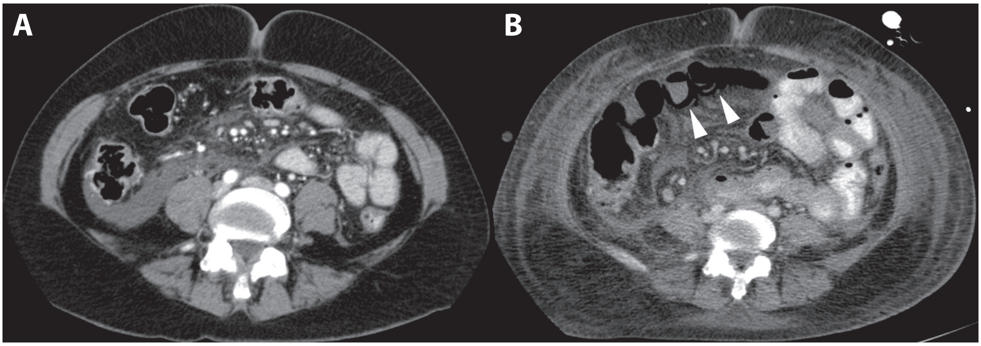

FIGURE 18 A 47-year-old woman with development of ACS occurring early in the course of acute necrotizing pancreatitis (same patient as Figure 6). **(A)** Contrast-enhanced CT (day 1) at the level of the umbilicus shows mesenterial and retroperitoneal inflammatory changes due to pancreatitis. Note, the normal configuration of the abdominal contour. **(B)** Repeat CT on day 4 shows a rounded appearance of the abdomen (round belly-sign). Also note, pneumatosis intestinalis and absent bowel wall enhancement of ileal loops (arrowheads), indicative for small bowel ischemia. Patient underwent emergency laparotomy.

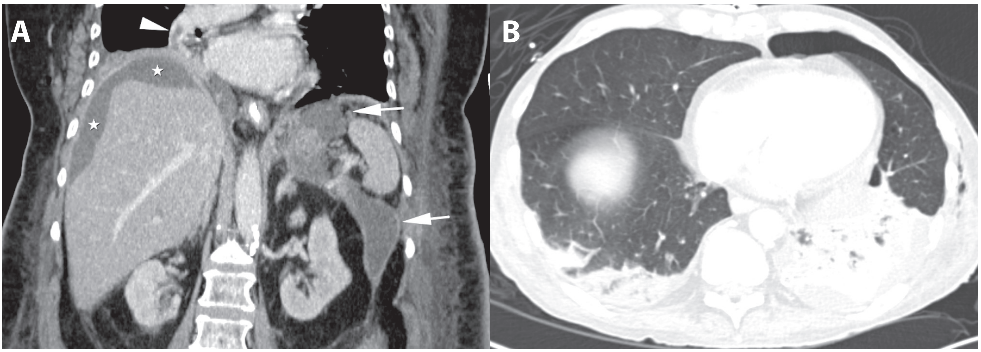

FIGURE 19 Two different patients (a, b) with pulmonary complications during an episode of acute pancreatitis. **(A)** Coronal reformatted contrast-enhanced CT in a 69-year-old woman shows signs of acute necrotizing pancreatitis with necrotic collections in the left retroperitoneum (arrows) and perihepatic fluid (white stars). As incidental finding, a thrombus was noted in the right pulmonary artery (arrowhead). **(B)** CT at the lung bases in an 80-year-old man with acute pancreatitis, who experienced a sudden onset of dyspnea and fever, demonstrates a left-sided pneumothorax and bilateral consolidations in the lower lobes, indicative for pneumonia.

CONCLUSION

Acute pancreatitis is a common but potentially devastating disease associated with significant morbidity, mortality, and public health impact in severe cases. Imaging-based predictive systems are useful for identifying groups of patients at risk for local complications or having severe disease rather than providing specific information changing clinical management on an individual basis. However, there are several individual CT features that may impact patient management significantly. Among these are the presence of significant necrosis (more than 30 %), especially in case of central gland necrosis (associated with increased need for intervention), imaging signs of infected necrosis (requiring empirical antibiotics or some kind of radiologic, endoscopic, or surgical intervention), massive hemorrhage or detection of an arterial pseudoaneurysm (indication for angiographic coiling or surgery), deep vein thrombosis (indication for anticoagulation), cholecystitis (amenable for percutaneous drainage), bowel ischemia or perforation (indication for surgery), and features of the ACS (requiring percutaneous drainage of ascites or surgery). The conveyance of these specific CT findings to clinicians caring for these challenging patients will have more clinical impact on patient management than providing any radiologic score.

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The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis

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ABSTRACT

Background. Diagnosing infected necrotizing pancreatitis (INP) may be challenging. The aim of this study was to determine the added value of routine fine-needle aspiration (FNA) in addition to clinical and imaging signs of infection in patients who underwent intervention for suspected INP.

Methods. We conducted a post hoc analysis of 208 consecutive patients from a prospective, multicenter database who underwent intervention because of suspected INP. In retrospect, 3 groups were constructed based on the patients preoperative characteristics: Clinical, imaging, and FNA. Patients in the clinical group had clinical signs of infection but no gas on preoperative computed tomography (CT) and no FNA performed before intervention. Patients in the imaging group had gas bubbles on the preoperative CT but no was FNA performed, whereas patients in the FNA group had a positive FNA before intervention. The reference standard for infection was the culture taken during the first intervention (either catheter drainage or necrosectomy).

Results. The initial intervention for INP was performed a median of 27 days (interquartile range, 20–39) after admission without difference between the 3 groups (P = .15). Infection was confirmed in 80% of 92 patients of the clinical group, in 94% of 88 patients of the imaging group, and in 86% of 28 patients of the FNA group (P = .07). Mortality was 19% and was not different between groups (P = .39).

Conclusion. INP can generally be diagnosed based on clinical or imaging signs of infection. FNA may be useful in patients with unclear clinical signs and no imaging signs of INP.

INTRODUCTION

Acute pancreatitis is the most common gastrointestinal condition requiring acute hospitalization in the United States.[1] Twenty percent of these patients have necrotizing pancreatitis.[2] The 2012 revised Atlanta Classification defines necrotizing pancreatitis by the presence of either pancreatic parenchymal or only peripancreatic necrosis.[3] In approximately 30% of these patients, infection of the necrosis occurs (infected necrotizing pancretitis [INP]), which requires radiologic or operative intervention in the vast majority of patients.[2,4] Interventions in these often critically ill patients carry a morbidity of 50–100% and a mortality of 15–25%.[4-9] Therefore, many studies have focused on prevention of INP. Surprisingly, few studies have addressed the topic of diagnosing INP.

Suspicion of infected necrosis can be based on clinical signs only (eg, fever, organ failure), on imaging signs of gas bubbles in peripancreatic collections on computed tomography (CT), on positive microbiologic culture obtained by fine-needle aspiration (FNA), or on a combinations of all these factors.[10,11] Since the initial Atlanta Classification[12] in 1993, only 1 retrospective study reported on the incidence of gas in peripancreatic collections (24% of 42 patients) in relation to patient outcome in patients with necrotizing pancreatitis.[10] In contrast, several studies reported on the use of FNA in diagnosing infected necrosis.[6,11,13-17] As a result of these studies, some authors propose routine FNA in patients with necrotizing pancreatitis, as reflected by the high use of FNA in the previous literature (40–100%).[5,17-19] The accuracy of FNA to diagnose infected necrosis may be high (range, 67–98%),[19-21] but, for several reasons, the added value of routine FNA may be limited.[7] First, with the current preferred approach of delayed intervention, even in case of infected necrosis, FNA seems to have limited therapeutic implications.[4,22] Second, false-negative and false-positive (contamination) rates have been reported up to be 25% and 15%, respectively.[7,18,23] Finally, although FNA is a considered to be a safe and minimally invasive procedure, it does carry a small risk of procedure-related complications (eg, bleeding, perforation, iatrogenic infection).[24]

The aim of this study was to determine the individual roles and (added) values of clinical and imaging signs and, especially, FNA in diagnosing INP.

PATIENTS AND METHODS

Patients

We performed a post hoc analysis in a prospective database of 639 patients with necrotizing pancreatitis, evaluated between March 2004 and November 2008 in all 8 Dutch university medical centers and 13 large teaching hospitals of the Dutch Pancreatitis Study Group. This cohort has been described previously.[4] During the study period, all patients admitted with acute pancreatitis were registered in a prospective database.[8,25] Patients were selected for the current study if they underwent intervention for suspected infection of peripancreatic or pancreatic necrosis. Patients were excluded if the intervention was performed for other indications than (suspected) infection (eg, abdominal compartment syndrome, bleeding, bowel ischemia, or perforation).

Definitions and groups

A definitive diagnosis of INP was established by a positive microbiologic culture obtained at the first intervention (either via percutaneous drainage or surgical necrosectomy). For this post hoc analysis, the intervention culture was considered to be the reference standard for infection, regardless of other subsequent cultures obtained by drainage or re-interventions. A positive FNA culture before intervention or the presence of gas in peripancreatic collections on CT was not considered definite proof for infection, being the diagnostic variables under study. In clinical practice, however, a positive FNA culture was indicative of infected necrosis. Patients without intervention for suspected infected necrosis were excluded from further analysis because the reference standard was lacking in these patients. All included patients were divided in 3 groups: (1) Clinical signs of infection (clinical group); (2) gas in peripancreatic collections on CT and clinical signs (imaging group); and (3) FNA and clinical signs (FNA group).

To facilitate the analysis between the study groups, patients who had both gas in peripancreatic collections on CT and in whom FNA cultures were performed (n = 16) were included in the imaging group, because FNA requires an additional intervention, whereas information on the presence of gas in peripancreatic collections can be derived from the CT that has already been performed routinely. In the clinical situation, however, this positive FNA was not ignored and used in the diagnostic workup to establish the diagnosis of infected necrosis; therefore, an additional sensitivity analysis was performed to determine the impact of including these 16 patients in the FNA group.

Treatment protocol

The treatment protocol has been described in detail previously.[4] In short, patients received broad-spectrum antibiotics in case of (suspected) INP initially. In case of clinical improvement, the antibiotic treatment regimen was narrowed based on culture results (if available). The majority of patients received broad-spectrum antibiotics for several weeks. Owing to the multicenter character of this study, it was not possible to record the exact use of antibiotics in all patients. Intervention was postponed if possible for ≥4 weeks after onset of symptoms to allow for demarcation and encapsulation of the infected collection, so-called walled-off necrosis. The minority of the present cohort (n = 88) was included in the PANTER trial and was randomized to open necrosectomy (n = 45) or to the step-up approach (n = 43).[8] Since 2006, a multidisciplinary expert panel, consisting of 8 gastrointestinal surgeons, 1 gastroenterologist, and 3 radiologists guided decisions on intervention. Patients with (suspected) INP were evaluated by the expert panel, and the treating physician was informed about the individual recommendations of the members of the panel. Notably, in every case, the ultimate decision for treatment and intervention was made by the treating physician.

Clinical group

Patients who had no gas in peripancreatic collections on CT and in whom no FNA was performed were classified as patients in whom the suspicion of INP was based on clinical signs. Unfortunately, no algorithm exists for establishing the diagnosis of infected necrosis only based on clinical signs; therefore, it is not possible to provide clear cutoff points of biochemical and mechanical outcome parameters to define infection. Usually, clinical deterioration was an important observation in patients with (suspected) infected necrosis. Examples of clinical signs were persisting sepsis, (new or prolonged) organ failure, increased need for cardiovascular and/or respiratory and/or renal support, leukocytosis, increased levels of C-reactive protein, and fever. Moreover, no other infectious focus must be found or held responsible for the clinical deterioration. Because experienced clinical judgment is needed in these complex and usually critically ill patients, in the majority of patients the decision to intervene was advised by the expert panel.

Imaging group

Patients with gas bubbles on CT were included in this group. CTs were performed at the discretion of the treating physician. One dedicated abdominal radiologist (T.L.B.) reviewed all CTs, and was blinded for the clinical background and treatment.

FNA group

With the policy of postponing intervention regardless the presence of (suspected) infection, routine FNA was not used routinely. The indication for performing FNA was left to the treating physician; therefore, FNA was only performed in case of unclear clinical and radiologic signs of infection. FNA was performed with ultrasound or CT guidance.

Data collection

The following data were extracted from the prospective database: Patient demographics, past medical history, American Society of Anesthesiologists class, etiology, day of hospital admission, duration of hospital stay, laboratory findings, CT findings from the initial hospitalization and second review by an experienced abdominal radiologist, presence of infectious complications, presence of (multiple) organ failure, clinical course, type of intervention(s), cultures from FNA and first intervention, and mortality.

Statistical analysis

All patients were analyzed in the 3 predefined groups. Per group, all data were pooled and baseline characteristics were listed. Percentages were calculated for baseline characteristics and all intervention cultures were compared. Continuous data were presented as mean values ± standard deviation (SD), whereas and non-normally distributed data were presented as median (interquartile range [IQR]). Differences were compared with the Chi-square or Mann- Whitney U tests, as appropriate. All statistical analyses were performed using SPSS for Windows version 16.0.2 (SPSS, Chicago, IL).

RESULTS

Baseline characteristics

Of 639 consecutive patients with necrotizing pancreatitis, 208 (32%) underwent either percutaneous drainage or operative necrosectomy for suspected INP, and could be evaluated for the reference standard of infected necrosis. Median age was 60 years (IQR, 48–69) with a male:female ratio of 2:1. The clinical group consisted of 92 of 208 patients (44%); these patients had neither gas bubbles on CT nor was FNA performed. Gas in peripancreatic collections on CT was seen in 88 of 208 patients (42%; imaging group) and FNA was performed in 28 of 208 patients (13%; FNA group). Baseline characteristics are shown in Table I.

Timing of intervention

There was no difference in timing of the first intervention between the 3 groups. In the clinical group ($n = 92$), intervention was performed at a median of 27 days (IQR, 21–38) after hospital admission, versus 31 days (IQR, 22–46) in the imaging group and 31 days (IQR, 18–38) in the FNA group ($P = .15$).

Gas in collections with necrosis ($n = 88$) was seen after a median of 22 days (IQR, 13–37) after hospital admission and the first intervention was performed a median of 10 days later. The first FNA ($n = 28$) was performed a median of 17 days (IQR, 10–28) after hospital admission and the first intervention was performed a median of 14 days later.

Diagnostic accuracy

Infected necrosis was documented by a positive culture of material obtained during the first intervention (ie, the reference standard) in 74 of 92 patients (80%) in the clinical group, in 83 of 88 patients (94%) in the imaging group, and in 24 of 28 patients (86%) of the FNA group ($P = .07$).

In 19 of the 28 patients (68%) in the FNA group, the FNA cultures matched with the intervention cultures. In 8 of 28 patients (29%), other (new) micro-organisms were found during intervention; in these patients, the FNA culture was considered to be false negative. In 1 patient (4%), a false-positive culture was found. When all 44 patients who underwent FNA before intervention were analyzed (including all 16 patients with both gas bubbles and FNA), 27% of FNA cultures (12/44 patients) did not match with cultures taken from the intervention, regardless of the presence of gas in peripancreatic collections on CT. In 11 of 44 patients (25%), other (new) micro-organisms were found during intervention compared with the FNA culture (median time between FNA and intervention 9 days; IQR, 5–20), and in 1 of 44 patients (2%), a positive FNA culture was found with subsequently a negative intervention culture. In this patient, the time interval between FNA and intervention was five days. These data are shown in detail in Table II.

TABLE I. Baseline characteristics

Characteristic	All patients (n = 208)	Clinical group (n = 92)	Imaging group (n = 88)	FNA group (n = 28)
Age (y)	60 (48–69)	58 (45–69)	61 (51–72)	57 (43–64)
Male gender	142 (68)	60 (64)	60 (68)	22 (79)
Etiology				
Biliary	101 (49)	36 (39)	49 (56)	16 (57)
Alcohol abuse	44 (21)	30 (33)	10 (11)	4 (14)
Other	18 (9)	6 (8)	7 (8)	5 (18)
Unknown	45 (21)	20 (21)	22 (25)	3 (11)
ASA class on admission				
I (healthy status)	57 (27)	21 (23)	22 (25)	14 (50)
II (mild systemic disease)	113 (54)	53 (59)	50 (57)	10 (36)
III (severe systemic disease)	38 (18)	18 (18)	16 (18)	4 (14)
Predicted severity of pancreatitis				
APACHE-II score on admission	8 (5–11)	9 (5–11)	8 (5–11)	6 (4–10)
APACHE-II score >8 on admission	95 (46)	47 (50)	42 (48)	6 (21)
Imrie-score on admission	4 (3–5)	4 (2–5)	3 (3–5)	4 (2–5)
Imrie-score ≥3 on admission	158 (76)	69 (75)	67 (76)	22 (79)
Highest CRP level in first 48h of admission (mg/L)	295 (212–380)	289 (210–372)	289 (205–381)	335 (245–438)
CRP >150 (mg/L)	179 (86)	77 (78)	77 (88)	25 (89)
CT severity index	8 (6–10)	8 (4–10)	6 (6–10)	7 (6–8)
Pancreatic necrosis	156 (75)	66 (72)	70 (80)	20 (71)
Peripancreatic necrosis alone	52 (25)	26 (28)	18 (20)	8 (29)
Extent of pancreatic necrosis (%)				
<30	102 (49)	40 (45)	46 (52)	16 (57)
30–50	53 (25)	28 (30)	17 (19)	8 (29)
>50	53 (25)	24 (25)	25 (28)	4 (14)

Continuous variables are presented as median values (interquartile range); percentages are in parenthesis.
APACHE, Acute Physiology And Chronic Health Evaluation; *ASA*, American Society of Anesthesiologists; *CRP*, C-reactive protein.

TABLE II. Data from 12 patients with discrepancy between FNA culture and intervention culture

Patient	FNA culture	Sensitivity profile	Antibiotics started after culture	Intervention culture	Sensitivity profile	Antibiotics started after culture	Time between FNA and intervention (d)
1	Moraxella spp.	PENI	IMIP, FLUCO	No growth	n.a.	IMIP, FLUCO	5
2	C albicans E faecium	VANCO, FLUCO	VANCO, FLUCO	*C albicans, E faecium, P aeruginosa,*	MERO, FLUCO	VANCO MERO, FLUCO	1
3	H influenza	Missing	Missing	*S salivarius, Prefotella* spp.	AUGM, PENI, COTRIM	Missing	1
4	No growth	n.a.	Missing	*Klebsi€ella* spp.	AUGM, CIPRO	MERO, CIPRO	5
5	P mirabilis	PENI, AUGM	IMIP	*C albicans*, E faecalis	AUGM, VANCO	IMIP	7
6	No growth	n.a.	None	*Enterococcus* spp.	VANCO	VACO	8
7	E cloacae	Missing	MERO	*E cloacae*, *E faecium*	Missing	VANCO, COTRIM	9
8	*Streptococcus* spp. *Enterococcus* spp.	Missing	VANCO, FLUCO, CEFTA	*B fragilis*, *E faecium*	Missing	VANCO	11
9	No growth	n.a.	None	*Citrobacter* spp., *E faecalis*	AUGM, IMIP	IMIP, TEICO, FLUCO	15
10	No growth	n.a.	TAZO	*Stenotrophomonas*	spp.	TAZO, COTRIM CLINDA, COTRIM	20
11	E coli	Missing	Missing	*E coli*, *E. cloacae*, *Streptococcus* spp.	Missing	Missing	36
12	No growth	n.a.	None	S aureus	FLUCLOX	FLUCLOX	44

CEFTA, Ceftazidim; CIPRO, ciproxin; CLINDA, clindamycin; COTRIM, cotrimoxazol; FLUCO, fluconazole; FLUCLOX, flucloxacilline; IMIP, imipenem; MERO, meroponem; n.a., not applicable; PENI, penicillin; TAZO, tazocin; TEICO, teicoplanine; UGM, augmentin; VANCO, vancomycin.

Mortality

Overall mortality was 19% (40/208 patients) without differences between the groups: 18% (17/92 patients) in the clinical group, 17% (15/88 patients) in the imaging group, and 28% (8/28 patients) in the FNA group ($P = .39$). Mortality in all 44 patients who underwent FNA before intervention was 27% (12/44 patients).

Microbiology

In 184 of 208 patients (88%), infected necrosis was confirmed by culture taken at the first intervention. In 114 of these 184 patients (62%), the infection was monomicrobial, whereas in 70 patients (38%), ≥ 2 bacteria/fungi were cultured. The mortality between these groups did not differ (18%; 21/114 patients) with monomicrobial culture versus 21% (15/70 patients) with polymicrobial culture ($P = .62$). *Escherichia coli* was cultured most frequently (40%), followed by *Staphylococcus spp.* (28%) and *Enterococcus spp.* (25%). Yeasts were cultured in 9% of patients, predominantly *Candida spp.* No data were available about the resistance pattern of microorganisms cultured from the necrosis.

DISCUSSION

This study suggests that the diagnosis of INP can be based on clinical and imaging signs in the majority of patients. FNA can be used selectively in patients in whom the clinical signs are unclear and have no imaging signs of infection.

Routine use of FNA has been advocated previously in patients suspected of having INP.[26,27] This recommendation dates from a time period where the diagnosis of infected necrosis was believed to require immediate operative treatment or interventional drainage. In current series, however, intervention was usually postponed if clinically possible until the necrosis had become walled off.[4,6,22,28] Thus, even after confirmation of the diagnosis of infected necrosis, intervention was postponed whenever possible. This attempt to put off the intervention for about 4 weeks is reflected by our data showing that the median timing of intervention was 29 (IQR, 22–41), without difference between the groups. Apparently, FNA did not necessarily prompt earlier intervention, whereas mortality was comparable between groups. Notably, no mortality was observed in the 11 patients with gas bubbles and/or positive FNA in whom intervention was postponed and ultimately waived because of successful conservative treatment.[4] These findings support the concept that the diagnosis of INP does not mandate an emergency intervention and are in line with previous studies.[4,7,29] Future studies should determine whether earlier intervention after positive FNA without the current 10- to 14-day delay can decrease morbidity or mortality.

The presence of gas in peripancreatic collections is considered by many as pathognomonic for INP.[11] Only 3 studies reported the incidence of gas in peripancreatic collections.[10,11,20] Two studies published before 1993 included only a small number of patients (<30).[11,20] The third study, describing 42 patients with pancreatic necrosis on CT, found gas bubbles in 20 patients (48%).[10] But, because no consecutive series was described, the actual incidence of gas bubbles in patients with necrotizing pancreatitis remained unclear. In the current study, only patients in whom an intervention was performed for suspected INP were included (208/639 patients). Even though this was a selected subgroup of patients, it enabled us to compare the CT (and FNA) findings with the reference standard.

