Acute Pancreatitis: Extrapancreatic Necrosis Volume as Early Predictor of Severity[1]

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Purpose: To determine the volume of extrapancreatic necrosis that predicts severe acute pancreatitis and to assess the reliability of this threshold in predicting severe acute pancreatitis compared with current scoring systems and C-reactive protein (CRP) levels.

Materials and Methods: This institutional review board–approved, HIPAA-compliant retrospective study included patients with acute pancreatitis who were examined with computed tomography (CT) 2–6 days after disease onset. Extrapancreatic necrosis volume, Balthazar score, and CT severity index (CTSI) were calculated. CRP levels 48 hours after the onset of symptoms were reviewed. Outcome parameters included organ failure, infection, need for surgery or percutaneous intervention, duration of hospitalization, and/or death. Receiver operating characteristic (ROC) curves were constructed to determine the optimal threshold for predicting clinical outcomes. Pairwise comparisons of areas under ROC curves (AUCs) from the different grading systems were performed. Interobserver and intraobserver agreement in the grading of extrapancreatic necrosis was assessed by using κ statistics.

Results: In 264 patients, significant relationships were found between extrapancreatic necrosis volume and organ failure, infection, duration of hospitalization, need for intervention, and death ($P < .001$ for all). The optimal threshold for predicting severe acute pancreatitis was 100 mL. Sensitivity and specificity were 95% (19 of 20) and 83% (142 of 172), respectively, for predicting organ failure (vs 100% [20 of 20] and 46% [79 of 172] for the Balthazar score and 25% [five of 20] and 95% [163 of 172] for the CTSI). The extrapancreatic necrosis AUC was the highest for all systems. Interobserver and intraobserver agreement based on the 100-mL threshold was considered to be excellent.

Conclusion: A simple grading system based on an objective criterion such as a threshold of 100 mL of extrapancreatic necrosis provides more reliable information for predicting acute pancreatitis outcomes than do the current scoring systems.

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Acute pancreatitis is a common inflammatory disease of the pancreas with increasing incidence in the Western world (1). It is a complex process in which pancreatic enzyme activation causes local pancreatic damage, resulting in an acute inflammatory response. Acute pancreatitis remains a disease of unpredictable outcome, with a mortality rate of between 10% and 15% (2). The most common causes of acute pancreatitis are biliary tract stones and alcohol abuse.

The widely accepted Atlanta classification, introduced in 1992, divided acute pancreatitis into mild and severe acute pancreatitis (3). This has recently been revised by international consensus, and there are now clearer definitions in which severe acute pancreatitis is classified on the basis of organ failure (4). Severe acute pancreatitis occurs in approximately 20% of patients and is associated with prolonged hospitalization, high morbidity, and high mortality, with death rates of 30%–50% (1). Mild acute pancreatitis responds well to supportive care, whereas severe acute pancreatitis requires monitoring and targeted therapies and has a poorer prognosis (5).

Improvements in therapeutics involve early risk assessment to allow appropriate therapeutic management and adequate allocation of hospital resources, with selective use of intensive care unit beds for patients at high risk.

Over recent decades, several clinical, biochemical, and radiologic scoring systems have been developed to predict adverse outcomes in acute pancreatitis. In 1985, Balthazar and colleagues introduced a scoring system (6) based on the presence of pancreatic and peripancreatic inflammation that uses a five-point scale (grades A–E). Later, this score was combined with an evaluation of the extent of pancreatic necrosis to create the computed tomography (CT) severity index (CTSI). This 10-point scale became a standard for assessing CT findings in acute pancreatitis. Since then, other radiologic scoring systems have been introduced (7). Nevertheless, the Balthazar scoring system and the CTSI remain the most widely used systems, despite only moderate interobserver agreement (5).

Some authors have questioned the validity of these scores as a prognostic tool for severity and outcome (1). Lankisch et al (8) stated that the presence and extent of extrapancreatic fluid collections were significantly correlated with a severe outcome. Furthermore, it has been reported that severe acute pancreatitis can occur in patients within Balthazar groups D and E without pancreatic necrosis (9). We propose that the outcome of acute pancreatitis could be associated with variations in the volume of extrapancreatic necrosis.

The purpose of this study was to determine the extrapancreatic necrosis volume that predicts severe acute pancreatitis and to assess the reliability of this simple new grading system in predicting severe acute pancreatitis, as compared with current scoring systems and C-reactive protein (CRP) levels.

Advances in Knowledge

- Extrapancreatic necrosis volume is associated with clinical outcome in patients with acute pancreatitis.
- The area under the receiver operating characteristic curve (AUC) of extrapancreatic necrosis for predicting organ failure was 0.94 (95% confidence interval [CI]: 0.90, 0.97), significantly higher than the AUCs of the Balthazar score (0.83 [95% CI: 0.76, 0.88]), CT severity index (0.84 [95% CI: 0.78, 0.89]), and C-reactive protein (CRP) level (0.78 [95% CI: 0.72, 0.84]).
- A 100-mL threshold of extrapancreatic necrosis yields better sensitivity and specificity combinations for predicting organ failure (95% [19 of 20] and 83% [142 of 172]) and infection (81% [26 of 32] and 86% [137 of 160]) than other grading systems, including CRP level.
- Risk assessment performed on the basis of extrapancreatic necrosis volume measurement had excellent interobserver and intraobserver agreement, with κ statistics of 0.810 and 0.816, respectively.