Infection of necrosis can occur at any time after onset of symptoms, but has a peak incidence between weeks 3 and 4.[30] Therefore, FNA performed early in the disease course often yields negative results. Moreover, negative FNA cultures are obviously only reliable for a short period of time. Cutoff points varying from 1 to 27 days have been reported,[19,21,31] but most studies do not actually report on the time between FNA culture and intervention.[6,11,13-17]

The role of antibiotics in patients with suspected INP remains a topic of debate. In the current study, almost all patients with suspicion of infected necrosis received broad-spectrum antibiotics as part of the conservative treatment strategy. Consequently, outcome of FNA cultures may be influenced and false-negative FNA cultures could occur. This possibility may be partly the reason for the high false-negative rate of 29%. Conversely, prolonged antibiotic treatment before intervention could result in a negative intervention culture and thus, false-positive FNA cultures and false-positive gas bubbles in peripancreatic collections. Whether antibiotics substantially influenced the intervention cultures remains unclear, although this possibility may explain in part the false-positive outcomes of both FNA and CT findings.

Our results show that in almost 40% of patients with INP, multiple micro-organisms were found at cultures taken from the first intervention and that in 27% of patients, these findings did not (fully) correspond with the micro-organisms found with FNA culture. This finding may indicate that translocation of other intestinal micro-organisms occurred in the time period between FNA and intervention. These findings do not support the routine narrowing of antibiotic treatment based on FNA cultures.

Our study has some limitations. First, because not all patients with necrotizing pancreatitis underwent a routine FNA and a subsequent intervention, this study cannot be seen as a purely diagnostic study; however, it seems rather unlikely that such a study will be ever performed given the clear ethical problems with such an approach. Second, both FNA and CT were performed at the discretion of the treating physician. We cannot exclude the possibility that only patients without obvious clinical signs and no gas bubbles on CT underwent FNA. This approach to treatment could lead to selection bias, but has no further implications for the management of the individual patient. The main strength of our report, however, lies in the use of a multicenter, prospective database focused specifically on intervention in necrotizing pancreatitis in a consecutive series of patients.

In conclusion, this study showed that in the majority of INP patients can be diagnosed based on clinical and imaging signs, and that FNA may be reserved for patients with unclear clinical signs without imaging signs of infection. Although FNA may lead to an earlier diagnosis of INP, it is unclear whether this is of additional value.

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An assessment of the severity of interstitial pancreatitis

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ABSTRACT

Background & aims: There is limited information on the incidence of and factors associated with severe disease among patients with interstitial pancreatitis (IP). We evaluated a large cohort of patients with IP and compared data with those from patients with extrapancreatic necrosis (EXPN).

Methods: We evaluated 149 consecutive patients with IP admitted over a 2.5-year period. Transferred patients were excluded. We collected data on age, Charlson comorbidity score (CCI), measures of severity on admission or within 24 hours (Acute Physiology and Chronic Health Evaluation II, bedside index for severity of acute pancreatitis scores), persistent (>48h) systemic inflammatory response syndrome, persistent organ failure, need for intensive care unit, length of hospital stay (in days), and mortality. We also analyzed levels of severity among those with IP and EXPN. Statistical analysis was performed using SAS version 9.1 (Cary, NC).

Results: Among the patients with IP, the median CCI score was 1, the median Acute Physiology and Chronic Health Evaluation II score was 7, and the median bedside index for severity of acute pancreatitis score was 1. In addition, the median length of hospital stay was only 4 days; only 1% had persistent organ failure and only 1% to 2% required intervention. The mortality rate of IP was 3%; it was associated significantly with comorbidity (the median CCI scores of non-survivors and survivors was 4 and 1, respectively, *P* .003). Patients with EXPN had greater levels of disease severity, compared with patients with IP.

Conclusions: IP is severe in only 1% to 3% of patients; mortality of IP is associated strongly with comorbidity. EXPN is more frequently severe than IP; EXPN must be distinguished from IP in clinical studies.

Introduction

Interstitial pancreatitis (IP) has been recognized as a distinct clinicopathologic form of acute pancreatitis for nearly 9 decades.[1] Although nearly 85% of patients hospitalized for acute pancreatitis have IP, most clinical studies over the past 2 decades have evaluated severity of necrotizing pancreatitis (NP).[2]

Early surgical[1,3] and autopsy series[4–6] of IP were limited by incomplete clinical data and their focus on small numbers of patients with the most severe form of disease. More recent surgical studies have reported mortality rates of 6.3% to 9.2% in IP.[7,8] More recent nonsurgical studies have reported mortality rates of 0% to 5.3%.[9–19] Several studies reported organ failure rates of 6.8% to 18%[9,18–20] but did not make the important distinction between transient and persistent organ failure.[21,22]

Key limitations to all prior studies evaluating severity in IP include the inclusion of transferred patients[23,24] and the likely inclusion of patients with extrapancreatic necrosis (EXPN).[17,25] Both groups have been shown to have increased severity of disease, and their inclusion in studies of IP tends to bias the results. These limitations make it difficult to draw conclusions regarding the severity of IP.

The primary aim of our study was to examine the severity of IP among a cohort of nontransferred consecutive patients. The secondary aim was to compare severity between patients with IP and EXPN.

METHODS

The demographic, clinical, laboratory, and radiologic data for all patients directly admitted to our institution with a diagnosis of acute pancreatitis between June 2005 and December 2007 were collected prospectively. All patients transferred from outside institutions were excluded from the study. Patients with radiographic evidence of chronic pancreatitis also were excluded from the study. Among patients with prior or multiple episodes of acute pancreatitis, only the first admission for acute pancreatitis at our institution was evaluated. Data for all patients were collected prospectively for 7 days or until discharge if fewer than 7 days. This Health Insurance Portability and Accountability Act–compliant study was approved by our institutional review board.

Acute pancreatitis was defined as 2 or more of the following: characteristic abdominal pain; serum amylase and/or lipase levels 3 times the upper limit of normal; a contrast-enhanced computed tomography (CECT) of the abdomen or magnetic resonance imaging within the first 7 days of hospitalization showing characteristic changes of acute pancreatitis. IP and NP were defined in accordance with the Atlanta Classification of acute pancreatitis.[26] EXPN was defined by the presence of normally enhancing pancreatic parenchyma surrounded by a heterogeneous collection consisting of liquid and nonliquid densities on at least 2 consecutive CECTs. A prior study showed correlation between radiologic and subsequent surgical findings in patients with EXPN.[25] The CT severity index (CTSI) was used to assess the severity of pancreatitis.[14] The decision to obtain imaging was at the discretion of the treating clinicians. All imaging studies were reviewed separately by 2 radiologists (T.L.B. and K.J.M.) who were blinded to the clinical data.

Risk factors for severity of acute pancreatitis on admission included age,[27,28] male sex,[29] alcohol use,[30,31] first episode,[32] and obesity (body mass index, >30).[33,34] Measures of severity at admission included increased blood urea nitrogen level (>25 mg/dL)[35,36] and hemoconcentration (hematocrit, >44).[18,37,38] Measures of severity within 24 hours of admission included Acute Physiology and Chronic Health Evaluation II[26] and bedside index for severity of acute pancreatitis scores.[39,40]

Markers of severity during hospitalization included persistent systemic inflammatory response syndrome (SIRS),[41–43] persistent organ failure,[21,22,41] length of stay, need for intensive care unit (ICU), development of hospital-acquired extrapancreatic infection,[44,45] and mortality.

Organ failure was defined as a score of 2 or greater in 1 or more of the 3 organ systems (cardiovascular, respiratory, and renal).[46] Organ failure was assessed for all patients during the first 7 days of hospitalization based on the most extreme laboratory value or clinical measurement in each 24-hour period. Duration of organ failure was defined as transient if lasting 48 hours or fewer, or persistent if lasting more than 48 hours.

SIRS was defined as 2 or more of the following: temperature lower than 36° or greater than 38°C; $PaCO_2$ less than 32 mm Hg or respiratory rate greater than 20 breaths/min; pulse greater than 90 beats/min; white blood count less than 4000 or greater than 12,000 cells/mm^3 or greater than 10% immature bands. SIRS scores were calculated on all patients during the first 7 days of hospitalization based on the most extreme laboratory value or clinical measurement in each 24-hour period. SIRS was defined as transient if lasting 48 hours or fewer or persistent if lasting more than 48 hours during the first 7 days of hospitalization.

Extrapancreatic infection (EI) was defined by the presence of a positive blood, sputum, and/or urine culture, and/or imaging showing a pulmonary infiltrate within the first 7 days of hospitalization.[45]

Mortality was defined as death occurring during hospitalization or within 30 days of hospital discharge.

The Charlson comorbidity index (CCI) score was used to quantify the burden of comorbid disease.[47] CCI as well as age-adjusted CCI (ACCI) scores were calculated for all patients in the study cohort.

Statistical Analysis

Statistical comparisons were performed using the chi-square or the Fisher exact tests for categoric variables, analysis of variance for normally distributed numeric variables, and the Wilcoxon rank sum test for non-normally distributed numeric variables. All statistical calculations were performed using SAS version 9.1 (Cary, NC).

RESULTS

Figure 1 shows the selection criteria of the study cohort. A total of 306 patients with acute pancreatitis were evaluated. We excluded 54 patients transferred from outside institutions. Among these 54 patients, 23 had NP, 25 had IP, and 6 had EXPN. Of the remaining 252 patients who were admitted directly to our institution, we excluded the 17 patients with an unenhanced computed tomography, 11 patients with NP, and 8 patients with EXPN. Among the 216

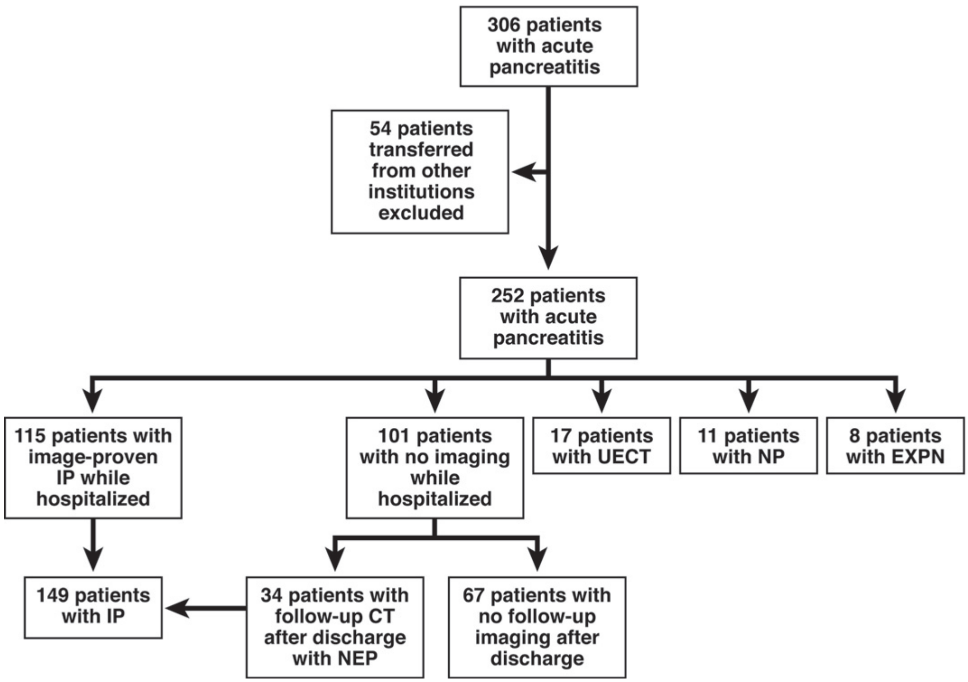

FIGURE 1. Selection criteria for study cohort. NEP, normally enhancing pancreas; UECT, unenhanced CT.

remaining patients, 115 underwent a CECT (n = 94) or magnetic resonance imaging (n = 21) showing IP, whereas 101 had no imaging while hospitalized. Among the 101 patients without imaging while hospitalized, 34 patients had a CECT after discharge from the hospital showing a normally enhancing pancreas. Therefore, a total of 149 patients had imaging consistent with interstitial pancreatitis.

TABLE 1. Severity and Interventions Among Total Patient Cohort and Among Patients With IP Confirmed by CT and Those With No CT

	Total (n = 216)	IP (n = 149)	No CT (n = 67)	P value[a]
Risk factors for severity on admission				
Age, y	52 ± 17	54 ± 17	48 ± 16	.35
Male sex	92 (43)	64 (43)	28 (42)	.88
BMI≥30	73 (35)	49 (33)	24 (39)	.53
Alcohol etiology	38 (18)	23 (15)	15 (22)	.25
First episode	155 (72)	107 (72)	48 (72)	1.00
CCI	0 [0, 2]	1 [0, 2]	0 [0, 1]	.001
ACCI	1 [0, 4]	2 [0, 4]	1 [0, 3]	.007
Measures of severity at admission or ≤ 24h				
BUN>25	23 (11)	16 (11)	7 (10)	1.00
HCT≥44	39 (18)	26 (17)	13 (19)	.71
APACHE II, ≤ 24h	7 [4, 10]	7 [5, 10]	6 [4, 9]	.03
BISAP, ≤ 24h	1 [1, 2]	1 [1, 2]	1 [1, 1]	.03
Markers of severity during hospitalization				
Persistent SIRS	48 (22)	42 (28)	6 (9)	.001
Persistent organ failure	4 (2)	2 (1)	2 (3)	.59
Length of stay, d	3 [2, 6]	4 [2, 7]	3 [2, 4]	.001
Need for ICU	15 (7)	10 (7)	5 (7)	.78
EI	34 (16)	27 (18)	7 (10)	.22
Death	6 (3)	5 (3)	1 (1.5)	.67
Interventions				
Need for intubation	3 (1)	3 (2)	0 (0)	.55
Need for dialysis	0 (0)	0 (0)	0 (0)	NA
Need for pressors	1 (0.5)	1 (1)	0 (0)	1.00
Received antibiotics	77 (36)	62 (42)	15 (22)	.009

NOTE. Values are expressed as mean ± standard deviation, median [Q1, Q3], and number (%).
APACHE, Acute Physiology and Chronic Health Evaluation; BISAP, bedside index for severity of acute pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; EI, extrapancreatic infection; HCT, hematocrit.
[a]P values reflect comparison between IP versus no CT.

Table 1 displays the severity and interventions of the full cohort of 216 patients and compares the severity of the 149 patients with imaging-confirmed IP with the 67 patients who did not have any imaging. The 149 patients with IP had significantly higher CCI, ACCI, Acute Physiology and Chronic Health Evaluation II, and bedside index for severity of acute pancreatitis scores, and had significantly higher rates of persistent SIRS and longer length of stay. Given the increased severity among patients with imaging compared with those who did not undergo imaging, patients without imaging most likely also had IP. However, we limited our evaluation to the 149 patients with imaging-proven IP. These data indicate that nearly all

TABLE 2. Comparisons Between IP Nonsurvivors and Survivors With Regard to Severity and Interventions

	IP (n = 149)		
	Nonsurvivors (n = 5)	Survivors (n = 144)	P value
Risk factors for severity on admission			
Age, y	58 ± 5	54 ± 17	.62
Male sex	3 (60)	61 (42)	.65
BMI ≥ 30	1 (20)	48 (33)	.67
Alcohol etiology	1 (20)	22 (15)	.57
First episode	4 (80)	103 (72)	1.00
CCI	4 [3, 6]	1 [0, 2]	.003
ACCI	5 [4, 7]	2 [0, 4]	.01
Measures of severity at admission or ≤ 24h			
BUN ≥ 25	1 (20)	15 (10)	.44
HCT ≥ 44	0 (0)	26 (18)	.59
APACHE II, ≤ 24h	11 [9, 14]	7 [5, 10]	.07
BISAP, ≤ 24h	1 [1, 1]	1 [1, 2]	.59
Markers of severity during hospitalization			
Persistent SIRS	5 (100)	37 (26)	.002
Persistent organ failure	2 (40)	0 (0)	.0001
Length of stay, d	10 [9, 19]	4 [2, 7]	.002
Need for ICU	3 (60)	7 (5)	.002
EI	1 (20)	26 (18)	1.00
Interventions			
Need for intubation	2 (40)	1 (0.7)	.003
Need for dialysis	NA	NA	NA
Need for pressors	1 (20)	0 (0)	.03
Received antibiotics	4 (80)	58 (40)	.16

NOTE. Values are expressed as mean ± standard deviation, median [Q1, Q3], and number (%).
APACHE, Acute Physiology and Chronic Health Evaluation; BISAP, bedside index for severity of acute pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; EI, extrapancreatic infection; HCT, hematocrit.

patients with interstitial pancreatitis have mild disease, with only 1% having persistent organ failure, a median length of stay of only 4 days, need for ICU in only 7%, mortality rate of only 3%, and minimal need for intervention (intubation, dialysis, or pressors).

Table 2 compares severity and interventions between nonsurvivors and survivors with IP. Nonsurvivors had a significantly higher median CCI and ACCI and significantly higher rates of persistent SIRS and persistent organ failure. They also had an increased need for ICU, longer length of stay, and increased need for intubation and pressor support. If the patients who did not undergo imaging while hospitalized (n = 67) are included in this comparison, the results do not change ($P > .05$) (data not shown).

Table 3 shows the clinical details of the 5 nonsurvivors with IP. The highest CTSI was only 2 within the first 7 days of hospitalization for all 5 nonsurvivors. Malignancy and severe liver disease were the comorbid conditions associated with death among the nonsurvivors. Among the 67 patients who did not undergo imaging, there was a single death as a result of severe liver disease.

Table 4 compares severity and interventions among the 149 patients with IP and the 8 patients with EXPN. The patients with EXPN were more likely to be male and have acute alcoholic pancreatitis compared with those with IP. There were no significant differences in measures of severity at admission or within 24 hours. Patients with EXPN had higher rates of persistent organ failure, increased need for ICU, a longer median length of stay, and increased need for intubation and pressor administration. The mortality rates were similar between both groups of patients.

TABLE 3. Clinical Characteristics of IP Nonsurvivors

Patient	Number of days from admission to death	Highest CTSI in first 7 days of hospitalization	Comorbid diseases	Cause of death
1	10	2	Severe liver disease	Fulminant liver failure
2	9	2	Metastatic solid malignancy, peptic ulcer disease	Metastatic esophageal cancer
3	18	2	Metastatic solid malignancy	Metastatic duodenal cancer
4	8	2	Diabetes	Sepsis
5	30	2	Lymphoma	Graft-vs-host disease

TABLE 4. Comparison of Severity and Interventions Among Patients With IP and EXPN

	IP (n = 149)	EXPN (n = 8)	P value
Risk factors for severity on admission			
Age, y	54 ± 17	46 ± 11	.18
Male sex	64 (43)	7 (88)	.01
BMI ≥ 30	49 (33)	4 (50)	.45
Alcohol etiology	23 (15)	4 (50)	.01
First episode	107 (72)	6 (75)	1.00
CCI	1 [0, 2]	1 [0, 3]	.58
ACCI	2 [0, 4]	2 [0, 4]	.80
Measures of severity at admission or ≤ 24h			
BUN ≥ 25	16 (11)	1 (13)	1.0
HCT 44	26 (17)	3 (38)	.17
APACHE II, ≤ 24h	7 [5, 10]	8 [5, 13.5]	.38
BISAP, ≤ 24h	1 [1, 2]	1 [1, 2]	.80
Markers of severity during hospitalization			
Persistent SIRS	52 (28)	5 (63)	.05
Persistent organ failure	2 (1)	2 (25)	.01
Length of stay, d	4 [2, 7]	9.5 [5.5, 13]	.004
Need for ICU	10 (7)	3 (38)	.02
EI	27 (18)	2 (25)	.64
Death	5 (3)	1 (13)	.27
Interventions			
Need for intubation	3 (2)	2 (25)	.02
Need for dialysis	0 (0)	1 (13)	.05
Need for pressors	1 (0.7)	2 (25)	.007
Received antibiotics	62 (42)	6 (75)	.08

NOTE. Values are expressed as number (%), median [Q1, Q3], or mean ±standard deviation.
APACHE, Acute Physiology and Chronic Health Evaluation; BISAP, bedside index for severity of acute pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; EI, extrapancreatic infection; HCT, hematocrit.

DISCUSSION

Our study systematically evaluated severity of IP in a cohort of consecutive nontransferred patients. We found that IP was a very mild disease in nearly all patients with a median length of stay of only 4 days, persistent organ failure in only 1%, and a mortality rate of only 3%.

Mortality in IP was associated significantly with increased comorbidity, persistent SIRS, and persistent organ failure. It appears that comorbidity played a more important role in mortality than the severity of underlying IP. This is supported by 2 findings. First, measures of severity at admission and within 24 hours were similar between nonsurvivors and survivors. Second, all of our nonsurvivors had a CTSI of only 2 during hospitalization. Because a CTSI of 2 represents pancreatic gland inflammation associated with only mild peripancreatic inflammation and no fluid collections, our nonsurvivors also clearly had very mild pancreatitis by imaging criteria.[14]

Prior autopsy studies[4–6] also have shown an increased prevalence of comorbid diseases in patients with IP but have focused on those with severe acute pancreatitis[4–6] and did not use a validated instrument to measure comorbidity. A few clinical studies of acute pancreatitis have used age as a surrogate for comorbidity.[27,28] Other clinical studies have used the CCI[48,49] and Elixhauser index[50,51] but focused on patients with severe acute pancreatitis[48,49] and did not differentiate between patients with IP and NP on the basis of imaging studies.[48–51]

The mortality of patients with EI has been reported to be 28% in 2 prior studies that included patients with NP as well as IP.[44,45] Our mortality rate of 3.7% among patients with IP who developed an EI was not significantly different from the overall IP mortality rate of 3% in our study. It would appear that EI has a stronger impact on mortality in NP than IP.

Prior studies evaluating disease severity in IP have had numerous methodologic limitations. First, these studies have included transferred patients who, in general, have more severe acute pancreatitis than direct admissions.[23,24,52,53] Second, there are no prior studies that have distinguished between transient and persistent organ failure among patients with IP.[9,18–20] Several studies have reported that persistent organ failure has a mortality rate of 35% to 55% compared with 0% to 1% with transient organ failure,[21,22,41] but failed to indicate how many patients had IP in their study cohorts. Third, prior studies have focused only on those patients who underwent radiologic imaging. The severity of those who did not undergo imaging was not determined. In the present study, we found that the severity of acute pancreatitis in patients without imaging was less than in those with imaging, suggesting that those without imaging likely had IP. Fourth, aside from a single study from Bruennler et al,[17] no other studies have distinguished between IP and EXPN.

Extrapancreatic necrosis is defined as necrosis of the peripancreatic fat and tissue with a normally enhancing pancreatic gland on contrast-enhanced imaging studies.[25] Although the accuracy of CT for diagnosing EXPN has not been studied in depth, a prior study showed correlation between CECT and surgical findings in patients with EXPN.[25] Patients with an alcohol etiology were more likely to present with EXPN than with IP. Alcohol use has been shown previously to be a risk factor for pancreatic necrosis,[54] and it also may be a risk factor for EXPN. There were no measures of severity at admission or within 24 hours of admission, which differentiated patients with EXPN from IP. However, patients with EXPN had increased severity of disease during hospitalization when compared with patients with IP. The likely inclusion of patients with EXPN in prior studies of IP is a potential explanation for the wide variation in rates of organ failure and mortality.

In 2 prior clinical studies that have evaluated EXPN, the mortality rate was 8% in one study[25] and 100% in the other study.[17] However, the results of these studies were limited by the inclusion of transferred patients.

The strengths of our study were as follows: (1) prospective data collection, (2) evaluation of a large number of consecutive direct admissions with exclusion of patients transferred from outside institutions, and (3) assessment of comorbidity using a prospectively validated scoring system that has been used previously in several other disease states.

The primary limitation of our study was that some patients did not undergo a CT scan to determine whether they had IP. However, if patients without imaging are combined with patients who underwent imaging, the rates of mortality and persistent organ failure were essentially the same as for patients who underwent imaging (Table 1).

In summary, almost all patients with IP experienced very mild disease. Comorbidity was a very important factor for mortality in IP. Because the severity of EXPN was greater than that of IP, EXPN must be distinguished from IP in clinical studies.

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13

Extrapancreatic necrosis without pancreatic parenchymal necrosis:

A separate entity in necrotising pancreatitis?

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ABSTRACT

Objective: In the revised Atlanta Classification of acute pancreatitis, the term necrotising pancreatitis also refers to patients with only extrapancreatic fat necrosis without pancreatic parenchymal necrosis (EXPN), as determined on contrast-enhanced CT (CECT). Patients with EXPN are thought to have a better clinical outcome, although robust data are lacking.

Methods: A post hoc analysis was performed of a prospective multicentre database including 639 patients with necrotising pancreatitis on contrast-enhanced CT. All CECT scans were reviewed by a single radiologist blinded to the clinical outcome. Patients with EXPN were compared with patients with pancreatic parenchymal necrosis (with or without extrapancreatic necrosis). Outcomes were persistent organ failure, need for intervention and mortality. A predefined subgroup analysis was performed on patients who developed infected necrosis.

Results: 315 patients with EXPN were compared with 324 patients with pancreatic parenchymal necrosis. Patients with EXPN less often suffered from complications: persistent organ failure (21% vs 45%, $p<0.001$), persistent multiple organ failure (15% vs 36%, $p<0.001$), infected necrosis (16% vs 47%, $p<0.001$), intervention (18% vs 57%, $p<0.001$) and mortality (9% vs 20%, $p<0.001$). When infection of extrapancreatic necrosis developed, outcomes between groups were equal (mortality with infected necrosis: EXPN 28% vs pancreatic necrosis 18%, $p=0.16$).

Conclusion: EXPN causes fewer complications than pancreatic parenchymal necrosis. It should therefore be considered a separate entity in acute pancreatitis. Outcome in cases of infected necrosis is similar.

INTRODUCTION

In a disease as complex as acute pancreatitis, correct terminology and clear definitions are essential in interdisciplinary communication among treating physicians as well as in reports of clinical research. In the 1992 Atlanta Classification, necrotising pancreatitis was defined as diffuse or focal area(s) of non-viable pancreatic parenchyma typically associated with extrapancreatic fat necrosis or non-enhanced pancreatic parenchyma >3 cm in length or involving >30% of the area of the pancreas.[1] This definition did not include patients with extrapancreatic necrosis only (EXPN). Over the years a few small case series have described patients undergoing surgical removal of extensive extrapancreatic necrosis while the pancreatic parenchyma appeared to be viable.[2–5] Since these first reports, no prospective study has compared the outcome of patients with EXPN with patients with pancreatic parenchymal necrosis (or, in short, pancreatic necrosis) in a large consecutive cohort.

The primary aim of this study was to investigate whether the rate of complications and mortality of patients with EXPN differs from that of patients with pancreatic necrosis with or without extrapancreatic necrosis. The second aim was to determine whether the rates of complications differ between patients with EXPN or pancreatic necrosis who develop infected necrosis.

METHODS

Patients

This was a post hoc analysis of a database of a prospective multicentre cohort study.[6] Patients with acute pancreatitis were included between March 2004 and November 2008 in all eight Dutch university medical centres and 13 large teaching hospitals of the Dutch Pancreatitis Study Group. During the study period, all patients admitted with acute pancreatitis were screened for eligibility for the Dutch PROPATRIA and PANTER trials.[7 8] Regardless of eligibility for the randomised trials, patients were asked for informed consent for registration in the prospective database on admission.

Details on the general treatment protocol, data collection and definitions of outcomes (eg, definition of primary infected necrosis or organ failure) of this cohort have been described previously.[6] Infected necrosis was defined as a positive culture of pancreatic or extrapancreatic necrosis obtained by means of fine needle aspiration or from the first drainage procedure or first necrosectomy, or the presence of gas in the peripancreatic collection on contrast-enhanced CT. In the current study, new analyses were performed specifically to compare patients with pancreatic necrosis (with or without extrapancreatic necrosis) with patients with EXPN as determined on CECT. Patients with interstitial pancreatitis were excluded. The following baseline parameters were assessed: age, aetiology, American Society of Anaesthesiologists (ASA) classification on admission, Acute Physiology, Age, and Chronic Health Evaluation

(APACHE)-II score on admission, Imrie or Modified Glasgow score, C reactive protein (CRP) during the first 48h of admission and number of transferred patients from other hospitals to one of the hospitals of the Dutch Pancreatitis Study Group. The following outcome parameters were assessed: organ failure, multiple organ failure, development of sterile or infected necrosis, conservative treatment or intervention and mortality.

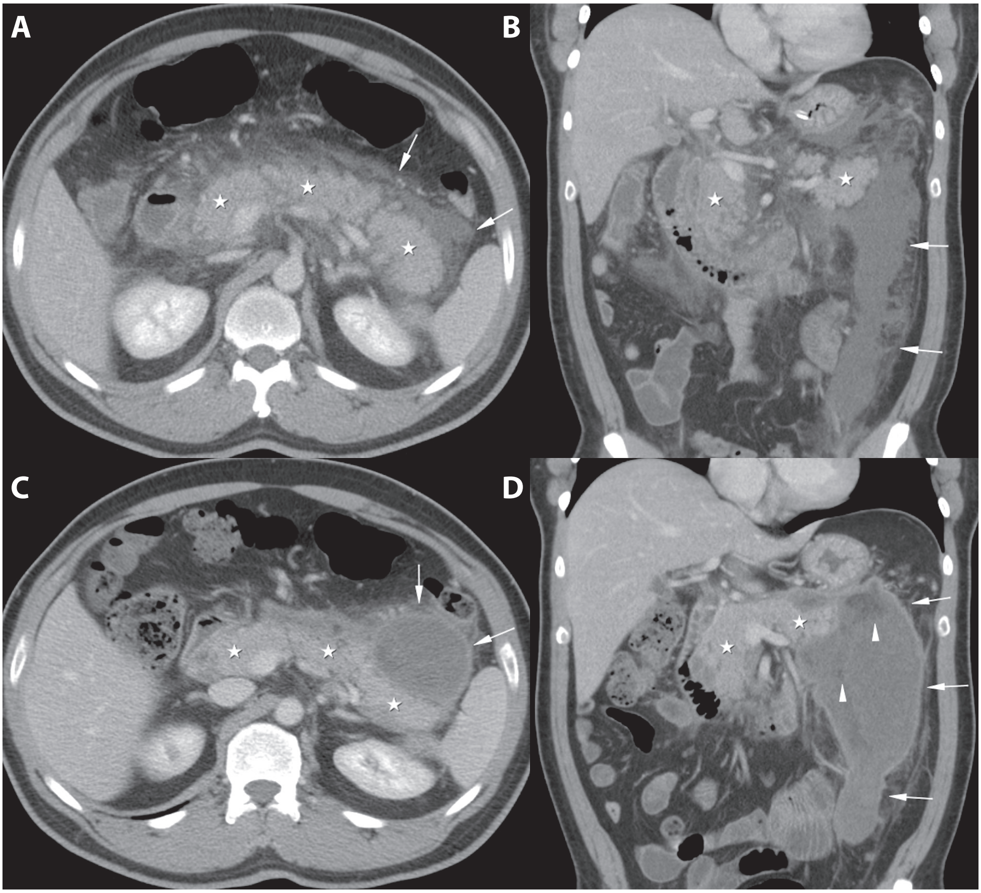

FIGURE 1 Extrapancreatic necrosis. **(A, B)** Axial and coronal reconstructed contrast-enhanced CT scans in a 37-year-old man with alcohol-induced pancreatitis 6 days after onset of symptoms. There is normal enhancement of the pancreatic parenchyma (white asterisks) with a poorly marginated peripancreatic collection (arrows) extending into the left anterior pararenal compartment. **(C, D)** Axial and coronal reconstructed contrast-enhanced CT scans 2 months later, again showing a normal enhancement of the pancreas surrounded by a well encapsulated heterogeneous peripancreatic collection (arrows) with areas of non-liquid (fat) densities (arrowheads) in the left anterior pararenal compartment. During surgery a large amountof necrotic material was debrided and pus was drained. The patient recovered uneventfully with preservation of normal pancreatic function.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was investigator-initiated and investigator-driven. The ethics review board of each participating hospital approved the study. Patients or their legal representatives gave written informed consent. We adhered to the STROBE statement guidelines for reporting on observational cohort studies.[9]

Definitions of extrapancreatic necrosis and pancreatic necrosis

Pancreatic necrosis was defined as focal or diffuse non-enhancement of the pancreatic gland as determined on CECT. Extrapancreatic necrosis only without pancreatic necrosis (ie, EXPN; figure 1) was defined as extrapancreatic morphological changes exceeding fat stranding with complete enhancement of the pancreatic parenchyma without signs of focal or diffuse non-enhancement able to be determined on the final CECT of hospitalisation or before any intervention. Patients with both pancreatic and extrapancreatic necrosis were included in the pancreatic necrosis group (figure 2). Patients with pancreatic necrosis without extrapancreatic necrosis, which is very rare, were also included in the group of patients with pancreatic necrosis.

FIGURE 2 Acute necrotising pancreatitis. Axial contrast-enhanced CT scan in a 45-year-old woman with acute biliary pancreatitis. There is non-enhancement of the neck and part of the body of the pancreas (white asterisk) indicative of parenchymal necrosis with normal enhancement of the tail of the pancreas (black asterisk).

Evaluation of imaging

CECT generally was performed approximately 7 days after admission. In patients with clinical deterioration or without clinical improvement, additional CECTs were performed. In patients participating in the PROPATRIA trial, a CECT after 7–10 days was part of the protocol. Radiologists in the participating centres assessed the CECT for the presence or absence of necrotising pancreatitis. Based on their evaluation, patients were included in the prospective database. After closure of the database following completion of the PANTER trial, all CECTs performed during and after hospitalisation were reviewed by a single experienced abdominal radiologist (TLB) who was unaware of the patients' clinical background, possible interventions and the initial radiology report. Because extrapancreatic or parenchymal necrosis can be missed on CECTs performed early in the disease course, all CECTs performed in each patient were reviewed. The final decision on the presence or absence of EXPN or pancreatic necrosis was based on the final CECT of hospitalisation or before any intervention.

Statistical analysis

Continuous data are presented as median with interquartile range (IQR). Differences were tested with the Mann–Whitney U test. Proportions were compared by the χ^2 test, the Fisher exact or the linear-by-linear association test, as appropriate. To assess whether EXPN is an independent predictor of clinical outcome, multivariable regression analysis was performed adjusting for potential confounders (eg, prognostic variables on admission such as age). The following clinical outcomes were analysed: persistent organ failure, persistent multiple organ failure, infected necrosis, the need for intervention and mortality. EXPN was entered into the model as the main factor. As co-variables, all prognostic variables that were potentially different between patients with EXPN and those with pancreatic necrosis on admission in univariable analysis (p<0.2) were included. The results are reported as adjusted odd ratios (ORs) with 95% confidence intervals (CIs). A two-sided p<0.05 was considered statistically significant. Analyses were performed with SPSS V.15.0 (SPSS).

RESULTS

Patients

Of the 639 patients included in the prospective database, 315 patients (49%) had EXPN (determined on CECT) and 324 patients (51%) had signs of pancreatic necrosis (with or without extrapancreatic necrosis) (figure 3). Only four of the 639 patients (0.6%) had pancreatic necrosis without any signs of peripancreatic necrosis and these patients were included in the pancreatic necrosis group. Patients with interstitial pancreatitis were excluded. Baseline characteristics are shown in table 1. No differences were seen in age, sex, aetiology, ASA classification and predicted severity based on APACHE-II scores and CRP levels. The median Imrie score at 48h after admission was higher in patients with pancreatic necrosis (4 vs 3, p<0.001). The percentage of transferred patients was also higher in patients with pancreatic necrosis (36% vs 13%, p<0.001).

Use of CECT

A median number of 2 (IQR 4–7) CECTs were performed in each patient (table 1). Patients with EXPN were scanned less frequently than those with pancreatic necrosis (median 2 (IQR 1–4) vs 6 (IQR 3–10), p<0.001). The overall median time between onset of symptoms and the final CECT of hospitalisation or before any intervention was 14 days (IQR 7–46). Patients with EXPN had their final CECT earlier than patients with pancreatic necrosis (median 9 days (IQR 5–21) after admission vs 34 days (IQR 9–71), p<0.001).

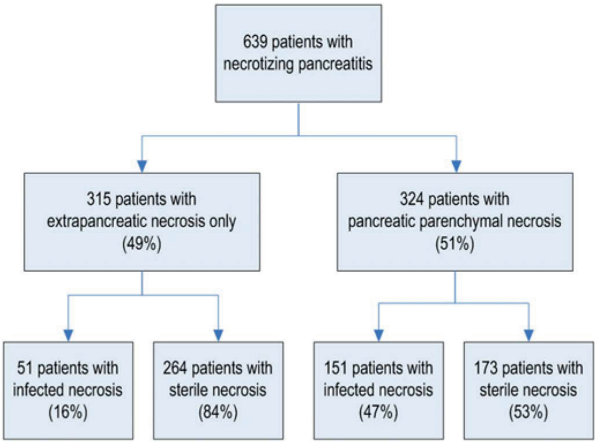

FIGURE 3. Study population.

TABLE 1. Admission characteristics of patients with extrapancreatic necrosis only (EXPN) compared with patients with pancreatic parenchymal necrosis

Characteristic	All patients (N=639)	EXPN (N=315)	Pancreatic necrosis (N=324)	p Value
Age (years)	58 (45–70)	58 (44–72)	58 (45–69)	0.24†
Male sex	398 (62%)	184 (58%)	214 (66%)	0.05‡
Aetiology				0.26§
Gallstones	304 (48%)	149 (47%)	155 (48%)	
Alcohol abuse	150 (24%)	76 (24%)	74 (23%)	
Other	63 (10%)	37 (12%)	26 (8%)	
Unknown	122 (19%)	53 (17%)	69 (21%)	
ASA class on admission				0.79¶
I (healthy status)	202 (32%)	97 (31%)	105 (32%)	
II (mild systemic disease)	347 (54%)	174 (55%)	173 (53%)	
III (severe systemic disease)	90 (14%)	44 (14%)	46 (14%)	
Predicted severity of pancreatitis				
APACHE-II score on admission	8 (5–11)	7 (5–10)	8 (5–11)	0.98†
Imrie/modified Glasgow score after 48h	3 (2–5)	3 (2–4)	4 (2–5)	<0.001†
Highest CRP level in first 48h	291 (216–382)	293 (216–278)	290 (215–388)	0.60†
Transferred from other hospital	156 (24%)	40 (13%)	116 (36%)	<0.001‡
No. of CECTs performed per patient*	2 (4–7)	2 (1–4)	6 (3–10)	<0.001†
Timing of final CECT* (days after admission)	14 (7–46)	9 (5–21)	34 (9–71)	<0.001†

Continuous variables are median (IQR). *Before discharge or any intervention. †Mann–Whitney U test. ‡Fisher exact test. §Pearson χ^2 test. ¶Linear-by-linear association. APACHE, Acute Physiology Age and Chronic Health Evaluation; ASA, American Society of Anaesthesiologists; CECT, contrast-enhanced CT; CRP, C-reactive protein.

Outcomes

The different outcomes of patients with pancreatic necrosis and EXPN are presented in table 2. All outcomes occurred less often in patients with EXPN. More specifically, patients with EXPN had a significantly lower risk of developing single or multiple organ failure. Twice as many patients with pancreatic necrosis developed persistent organ failure during admission (21% vs 45%, p<0.001). Persistent multiple organ failure was also seen in twice as many patients with pancreatic necrosis (15% vs 36%, p<0.001). Patients with EXPN had a lower risk of developing infected necrosis (16% vs 47%, p<0.001). The need for intervention was lower in patients with EXPN (18% vs 57%, p<0.001). Finally, the death rate in patients with EXPN was significantly lower (9% vs 20%, p<0.001).

TABLE 2. Outcome of patients with extrapancreatic necrosis only (EXPN) compared with patients with pancreatic parenchymal necrosis

Characteristic	EXPN (N=315)	Pancreatic necrosis (N=324)	p Value†
Organ failure			
At any time during admission	77 (24%)	163 (50%)	<0.001
At any time during admission, persistent	66 (21%)	147 (45%)	<0.001
In the first week of admission	47 (15%)	93 (29%)	<0.001
Multiple organ failure			
At any time during admission	56 (18%)	138 (43%)	<0.001
At any time during admission, persistent	46 (15%)	115 (36%)	<0.001
In the first week of admission	30 (10%)	64 (20%)	<0.001
Sterile or infected necrosis			
Sterile necrosis	264 (84%)	173 (54%)	<0.001
Primary infected necrosis	51 (16%)	151 (47%)	<0.001
Conservative treatment or intervention			
Conservative treatment	258 (82%)	139 (43%)	<0.001
Any intervention*	57 (18%)	185 (57%)	<0.001
Emergency laparotomy	3 (1%)	29 (9%)	<0.001
PCD (as first intervention)	37 (12%)	94 (29%)	<0.001
Necrosectomy‡	40 (13%)	129 (40%)	<0.001
Mortality	29 (9%)	64 (20%)	<0.001

*Emergency laparotomy, PCD or necrosectomy.
†Fisher exact test.
‡With or without previous PCD or emergency laparotomy. PCD, percutaneous catheter drainage.

After adjustment for potential confounding factors with multi-variable regression, patients with EXPN still had better clinical outcomes. After adjusting for male sex, Imrie score and transferred patients, EXPN was independently associated with a lower risk of organ failure (adjusted OR 0.53, CI 0.37 to 0.78, p<0.001), multiple organ failure (adjusted OR 0.48, CI 0.32 to 0.72, p<0.001), infected necrosis (adjusted OR 0.30, CI 0.20 to 0.45, p<0.001), any intervention (adjusted OR 0.25, CI 0.17 to 0.38, p<0.001) and mortality (adjusted OR 0.59, CI 0.35 to 0.97, p=0.04).

TABLE 3. Outcome in subgroup of patients with primary infected extrapancreatic necrosis only (EXPN) or pancreatic parenchymal necrosis

Characteristic	Infected EXPN (N=51)	Infected pancreatic necrosis (N=151)	p Value‡
Organ failure			
At any time during admission	31 (61%)	101 (67%)	0.50
At any time during admission, persistent	28 (55%)	90 (60%)	0.62
Multiple organ failure			
At any time during admission	26 (51%)	86 (57%)	0.52
At any time during admission, persistent	21 (41%)	70 (46%)	0.63
Conservative treatment or intervention			
Conservative treatment	4 (8%)	9 (6%)	0.74
Any intervention*	47 (92%)	142 (94%)	0.74
Emergency laparotomy	0 (0%)	4 (3%)	0.58
PCD (as first intervention)	32 (63%)	84 (56%)	0.42
PCD only†	14 (28%)	34 (23%)	0.57
Necrosectomy§	33 (65%)	108 (72%)	0.23
Mortality	14 (28%)	27 (18%)	0.16

*Emergency laparotomy, PCD or necrosectomy.
†In subgroup of patients with PCD as first intervention.
‡Fisher exact test.
§With or without previous PCD or emergency laparotomy. PCD, percutaneous catheter drainage.

Subgroup analysis of primary infected necrosis

The subgroup of 202 patients who developed infected necrosis was separately analysed. There were no significant differences between patients with infected EXPN and patients with infected pancreatic necrosis regarding all the aforementioned clinical outcomes (table 3). The incidence of persistent organ failure (55% of EXPN vs 60% of pancreatic necrosis, p=0.62) and persistent multiple organ failure (41% of EXPN vs 46% of pancreatic necrosis, p=0.63) was similar. Almost all patients with infected necrosis required an intervention (92% vs 94%, p=0.74). The likelihood of recovery following percutaneous catheter drainage without the need for additional necrosectomy was 28% versus 23% (p=0.57). Mortality did not differ significantly between the two groups (28% vs 18%, p=0.16).

DISCUSSION

This study, evaluating the clinical outcome of a large prospective cohort of patients with necrotising pancreatitis, shows that patients with EXPN (as determined on CECT) have a better prognosis than patients with pancreatic necrosis. However, in case of infected necrosis, rates of complication and mortality are similar. To our knowledge, this is the first report on clinical outcomes of EXPN in a large unselected cohort of patients with acute necrotising pancreatitis.