Implication for Patient Care

- Extrapancreatic necrosis volume measurement is a promising technique for the evaluation of the severity of acute pancreatitis and provides valuable information that could improve early risk assessment without modifying prescription habits.

Materials and Methods

This study was performed with the approval of our institutional review board and was compliant with Health Insurance Portability and Accountability Act regulations.

Patients

We performed a retrospective review that included all patients admitted to and treated in our university hospital between 2004 and 2009 with a confirmed diagnosis of acute pancreatitis and an early CT study. Diagnosis was based on the association of abdominal

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Abbreviations:
AUC = area under the ROC curve
CI = confidence interval
CRP = C-reactive protein
CTSI = CT severity index
ROC = receiver operating characteristic

Author contributions:
Guarantors of integrity of entire study, O.M., S.L., B.B., H.R., P.O.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, O.M., S.L., L.B., H.R., P.O.; clinical studies, O.M., S.L., B.B., L.B., H.R., P.O.; experimental studies, S.L.; statistical analysis, O.M., S.L., H.R.; and manuscript editing, O.M., S.L., F.Z.M., H.R., P.O.

Conflicts of interest are listed at the end of this article.

Figure 1

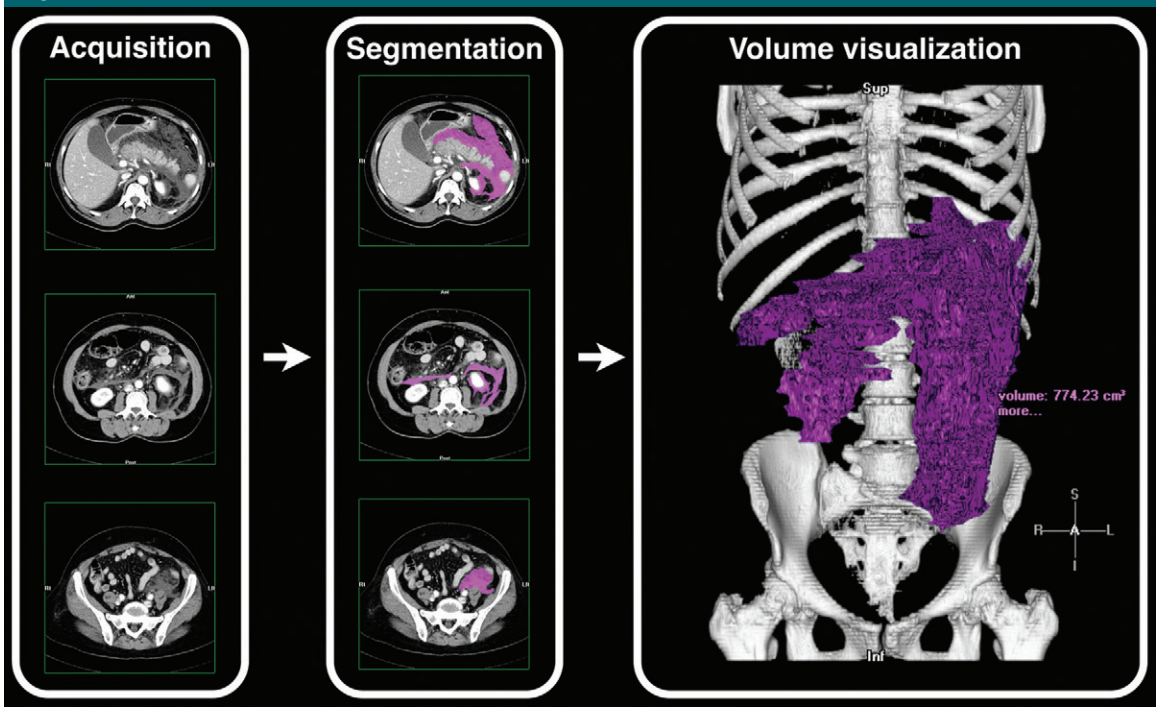


Figure 1: Axial CT images show volume measurement workflow.

pain consistent with acute pancreatitis (acute onset of persistent severe epigastric pain) and elevated serum lipase levels (at least three times greater than the upper limit of normal). An early CT study was defined by a delay of between 2 and 6 days after symptom onset. In our institution, an early CT study is routinely performed in all patients with a confirmed diagnosis of acute pancreatitis, regardless of its severity. Patients who had been transferred from another hospital without an early CT study were not be included. There was no exclusion criterion. Baseline data collected included sex, age, etiology, and time between admission and CT examination.

CT Technique

All CT examinations were performed by using a 16–detector row CT scanner (Sensation 16; Siemens, Erlangen, Germany). CT examinations were enhanced with contrast material and were performed with a 70-second scanning delay after intravenous injection of 100 mL of iopromide (300 mg iodine per milliliter, Ultravist 300; Berlex Laboratories, Wayne, NJ) injected at a rate of 3 mL/sec. Seventeen of the examinations were not contrast material enhanced because of renal dysfunction or an allergy. The imaging parameters were as follows: tube voltage, 120 kV; tube current, 200 mAs per section; field of view, 42 cm; reconstruction thickness, 2 mm; reconstruction increment, 1 mm; and matrix, 512 × 512. The area scanned extended from the diaphragmatic domes to the ischium.

Image Analysis and Measurement of Extrapancreatic Necrosis Volume and CRP Levels

CT studies were retrospectively reviewed on picture archiving and communication system workstations (McKesson Radiology Station 11; McKesson Medical Imaging Group, Richmond, British Columbia, Canada). Whenever possible, Balthazar score and CTSI were calculated for each patient. Pancreatic necrosis was defined as an area of diminished or no enhancement of the pancreatic parenchyma after intravenous administration of contrast material. With the CTSI, predicted severity was graded as mild (0–3 points), moderate (4–6 points), or severe (7–10 points). The volume of extrapancreatic necrosis, where present, was measured with manual segmentation (Voxar 3D ActiveX; Toshiba Medical Visualization Systems, Edinburgh, Scotland). Extrapancreatic necrosis included peripancreatic and contiguous retroperitoneal fat necrosis defined by fat infiltration, collection of fluid, or collection of both fluid and solid components (Fig 1, Appendix E1 [online]). Peritoneal fluids were not included. The results were expressed in milliliters. All the CT studies were reviewed by a senior radiologist specializing in abdominal imaging (S.L.) who had 6 years of experience. To assess interobserver and intraobserver agreement, a junior radiologist (O.M.) with 3 years of experience independently performed two other reviews, in a random sample of 50 patients. These reviews were separated by a 6-month interval to avoid potential recall bias. Both radiologists were blinded to clinical data and the

outcome parameters. The time taken for each measurement was calculated in seconds. CRP levels 48 hours after the onset of symptoms were retrieved from the medical records.

Outcome Parameters

Outcome parameters were collected from the hospital information system and included the length of hospital stay (in days), the need for surgical intervention (surgical débridement, excluding delayed cholecystectomy) or percutaneous intervention (CT-guided catheter drainage of pancreatic fluid or fat necrosis), evidence of infection in any organ system (positive results after a Gram stain or culture or the combination of a fever > 37.8°C and a white blood cell count of > 15 000/mm^3), and organ failure or death. Organ failure was defined as follows: for the cardiovascular system, hypotension requiring vasoactive medication; for the renal system, a serum creatinine level of more than 300 μmol/L or the need for hemo- or peritoneal dialysis; for the respiratory system, an arterial partial pressure of oxygen of less than 60 mm Hg or the need for ventilatory support; for the neurologic system, a Glasgow Coma Scale score of less than 6 in the absence of sedation; and for the hematologic system, a platelet count of 100 000/mL or less.

Statistical Analysis

Statistical analysis was performed by using Stata software (Stata, College Station, Tex) after converting the Excel database with Stat/Transfer (Circle Systems, Seattle, Wash), and MedCalc 12.2.1 (MedCalc, Mariakerke, Belgium). Qualitative variables were compared by using the parametric Student *t* test or the Mann-Whitney *U* test, as appropriate. The normalities of necrosis volume and hospital stay distributions were analyzed by using a Shapiro-Wilk test. Because both were characterized by non-Gaussian distribution, the correlation between the volume of necrosis and hospital stay was analyzed by using the Spearman rank correlation coefficient. $P < .05$ was considered to indicate a statistically significant difference.

Table 1

Baseline Demographic and Clinical Characteristics of 264 Patients Who Underwent CT for Acute Pancreatitis

Parameter	Datum
Patient characteristics	
Age (y)*	55.3 (17–93)
Women	58.5 (19–93)
Men	53.1 (17–85)
Female-to-male ratio	0.65 (104/160)
No. of women	104 (39)
Cause of acute pancreatitis	
Gallstone	90 (34)
Alcohol abuse	58 (22)
Ampullary tumor	20 (8)
After endoscopic retrograde cholangiopancreatography	13 (5)
Other	3 (1)
Unknown	69 (26)
Severity outcomes	
Clinical outcomes	
Duration of hospitalization (d)*	15 (2–240)
Infection	46 (17)
Organ failure	36 (14)
Need for intervention	27 (10)
Percutaneous catheter drainage	22 (8)
Surgical necrosectomy	14 (5)
Both	9 (3)
Death	9 (3)
CT scanning	
Time to CT (d)*	2.9 (2–6)
Contrast enhancement used	247 (94)
Balthazar score	
A	62 (24)
B	12 (5)
C	41 (15)
D	47 (18)
E	102 (38)
CTSI	
Mild (0–3)	148 (60)
Moderate (4–6)	83 (34)
Severe (7–10)	16 (6)
CRP level (mg/L)†	154 ± 129

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

* Data are means, with ranges in parentheses.

† Data are the mean ± the standard deviation.

A receiver operating characteristic (ROC) curve was constructed to determine the optimal threshold point for predicting organ failure and infection from volume. For the same events, ROC curves were also constructed for the Balthazar score, the CTSI, and CRP level. The area under the ROC curve (AUC) was calculated and was used as a measure of diagnosis accuracy. Pairwise comparisons of the AUCs were performed by using the method of Delong et al in the group of patients who had undergone both contrast-enhanced CT and assessment of CRP levels 48 hours after the onset of symptoms. Sensitivity, specificity, positive likelihood ratio, positive

predictive value, negative predictive value, and diagnostic odds ratio were also calculated in the same population. In secondary analysis, correction for the optimism of the AUC was performed by using the bootstrapping method (10,11). We produced two statistical models using binary logistic regression to compute the predicted probability of outcome separately for organ failure and infection, as a function of both CRP level and extrapancreatic necrosis volume (Appendix E2 [online]). ROC analysis was used to assess the predictive utility of the combined models. As previous investigators have done, we used κ statistics for interobserver and intraobserver agreement for assessing the severity of acute pancreatitis on the basis of extrapancreatic necrosis volume (5). A κ statistic of 0.41–0.60 was considered to indicate moderate agreement, 0.61–0.80 was considered to indicate good agreement, and 0.81–1.00 was considered to indicate excellent agreement (12).