The presence of extrapancreatic necrosis as a separate entity in the absence of pancreatic necrosis was first recognised by Howard and Wagner in 1989.[2] In a group of 13 patients, pancreatography after debridement of necrosis showed an intact pancreatic duct in most patients. Subsequently, Madry and Fromm reported the results of 40 patients operated for infected necrosis.[4] Patients were described as having necrotic retroperitoneal fat without overt pancreatic necrosis. Sakorafas and colleagues were the first to report a better outcome in patients with EXPN who underwent surgical debridement.[5] Operative and CT findings of 12 patients operated for necrotising pancreatitis between 1983 and 1997 suggested that necrotising pancreatitis did not always involve the pancreatic parenchyma. In contrast to the current study, this retrospective study only reported the outcome of patients who underwent surgical debridement for necrotising pancreatitis and did not provide the clinical outcome of the total group of patients (with or without organ failure, sterile or infected, conservative treatment or after intervention). In their study, including 12 patients with EXPN, mortality was 8% which is comparable to the 9% death rate found in 315 patients with EXPN in this study. In both studies the death rate in patients with pancreatic necrosis was 20%. Accurate comparison of death rates between the two studies, however, is hampered by differences in patient characteristics, CECT assessment of EXPN, and study design (ie, experienced single-centre study vs multicentre study with academic and non-academic hospitals).

In the present study EXPN was diagnosed if CECT showed extrapancreatic fat with morphological changes that exceeded fat stranding and if the pancreatic parenchyma did not show any signs of necrosis as determined on the last CECT of hospitalisation or before any intervention. We cannot exclude, however, that small focal areas of parenchymal necrosis were overlooked on CT in patients with EXPN. Inversely, extrapancreatic morphological changes could also consist of fluid only instead of fat necrosis. Previous studies have indeed questioned the accuracy of CECT for diagnosing EXPN.[10 11] Small extrapancreatic collections (eg, <2 cm in diameter) most likely contain fluid which can easily be absorbed while large extrapancreatic effusions (eg, >5 cm in diameter) are less easily absorbed.[12] Collections that do not dissolve early in the course of the disease will most likely contain some degree of peripancreatic tissue necrosis and, hence, have a greater chance of being detected. If extrapancreatic changes have been overestimated and incorrectly scored as EXPN (while those patients actually had interstitial pancreatitis without necrosis), this could potentially question the validity of the differences found in this study. It is known that patients with interstitial pancreatitis have a better prognosis than patients with EXPN. A recent study from Boston compared the outcome of patients with interstitial pancreatitis with that of eight patients with EXPN.[13] Patients with interstitial pancreatitis had a better outcome in terms of organ failure, length of hospital stay, need for interventions and mortality, but this study did not include patients with pancreatic necrosis.

However, we have several reasons to believe that the presence of EXPN has not been overestimated in this study. First, several studies have actually demonstrated a good accuracy of CECT for EXPN when CECT findings were compared with the presence of fat necrosis at operation or autopsy.[14–16] Second, in patients with EXPN the median time between onset of symptoms and the last CECT before discharge was 9 days. Extrapancreatic collections that persist throughout the second week after onset of symptoms will, in the majority of cases, contain some amount of fat necrosis.[17 18] Third, the APACHE-II scores on admission and CRP levels after 48h did not differ between patients with EXPN and those with pancreatic necrosis. If patients with interstitial disease (with extrapancreatic fluid instead of extrapancreatic necrosis) had been incorrectly scored as EXPN and included in the study, one could speculate that the median severity scores on admission in the EXPN group would have been lower than the median severity scores of patients with pancreatic necrosis. However, as patients with interstitial disease (based on CECT) were not included in the study, we did not investigate whether the severity scores in this group of patients is actually lower than in patients with EXPN. In a previous multicentre study we found a death rate of 0.8% in patients with interstitial pancreatitis (the death rate in patients with EXPN in this study was 9%).[19] Although the Imrie scores did differ significantly after 48h, these scores reflect the ongoing inflammatory response and are likely to be more severe in patients with parenchymal necrosis. The same difference in ongoing inflammatory response between groups was seen in patients with organ failure during the first week.

The pathophysiological explanation for the better outcome of patients with EXPN remains speculative. It is generally believed that trypsin activation within pancreatic acinar cells leads to autodigestion and local inflammation.[20 21] Following a cascade of intracellular events, the pancreatic acinar cells may become necrotic. In some patients, extensive local inflammation causes a severe systemic inflammatory response syndrome that may lead to organ failure.[22 23] In EXPN, necrosis of the acinar cells does not seem to occur and the pancreatic parenchyma is preserved (at least on CECT). This might be indicative of a less severe local inflammatory response. Subsequently, a less severe *local* inflammatory response could explain the less severe *systemic* inflammatory response in patients with EXPN. Another potential explanation may be that the amount of released inflammatory mediators or cytokines in EXPN is lower. The concentration of inflammatory mediators might be higher in the pancreatic acinar cells than in the extrapancreatic fatty tissue. Parenchymal necrosis causes these mediators to be released into the systemic circulation. Conceivably, the higher the amount of mediators released, the more severe the systemic inflammatory response will be.[24] Lastly, it might be possible that ductal disruption, which may occur with parenchymal necrosis, causes more complications. Ductal disruption could facilitate bacterial invasion of pancreatic tissue. In this study we found that patients with pancreatic necrosis developed infection significantly more often (47% vs 16%).

In patients with necrotising pancreatitis, pancreatic exocrine and endocrine insufficiencies and pancreatic fistulas following interventions are common long-term complications.[8 25 26] In theory, EXPN will not cause these complications. None of the patients with EXPN in the study by Sakorafas developed endocrine or exocrine insufficiency during long-term follow-up. In a previous study, pancreatic fistulas were shown to cause considerable morbidity.[27] For this cohort, however, our prospective database did not include data on exocrine and endocrine insufficiency or pancreatic fistulas.

This clinical study does not necessarily prove, in terms of biology, that EXPN is a separate entity. Based on the results of this study, however, EXPN should be recognised as a different clinical entity within necrotising pancreatitis (compared with parenchymal necrosis) because it heralds several significant clinical implications. First, in cases of EXPN determined on CECT, surgeons should refrain from debridement of the pancreas during necrosectomy (eg, in case of infected necrosis) to prevent iatrogenic pancreatic injury. This knowledge is crucial as during surgery the differentiation between necrotic pancreatic parenchyma and peripancreatic fat necrosis can be difficult. Second, to compare reports of clinical studies on new interventions in necrotising pancreatitis accurately, future studies should report the number of patients with EXPN. Third, the presence of EXPN is a favourable prognosticator compared with pancreatic necrosis. The presence of EXPN should not change overall management but does provide the clinician with information for risk stratification. Fourth, our finding that infected EXPN has a similar poor outcome to that of infected pancreatic necrosis underlines the importance of adequate monitoring and timely recognition and treatment of sepsis in all patients with necrotising pancreatitis.

In summary, this study provides necessary data on the outcome of patients with EXPN. The prognosis of patients with non-infected EXPN has been shown to be significantly better than that of patients with non-infected pancreatic necrosis and could be considered a different clinical entity in acute pancreatitis. In case of infection, however, the prognosis is similar among patients with EXPN and those with parenchymal necrosis.

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14

Location of Pancreatic Parenchymal Necrosis determines Clinical Outcome in Necrotizing Pancreatitis

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SUBMITTED

ABSTRACT

Introduction: In acute pancreatitis, the extent of pancreatic parenchymal necrosis is deemed an important determinant of clinical outcome. Data on the impact of location of pancreatic necrosis is lacking. We investigated the clinical impact of both extent and location of pancreatic necrosis in a large cohort.

Material and Methods: This was a prospective observational cohort study. During a 4.5-year study period, all consecutive patients with pancreatic necrosis on contrast-enhanced computed tomography (CT) were included in 21 Dutch hospitals. Two radiologists, blinded to clinical outcome, independently reviewed all CTs and classified pancreatic necrosis with respect to its extent and location (i.e. the pattern of involvement) according to predefined criteria. Clinical severity parameters were available from a prospective database and included persistent organ failure, infected pancreatic necrosis, invasive intervention, and death.

Results: A total of 324 patients with pancreatic necrosis were included. Extent of pancreatic necrosis was less than 30% in 132 patients (40%), between 30-50% in 83 patients (26%), and over 50% in 109 patients (34%). All severity parameters, except mortality, differed significantly ($p<0.001$) between patients with less than 30% compared with over 30% pancreatic necrosis, but not between patients with 30 to 50% versus those with over 50% pancreatic necrosis.

Central gland necrosis was the most frequent pattern of necrosis encountered. All outcomes studied were significantly associated with location of pancreatic necrosis ($p<0.001$). Outcomes were poorer in patients with right-sided, central gland, and subtotal necrosis. In most multivariable analyses, the location of pancreatic necrosis was independently and most strongly associated with clinical outcomes.

Conclusion: Clinical severity of necrotizing pancreatitis is most strongly associated with location of pancreatic necrosis. Patients with right-sided, central gland, and subtotal necrosis have the poorest outcomes.

INTRODUCTION

Around one in five patients with acute pancreatitis develops pancreatic parenchymal necrosis (in short, pancreatic necrosis). These patients suffer frequently from local and systemic complications with an overall mortality of 5-10% [(1,2)]. Computed tomography (CT) is regarded the standard technique for imaging patients with severe acute pancreatitis [(3,4)]. CT is used for diagnosis and severity classification of the disease and its complications. Local complications depicted on CT that influence clinical outcome are the presence of pancreatic necrosis and associated peripancreatic collections [(4-6)]. Several studies have evaluated the association between extent of pancreatic necrosis and clinical outcomes, with varying results. Some have found a strong linear correlation between extent of pancreatic necrosis and clinical outcome [(7-18)], others did not [(19-28)]. Particularly, varying associations have been reported for patients with 30-50% versus those with more than 50% pancreatic necrosis. Several reports have also studied the clinical significance of location of pancreatic necrosis [(7-9,20,29-33)], again, with conflicting results. Previous studies on extent and location of pancreatic necrosis are limited due to smaller study populations (median 82, range 32-161 patients), retrospective acquisition of clinical data, selected study populations (e.g. alcoholic etiology or cohorts undergoing invasive therapy or managed non-operatively), heterogeneity of study outcomes and severity parameters (varying from differing criteria for organ failure, admission to intensive care unit or length of hospital stay to need for intervention), use of outdated imaging techniques (before the era of multisclice CT technique), performed in an era of different invasive intervention criteria (for example, early surgical intervention), or spanning longer time periods (median 7 years, range 2-12 years). Hence, we performed this study with the following aims; (a) to analyze and classify the extent and location of pancreatic necrosis and (b) to study the association between extent and location of pancreatic necrosis (based on the pattern of involvement) and clinical outcome.

MATERIALS AND METHODS

Study Design

This was an observational cohort study using a prospectively collected database of patients with a primary episode of necrotizing pancreatitis enrolled between March 2004 and November 2008 at 21 centers of the Dutch Pancreatitis Study Group. The ethics review board of all participating hospitals approved the study protocol. Written informed consent was obtained from all patients or their legal representatives. The original cohort consisted of 639 patients with necrotizing pancreatitis, including those with extrapancreatic necrosis alone. The clinical outcomes of these patients have been described previously [(34)]. For the current study, the subset of patients who had pancreatic necrosis was selected from this cohort.

Pancreatic Necrosis

Pancreatic necrosis was defined as areas of nonenhancement of pancreatic parenchyma on contrast-enhanced CT (CECT) [4-6]. The extent and anatomic location of pancreatic necrosis were recorded on all CECTs before any kind of intervention or death.

Extent of necrosis: The full extent of pancreatic necrosis was estimated visually as <30%, between 30-50%, and >50% [5,6].

Anatomic location of necrosis: Per pancreatic region (head, neck, body, and tail) the extent of involvement of necrosis was estimated visually as <50%, between 50% and 100%, and 100%.

The porto-mesenteric confluence was used as an anatomic landmark for subdividing the pancreas into four regions [35,36]. The pancreatic head (including the uncinate process) was defined as the portion of the pancreas right of the porto-mesenteric confluence. The pancreatic neck was defined as the portion of pancreas ventral to the porto-mesenteric confluence. The pancreatic body and tail was defined as the portion of the pancreas left to the pancreatic neck. The border between the body and tail was defined as halfway between the pancreatic neck and the left margin of the pancreas [35].

Pattern of necrosis: Subsequently, pancreatic necrosis was classified in the following five categories based on the dominant location of involvement, modified from Kemppainen et al [8]; right-sided necrosis, central gland necrosis, left-sided necrosis, subtotal necrosis, and scattered necrosis (Fig. 1). Right-sided necrosis was defined as lack of enhancement primarily in the pancreatic head (at least 50% of area involved) with or without little necrosis of other parts of the pancreas (Fig. 2). Central gland necrosis was defined as transparenchymal (necrosis of the entire anteroposterior width and craniocaudal length of the pancreas) lack of enhancement of pancreatic neck and/or body with normal enhancement of pancreatic head and viable upstream tail of at least 3 cm (Fig. 3). Left-sided necrosis was defined as lack of enhancement of pancreatic tail with or without involvement of the body and normal enhancement of head and neck of the pancreas (Fig. 4). Subtotal necrosis was defined as lack of enhancement of pancreatic neck, body and greater part of pancreatic head and tail (with or without sparing of small part of pancreatic head and tail) (Fig. 5). Scattered necrosis was defined as uni- or multifocal area(s) of lack of enhancement throughout the pancreas, without complete thickness or transparenchymal necrosis (i.e. partial thickness necrosis) (Fig. 6).

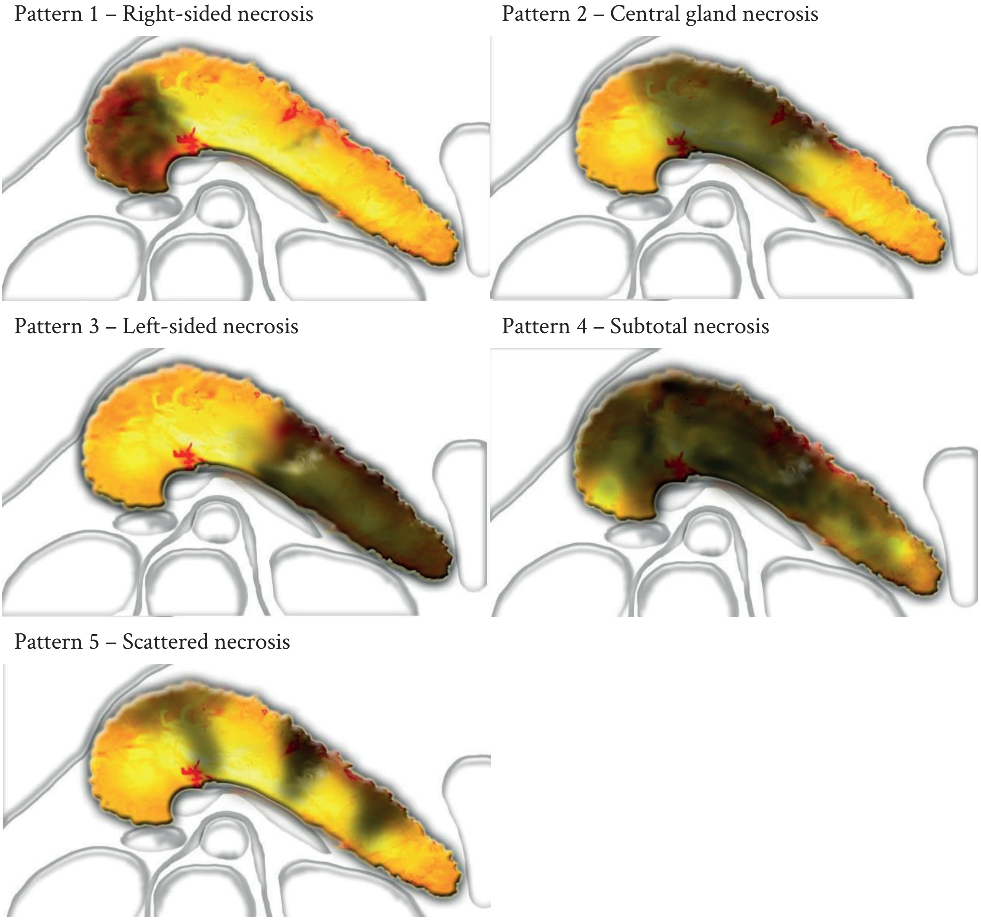

FIGURE 1. Patterns of pancreatic necrosis

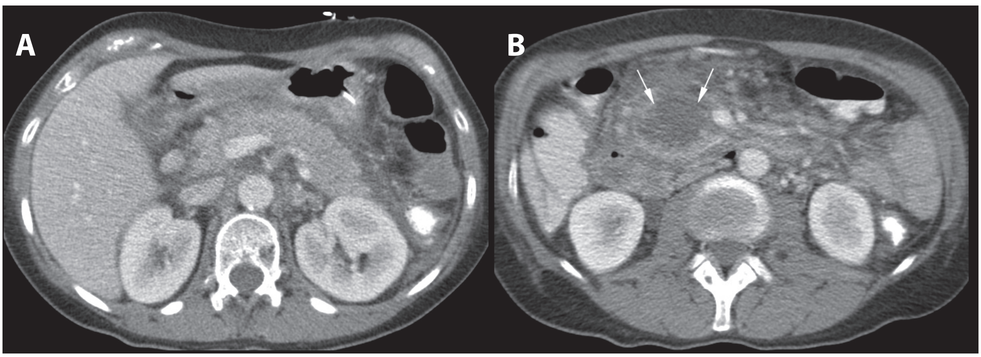

FIGURE 2A and B. Right sided necrosis – pattern 1. (**A**) CT showing normal enhancement of pancreatic body and tail, whereas the greater part of the pancreatic head (**B**) shows non-enhancement (small arrows).

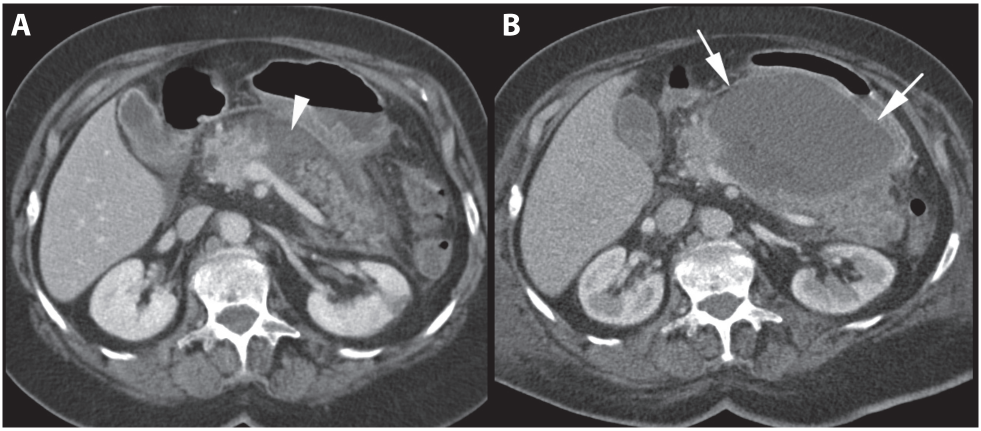

FIGURE 3A and B. Central gland necrosis – pattern 2. (**A**) CT depicts an area of non-enhancement at the body of the pancreas (arrowhead) representing <30% extent of necrosis with viable upstream pancreatic tissue. (**B**) Follow-up CT at day 17 shows a significant enlargement of the associated necrotic collection (arrows) abutting the stomach, likely related to a disrupted pancreatic duct.

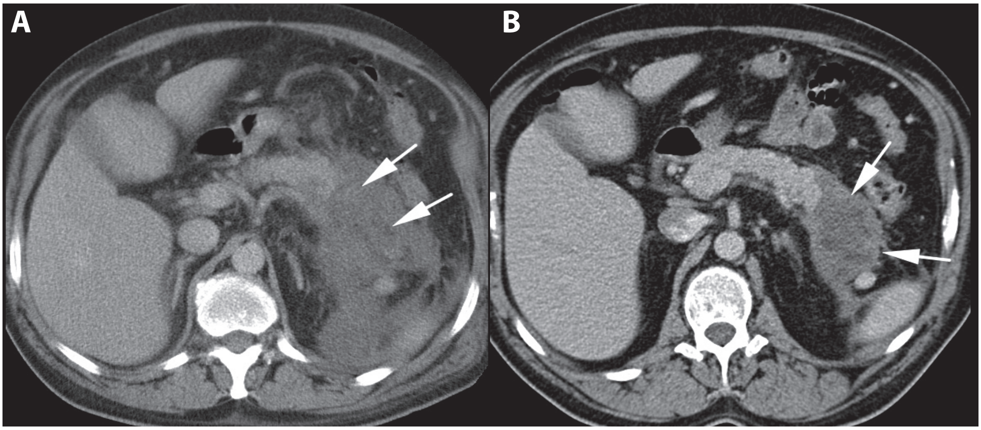

FIGURE 4A and B. Left sided necrosis – pattern 3. (**A**) CT shows an area of necrosis at the pancreatic tail with associated necrotic collection in the left retroperitoneal space (arrows). (**B**) Follow-up CT at day 24 shows stable non-enhancement of pancreatic tail with associated heterogeneous necrotic collection (arrows) which has diminished in size.

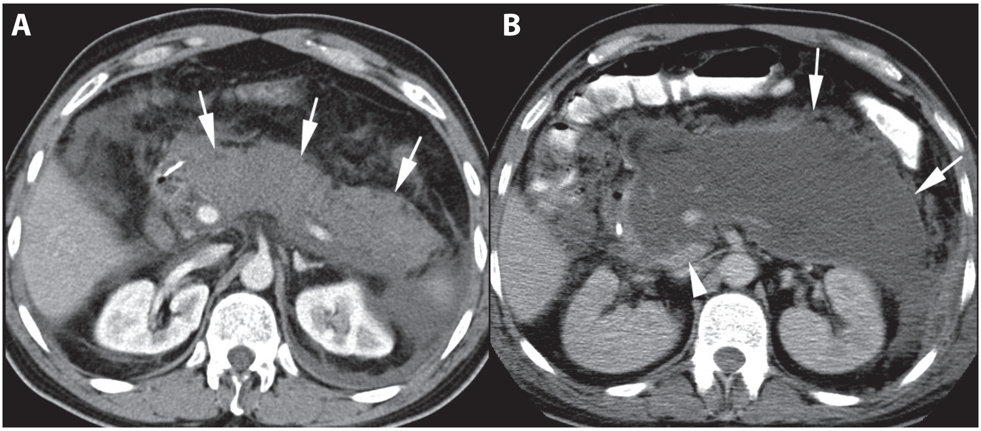

FIGURE 5A and B. Subtotal necrosis – pattern 4. (**A**) CT on the day of admission shows a large area of hypo-perfusion of the pancreatic body and tail and part of the head, likely representing >90% necrosis (arrows). (**B**) Follow-up CT on day 14 confirms necrosis of the pancreatic parenchyma for more than 90% with small area of remaining vital pancreatic parenchyma in the pancreatic head (arrowhead). There is an associated heterogeneous partially encapsulated acute necrotic collection (arrows).