Results

Population

A total of 264 patients were included. Baseline demographic and clinical characteristics are depicted in Table 1 . Contrast enhancement was not performed in 17 patients because of renal dysfunction in 14 patients and an iodine allergy in three patients, which contraindicated administration of the contrast material. CRP levels were obtained for 206 patients (Fig 2).

Extrapancreatic Necrosis Volume

The mean extrapancreatic necrosis volume was 114 mL (median, 12 mL; range, 0–1596 mL) (Fig 1). The mean time taken to measure extrapancreatic necrosis volume was 139 seconds (range, 10–304 seconds). We found a significant correlation between extrapancreatic necrosis volume and the length of the hospital stay (Spearman correlation coefficient, 0.75; $P < .0001$) (Fig 3). Increased extrapancreatic necrosis volume was associated with the occurrence of organ failure ($P < .001$), infection ($P < .001$), the need for surgical or percutaneous intervention ($P < .001$), and death ($P < .001$) (Fig 4). We focused on the occurrence of organ failure or an infection to distinguish mild and moderate acute pancreatitis from severe acute pancreatitis. Duration of

Figure 2

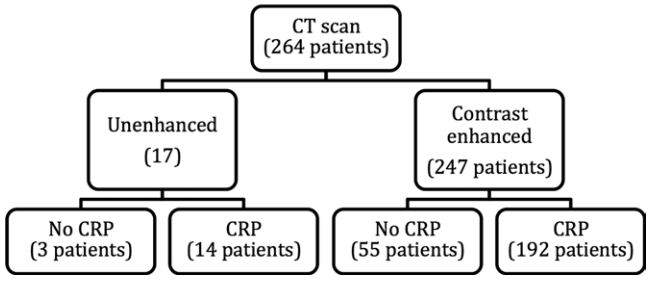


Figure 2: Flowchart of the study population.

Figure 3

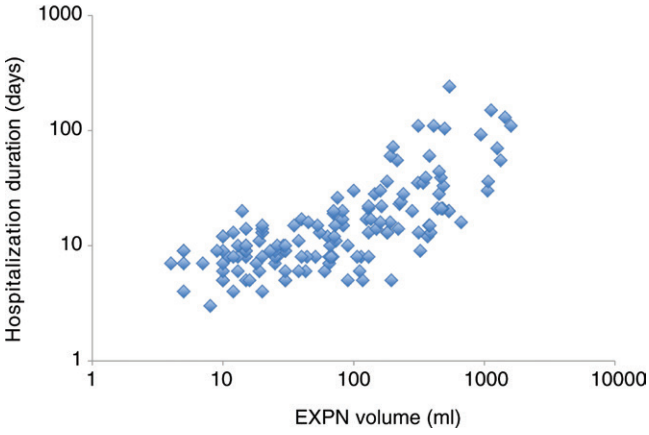


Figure 3: Graph shows correlation between extrapancreatic necrosis *(EXPN)* volume and duration of hospitalization.

Figure 4

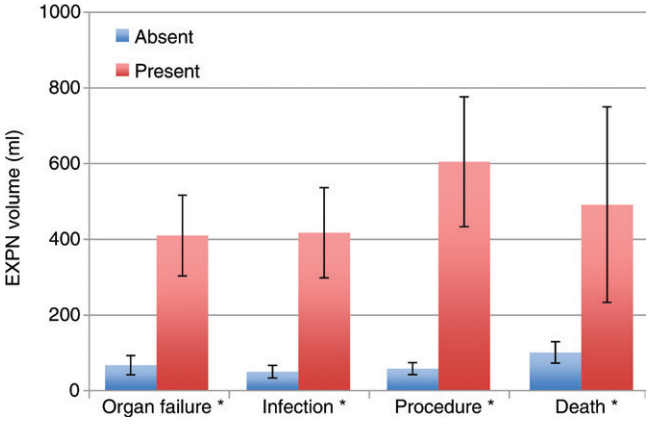


Figure 4: Bar graph shows mean extrapancreatic necrosis *(EXPN)* volume in milliliters (error bars = 95% CIs) for each clinical outcome. * = $P < .05$.

Figure 5

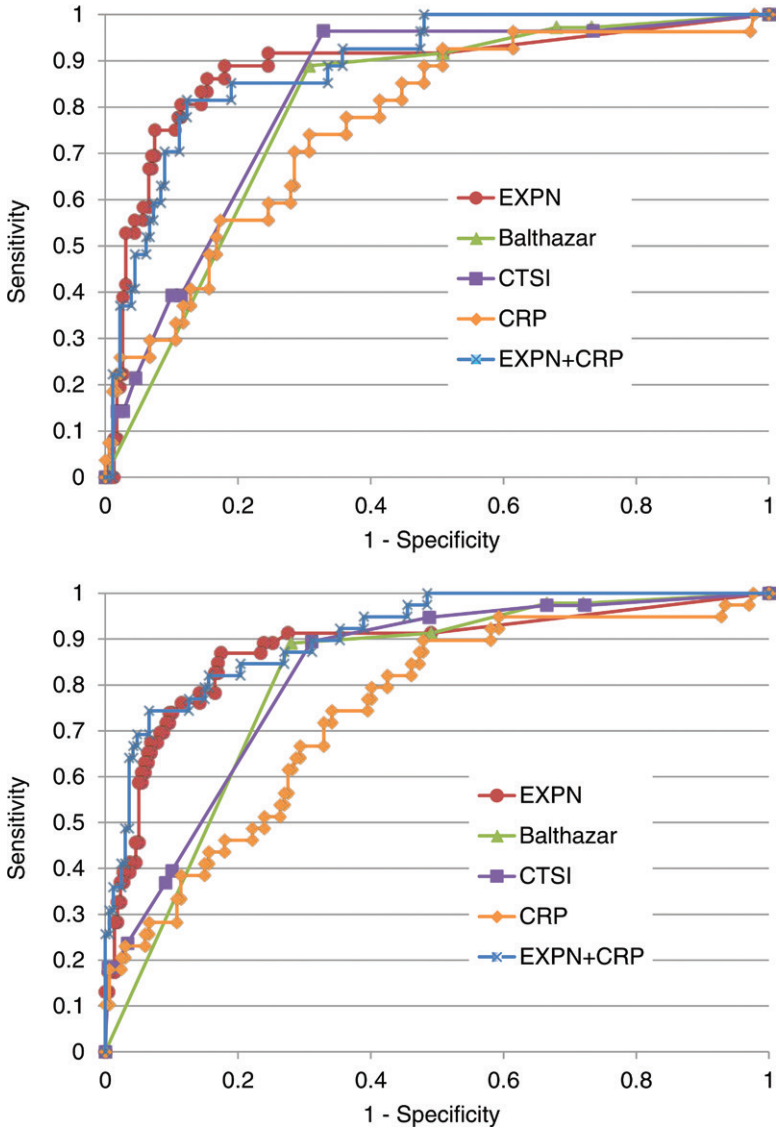


Figure 5: ROC curves of the different scoring systems and CRP level in predicting organ failure (top graph) or infection (bottom graph). *EXPN* = extrapancreatic necrosis.

hospitalization was not considered because it may not accurately represent morbidity because other factors may prolong the length of stay. Data for in-hospital mortality and the need for surgical or percutaneous procedures were too low in our series and were therefore not used for ROC analysis. On the basis of extrapancreatic necrosis volume, the ROC curves yielded an AUC of 0.94 (95% confidence interval [CI]: 0.90, 0.97) in predicting organ failure and 0.92 (95% CI: 0.87, 0.95) for infection (Fig 5; Tables 2, 3). Even after correction for optimism, the ROC curves still yielded an AUC of 0.89 (95% CI: 0.83, 0.98) in predicting organ failure and 0.88 (95% CI: 0.83, 0.96) for infection (Table E1 [online]). The optimal threshold value for predicting severe acute pancreatitis was 100 mL. Statistical analysis revealed significant differences for each clinical outcome between the two groups on the basis of this threshold (Table 4). Interobserver and intraobserver agreement, based on this 100-mL threshold, were considered excellent, with κ statistics of 0.810 and 0.816, respectively. Sensitivity and specificity were, respectively, 95% (19 of 20 [95% CI: 75%, 100%]) and 83% (142 of 172 [95% CI: 76%, 88%]) for predicting organ failure and 81% (26 of 32 [95% CI: 64%, 93%]) and 86% (137 of 160 [95% CI: 80%, 91%]) for infection (Table 5).

Comparison of Extrapancreatic Necrosis with Other Scoring Systems

The AUCs for organ failure and infection were considered to compare the scoring systems for predicting clinical severity. Extrapancreatic necrosis volume demonstrated the highest AUC of all the scoring systems for both organ failure and infection (Fig 5; Tables 2, 3). This AUC was statistically higher than those of both the Balthazar score and the CTSI for predicting organ failure or infection. There was no significant difference between Balthazar score and CTSI (Tables 2, 3).

On the basis of the ROC analysis, the following thresholds were selected: a Balthazar score of E or greater and a CTSI of 4 or greater. As shown in Table 5, sensitivity values, especially for predicting organ failure, were slightly higher than those for extrapancreatic necrosis, but specificity values were lower: 65% (112 of 172 [95% CI: 57%, 72%]) for Balthazar score and 63% (108 of 172 [95% CI: 55%, 70%]) for CTSI, versus 83% (142 of 172 [95% CI: 76%, 88%]) for extrapancreatic necrosis. When we considered the usual threshold values—that is, a Balthazar score of D or greater and a CTSI of 7 or greater, sensitivity and specificity, respectively, displayed opposing tendencies, with 100% (20 of 20 [95% CI: 83%, 100%]) and 46% (79 of 172 [95% CI: 38%, 54%]) for Balthazar score but 25% (five of 20 [95% CI: 9%, 49%]) and 95% (163 of 172 [95% CI: 90%, 98%]) for CTSI (Table 5). Use of these thresholds leads to false-positive cases with the Balthazar score (Fig 6) and false-negative cases with the CTSI (Fig 7). As shown in Table 4, CTSI revealed no

Table 2

AUCs of the Different Scoring Systems and CRP Level in Predicting Organ Failure or Infection in the 192 Patients Who Underwent Contrast-enhanced CT and CRP Level Evaluation

Grading System	Organ Failure	Infection
Extrapancreatic necrosis volume	0.94 (0.90, 0.97)	0.92 (0.87, 0.95)
Balthazar score	0.83 (0.76, 0.88)	0.82 (0.76, 0.87)
CTSI	0.84 (0.78, 0.89)	0.83 (0.77, 0.88)
CRP level	0.78 (0.72, 0.84)	0.77 (0.70, 0.82)
Extrapancreatic necrosis volume plus CRP level	0.92 (0.88, 0.96)	0.92 (0.87, 0.95)

Note.—Data in parentheses are 95% CIs.