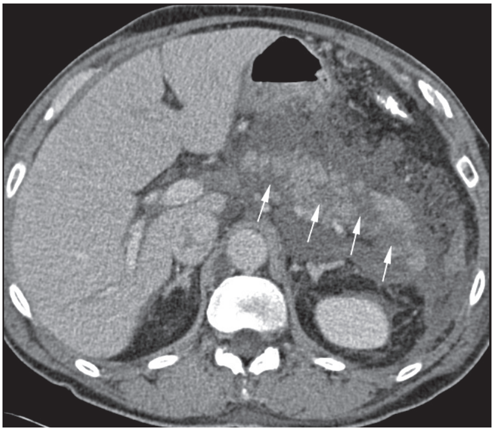

FIGURE 6. Scattered necrosis – pattern 5. CT depicts multifocal small areas of non-enhancement in pancreatic body and tail (small arrows) with associated peripancreatic necrotic collections.

CT Acquisition and Analysis

CECTs from all registered patients (including imaging performed at referring centers) performed during hospitalization was retrieved and reviewed soft copy using open source DICOM viewer software (32-bit OsiriX version 3.3, Geneva, Switzerland). Because this was a multicenter study, a variety of CT scanners (all performed on multidetector CT; 16-slice or higher) with varying CT parameters had been used. In all patients, at least one CECT in the pancreatic or portal venous phase was performed and available for review during hospitalization. The decision to perform the index CECT and all consecutive CECTs was made by discretion of the attending physicians, in general because of deteriorating clinical condition of the patient. In the PROPATRIA trial, CECT was performed per protocol 7-10 days after admission and on demand therefore and thereafter [37]. The first CECT performed after 72 hours after symptom onset was used for assessment of pancreatic necrosis, since early CT may miss the presence and extent of pancreatic necrosis [3-6]. All subsequent CTs were reviewed for progressive or late onset of pancreatic necrosis. All digitalized CECTs were reviewed retrospectively and independently by two radiologists (T.L.B. and I.G.S., with 10 and 5 years experience in abdominal imaging, respectively), blinded to clinical outcome, for assessment of extent, location, and pattern of pancreatic necrosis. Consensus between the two observers was reached when discrepant results were obtained.

Clinical Data and Outcome

The demographic, laboratory, and clinical data until discharge or death were recorded prospectively. The following predefined clinical outcome parameters were collected: in-hospital mortality, persistent organ failure (lasting more than 48 hours), infection of pancreatic or extrapancreatic necrosis (infected necrosis), need for invasive intervention (endoscopic or percutaneous drainage, surgical, or endoscopic necrosectomy), and the composite of major morbidity and death (presence of at least one of the aforementioned clinical outcome parameters). Severe acute pancreatitis was defined as persistent organ failure adopted from the 2012 Revised Atlanta Classification [38].

Data Analysis

Analyses were performed with SPSS version 22.0 (Chicago, IL). The Kolmogorov–Smirnov test was used to assess whether continuous data were distributed normally ($p<0.05$). Kappa statistics were used to calculate the interobserver agreement between the two radiologists. Continuous data are presented as mean ± SD and in case of non-normal distributions as median with interquartile range (IQR). A kappa of less than 0.00 represents no agreement, 0.0-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1.00, excellent agreement [39]. In the entire study population, the following variables were compared with clinical outcomes: extent and pattern (based on dominant location) of pancreatic necrosis. Differences were tested by the Student's T-test or Mann–Whitney U test. Proportions were compared by the Chi-square test. Various multivariable logistic regression analyses were performed with the clinical outcomes as dependent outcomes and extent of pancreatic necrosis and pattern of pancreatic necrosis as co-variates, to determine whether pattern and extent were independently associated with severity parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

Patients

Among 639 patients with necrotizing pancreatitis, some 324 patients had pancreatic necrosis on CECT and, hence, constitute the final study cohort of whom 214 patients (66%) were male (median age 58 years, IQR 45 - 69). The etiology of pancreatitis was biliary in 155 (48%) patients, alcohol in 74 (23%) patients, other causes (including hyperlipidaemia, hypercalcemia, post-ERCP) in 26 (8%) patients, and idiopathic in 69 (21%) patients. A total of 1164 CECTs in 324 patients were available for review (median of 6, IQR 3 - 10). Data on patient outcome of the study cohort are summarized in Table 1.

TABLE 1. Patient characteristics

Characteristic	Pancreatic necrosis N = 324
Age – yr	58 (45 – 69)
Male sex	214 (66%)
Etiology	
Gallstones	155 (48%)
Alcohol abuse	74 (23%)
Other	26 (8%)
Unknown	69 (21%)
ASA[#] class on admission	
I (healthy status)	105 (32%)
II (mild systemic disease)	173 (53%)
III (severe systemic disease)	46 (14%)
Predicted severity of pancreatitis	
APACHE-II[†] score on admission	8 (5 – 11)
Imrie / modified Glasgow score after 48 hours	4 (2 – 5)
Highest CRP[‡] level in first 48h	290 (215 – 388)
Transferred from another hospital	116 (36%)
No. of CECTs performed per patient*	6 (3 – 10)

Continuous variables are median (interquartile range). [#]ASA, American Society of Anaesthesiologists; [†]APACHE, Acute Physiology Age and Chronic Health Evaluation; [‡]CRP, C-reactive protein; CECT, contrast-enhanced CT; *After 72h of symptom onset and before discharge or any intervention.

Extent of Pancreatic Necrosis and Clinical Outcome

Interobserver agreement for assessing the extent of pancreatic necrosis was 0.79 (95% CI: 0.71-0.84), indicating substantial correlation. The extent of pancreatic necrosis in the 324 patients was as follows: <30% necrosis; 132 patients (40%), 30-50%; 83 patients (26%), and >50%

TABLE 2. Anatomic region of pancreatic necrosis

Anatomic region N = 324	Involvement (%)	Extent of involvement per region		
		<50%	50-100%	100%
Head	184 (57%)	142 (77%)	42 (23%)	0
Neck	240 (74%)	65 (27%)	21 (9%)	154 (64%)
Body	229 (71%)	96 (42%)	39 (17%)	94 (41%)
Tail	159 (49%)	78 (49%)	39 (25%)	42 (26%)

TABLE 3. Pattern in relation to extent of pancreatic necrosis

Pattern N = 324	Number (%)	Extent of involvement of total parenchyma		
		<30% n = 132	>30-50% n = 83	>50% n = 109
Right	17 (5%)	15 (88%)	2 (12%)	0
Central	128 (40%)	25 (20%)	55 (43%)	48 (37%)
Left	35 (11%)	17 (49%)	6 (17%)	12 (34%)
Subtotal	47 (14%)	0	0	47 (100%)
Scattered	97 (30%)	75 (77%)	20 (21%)	2 (2%)

TABLE 4. Association of extent of pancreatic necrosis with clinical outcome

Clinical Outcome N = 324	Extent of involvement of total parenchyma		
	<30% n = 132	>30-50% n = 83	>50% n = 109
Persistent organ failure	42 (32%)*¶	42 (51%)*†	63 (58%)†¶
Infected necrosis	52 (39%)*¶	46 (55%)*†	53 (49%)†¶
Invasive intervention	61 (46%)*¶	58 (70%)*†	66 (61%)†¶
Mortality	23 (17%)†	15 (18%)†	26 (24%)†
Composite endpoint#	76 (58%)*¶	62 (75%)*†	83 (76%)†¶

*,¶, significant differences between groups (p<0.05)
†, no significant differences between groups
#, presence of any of the following severity parameters: persistent organ failure, infected necrosis, invasive intervention, or mortality

TABLE 5. Association of pattern of pancreatic necrosis with clinical outcome

Clinical Outcome N = 324	Pattern of pancreatic necrosis				
	Right n = 17	Central n = 128	Left n = 35	Subtotal n = 47	Scattered n = 97
Persistent organ failure	9 (53%)	77 (60%)	8 (23%)	29 (62%)	24 (25%)
Infected necrosis	8 (47%)	76 (59%)	10 (29%)	20 (43%)	37 (38%)
Invasive intervention	11 (65%)	99 (77%)	12 (34%)	25 (53%)	38 (39%)
Mortality	7 (41%)	34 (27%)	3 (9%)	13 (28%)	7 (7%)
Composite endpoint#	14 (82%)	108 (84%)	14 (40%)	38 (81%)	47 (49%)

P<0.001
#, presence of any of the following severity parameters: persistent organ failure, infected necrosis, invasive intervention, or mortality

necrosis; 109 patients (34%). Once pancreatic necrosis was established on a CECT at a median of 6 days (IQR 4 - 12 days) after symptom onset, no late onset or increase in extent of pancreatic necrosis was observed on follow-up CECTs. The association between clinical outcome and extent of pancreatic necrosis is shown in Table 4. For all severity parameters studied there was a significant relationship between extent of pancreatic necrosis and clinical outcome, except for mortality. Patients with <30% pancreatic necrosis had a significantly better outcome than those with >30% pancreatic necrosis ($p<0.001$). No significant differences in clinical outcome, however, was seen in patients with 30-50% versus those with >50% pancreatic necrosis ($p=0.37$). Moreover, for infected necrosis and need for invasive intervention a stronger association was seen in patients with 30-50% versus those with >50% pancreatic necrosis, albeit without reaching statistical significance.

Location and Pattern of Pancreatic Necrosis and Clinical Outcome

Interobserver agreement for assessing location and pattern of pancreatic necrosis was 0.81 (95% CI: 0.73-0.86), indicating excellent correlation. The location of pancreatic necrosis, including the percentage of involvement per region is depicted in Table 2. Pancreatic necrosis occurred most often in the pancreatic body and neck in 71% and 74% of patients, respectively. Accordingly, central gland necrosis was the most frequent pattern observed (128 patients, 40%), followed by scattered necrosis (97 patients, 30%), and subtotal necrosis (47 patients, 14%) (Table 3). The extent of pancreatic necrosis involved per pattern of pancreatic necrosis is shown in Table 4. In Table 5, clinical outcome according to the pattern of pancreatic necrosis is depicted. A significant association was observed between all outcomes studied with pattern of pancreatic necrosis ($p<0.001$). The highest association of all severity parameters, including the composite endpoint, occurred in patients with right-sided, central gland, and subtotal necrosis. Patients with right-sided necrosis had the highest mortality rates (41%). Patients with left-sided and scattered necrosis had significantly lower rates of persistent organ failure, infected necrosis, need for intervention, mortality, including the composite of major morbidity and death. The multivariable analyses generally demonstrated that the pattern of pancreatic necrosis was independently and most strongly associated with severity parameters (data not shown).

DISCUSSION

This is the largest cohort study focusing on extent and location of pancreatic necrosis and their association with clinical outcome. Major findings are that: a) a significant correlation exists between extent of pancreatic necrosis and clinical outcome (mortality, infected necrosis, persistent organ failure, and need for intervention), albeit no significant differences were observed when comparing outcomes in patients with 30-50% and >50% pancreatic necrosis; b) central gland necrosis is the dominant pattern of pancreatic necrosis (occurring in 40% of patients) with significant association with infected necrosis and need for invasive intervention;

c) patients with right-sided, central gland, and subtotal necrosis have the poorest clinical outcome compared with patients with left-sided and scattered necrosis; and d) in multivariable analysis, the pattern of pancreatic necrosis was most strongly associated with clinical outcome.

The pathophysiology of parenchymal necrosis is thought of as an ischemic event caused by vascular changes of intrapancreatic vessels following acinar cell injury. After cytolysis, the activated pancreatic enzymes incite an inflammatory reaction leading to vasospasm, vascular stasis and thrombosis [(7,40-42)]. Although it has been reported that the pancreatic head is often spared in necrotizing pancreatitis [(7,8,21,43)], we found that this part is involved in over half the cases. However, complete necrosis of the pancreatic head does not occur as areas of the pancreatic head were spared in all patients studied. Conversely, other pancreatic regions frequently showed complete necrosis (Table 2). It is believed that the large number of collaterals in the pancreatic head (i.e. an anatomically and functionally important area) is protective for complete necrosis [(21,44,45)]. In our study, the pancreatic neck and body were the most vulnerable areas to undergo necrosis (with complete necrosis in 66% and 40%, respectively), most likely attributed to a lack of a satisfactory collateral network. Indeed, these regions are regarded as the 'watershed areas' between the proximal and distal pancreas and, therefore, are more susceptible to perfusion alterations [(45-49)]. This clarifies the high prevalence of central gland necrosis and the relatively low prevalence of isolated right- or left-sided necrosis. Opposed to what is reported by some [(7,8,21,48)], we found that even in case of extensive necrosis, areas of the pancreatic gland remained viable (primarily in the pancreatic head and tail) and, hence, 'complete necrosis' of the whole pancreatic gland was not seen. Presumably, advances of CT technique have contributed to improved assessment of the pancreas; i.e. all patients in our study underwent multislice CT examinations with probably better detection of remaining viable pancreatic tissue. Furthermore, different from several groups of investigators [(6,7,8,10,50)], we did not observe an increase or late onset of pancreatic necrosis once necrosis was definitively established on the index CECT. This is in keeping with the assumption that pancreatic necrosis develops within the first 72 hours after symptom onset [(51)]. In some patients, close analysis of successive CTs revealed a decrease in pancreatic volume in the later phase of disease due to subsidence of initial pancreatic swelling [(43)]. Also, during follow-up enlarging peripancreatic collections may compress remaining viable pancreatic tissue with restoration after resolution of collections by drainage or necrosectomy [(52)]. Both latter manifestations may simulate an 'increase' in extent of pancreatic necrosis. Alternatively, the differing findings can be ascribed to differences in timing of CECT on which pancreatic necrosis is assessed (i.e. an early CT within 48-72 hours following symptom onset may underrate the degree and extent of pancreatic necrosis) or in the event of repeated pancreatic insults during the same hospitalization.

Most studies have shown a clear correlation between presence of pancreatic necrosis and increased morbidity and mortality [(7-18)]. But, some have questioned the linear relationship between extent of pancreatic necrosis and clinical outcome [(19-28)]. Balthazar and colleagues classified the extent of pancreatic necrosis into 3 categories (i.e. <30%, 30-50%, and >50%) and incorporated the presence and extent of parenchymal necrosis in the CT Severity Index (CTSI) [6]. The CTSI represents a numeric CT-based predictive scoring system on a 10-point scale implying that prognosis is directly correlated with extent of pancreatic necrosis [6]. Yet, our results and other studies do not support this premise [9,19,20,26,27]. In their original study, Balthazar and colleagues reported minor morbidity in patients with <30% pancreatic necrosis compared with 40% morbidity in patients with >30% pancreatic necrosis [6]. Differences in morbidity and mortality between the groups with 30-50% and >50% pancreatic necrosis, however, were not statistically significant. We also found a modest correlation between extent of pancreatic necrosis and clinical outcome. Noteworthy, an even stronger association was observed in the group with 30-50% pancreatic necrosis for infected necrosis and need for invasive intervention compared with those with >50% pancreatic necrosis. In multivariable analysis, the pattern of pancreatic necrosis appeared to be more strongly correlated with clinical outcome than its extent. We found that patients with right-sided, central gland, and subtotal necrosis had significantly higher morbidity and mortality rates than patients with left-sided and scattered necrosis. Our results are comparable with previous reports that studied smaller cohorts or were biased towards a high prevalence of alcohol-related disease [7,53]. From a pathophysiological perspective, there is a plausible explanation for the clinical impact of pattern of pancreatic necrosis. In recent reports, the integrity of the main pancreatic duct is regarded as a major determinant in clinical course and kind of treatment applied in patients with acute pancreatitis [46,47,54-56]. Patients with right-sided and central gland necrosis (with significant remaining viable pancreatic tissue proximal to the blockage, often >50% of parenchyma) are at highest risk of disruption of the pancreatic duct resulting in continued leakage of pancreatic enzymes in and outside the pancreas (also known as 'disconnected duct syndrome') [46,47,49,54-58]. Interestingly, the incidence of main pancreatic duct disruption in necrotizing pancreatitis is reported to be around 40%, which corresponds to the incidence of central gland necrosis observed in our study [46,59,60]. The diagnosis of a disrupted pancreatic duct depends on clinical and endoscopic retrograde cholangiography criteria. This entity can, however, be inferred from CT when right-sided necrosis or transparenchymal central gland necrosis of the pancreas is seen, especially when the segment involved measures more than 2 cm and an increase of necrotic collections is observed on sequential CTs [61]. Furthermore, in right-sided necrosis vital structures surround the pancreatic head in a constrained anatomic compartment that likely provokes increased inflammatory stress, locally and systemically, manifested clinically as systemic inflammatory response syndrome and prolonged organ dysfunction [8,9].

Our results might clarify the non-linear relationship between extent of pancreatic necrosis and clinical outcome. All patients with right-sided necrosis and 63% of patients with central gland necrosis had <50% pancreatic necrosis (Table 4), but a strong association was observed with all clinical outcome parameters studied, in particular rate of infected necrosis and the need for invasive intervention. Notably, 24% of patients with extensive necrosis (>50% pancreatic necrosis) had a relatively clinically mild course; i.e. these patients did not die, did not develop persistent organ failure or infected necrosis, and did not need invasive intervention (Table 5). The absence of significant vital upstream pancreatic parenchyma (and, hence, the leakage of pancreatic enzymes) likely precludes the development of complications in these patients. Conversely, it is also important to identify those with left-sided and scattered necrosis as these have a significant better outcome regardless of extent of pancreatic necrosis, probably related to the absence of pancreatic duct disruption.

The strengths of this study are the large study population on necrotizing pancreatitis with CT correlation (previous studies included smaller study populations [7,29-32], the prospective acquisition of clinical data, and the recruitment of a large cohort in a relatively small time period of 4.5 years receiving similar management [34]. Prior studies used outdated CT equipment or evaluated long time intervals ranging up to 9-12 years despite major improvement in imaging techniques and advanced management of severe acute pancreatitis [7-9,30]. However, our study has some limitations. First, because this was a multicenter study, CTs were performed with a variety of CT scanners with varying protocols. However, all CTs were performed on multidetector CT scanners and, in the majority of patients, multiple CECTs were available for determining the location and extent of pancreatic necrosis. Hence, we feel that this did not influence our findings significantly. Second, most CTs were performed on discretion of the clinician with no standardized timing. This reflects common and current practice; given the high costs and radiation issues associated with CT, judicious use of this modality is recommended [62-64]. Third, as with all classification systems, there is clearly some subjectivity in grading the pattern of pancreatic necrosis. Although, we found a good interobserver agreement between two experienced readers, additional studies are needed in a different cohort and readers with varying experience.

In summary, the pancreatic neck and body are the most vulnerable regions to undergo necrosis, with central gland necrosis being the dominant pattern of necrosis occurring in 40% of patients presenting with pancreatic necrosis. Extent of pancreatic necrosis is associated with most severity parameters studied (except mortality) with significant better clinical outcome in patients with <30% versus those with >30% pancreatic necrosis. Furthermore, the pattern of pancreatic necrosis is associated most strongly with all severity parameters studied, especially when involving primarily the head or central part of the pancreas (likely related to a disrupted pancreatic duct) with an upstream vital pancreatic parenchyma.

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PART III

Appendices

15

Summary

This thesis had two main objectives pertaining to the classification and severity prediction of acute pancreatitis. We evaluated the previous classification system on acute pancreatitis (1992 Atlanta Classification) extensively by means of two literature reviews and interobserver agreement studies and studied the morphologic part of the most recent Revised Atlanta Classification constructed in 2012. The predictive accuracy of imaging-based scoring systems was addressed in two comparative studies and a severity assessment of interstitial edematous pancreatitis and necrotizing pancreatitis was performed in two different cohorts.

In ***Chapter 2***, we performed an interobserver agreement study among 5 experienced abdominal radiologists for categorizing pancreatic (fluid) collections on CT using the 1992 Atlanta Classification. To this end, preoperative contrast-enhanced CTs from 70 consecutive patients operated for acute necrotizing pancreatitis were reviewed. Results of this study showed a poor interobserver agreement among the five radiologists as in only three out of 70 cases (4%) the same Atlanta definition was chosen and in 42 out of 70 cases (42%), three radiologists agreed on the same Atlanta definition. We concluded that the 1992 Atlanta definitions should not be used for categorizing pancreatic collections on CT.

In a complex disease such as acute pancreatitis, correct terminology and clear definitions are important. The clinically based Atlanta Classification was formulated in 1992, but in recent years it has been criticized increasingly. In two literature reviews, an extensive evaluation was undertaken to assess the use and acceptance of the 1992 Atlanta definitions in medical literature. In ***Chapter 3***, a Medline search strategy (during the period 1993-2006) was conducted that included terms abandoned by the 1992 Atlanta Classification: 'phlegmon', 'infected pseudocyst', 'hemorrhagic pancreatitis', and 'persistent pancreatitis'. Also, new terms that have emerged in literature after the publication of the 1992 Atlanta Classification were categorized. In total 239 articles were reviewed, including 10 guidelines and 42 reviews. We found that the abandoned terms 'hemorrhagic pancreatitis' and 'persistent pancreatitis' were discarded effectively, whereas 'infected pseudocyst' and 'phlegmon' were encountered frequently with several authors openly questioning their abandonment. New terms identified were 'organized pancreatic necrosis', 'necroma', 'extrapancreatic necrosis', and 'central gland necrosis'. Some of these are manifestations of acute pancreatitis that were not addressed adequately by the 1992 Atlanta Classification. In ***Chapter 4***, a formal evaluation of the use of the 1992 Atlanta definitions in the literature was performed. A Medline literature search sought studies published between 1993 and 2006. In total, 447 articles were identified, including 12 guidelines and 82 review articles. Alternative definitions of predicted severity of acute pancreatitis, actual severity, and organ failure were used in more than half of the studies. There was a large variation in the interpretation of the 1992 Atlanta definitions of local complications, especially relating to the content of peripancreatic collections. Both literature reviews revealed that the 1992 Atlanta Classification was outdated and was in need for revision.

To that purpose, a new set of morphologic terms to describe pancreatic collections in acute pancreatitis on CT was developed. The morphologic terms consisted of: presence of a collection, relation with the pancreas, content, shape, mass effect, loculated gas bubbles, gas-fluid level, encapsulation and presence and extent of concomitant pancreatic non-enhancement. Because the terms proposed by the 1992 Atlanta Classification (e.g. pseudocyst, pancreatic abscess) had shown a very poor interobserver agreement (Chapter 2), creating the potential for patient mismanagement, in ***Chapter 5*** we performed an interobserver agreement study for the above mentioned new set of morphologic terms to describe pancreatic collections in acute pancreatitis on CT. Among 17 readers (9 clinicians and 8 radiologist from US and Europe), the overall interobserver agreement was good to excellent for these individual morphologic terms. Thus, we advocate to use these descriptive terms to describe CT morphology of acute pancreatitis rather than using the 1992 Atlanta definitions.

Although the 1992 Atlanta Classification of acute pancreatitis enabled standardized reporting of research and aided communication between clinicians, it became increasingly clear over the years that a revision was necessary based on improved understanding of acute pancreatitis and to overcome the deficiencies identified. An international iterative web-based consultation was undertaken in 2007 to ensure wide participation of pancreatologists. After five years of discussion, a consensus document (the 2012 Revised Atlanta Classification) was constructed and presented in ***Chapter 6***. The 2012 Revised Atlanta Classification defines criteria for the diagnosis of acute pancreatitis and identifies two phases of disease: early and late. Acute pancreatitis can be either interstitial pancreatitis without tissue necrosis, or necrotizing pancreatitis, with necrosis of pancreatic parenchyma, peripancreatic tissue, or both. Severity of acute pancreatitis is categorized into three grades: mild, moderate severe, and severe, depending upon presence of organ failure and local or systemic complications. For the first time, a imaging-based classification has been added based on morphologic CT criteria. The nomenclature of pancreatic collections was divided into four subsets: acute peripancreatic fluid collection, pseudocyst, acute necrotic collection, and walled-off necrosis, based on their composition and morphology on CT. The wide consultation among pancreatologists to reach this consensus should encourage widespread adoption.

An important aim of the 2012 Revised Atlanta Classification was to facilitate consistent reporting and better comparison of data, obtained in clinical research. Therefore, new CT based criteria were proposed to describe the morphology of acute pancreatitis. In ***Chapter 7***, the interobserver agreement in evaluating the new CT criteria was assessed among radiologists in 285 consecutive patients with acute pancreatitis who underwent a CT during their admission. For most of the newly introduced CT criteria, the interobserver agreement was moderate to substantial. In four categories, the interrater agreement was only fair: extrapancreatic necrosis (EXPN) (0.326), type of pancreatitis (0.370), characteristics of collections (0.408), and appropriate term of collections (0.356). The fair kappa values were related to discrepancies in the identification of extrapancreatic necrotic material. This is an increasingly acknowledged limitation of CT and the 2012 Revised Atlanta Classification. Consequently, further adjustments to the new criteria are likely to be expected.

The severity prediction of acute pancreatitis has engendered as much attention as its classification. A decade after the development of the first predictive clinical scoring, the Ranson score in 1974 (1), Balthazar and colleagues proposed a radiologic scoring system in 1985 based on an unenhanced CT (2). Some 5 years later, the same authors updated this grading system by adding presence and extent of parenchymal necrosis on an contrast-enhanced CT to the Balthazar score, resulting in the CT Severity Index (CTSI), which is still the most frequently used CT scoring system to date (3). In 2004, this scoring system was modified by Mortele and colleagues (the Modified CT Severity Index or MCTSI) by incorporating some simplifications and subsequently tested in a small cohort of 66 patients (4). In ***Chapter 8***, we compared the MCTSI with the original CTSI regarding assessment of severity parameters in 196 acute pancreatitis patients who underwent a contrast-enhanced CT or MRI within 1 week of symptom onset. Both CT indexes were also compared with the Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II index. Two abdominal radiologists scored both CT indexes independently. Severity parameters included mortality, organ failure, pancreatic infection (infected necrosis), admission to and length of ICU stay, length of hospital stay, need for intervention, and clinical severity of acute pancreatitis. Although, for both CT indexes a significant relationship was observed between the score and each severity parameter ($p < 0.0001$), no significant differences were seen between the CT indexes. Compared with the APACHE II index, both CT indexes more accurately correlated with the need for intervention (CTSI, $p = 0.006$; MCTSI, $p = 0.01$) and pancreatic infection (CTSI, $p = 0.04$; MCTSI, $p = 0.06$) and more accurately diagnosed clinically severe disease (area under the curve, 0.87; 95% CI, 0.82-0.92). Interobserver agreement was excellent for both indexes: for CTSI, 0.85 (95% CI, 0.80-0.90) and for MCTSI, 0.90 (95% CI, 0.85-0.95). Thus, in clinical practice, both indexes can be used interchangeably for grading the morphologic severity of disease.

It is generally acknowledged that early identification of patients with clinically severe acute pancreatitis is critical for triage and individualized treatment. In ***Chapter 9***, we compared the predictive accuracy of CT and clinical scoring systems in their severity assessment on admission. During a two-and-half-year period all consecutive patients with a primary diagnosis of acute pancreatitis were enrolled prospectively for this study. Of these, 150 patients (159 episodes of pancreatitis) received a (unenhanced or contrast-enhanced) CT on the day of admission. A retrospective analysis of the abdominal CT data was performed. Seven CT scoring systems (CT severity index (CTSI), modified CT severity index (MCTSI), pancreatic size index (PSI), extrapancreatic score (EP), "extrapancreatic inflammation on CT" score (EPIC), "mesenteric edema and peritoneal fluid" score (MOP), and Balthazar grade) as well as two clinical scoring systems: Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II and Bedside Index for Severity in AP (BISAP) were compared with regard to their ability to predict disease severity on admission (i.e. first 24h of hospitalization). Clinically severe acute pancreatitis was defined as one or more of the following: mortality, persistent organ failure and/or the presence of local pancreatic complications that require intervention. At the time of this study, the definitive parameters of disease severity were not yet defined, therefore, definitions for disease severity differ slightly from the 2012 Revised Atlanta Classification. All CTs were reviewed in consensus by 2 abdominal radiologists, each blinded to patient outcome. The accuracy of each CT and clinical scoring system for predicting the severity of acute pancreatitis was assessed using receiver operating curve analysis. Overall, the Balthazar grading system (any CT technique) and CTSI (contrast-enhanced CT only) demonstrated the highest accuracy among all 7 CT scoring systems for predicting disease severity, but this was not statistically significant. The predictive accuracy of CT scoring systems for severity of AP was, however, similar to clinical scoring systems. Hence, a CT on admission solely for disease severity assessment is not recommended.

In the radiologic literature, however, it is often acclaimed that CT should be performed early in acute pancreatitis to evaluate morphologic severity of acute pancreatitis (5-7), but this is not supported by clinical guidelines and most clinicians (6-12). In ***Chapter 10***, an overview of existing radiologic scoring systems (mostly based on CT) is presented combined with their strengths and limitations in predicting ultimate severity. The primary limitation of imaging scoring systems is that they better correlate with local complications than with systemic complications (particularly persistent organ failure which is the defining feature of severe acute pancreatitis). Besides providing a radiologic score in a CT report, a list of possible complications are reviewed that may be encountered on CT for evaluation of acute pancreatitis. These include imaging signs of infected necrosis (gas bubbles within necrotic collections), massive hemorrhage or detection of an arterial pseudoaneurysm, deep vein thrombosis or pulmonary emboli, cholecystitis, bowel ischemia or perforation, and imaging features of abdominal compartment syndrome ('round-belly sign' or increasing girth on serial CT). Most of these complications are not part of any imaging scoring system, but nonetheless have a significant and direct impact on patient management.

One of the most severe local complication of acute pancreatitis is infected necrosis, which is associated with significant morbidity and mortality rates of around 20-30% (12, 13). The depiction of gas configurations within necrotic collections on CT represents a virtually pathognomonic feature of infected necrosis, but is not always present. Diagnosing infected necrosis clinically may be challenging as severe SIRS may present with a septic profile as well. In ***Chapter 11***, we determined the added value of routine fine-needle aspiration (FNA) in addition to clinical and imaging signs of infection in patients who underwent intervention for suspected infected necrosis. We conducted a post hoc analysis of 208 consecutive patients from a prospective, multicenter database who underwent intervention because of suspected infected necrosis. In retrospect, three groups were constructed based on patients' preoperative characteristics: clinical profile, imaging findings, and results of FNA. Patients in the clinical group had clinical signs of infection but no gas on preoperative CT and no FNA performed before intervention. Patients in the imaging group had gas bubbles on the preoperative CT but no FNA was performed, whereas patients in the FNA group had a positive FNA before intervention. The reference standard for infection was the culture taken during the first intervention (either catheter drainage or necrosectomy). The initial intervention for infected necrosis was performed a median of 27 days (interquartile range, 20-39) after admission without difference between the 3 groups (p = .15). Infection was confirmed in 80% of 92 patients of the clinical group, in 94% of 88 patients of the imaging group, and in 86% of 28 patients of the FNA group (p = .07). Mortality was 19% and was not different between groups (p = .39). We conclude that infected necrosis can generally be diagnosed based on clinical or imaging signs of infection. FNA is useful in patients with equivocal clinical signs and no imaging signs of infected necrosis.

There is limited information on the incidence of factors associated with clinically severe disease among patients with interstitial pancreatitis. In ***Chapter 12***, we evaluated 149 consecutive patients with interstitial pancreatitis admitted over a 2.5-year period and compared data with those from patients with EXPN. We assessed the Charlson comorbidity score (CCI) and some measures of severity on admission or within 24 hours (APACHE II, BISAP scores). Furthermore, we assessed the incidence of persistent (>48h) systemic inflammatory response syndrome, persistent organ failure, need for intensive care unit, length of hospital stay (in days), and mortality among patients with interstitial pancreatitis and those with EXPN. Among the patients with interstitial pancreatitis, the median APACHE II score was 7, and the median BISAP score was 1. In addition, the median length of hospital stay was only 4 days; only 1% had persistent organ failure and only 1% to 2% required intervention. The mortality rate of interstitial pancreatitis was 3% and this was associated significantly with comorbidity (the median CCI scores of nonsurvivors and survivors was 4 and 1, respectively, p = 0.003). Patients with EXPN had greater levels of disease severity, compared with patients with interstitial pancreatitis and, therefore, should be distinguished from interstitial pancreatitis in clinical studies.

In the 2012 Revised Atlanta Classification of acute pancreatitis, the term necrotizing pancreatitis also refers to patients with only EXPN without pancreatic parenchymal necrosis, as determined on CECT. Patients with EXPN are thought to have a better clinical outcome compared with those with parenchymal necrosis, although robust data are lacking. In ***Chapter 13***, we performed a post hoc analysis of a prospective multicenter database including 639 patients with necrotizing pancreatitis on CECT. All CTs were reviewed by a single radiologist blinded to the clinical outcome. Some 315 patients with EXPN were compared with 324 patients with pancreatic parenchymal necrosis (with or without extrapancreatic necrosis). Outcomes were persistent organ failure, need for intervention, and mortality. A predefined subgroup analysis was performed on patients who developed infected necrosis. Patients with EXPN less often suffered from complications: persistent organ failure (21% vs 45%, p < 0.001), persistent multiple organ failure (15% vs 36%, $p < 0.001$), infected necrosis (16% vs 47%, $p < 0.001$), intervention (18% vs 57%, $p < 0.001$), and mortality (9% vs 20%, $p < 0.001$). When infection of extrapancreatic necrosis developed, outcomes between groups were similar (mortality with infected necrosis: EXPN 28% vs pancreatic necrosis 18%, $p = 0.16$). Based on these and other data we propose that EXPN should be regarded a separate entity within the morphological spectrum of acute pancreatitis.

In acute pancreatitis, the extent of pancreatic parenchymal necrosis is deemed an important determinant of clinical outcome. Data on the impact of location of pancreatic necrosis is lacking. In ***Chapter 14***, we investigated the clinical impact of both extent and location of pancreatic necrosis in a large cohort. Clinical severity parameters included persistent organ failure, infected pancreatic necrosis, invasive intervention, and death. A total of 324 patients had pancreatic necrosis. Extent of pancreatic necrosis was less than 30% in 132 patients (40%), between 30-50% in 83 patients (26%), and over 50% in 109 patients (34%). All severity parameters, except mortality, differed significantly ($p<0.001$) between patients with less than 30% compared with over 30% pancreatic necrosis, but not between patients with 30 to 50% versus those with over 50% pancreatic necrosis. Central gland necrosis was the most frequent pattern of pancreatic necrosis encountered (40%). All outcomes studied were significantly associated with location of pancreatic necrosis ($p<0.001$). The strongest association was found in patients with right-sided, central gland, and subtotal necrosis. After multivariable analysis, the pattern of pancreatic necrosis (based on location) was associated most strongly with all severity parameters studied, especially when involving primarily the head or central part of the pancreas (likely related to a disrupted pancreatic duct) with an upstream vital pancreatic parenchyma. We conclude that the location of pancreatic necrosis is an important prognostic factor determining the clinical course of patients with acute necrotizing pancreatitis.

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16

General Discussion and Future Perspectives

PART I - CLASSIFYING AN UNCLASSIFIABLE DISEASE?!

Classification of acute pancreatitis is important for improvement of individual clinical care and for advancement of clinical research. For clinicians from various disciplines it is imperative to agree on terminology to apply appropriate therapy in an effective manner, including medical, surgical, and radiologic options (1). For example, if acute peripancreatic fluid collections are referred to as 'pseudocysts' by the reporting radiologist there is a tendency for the clinician to think immediately of interventional techniques (2-5). Many of these acute peripancreatic fluid collections, however, regress spontaneously without need for specific treatment (6,7). But if the collection contains necrotic material and is classified erroneously as a 'pseudocyst', the clinician is misled, potentially leading to therapeutic misadventures (2,4,8,9). Accurate disease classification and broad consensus on terminology is equally important for improvement of the quality of clinical research. In the past, communication between clinicians treating and studying acute pancreatitis and assessment of various methods of therapy has been hampered greatly by the use of varying definitions for disease severity, incomplete data reporting, and lack of comparable data (10,11). Moreover, misclassification errors occur in up to a quarter or a third of patients enrolled in clinical studies (i.e. patients with predicted severe acute pancreatitis experience a mild clinical course and vice versa), which further impedes the assessment of efficacy of new therapies (12-14). Classification systems have been constructed and recently modified to help in guiding and selecting homogeneous patient populations. For these reasons, some 40 pancreatologists from 15 countries involving 6 different disciplines convened at the 1992 International Symposium on Acute Pancreatitis, held in Atlanta, Georgia, USA. This symposium resulted in a *clinically* based classification system for acute pancreatitis, which more precisely defined the diagnosis, the subtypes, and complications of acute pancreatitis (15).

Over the ensuing decades, the shortcomings of the 1992 Atlanta Classification became increasingly apparent and were addressed resulting in the Revised Atlanta Classification.

Limitations of 2012 Revised Atlanta Classification and how to proceed

Since its publication several studies have been performed showing that the 2012 Revised Atlanta Classification better correlates with clinical outcome than the 1992 Atlanta Classification (16-24). Although the 2012 Revised Atlanta Classification represents a major advancement in the field of pancreatology incorporating the latest understandings of the disease, some studies and editorials have identified a number of shortcomings.

Some claim that the 2012 Revised Atlanta Classification failed to acknowledge a subgroup of patients with very early severe acute pancreatitis (i.e. those with severe organ failure at admission with high mortality and morbidity) within the subgroup of patients with severe acute pancreatitis (25-27). They advocate that this subgroup deserves separate grouping because the conventional and largely supportive treatment is mostly ineffective due to the lack of knowledge of this intense and disproportionate inflammatory response.

The impact of extrapancreatic infection on the clinical course of acute pancreatitis has been subject of several studies, but is not addressed in the 2012 Revised Classification (28,29). Others state that the 2012 Revised Atlanta Classification also failed to acknowledge infected necrosis as determinant of severe disease and cause of most of late mortality in acute pancreatitis (18,23). The Determinant-Based Classification or DBC (published in 2012) postulates that there are two fundamental determinants of severity; both local (presence of necrosis and/or infection) and systemic (organ failure) and these can both occur in the early and late phases (30). An interaction between these determinants exists as it is claimed that the risk of mortality doubles if both infected necrosis and organ failure are present together (18,23,31-36).

The dynamic nature of organ failure is addressed only moderately in the 2012 Revised Atlanta Classification that merely discriminated transient and persistent organ failure. Some claim that a severity classification should incorporate the number of organs failing, the degree and timing of organ dysfunction, and the impact of ongoing deterioration (beyond 48h) or improvement of organ dysfunction on clinical outcome (37-42).

Another limitation pertains to the rather 'simplistic' approach of the 'two-phase theory' (42). In the early phase, most of the systemic manifestations of acute pancreatitis are a consequence of the host response to pancreatic injury (activation of cytokine cascade manifesting as SIRS and/or compensatory anti-inflammatory response syndrome (CARS). In the late phase, persistence of systemic signs of ongoing inflammation may result from infection of necrosis (43). The 2012 Revised Atlanta Classification predicates strongly on the notion of these two distinct phases in the evolution of acute pancreatitis and states that "these two phases of the disease have a distinct pathophysiology, need for different therapies, and different ways of describing severity". In practice, however, there is considerable overlap in the pathophysiological drivers early in the disease (e.g. cytokines not associated with infection) and late in the disease (e.g. cytokines associated with infection) (42-44). In a distinct proportion of patients, early infection of pancreatic and peripancreatic tissue occurs belying in essence the two-phase theory (45-47). Future large-scale prospective multicenter studies from different centers worldwide should investigate the impact of the dynamic nature of organ failure and elucidate whether the interaction between organ failure and infected necrosis and the two-phase theory pertaining to organ failure truly exists.

In the 2012 Revised Atlanta Classification, the presence of extrapancreatic tissue necrosis (EXPN) is headed under necrotizing pancreatitis. Based on this definition, the incidence of necrotizing pancreatitis will likely rise considerably by including patients with limited or moderate extensive EXPN, many of whom have a mild course clinically. Hence, the disparity between the morphologic and clinical severity of acute pancreatitis will become more pronounced. Furthermore, the role of EXPN has been studied increasingly over the past years with mounting evidence that patients with EXPN have distinct outcomes compared with those with interstitial disease and those with pancreatic parenchymal necrosis (48-53).

A 3-tier morphological classification system (with EXPN regarded as a separate entity within the morphological spectrum of acute pancreatitis) has, therefore, been proposed (54-56). More data from large scale studies are awaited.

The final shortcoming reported relates to the moderate severe group, which is composed of a heterogeneous group of patients with wide spectrum of severity: patients with varying local complications (with varying prognostic significance; e.g. sterile acute peripancreatic fluid collections versus infected necrotic collections), patients with transient organ failure, and those with deterioration of pre-existing comorbidities (regarded as a consequence rather than a cause of acute pancreatitis severity) (57). Also, the number and degree of existing comorbidities might influence the clinical course of acute pancreatitis.

Although the 2012 Revised Atlanta Classification has incorporated current clinical knowledge, there remains a lack of complete understanding of the pathophysiology of acute pancreatitis and a number of limitations pertaining to this new classification have been raised. To improve the 2012 Revised Atlanta Classification, future observational multicenter studies and disease registries (preferably from different centers from different countries across the world) should record and report data of organ failure (any, transient, persistent, single or multi-organ, organ type, and timing) and tissue necrosis (yes or no, pancreatic, peripancreatic and/or both, infected or not), as well as information on the details of the frequency of and outcomes within subgroups of patients in the moderate severe and severe categories to allow for future reliable comparisons. More reliable data is needed on the clinical outcome of the 'critical' disease category, i.e. patients with combined persistent organ failure and infected necrosis. As such new data become available, adjustments to the current classification should be made according to the principle: progress mandates change. The Dutch Pancreatitis Study Group has had major input in the 2012 Revised Atlanta Classification and has a recognized track record in performing randomized controlled clinical trials to elucidate longstanding enigmas, and, hence, is the endorsed authority to take the lead in executing this task.

Remaining issues in nomenclature of morphologic definitions

Lack of histopathologic evidence

Much of our current understandings of the dynamic process of acute pancreatitis stems from serial cross-sectional imaging, primarily in those with severe disease. In the 2012 Revised Atlanta Classification, the pathogenesis of pancreatic collections is based on several assumptions with lack of histopathologic proof. It is assumed that in acute pancreatitis pancreatic collections develop from rupture of the pancreatic duct or its side-branches or from edema. In the 2012 Revised Atlanta Classification, a divergent pathogenesis of pseudocyst and WON is presumed. But, the reverse may also be true; both may develop from damage of pancreatic tissue with leakage of pancreatic juice in damaged areas and formation of a fibrous capsule around such collections. Furthermore, the natural evolution and exact composition of pancreatic collections may vary for different patients in different anatomic locations at different stages of disease. Unfortunately, there is lack of data on the exact composition of these collections early as well as later in the disease course. Also, the process and rate of liquefaction of pancreatic and peripancreatic tissues remains an area of enigma. Finally, it is not clearly understood why some collections resolve or regress and some persist.

Differentiating fat stranding from collection

Pancreatic collections may range from rather discrete to extensive in size and extension. The distinction between 'extensive fat stranding' and a 'collection' is subjective and arbitrarily. In the 2012 Revised Atlanta Classification, the term 'collection' is used for any peripancreatic abnormality, which is more than simple fat stranding comparable to conditions like uncomplicated appendicitis or diverticulitis, even when no well-defined wall is seen.

Diagnosis of isolated EXPN

Activated pancreatic enzymes (such as lipase) that intersperse with anatomic areas containing fat (primarily in the retroperitoneum and mesenteries) may lead to lipolysis of extrapancreatic fat with development of EXPN. It is a difficult diagnosis to make at cross-sectional imaging since current imaging techniques are not able to demonstrate fat perfusion or lack thereof. Moreover, CT cannot reliably distinguish peripancreatic fat necrosis (EXPN) from other causes of peripancreatic fluid (interstitial pancreatitis). At early baseline CT, the diagnosis of EXPN is suggested by the presence of collections that show increased attenuation and fluid densities interspersed among fat present in the retroperitoneum and mesenteries. At follow-up CT, EXPN becomes more apparent when pancreatic collections have a more heterogeneous appearance with varying densities (i.e. acute necrotic collections). The morphologic type of acute pancreatitis, however, may remain indeterminate in those patients who have only one early CT available for severity evaluation showing equivocal findings.