Table 3

Pairwise Comparison *P* Values for AUC in Predicting Infection or Organ Failure

	Organ Failure				
Infection	Extrapancreatic Necrosis Volume	Balthazar Score	CTSI	CRP Level	Extrapancreatic Necrosis Volume plus CRP Level
Extrapancreatic necrosis volume		<.0001	.0013	.0015	.3990
Balthazar score	<.0001		.6188	.3665	.0007
CTSI	.0003	.7899		.2395	.0069
CRP level	.0017	.2261	.1520		.0001
Extrapancreatic necrosis volume plus CRP level	.9173	.0001	.0005	.0001	

Table 4

Relationship between CTSI or Extrapancreatic Necrosis Volume Grading System and Clinical Outcome

	Extrapancreatic Necrosis Volume		CTSI		
Clinical Outcome	<100 mL (*n* = 197)	≥100 mL (*n* = 67)	Mild (*n* = 148)	Moderate (*n* = 83)	Severe (*n* = 16)
Length of hospital stay (d)*	7.6†	39.2†	6.3	20.9†	59.8†
Organ failure	5 (3)†	31 (46)†	1 (1)	25 (21)	37 (6)
Infection	10 (5)†	36 (53)†	3 (4)	30 (25)	56 (9)
Surgery	1 (1)†	13 (19)†	0	7 (6)†	37 (6)†
Percutaneous intervention	1 (1)†	21 (31)†	0	17 (14)†	37 (6)†
Death	0†	9 (13)†	0	4 (3)†	18 (3)†

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Data are means.

† $P < .05$ for significant differences between the < 100-mL group and the ≥ 100-mL group for extrapancreatic necrosis volume and between the moderate and severe groups for CTSI.

significant differences between the moderate and severe pancreatitis groups in terms of development of infection ($P = .055$) or organ failure ($P = .18$), whereas there was a difference between the two groups on the basis of extrapancreatic necrosis. Compared with other scoring systems, extrapancreatic necrosis volume had the best positive likelihood ratio (5.4 [95% CI: 3.9, 7.7]) and diagnostic odds ratio (90 [95% CI: 12, 698]) for predicting organ failure.

Comparison of Extrapancreatic Necrosis with CRP Level

The most striking observation to emerge from this data was that CRP level yielded the smallest AUCs for predicting organ failure (0.78 [95% CI: 0.72–0.84]) or infection (0.77 [95% CI: 0.70–0.82]). The AUC of extrapancreatic necrosis volume was significantly higher than that of CRP level for predicting organ failure or infection ($P < .01$). There were no significant differences between the AUCs of CRP level and those of both Balthazar score and CTSI (Tables 2, 3). On the basis of the ROC analysis, a threshold value of 199 mg/L or greater was selected. With this threshold, sensitivity and specificity for predicting organ failure were 75% (15 of 20 [95% CI: 51%, 91%]) and 67% (116 of 172 [95% CI: 60%, 74%]), respectively. When we considered the usual threshold value (≥150 mg/L), there was a slight increase in sensitivity at the expense of specificity. Extrapancreatic necrosis presented better test characteristics than both CRP threshold values (Table 5).

Combining CRP Level and Extrapancreatic Necrosis Volume

Statistical models provided AUCs of 0.92 (95% CI: 0.88, 0.96) for predicting organ failure and 0.92 (95% CI: 0.87, 0.95) for predicting infection. On the basis of ROC analysis, there was no statistical difference from extrapancreatic necrosis volume (Fig 5; Tables 2, 3). For predicting organ failure, the optimal cutoff value showed only a slight increase in the positive likelihood ratio compared with the ratio for extrapancreatic necrosis volume alone (7.4 vs 5.4). Furthermore, it showed decreased sensitivity (90%, 18 of 20 [95% CI: 68%, 99%] vs 95%, 19 of 20 [95% CI: 75%, 100%]) and diagnostic odds ratio (64 vs 90), with only slightly improved specificity (88%, 151 of 172 [95% CI: 82%, 92%]

Table 5

Main Characteristics of Different Scoring Systems and CRP Level in 192 Patients Who Underwent Contrast-enhanced CT and CRP Level Evaluation