Differentiating liquid from necrotic collections

The 2012 Revised Atlanta Classification relies heavily on CT criteria for defining the four subsets of pancreatic collections based on content and maturation. Although CT elegantly depicts the extent of pancreatic collections and degree of encapsulation, it is limited in the accurate assessment of internal contents of pancreatic collections (58,59). Peripancreatic collections may display attenuation values approaching water densities on CT; the actual fluid content of such collections may be minimal. In particular, collections developing in the first week of acute pancreatitis may have an equivocal appearance on CT (i.e. homogeneous fluid attenuation) where it is impossible to distinguish an acute peripancreatic fluid collection from an acute necrotic collection and thus, in determining the type of pancreatitis (interstitial or necrotizing pancreatitis).

Some unanswered questions remain specifically pertaining to the local complications in acute pancreatitis. What is the prognostic significance of acute peripancreatic fluid collections? Should acute peripancreatic fluid collection be regarded as a local complication or as an insignificant local event? What is the frequency of infection of such acute peripancreatic fluid collections? How many of these acute peripancreatic fluid collections turn into pseudocysts (i.e. fluid collections in absence of necrotic material)? Also, there are a number of outstanding issues that relate to the relative prognostic significance of presence and extent of both pancreatic parenchymal necrosis and EXPN and issues pertaining to the timing, diagnosis, and risk factors for infected necrosis.

Some of these questions demand a different approach of imaging patients with acute pancreatitis as CT is not able to elucidate the aforementioned enigmas. Compared with CT, MRI is superior for differentiating liquid from necrotic collections due to its superior tissue contrast resolution capabilities. With increasing use and availability of MR imaging in acute pancreatitis, some of these questions may, therefore, be answered in large prospective longitudinal studies using serial MRIs, preferably performed standardized and periodically (e.g. weekly).

PART II - PREDICTING AN UNPREDICTABLE DISEASE?!

Acute pancreatitis is one of the least predictable acute gastrointestinal disorders. The clinical course of acute pancreatitis is highly variable, ranging from mild self-limiting symptoms to rapidly progressive organ dysfunction, potentially culminating in death if not treated appropriately (60,61). Since nearly half a century, an exhaustive search for the ideal scoring system has been undertaken to identify those who will develop organ failure in the early stages and infected necrosis and sepsis in the later phase. An ideal prognostic scoring system should be simple and easy to use in clinical practice, widely available, objective, reproducible, sufficiently accurate in differentiating mild from severe disease in individual patients, and applicable early in the disease process, preferably on the day of admission (or better within a few hours of admission), such that patients at risk for severe acute pancreatitis are more closely monitored for supportive treatment (in medium or intensive care units), empirically treated (i.e. institution of tailored fluid resuscitation, endoscopic intervention, enteral nutrition, or new therapies as they become available), or transferred to specialized centers. These predictive tools should assist clinicians in identifying patients who are at risk of developing complications to be able to initiate effective therapies *before* those complications develop. In contrast, patients with mild acute pancreatitis have no need of specific treatment, except for a cholecystectomy during hospitalization in those with predicted mild biliary pancreatitis (62).

Reports on the discriminatory power of clinical and imaging-based scoring systems all show a positive correlation between the scoring system studied and patient outcome. Comparison of these studies is, rendered difficult because of the profound lack of homogeneity in study design, differences in methodology used and the wide diversity in definitions for severe acute pancreatitis and clinical end points (e.g. variation in defining organ failure and systemic complications). Two recent studies accounted for these shortcomings by using the 2012 Revised Atlanta definitions and compared the accuracy of several imaging-based scoring systems (including the CTSI) at admission (63,64). Results of these studies showed comparable performance characteristics among the imaging-based scoring systems studied in the prediction of disease severity and overall mortality. Also, these studies showed that imaging-based scoring systems did not perform better than commonly used clinical scoring systems, such as the BISAP and APACHE II score.

Shortcomings of all predictive systems

Despite the plethora of clinical, biochemical, and imaging-based scoring systems, none qualifies as the ideal prognostic system. Several shortcomings are shared by all staging systems. The available staging systems were devised to identify groups of patients at risk for developing organ failure or clinically severe disease rather than identifying individual patients (65). Furthermore, one-fifth to one-third of patients with potentially fatal severe acute pancreatitis is identified inappropriately using the traditional scoring systems (66-69). Indeed, scoring systems perform best at the extremes of the prediction range, while the discriminatory power is moderate at best in the middle prediction range; i.e. the range where the clinician needs most assistance. Additionally, the variable timing of patient admission to the hospital affects the clinical, laboratory, and imaging parameters, which may explain the interinstitutional variability in scores obtained. Moreover, all scoring systems identify those with severe disease only as it develops and do not predict severe disease with enough lead time for potential intervention. Several simple, routinely available clinical measures, such as serum hematocrit, elevations in blood urea nitrogen, and presence of systemic inflammatory response syndrome (especially lasting more than 48h), may be as accurate as the more complex multiple-factor scoring systems in predicting severe acute pancreatitis (67). From an imaging perspective; the degree of morphologic abnormalities is influenced largely by the time interval between symptom onset and performance of the imaging study with increasing changes seen with increasing time interval (with correspondent higher scores or grades). Finally, scoring systems (imaging-based and biochemical systems alike) do not correlate with the risk of particular extrapancreatic complications (e.g. abdominal compartment syndrome, bowel ischemia or perforation or hemorrhage from an arterial pseudoaneurysm) and, therefore, fail to provide detailed information that influences patient management on an individual basis.

Shortcomings of imaging-based versus clinical scoring systems

Imaging-based systems have their specific shortcomings compared with clinical and biochemical scoring systems. Severe acute pancreatitis may run a highly variable clinical course; it may manifest early with SIRS, organ failure, and death in the first week or late with local complications demanding intervention. Compared with imaging-based systems, biochemical scoring systems correlate better with early systemic effects of pancreatic injury (i.e. organ failure; the main determinant for severity of disease in the 2012 Revised Atlanta Classification) and are in general better in predicting clinical severity early in the disease course (69). Conversely, imaging-based scoring systems are best in predicting late local complications (infected necrosis, need for intervention) (70,71). Second, imaging-based scoring systems are largely based on visual assessment and, therefore, are subject to variable interpretation, which likely relates to readers' expertise and familiarity of imaging findings of acute pancreatitis. In contrast, most biochemical scoring systems are derived from objective parameters. Third, imaging-based scoring systems do not account for patients pre-existing clinical status; such as age, co-morbid disease, and obesity which are well-known prognostic risk factors for morbidity and mortality (60,61). Fourth, as opposed to clinical scoring systems, imaging-based scoring systems are not repeated routinely within a short time period such that an interval change in significant morphology may go unnoticed (e.g. interval detection of parenchymal necrosis on serial CT not visible on the index CT). Fifth, institution of preventative measures requires early identification of patients with severe disease before the development of a complication. The timing of the CT scan in studies on the predictive power of imaging-based scoring systems, however, has varied from at admission to 10 days after admission. Conversely, clinical and biochemical scoring systems are tested mostly early in the clinical course (within the first 24-48h); i.e. in a timeframe where severity stratification is most useful. Finally, studies on imaging-based systems are biased toward more severe disease because cross-sectional imaging is usually not performed in patients with mild or minimal symptoms as they do not require imaging for clinical management, while clinical and biochemical scoring systems are tested and applicable in all patients presenting with acute pancreatitis.

Specific shortcomings of imaging-based scoring systems

The use of early imaging for prognostication is limited by several other factors specifically related to imaging-based scoring systems. First, in most imaging-based systems the rating of peripancreatic inflammation and fluid is determined based on their presence rather than extent; the latter may vary considerably among patients appreciated with similar grades. Second, morphologic signs of severe disease are a time-dependent phenomenon. CT only takes a snapshot at a moment in time whilst acute pancreatitis is a continuously evolving disease process, especially in the early phase. Consequently, patients may progress from mild to severe grades of CT severity. Third, the extent of parenchymal necrosis may not be evident until after 48h and, thus, may be underrated on early imaging (72,73). Fourth, in a definite percentage of patients with acute pancreatitis, there is a non-linear relationship between morphologic findings and clinical severity. CT may demonstrate little morphologic signs of severe disease early in disease process (i.e. on day of admission) in patients who already have organ failure as sign of a severe attack. Conversely, some 30% of patients with parenchymal necrosis will have a relatively benign clinical course (without organ dysfunction or systemic complications) (74,75). Finally, the fallacy of linking one imaging feature or a constellation of imaging features to severe clinical outcome falls short simply because of the intrinsic morbidity and mortality, albeit low in numbers, in patients with interstitial pancreatitis. In the minority of patients with interstitial pancreatitis with dismal outcome, grave CT-imaging features tend to be absent.

Clinicians need a powerful, simple, and easy to use predictive system early in the disease process, preferably within several hours after admission, for triaging patients to different levels of care. Cross-sectional imaging studies performed within this timeframe will unlikely surpass clinical scoring systems as has been shown in aforementioned reports comparing the various imaging-based scoring systems on day of admission (63,64). In view of the abovementioned limitations of imaging-based scoring systems, the added costs, efforts, and radiation burden associated with CT, and the ease of use of some of the clinical scoring systems, it is, therefore, unlikely that imaging-based scoring systems will ever serve as an accurate means of correctly identifying all those with severe acute pancreatitis early on in the disease process. The limited efficacy of imaging-based scoring systems reflects the complexity, variability, and heterogeneity of acute pancreatitis with its myriad possible clinical expressions.

Based on current evidence, the initial severity assessment of patients with acute pancreatitis should be based on laboratory and/or clinical scoring systems rather than relying on imaging parameters. The decision if and when to perform CT depends, therefore, on the overall clinical presentation. Undeniably, CT has its greatest merits in the later phase of the disease in those who have predicted moderate severe or severe acute pancreatitis by clinical assessment or those who do not improve clinically despite appropriate therapy when local complications, most commonly infection of necrotic tissue, largely affect clinical decision-making.

Future perspectives

Predicting the severity, prognosis, and clinical course of acute pancreatitis in individual patients remains important to clinicians. As aforementioned, the disease course of acute pancreatitis is highly variable and driven mainly by differences in individual susceptibility, general health, physiologic reserve, and by variations in the processes and pathogenicity of acute pancreatitis (primarily the occurrence of SIRS, organ dysfunction, tissue necrosis, and infected necrosis). Although there are many approaches to severity prediction, the continuing fundamental problem is that misclassification error occurs in 20-30% of patients. This limits the usefulness of any predictive system in an individual patient. Yet, there is still some value in predicting disease severity and this relates to triage, transfer, treatment, and trials.

To date, probably the best predictor of disease severity in clinical practice is not one of the multiple-factor systems, but rather an experienced clinician who is informed by patient- and disease-related risk factors, such as older age, (morbid) obesity, comorbidities, and who is familiar with the predictive value of the simple measures such as, SIRS, blood urea nitrogen, creatinine, and hematocrit levels. All of these factors are associated with worse outcomes and help in making decisions pertaining to patient triage and care. With reference to scientific research, it is doubtful that new multiple-factor clinical scoring systems (whether or not combined with other clinical or imaging systems) will increase the predictive accuracy any further. Future studies should, therefore, focus on the translational research to find better biological markers (i.e. sophisticated analytical technologies such as serum proteomic pattern analysis, genetic polymorphisms, metabolomics, and cytokine profiles, among others) of the primary factors determining clinical outcome (organ failure and (infected) pancreatic necrosis), as well as host-related factors that influence the severity of SIRS. Such an approach might help in understanding the mechanisms of severe acute pancreatitis, in identifying patients who are at-risk soon after or before pancreatic injury occurs, and in developing new therapies to mitigate the severity of acute pancreatitis. Notably, the latter is still not available and, therefore, it remains uncertain whether any future accurate prognostic indicator will actually decrease the severity of acute pancreatitis during hospitalization. Another approach to predicting severity of disease will likely come from analytic methods (e.g. artificial neural networks) and primarily intelligence-based data (artificial intelligence). Contemporary cross-sectional images (stored as DICOM) contain much metadata (e.g., imaging abnormalities, age, compression thickness, radiation dose, among others parameters), but very little of the vast amount of information contained in an individual imaging study is being used currently (76,77). Future advancements in imaging analytic tools, such as computer aided diagnosis, image segmentation, automated analysis tools (e.g. automatic assessment of 'bone density', quantification of visceral and subcutaneous fat, and measurements of muscle mass and density), and deep learning algorithms, will enable the integration of clinical data derived from hospital information systems, including imaging data, combined with genomic analysis, and lifestyle information. Furthermore, future advances in machine learning (a subfield of artificial intelligence that gives computers the ability to learn without being explicitly programmed) and data mining (identifying unanticipated associations in unstructured and seemingly unrelated datasets) will likely result in the identification of previously unrecognized patterns, risk factors, and relationships in complex diseases such as acute pancreatitis (78-80). In view of these advances in the field of medical technology, future breakthroughs are foreseen in creating new highly refined models for accurately predicting individual acute pancreatitis severity.

Finally, it is pivotal that future studies on pancreatitis severity prediction use similar definitions of severity in line with the 2012 Revised Atlanta Classification, including the presence of parenchymal necrosis (representing moderately severe acute pancreatitis) and persistent organ failure (representing severe acute pancreatitis). Other surrogate severity parameters, such as mortality (the end result of severity) and length of hospital or intensive care stay and need for intervention (among other variables) should be regarded as consequences of severity. Lack of using uniform definitions in the past has hampered comparison of interinstitutional data. It is to be hoped that with increased awareness within the scientific pancreatic community, pancreatologists worldwide comply with standardized definitions of disease severity.

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17

Nederlandse Samenvatting

Acute pancreatitis is een acute ontsteking van het pancreas, welke in de Westerse wereld voornamelijk wordt veroorzaakt door galstenen (40-50%) en alcohol (10-40%). Andere oorzaken zijn o.a. geneesmiddelen, hypertriglyceridemie, hypercalciëmie en na een ingreep (ERCP-procedure en na abdominale of thoracale chirurgie). In 10-20% van de gevallen blijft de oorzaak echter onbekend. De incidentie van acute pancreatitis neemt wereldwijd toe, waarschijnlijk door de toename van obesitas en incidentie van galstenen. In de Verenigde Staten is acute pancreatitis verantwoordelijk voor meer dan 200.000 opnames per jaar. In Europa varieert de incidentie van 4 tot 45 per 100.000 patiënten per jaar. In Nederland ziet een gemiddeld ziekenhuis jaarlijks 5 tot 10 patiënten met de ernstige vorm van acute pancreatitis. Acute pancreatitis gaat gepaard met hoge kosten; in de Verenigde Staten wordt jaarlijks ruim 2 miljard dollar uitgegeven aan acute pancreatitis, terwijl in Nederland de gemiddelde kosten van een ernstige necrotiserende pancreatitis, inclusief interventie, ongeveer 80.000 Euro bedraagt. Traditioneel wordt de klinische ernst van acute pancreatitis onderverdeeld in een milde en een ernstige vorm, terwijl op beeldvorming de interstitiële (met behoud van vitaal pancreasweefsel en omgevend weefsel) en necrotiserende (het afsterven van pancreas en/of omgevend weefsel) vorm wordt onderscheiden.

Dit proefschrift heeft 2 doelen betreffende de classificatie en het voorspellen van ernst van acute pancreatitis. Het oude classificatie systeem van acute pancreatitis (1992 Atlanta Classificatie) werd geëvalueerd door literatuuronderzoek en zogenaamde 'interobserver-overeenstemming' studies. Tevens werd een studie gedaan naar het morfologische deel van het nieuwe classificatiesysteem (Gereviseerde Atlanta Classificatie uit 2012). De voorspellende waarde voor het inschatten van ernst van ziekte door beeldvormende scoringssystemen werd gedaan door 2 studies. Tenslotte, zijn in 2 verschillende cohorten de ernst van de interstitiële en necrotiserende vorm van acute pancreatitis in kaart gebracht.

In ***hoofdstuk 2*** beschrijven we de resultaten van een 'interobserver-overeenstemming' studie tussen 5 abdominale radiologen voor het categoriseren van peripancreatische collecties op CT door gebruik te maken van de 1992 Atlanta Classificatie. De preoperatieve CT scans van 70 patiënten met necrotiserende pancreatitis werden hiervoor gebruikt. De interobserver-overeenstemming was slecht (kappa van 0.144 met standaarddeviatie van 0.095). In slechts 3 van de 70 patiënten kozen de 5 radiologen dezelfde definitie, terwijl 3 radiologen dezelfde definitie kozen in 42 van de 70 casus (42%). Conclusie van deze studie was dat de Atlanta definities uit 1992 niet gebruikt moeten worden voor het categoriseren van peripancreatische collecties op CT.

In een complex ziektebeeld zoals acute pancreatitis is het gebruik van correcte terminologie en gestandaardiseerde definities erg belangrijk zowel in de klinische praktijk als in wetenschappelijk onderzoek. Het 1992 Atlanta Classificatie systeem was een *klinisch* georiënteerd systeem en werd in toenemende mate bekritiseerd. In 2 uitgebreide literatuuronderzoeken werd de acceptatie en het gebruik van de 1992 Atlanta definities in de medische literatuur geanalyseerd.

In ***hoofdstuk 3*** beschrijven we een uitgebreid literatuuronderzoek gedurende de periode 1993 – 2006 waarbij gezocht werd naar termen die afgeraden werden te gebruiken door de 1992 Atlanta Classificatie: de verbannen terminologie betroffen 'phlegmone', 'geïnfecteerde pseudocyste', 'hemorragische pancreatitis', en 'persisterende pancreatitis'. Verder werden nieuwe termen gerubriceerd die opdoemden in de medische literatuur sinds de publicatie van de 1992 Atlanta Classificatie. In totaal werden 239 artikelen bestudeerd, inclusief 10 richtlijnen en 42 overzichtsartikelen. Uit ons onderzoek bleek dat 2 oude termen definitief uitgebannen waren ('hemorragische pancreatitis' en 'persisterende pancreatitis'), terwijl de verbanning van de termen 'geïnfecteerde pseudocyste' en 'phlegmone' het minst geaccepteerd is. Tegelijkertijd zijn er in dezelfde periode nieuwe termen geïntroduceerd. Dit betreffen de termen: 'organized pancreatic necrosis', 'necroma', extrapancreatic necrosis', en 'central gland necrosis'. Deze termen zijn geopperd om entiteiten te beschrijven die volgens de auteurs onvoldoende waren geadresseerd door de 1992 Atlanta Classificatie.

In ***hoofdstuk 4*** rapporteren we de uitkomsten van een systematisch literatuuronderzoek over het gebruik van de 1992 Atlanta definities sinds de publicatie van deze classificatie tot 2006 in de medische literatuur. In totaal werden 447 artikelen geanalyseerd, inclusief 12 richtlijnen en 82 overzichtsartikelen. In meer dan de helft van de gepubliceerde artikelen werden alternatieve definities gebruikt voor de voorspelde ernst van ziekte, de daadwerkelijke ernst van ziekte en criteria voor orgaanfalen. Ook de 1992 Atlanta definities voor wat betreft de lokale complicaties in en rondom het pancreas werden vrij geïnterpreteerd, vooral daar waar het ging om de inhoud van peripancreatische collecties. Beide literatuuronderzoeken toonden aan dat de 1992 Atlanta Classificatie gedateerd was en gereviseerd diende te worden.

Vanwege de gevonden beperkingen van de 1992 Atlanta Classificatie voor de lokale complicaties werd een nieuwe set van morfologische termen ontwikkeld om peripancreatische collecties op CT te beschrijven. Deze morfologische termen betroffen: de aan- of afwezigheid van een collectie, de relatie van de collectie met het pancreas, de inhoud, de vorm, het massa-effect, de aanwezigheid van geïmpacteerde gasbellen, gas-vocht niveau beeld, de mate van afkapseling en aanwezigheid en uitgebreidheid van niet-aankleurend pancreas parenchym. Omwille van het feit dat er een slechte interobserver-overeenstemming was bij gebruik van de 1992 Atlanta definities (zie hoofdstuk 2), beschrijven we in ***hoofdstuk 5*** een vergelijkbare studie bij gebruik van deze nieuwe set van morfologische termen om peripancreatische collecties op CT te beschrijven. De interobserver-overeenstemming tussen 17 pancreatologen (waaronder 7 gastro-intestinale chirurgen, 2 gastro-enterologen en 8 radiologen uit 3 Amerikaanse en 5 Europese gespecialiseerde ziekenhuizen) voor de nieuwe set van morfologische termen voor het beschrijven van peripancreatische collecties bij acute pancreatitis was goed tot uitstekend. Daarom adviseren wij om bij het beschrijven van morfologische afwijkingen van acute pancreatitis op CT de nieuwe descriptieve termen te gebruiken in plaats van de 1992 Atlanta definities.

De 1992 Atlanta Classificatie heeft ervoor gezorgd dat er meer gestandaardiseerd over acute pancreatitis werd gerapporteerd dan in de periode voorafgaande aan de introductie van dit classificatie systeem en dit zowel in wetenschappelijk onderzoek als in de dagelijkse communicatie tussen clinici onderling. Gaandeweg werd echter ook duidelijk dat de 1992 Atlanta Classificatie gedateerd was en aan revisie toe was door de vastgestelde tekortkomingen en door verbeterde ziekte inzichten over acute pancreatitis. Dit was de drijfveer om in 2007 een internationale consultatie via het internet op te zetten met medewerking van pancreatologen uit alle delen van de wereld, waaronder leden van de Dutch Pancreatitis Study Group. Na 5 jaar discussie resulteerde dit in een consensus document (de 2012 Gereviseerde Atlanta Classificatie) welke wordt gepresenteerd in ***hoofdstuk 6***. De 2012 Gereviseerde Atlanta Classificatie heeft criteria voor de diagnose van acute pancreatitis gedefinieerd en onderscheidt het verloop van de ziekte in 2 fasen: de vroege en late fase. Morfologisch wordt acute pancreatitis onderverdeeld in de interstitiële vorm en necrotiserende vorm waarbij de necrose kan bestaan uit pancreas parenchym, peripancreatisch vetweefsel of beide. De onderverdeling van de aanwezigheid van peripancreatische necrose onder de necrotiserende vorm is nieuw ten opzichte van de oude definitie van necrotiserende pancreatitis. De ernst van acute pancreatitis wordt, in plaats van 2 gradaties, nu gecategoriseerd in 3 gradaties: mild, matig ernstig en ernstig, afhankelijk van het optreden van orgaanfalen en lokale en systemische complicaties. Tenslotte is voor het eerst een beeldvormende classificatie toegevoegd voor de beschrijving van de lokale complicaties gebaseerd op morfologische CT criteria. De naamgeving van peripancreatische collecties is onderverdeeld in 4 types: acute peripancreatische vocht collectie (APFC), pseudocyste, acute necrotische collectie (ANC) en walled-off necrosis (WON) gebaseerd op de samenstelling van de collectie en de mate van afkapseling. De wereldwijde consultatie van pancreatologen om tot overeenstemming te komen die geleid heeft tot dit consensus document zou moeten leiden tot universele aanvaarding en gebruik van het nieuwe classificatie systeem.