Characteristic	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Diagnostic Odds Ratio
Organ failure				
Extrapancreatic necrosis volume ≥ 100 mL	95 (75, 100)	83 (76, 88)	5.4 (3.9, 7.7)	90 (12, 698)
Balthazar score				
≥D*	100 (83, 100)	46 (38, 54)	1.8 (1.6, 2.1)	35 (2, 586)
≥E	100 (83, 100)	65 (57, 72)	2.9 (2.3, 3.5)	76 (5, 1283)
CTSI				
≥7*	25 (9, 49)	95 (90, 98)	4.8 (1.8, 12.9)	6 (2, 20)
≥4	100 (83, 100)	63 (55, 70)	2.7 (2.2, 3.3)	69 (4, 1159)
CRP level				
≥150 mg/L*	80 (56, 94)	58 (50, 65)	1.9 (1.4, 2.5)	5 (2, 17)
≥199 mg/L	75 (51, 91)	67 (60, 74)	2.3 (1.6, 3.2)	6 (2, 18)
Extrapancreatic necrosis volume plus CRP level	90 (68, 99)	88 (82, 92)	7.4 (4.8, 11.3)	64 (14, 299)
Infection				
Extrapancreatic necrosis volume ≥ 100 mL	81 (64, 93)	86 (80, 91)	5.6 (3.7, 8.5)	26 (10, 70)
Balthazar score				
≥D*	97 (84, 100)	49 (41, 57)	1.9 (1.6, 2.2)	29 (4, 221)
≥E	94 (79, 99)	69 (61, 76)	3.0 (2.3, 3.8)	33 (8, 144)
CTSI				
≥7*	28 (14, 47)	97 (93, 99)	9.0 (3.2, 25.1)	12 (4, 39)
≥4	85 (69, 95)	66 (58, 73)	2.5 (1.9, 3.2)	18 (5, 63)
CRP level				
≥150 mg/L*	78 (60, 91)	60 (52, 68)	1.9 (1.5, 2.5)	5 (2, 13)
≥199 mg/L	69 (50, 84)	69 (62, 76)	2.2 (1.6, 3.1)	5 (2, 11)
Extrapancreatic necrosis volume plus CRP level	75 (57, 89)	93 (88, 97)	10.9 (6, 20)	40 (15, 111)

Note.—Data in parentheses are 95% CIs.

* Commonly used threshold for diagnosing severe acute pancreatitis.

vs 83%, 142 of 172 [95% CI: 76%, 88%]). Similar variations were observed for predicting infection (Table 5).

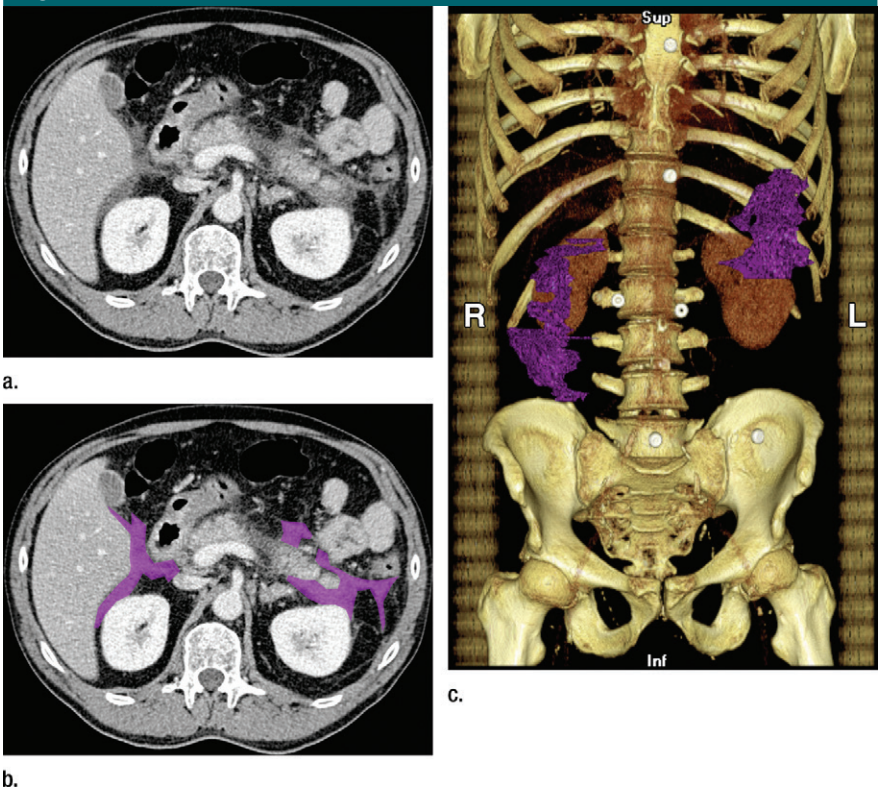
Discussion

In current practice, an early CT examination performed 48–72 hours after onset of symptoms is commonly prescribed. In this study, we demonstrated that extrapancreatic necrosis volume is highly correlated with patient outcomes, especially when considering the occurrence of organ failure and infection. The recent revision of the Atlanta classification established the presence of organ failure as the main criterion for defining severe acute pancreatitis (4). We are hereby proposing a new and much simpler method of grading pancreatitis on the basis of extrapancreatic necrosis volume, which continues the practice of performing an early CT study between 48 and 72 hours. A threshold of 100 mL offers great sensitivity and specificity for predicting the occurrence of organ failure or infection. It provides higher positive likelihood and diagnostic odds ratios than do the original Balthazar score, the CTSI, or even CRP level. Furthermore, it does not require administration of iodinated contrast material, and the use of only one simple criterion generates excellent inter- and intraobserver agreement.

Previous authors have shown the presence of infected necrosis to be an essential factor determining the occurrence of organ failure (13). The introduction of early CT evaluation using the Balthazar scoring system and later the CTSI has resulted in substantial progress in assessing patients with acute pancreatitis (6,9). Nevertheless, localization of fluid collections is frequently ambiguous, and simple thickening of fascia, caused by a small amount of fluid, can be difficult to incorporate into the classification (14). Pancreatic enlargement is left to subjective assessment (15), which probably explains the low number of grade Bs in our study and could explain an excess of false-positive cases. Lecesne et al (16) described poor interobserver agreement, particularly between grades C and D and between grades D and E. With CTSI, estimation of degree of necrosis is also subjective. It is not based on a computerized calculation and can be imprecise, especially for grades that are less than 30% or between 30% and 50%. Consequently, interobserver agreement for the CTSI score is not optimal, with a κ statistic ranging between 0.48 and 0.70 (5). Extrapancreatic necrosis volume provides one single objective criterion for grading acute pancreatitis at an early CT examination.

Other authors have questioned the usefulness of CTSI in terms of the clinical treatment of patients with an intermediate score (ie, 3–6) (15). The absence of any significant difference between patients with moderate predicted acute pancreatitis and those with severe acute pancreatitis as regards development of infection or organ failure support these reservations. Additionally, results of correlation between necrosis and organ failure in acute pancreatitis are controversial (17–19), and the injection of contrast material may have a deleterious effect on patients with acute pancreatitis (16). Moreover, with the CTSI, six points out of 10 come from pancreatic parenchymal necrosis grading. The weight of pancreas

Figure 6



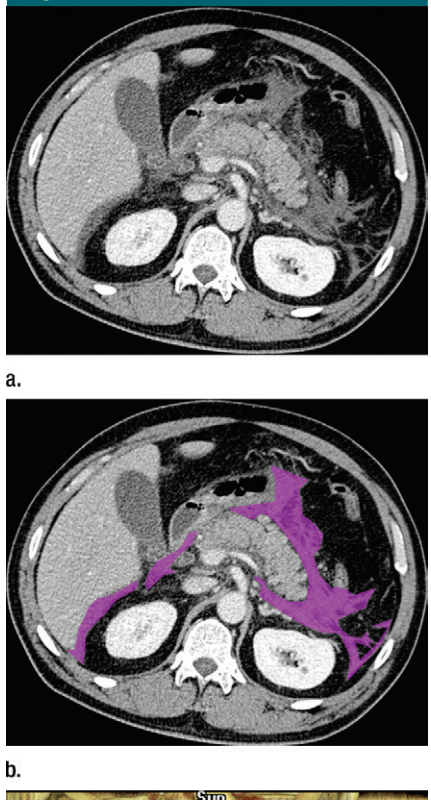
a.

b.

c.

Figure 6: Images show grade E acute pancreatitis with only 80 mL of extrapancreatic necrosis (<100 mL) in a patient with no organ failure or infection at follow-up. **(a, b)** Axial reconstructions from a CT study show segmentation of extrapancreatic necrosis in purple. **(c)** Three-dimensional model produced from segmentation of extrapancreatic necrosis.

Figure 7



a.

b.

c.

Figure 7: Images show acute pancreatitis graded as mild by using the CTSI (score = 4 for two or more fluid collections) with 1326 mL (>100 mL) of extrapancreatic necrosis in a patient with severe organ failure at follow-up. **(a, b)** Axial reconstructions from a CT study show segmentation of extrapancreatic necrosis in purple. **(c)** Three-dimensional model produced from segmentation of extrapancreatic necrosis.

necrosis in the score can lead to false-negative cases. Measurement of extrapancreatic necrosis volume does not require contrast enhancement and provides better test characteristics without considering parenchymal necrosis.

Currently, clinical care of patients with acute pancreatitis relies more on symptoms and serum analysis than on evaluation of an early CT study (20,21). CRP level is the best-known single simple serologic marker for predicting severe acute pancreatitis (22). It is probably the most widely prescribed and is considered to be the reference for predicting the severity of acute pancreatitis (23). In contrast to earlier studies (24–27), one unanticipated finding in our study was that CRP level yielded the smallest AUC of all grading systems. However, different definitions of severe acute pancreatitis and particularly the inclusion of acute fluid collection as a criterion may have introduced biases. This suggests that no grading system is self sufficient. Our study needs validation through a prospective evaluation, followed ideally by an interventional study based on these findings. For example, Lenhart and Balthazar (28) suggest that routine follow-up examinations be performed for patients with severe acute pancreatitis; thus, patients with fluid collections of 100 mL or greater might benefit from a follow-up CT examination, transfer to the intensive care unit, or both, relying on the integration of early clinical and biochemical parameters.

While showing the usefulness of extrapancreatic necrosis volume measurement for early acute pancreatitis severity grading, our study had some limitations. Only patients who underwent an early abdominal CT study were

included in the analysis, introducing a selection bias. We restricted our grading system to the detection of severe acute pancreatitis and made no distinction between mild and moderate acute pancreatitis. However, there is no proven benefit to different treatment of these patients. CRP levels were obtained for only 206 patients, but outcomes in these patients were comparable to those in the entire population. Estimates of sensitivity and specificity were derived from the same data used to identify an optimal ROC threshold for extrapancreatic necrosis and were therefore upwardly biased. Nevertheless, cross validation with bootstrapping showed little difference between AUCs from original data and AUCs corrected for optimism.

In conclusion, extrapancreatic necrosis volume is highly correlated with outcome in acute pancreatitis. A simple, highly reproducible grading system, based on an objective criterion such as a threshold of 100 mL of extrapancreatic necrosis, provides more reliable information than do the current scoring systems for predicting the occurrence of organ failure and infection in acute pancreatitis.

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