Een belangrijk doel van de 2012 Gereviseerde Atlanta Classificatie is om consistente rapportage te vergemakkelijken en om onderzoeksgegevens voortvloeiend uit klinisch onderzoek beter onderling te kunnen vergelijken. Dit was de reden om morfologische criteria te introduceren om de afwijkingen van acute pancreatitis op CT te beschrijven. In ***hoofdstuk 7*** testen we de interobserver-overeenstemming tussen radiologen bij gebruik van deze nieuwe CT criteria in 285 consecutieve patiënten met acute pancreatitis die gedurende hun ziekenhuisverblijf een of meer CT scans hebben ondergaan. Voor de meeste nieuw geïntroduceerde CT criteria was de interobserver-overeenstemming matig tot substantieel. Vier criteria toonden beperkte interobserver-overeenstemming: extrapancreatische necrose (EXPN) (kappa van 0.326), type van pancreatitis (kappa van 0.370), karakteristieken van collecties (kappa van 0.408), en juiste term van collecties (kappa van 0.356). De matige kappa waarden kunnen worden toegeschreven aan de moeilijkheid om necrotisch materiaal op CT te onderscheiden. Dit is een in toenemende mate gekende beperking van CT en dus van de 2012 Gereviseerde Atlanta Classificatie. Het is aannemelijk dat er in de toekomst verdere aanpassingen aan de nieuwe morfologische criteria zullen worden doorgevoerd.

Het voorspellen van de ernst van acute pancreatitis heeft ongeveer evenveel aandacht gekregen in de medische literatuur als de classificatie van ziekte. Een decade na de ontwikkeling van het eerste klinische scoringssysteem om de ernst van ziekte te voorspellen (de 'Ranson score' uit 1974) (1), hebben Balthazar en collega's in 1985 een radiologisch scoringssysteem bedacht gebaseerd op basis van een blanco CT (2). Dezelfde radiologen hebben 5 jaar later een vernieuwde scoringssysteem ontwikkeld waarbij de aanwezigheid en uitgebreidheid van parenchymnecrose geïncorporeerd werd door gebruik te maken van een intraveneus contrast versterkte CT. Dit heeft geresulteerd in de 'CT severity index' ofwel CTSI wat heden ten dage de meest gebruikte CT scoringssysteem wereldwijd is (3).

In 2004 hebben Mortele en collega's enkele modificaties aangebracht aan de bestaande CTSI (de zogenaamde 'modified CTSI' ofwel MCTSI) en getest in een klein cohort van 66 patiënten waarbij de MCTSI beter correleerde met uitkomstmaten dan de originele CTSI (4). In ***hoofdstuk 8*** hebben we de MCTSI vergeleken met de originele CTSI voor wat betreft diverse parameters die correleren met de ernst van acute pancreatitis in een groter cohort van 196 patiënten die gedurende de eerste week van opname een contrast versterkte CT of MRI hebben ondergaan. Beide radiologische scoringssystemen werden vergeleken met een vaak gebruikte klinisch scoringssysteem (APACHE-II score). Twee radiologen beoordeelden onafhankelijk van elkaar beide radiologische scoringssystemen. De scoringssystemen werden gecorreleerd met diverse parameters voor de ernst van acute pancreatitis, inclusief mortaliteit, orgaanfalen, geïnfecteerde necrose, opname en duur van intensive care periode, nood aan interventie en klinische ernst van acute pancreatitis. Voor beide radiologische scoringssystemen werd een significante correlatie gevonden tussen de score en elke afzonderlijke parameter ($p < 0.001$), echter zonder significant verschil. Vergeleken met de APACHE-II index, was de correlatie tussen beide radiologische scoringssystemen significant beter voor de parameters nood aan interventie (CTSI, $p = 0.006$; MCTSI, $p = 0.01$), geïnfecteerde necrose (CTSI, $p = 0.04$; MCTSI, $p = 0.06$), en klinische ernst van acute pancreatitis (receiver operator curve, 0.87; 95%, 0.82-0.92). De interobserver-overeenstemming voor beide radiologische scoringssystemen was uitstekend tussen beide radiologen: voor CTSI, 0.85 (95% CI, 0.80-0.90) en voor MCTSI, 0.90 (95% CI, 0.85-0.95). Concluderend stellen we dat in de klinische praktijk beide radiologische scoringssystemen willekeurig gebruikt kunnen worden voor het inschatten van de ernst van ziekte.

Het wordt algemeen onderkend dat vroege herkenning van patiënten met klinisch ernstige pancreatitis cruciaal is voor de triage van patiënten en voor geïndividualiseerde behandeling. In ***hoofdstuk 9*** vergeleken we de voorspellende accuratesse van verschillende CT en klinische scoringssystemen voor het bepalen van ernst van ziekte op de dag van ziekenhuisopname (gedefinieerd als: binnen 24 uur na opname). Gedurende een periode van twee-en-een-half jaar werden alle patiënten die opgenomen werden met de diagnose van acute pancreatitis prospectief geregistreerd. Van dit cohort ontvingen 150 patiënten (in totaal 159 episodes van pancreatitis) een niet-contrast versterkte of contrast-versterkte CT op de dag van opname. De CT scans werden retrospectief gescoord door 2 radiologen geblindeerd voor de klinische uitkomstmaten. In totaal werden 7 verschillende CT scoringssystemen (CTSI, MCTSI, 'pancreatic size index' (PSI), 'extrapancreatic score' (EP), 'extrapancreatic inflammation on CT' (EPIC), 'mesenteric edema and peritoneal fluid' score (MOP), en Balthazar gradering) en 2 klinische scoringssystemen (APACHE-II en 'Bedside Index for Severity in AP' (BISAP)) onderling met elkaar vergeleken in hun voorspellend vermogen om de ernst van acute pancreatitis in te schatten op de dag van ziekenhuisopname. Klinisch ernstige pancreatitis werd gedefinieerd indien werd voldaan aan 1 van de navolgende criteria: mortaliteit, persisterend orgaanfalen (langer dan 48 uur) en/of lokale complicaties waarvoor een invasieve interventie noodzakelijk werd geacht. Ten tijde van deze studie was de definitie van ernstige pancreatitis nog niet helemaal uitgekristalliseerd, zodoende verschilt deze definitie enigszins van de 2012 Gereviseerde Atlanta Classificatie. De accuratesse van alle scoringssystemen voor het voorspellen van de ernst van acute pancreatitis werd bepaald door middel van receiver operating curve analyse. Van alle 7 CT scoringssystemen toonden de Balthazar gradering (voor elke CT techniek) en CTSI (voor enkel contrast-versterkte CT) de hoogste accuratesse voor het voorspellen van ernst van ziekte, evenwel zonder significante verschillen. Daarbij was de voorspellende accuratesse van CT scoringssystemen en klinische scoringssystemen vergelijkbaar. Wij concludeerden dat vanwege kostenbesparende en stralingshygiënische overwegingen een CT op de dag van opname voor het inschatten van ernst van ziekte niet is geïndiceerd.

In de radiologische literatuur wordt vaak vernoemd dat een CT vroeg in het beloop van de ziekte aangeraden is voor het evalueren van de morfologische ernst van acute pancreatitis (5-7), echter dit wordt niet ondersteund door klinische richtlijnen noch onderschreven door de meeste clinici (6-12). ***Hoofdstuk 10*** bevat een overzicht van de meest gebruikte radiologische scoringssystemen (voornamelijk gebaseerd op CT), inclusief de voordelen en beperkingen voor het voorspellen van de ernst van acute pancreatitis. De voornaamste beperking van alle scoringssystemen is dat ze beter met lokale complicaties correleren dan met systemische complicaties (vooral persisterend orgaanfalen, welke de voornaamste component vormt voor ernstige acute pancreatitis). In een CT verslag bij een patiënt met acute pancreatitis is het daarom belangrijker om complicaties als gevolg van acute pancreatitis te beschrijven dan het benoemen van een CT score. In hoofdstuk 10 wordt verder een overzicht gegeven van dergelijke bevindingen en dit omvat o.a. tekenen van geïnfecteerde necrose (gasbellen binnen necrotische collecties), tekenen van hemorragie of het detecteren van een arterieel pseudoaneurysma, diepe veneuze trombose of longembolieën, acute cholecystitis, darmischemie of perforatie, en CT kenmerken van het abdominaal compartiment syndroom (zoals 'round-belly sign' ofwel de toenemende ronding van een buik op opeenvolgende CT scans). De meeste van deze complicaties maken geen onderdeel uit van een CT scoringssysteem maar hebben wel een directe en significante impact op de behandeling van een patiënt met acute pancreatitis.

Een van de meest ernstige lokale complicatie van acute pancreatitis is geïnfecteerde necrose welke gepaard gaat met hoge morbiditeit en een mortaliteit van ongeveer 20-30% (12,13). De waarneming van gasbellen binnen een necrotische collectie op CT is nagenoeg pathognomonisch voor geïnfecteerde necrose. De diagnose van geïnfecteerde necrose is in de klinische praktijk echter niet eenvoudig. In ***hoofdstuk 11*** beschrijven we de toegevoegde waarde van het routinematig verrichten van een fijne naald aspiratie (FNA) van peripancreatisch vocht in combinatie met klinische en beeldvormende kenmerken van geïnfecteerde necrose bij alle patiënten die een interventie hebben ondergaan voor de verdenking van geïnfecteerde necrose. Daartoe deden we een post-hoc analyse bij 208 patiënten uit een prospectief bijgehouden multicentrische database bij wie een invasieve interventie werd verricht voor geïnfecteerde necrose. Retrospectief werden 3 groepen gereconstrueerd gebaseerd op basis van preoperatieve patiënt karakteristieken: klinisch beeld, bevindingen op beeldvorming, en resultaten van FNA. Patiënten in de klinische groep hadden klinische tekenen van infectie bij wie geen FNA werd verricht en bij wie geen gasbellen op een preoperatieve CT aanwezig waren. Patiënten in de beeldvormende groep hadden gasbellen op een preoperatieve CT bij wie geen FNA is verricht. Patiënten in de FNA groep hadden een positief resultaat voor geïnfecteerde necrose. Als gouden standaard voor geïnfecteerde necrose gold een positieve kweek verkregen tijdens de eerste invasieve interventie (ofwel via percutane drainage ofwel gedurende een necrosectomie). De initiële interventie voor geïnfecteerde necrose werd gemiddeld 27 dagen na opname uitgevoerd zonder significante verschillen tussen de 3 groepen ($p = 0.15$). Infectie werd bevestigd in 80% van de 92 patiënten in de klinische groep, in 94% van de 88 patiënten in de CT groep en in 86% van de 28 patiënten in de FNA groep ($p = 0.07$). Mortaliteit was 19% en verschilde niet tussen de groepen ($p = 0.39$). De diagnose van geïnfecteerde necrose kan doorgaans gesteld worden op basis van de kliniek of CT kenmerken van infectie. FNA is voorbehouden en nuttig bij patiënten met een onduidelijke kliniek zonder CT kenmerken van geïnfecteerde necrose.

In de medische literatuur is er veel beschreven over de uitkomsten van patiënten met necrotiserende pancreatitis, echter beperkt over factoren die geassocieerd zijn met klinisch ernstige pancreatitis bij patiënten met een interstitiële pancreatitis op beeldvorming. In ***hoofdstuk 12*** presenteren we de resultaten van een cohort van 149 patiënten die gedurende een periode van twee-en-een-half jaar opgenomen werden met de diagnose interstitiële pancreatitis op beeldvorming en dit cohort werd vergeleken met patiënten met extrapancreatische necrose (EXPN). Daartoe bepaalden we de Charlson co-morbiditeit score (CCI), de APACHE-II en BISAP score op de dag van opname (de eerste 24 uur van opname). Bovendien evalueerden we de incidentie van persisterend systemische inflammatoire response syndroom (SIRS), persisterend orgaanfalen (langer dan 48 uur), nood aan ICU opname, duur van hospitalisatie (in dagen) en mortaliteit bij patiënten met interstitiële pancreatitis en bij patiënten met EXPN. De mediane

APACHE-II score en BISAP score bij patiënten met interstitiële pancreatitis was respectievelijk 1 en 7. De mediane ziekenhuisopnameduur bedroeg 4 dagen, 1% had persisterend orgaanfalen en 1-2% had nood aan een vorm van interventie. De mortaliteit bij patiënten met interstitiële pancreatitis was 3% en dit was geassocieerd met significante co-morbiditeit (mediane CCI score voor degenen die overleden en overleefden bedroeg respectievelijk 4 en 1, p = 0.003). Patiënten met EXPN verschilden significant ten opzichte van patiënten met interstitiële pancreatitis voor alle parameters. In klinische studies dient derhalve een onderscheid gemaakt te worden tussen deze 2 groepen patiënten.

In de 2012 Gereviseerde Atlanta Classificatie is de term necrotiserende pancreatitis gedefinieerd als necrose van het extrapancreatisch vetweefsel (EXPN), van het pancreas parenchym of beide. Het wordt verondersteld dat patiënten met EXPN een betere uitkomst hebben dan patiënten met parenchymnecrose, echter betrouwbare data om dit te staven ontbreken. In ***hoofdstuk 13*** beschrijven we een post-hoc analyse van een prospectief bijgehouden multicentrische database van 639 patiënten met necrotiserende pancreatitis op CT. Alle CT scans werden geblindeerd voor klinische uitkomsten beoordeeld door 1 radioloog. Van het cohort van 639 patiënten waren er 324 met necrose van pancreas parenchym (met of zonder begeleidende EXPN) en 315 met necrose van alleen EXPN (dus zonder parenchymnecrose). Klinische uitkomstmaten omvatte persisterend orgaanfalen, nood aan invasieve interventie en mortaliteit. Een vooraf opgestelde subgroep analyse werd verricht bij patiënten die geïnfecteerde necrose ontwikkelden. Resultaten lieten zien dat patiënten met EXPN minder complicaties kregen ten opzichte van patiënten met parenchymnecrose: persisterend orgaanfalen (21% versus 45%, p < 0.001), persisterend multi-orgaanfalen (15% versus 36%, p < 0.001), geïnfecteerde necrose (16% versus 47%, p < 0.001), nood aan invasieve interventie (18% versus 57%, p < 0.001) en mortaliteit (9% versus 20%, p < 0.001). Echter indien patiënten met EXPN geïnfecteerde necrose ontwikkelden waren de klinische uitkomsten gelijkwaardig aan die van patiënten met infectie van parenchymnecrose (mortaliteit bij geïnfecteerde necrose: EXPN 28% versus parenchymnecrose 18%, p = 0.16). Wij concluderen dat op basis van deze studie patiënten met EXPN tot een aparte categorie dienen te horen binnen het morfologische spectrum van acute pancreatitis.

Bij acute pancreatitis wordt de uitgebreidheid van parenchymnecrose als een belangrijk uitkomstmaat beschouwd. Echter er is weinig informatie over de locatie (patroon) van parenchymnecrose en diens correlatie met diverse uitkomstmaten. In ***hoofdstuk 14*** analyseren wij de klinische impact van zowel uitgebreidheid van parenchymnecrose als de locatie (patroon) van necrose in een cohort van 324 patiënten. Klinische uitkomstmaten waren persisterend orgaanfalen, geïnfecteerde necrose, nood aan invasieve interventie en mortaliteit. De uitgebreidheid van parenchymnecrose was minder dan 30% in 132 patiënten (40%), tussen de 30 en 50% in 83 patiënten (26%) en meer dan 50% in 109 patiënten (34%). Op alle klinische uitkomstmaten, behalve voor mortaliteit, zagen we een significant verschil (p<0.001) tussen patiënten met minder dan 30% necrose ten opzichte van patiënten met meer dan 30%

necrose, echter niet tussen patiënten met 30-50% necrose en die met meer dan 50% necrose. Qua locatie van parenchymnecrose stelden we vast dat het centrale deel van het pancreas het vaakst necrose ondergaat (40%). Alle uitkomstmaten waren significant gecorreleerd met locatie van parenchymnecrose ($p<0.001$). De sterkste associatie werd gezien bij patiënten met rechtszijdige, centrale deel en subtotale necrose. Na multivariabele analyse bleek dat de patroon van parenchymnecrose (gebaseerd op locatie) het sterkst was geassocieerd met klinische uitkomsten, vooral wanneer de parenchymnecrose de pancreaskop of het centrale deel betrof (gerelateerd aan een disruptie van de ductus pancreaticus) met vitaal pancreasweefsel stroomopwaarts. Derhalve concluderen wij dat de locatie van parenchymnecrose een belangrijke prognostische factor is die van invloed is op het klinisch beloop van patiënten met acute necrotiserende pancreatitis.

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Geachte promotor Prof. Dr. H.G. Gooszen, beste Hein. Ergens in 2005 alweer zijn we rond de tafel gaan zitten om het promotietraject vorm te geven op 1 A-4tje. Sindsdien zijn er talloze mutaties en versies geweest. Je bent de grondlegger van de Pancreatitis Werkgroep Nederland (of in het Engels: Dutch Pancreatitis Study Group, kortweg DPSG) en pancreatoloog van het eerste uur. Met gevoel voor eufemisme durf ik te stellen dat ik niet bepaald de meest snelle promovendus onder je bezielende leiding ben geweest, maar wellicht wel de meest eigengereide. Ik ben je zeer dankbaar voor het grote vertrouwen, de ruimte en vrijheid die je mij hebt gegund bij het bedenken, opzetten en uitvoeren van de verschillende studies. Ik waardeer je toegewijde begeleiding van een onconventionele promovendus van een 'perifere' proefschrift, je nadruk op klinische relevantie van diverse onderzoeksprojecten en je rotsvast geloof in een goede afloop. Je was er als ik erom vroeg en gaf me wijze raad en advies waar nodig. Ik heb dit als bijzonder prettig ervaren en heb dat enorm gewaardeerd. "Lang gewacht, stil gezwegen, nooit gedacht, toch gekregen". Precies deze door jouw gebezigde zinsnede typeert jou als promotor. Heel veel dank!

Copromotor Dr. M.S. van Leeuwen, beste Maarten. Ons gezamenlijke interesse in de beeldvorming van het pancreas heeft ons inmiddels alweer 15 jaar geleden bij elkaar gebracht. Je bent een man van vele ideeën, soms onnavolgbaar en lastig uitvoerbaar maar altijd kritisch en beschouwend met oog voor detail. Dank voor je belangrijke wetenschappelijke en inhoudelijke toevoegingen en kritische beoordelingen van de manuscripten welke hebben bijgedragen aan de kwaliteit van dit proefschrift. Ik waardeer je oprechte sociale betrokkenheid bij mijn wel en wee en voel me altijd hartelijk welkom bij de RAKU besprekingen.

Copromotor Dr. H.C. van Santvoort, beste Hjalmar. Op een herfstavond in het begin van deze eeuw kwam jij als jonge arts-onderzoeker bij mij langs om over een onderzoekje te praten. Ik kon toen niet bevroeden dat jij mij de erop volgende jaren zou gaan 'stalken' over alles wat met beeldvorming van acute pancreatitis vandoen heeft. Wees gerust, ik heb het met plezier gedaan! Je was de ideale opvolger van Marc Besselink, de denker versus de doener, een groter contrast tussen jullie is nauwelijks denkbaar behalve jullie gedeelde passie voor het pancreas. Discussiëren is je 2de natuur en toch knopen doorhakken; een opmerkelijke combi voor een chirurg! Je bent een betrokken clinicus en wetenschapper pur sang, toegewijd en gepassioneerd met oog voor detail en je bent behept met een scherp analytisch vermogen. Je bent uitgebreid betrokken geweest bij het afronden van het laatste hoofdstuk. Je kritische vragen en beschouwingen hebben geleid tot verdere diepgang die ten goede zijn gekomen aan de kwaliteit van diverse manuscripten. Bijzonder knap hoe je werk en privé weet te combineren gezien de bulk werk die je op je neemt. Daarnaast ben je altijd geïnteresseerd, sociaal betrokken en kan ik met jou over van alles en nog wat discussiëren. Ik zie uit naar onze verdere samenwerking en vriendschap.

Leden van de manuscriptcommissie en promotiecommissie:

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Curriculum Vitae

CURRICULUM VITAE

Thomas Bollen was born on March 30th, 1973 in Nijmegen. He spent most of his childhood in Pesse in the provence of Drenthe. He graduated from secondary school at the Menso Alting College in Hoogeveen in 1992. Due to numerus fixus he was not selected for medical school and, therefore, started (and finished) his medical training in Ghent, Belgium, at Ghent University. He graduated from medical school in 1999 and started his working career as surgical resident (not in training) at the St. Antonius Hospital in Nieuwegein for the following 18 months. In July 2001, he started his training in Radiology at the St. Antonius Hospital in Nieuwegein (dr. J.C. de Valois and dr. J.P.M. van Heesewijk). As radiology resident, he joined the Dutch Pancreatitis Study Group (DPSG) in 2003. For all randomized clinical trials conducted by the DPSG (i.e. PROPATRIA, PANTER, PENGUIN, PYTHON, PONCHO, and TENSION trial), he reviewed the imaging (primarily CTs) of randomized patients. After finishing his training in radiology, he followed a 3-month research fellowship at the Division of Abdominal Imaging & Intervention, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA (Associate Professor K.J. Mortele). After 2 years as junior staff member, he became a senior staff radiologist at the St. Antonius Hospital in Nieuwegein. As of 2011, he is the Abdominal Imaging Fellowship Program Director at St Antonius Hospital and since then he has trained 8 fellows. Thomas Bollen is (co-)author of over 100 peer-reviewed articles and 5 book-chapters. Since January 2018, he is chairman-person of the abdominal section of the Dutch Society of Radiology (NVvR). Thomas is father of his eldest son Xafier. He lives with his girlfriend Elvin and their two children Mila and Tobias.