Factors Predicting the Development of Necrosis in Patients Presenting With Edematous Acute Pancreatitis

Fatih Acehan, MD, Mustafa Comoglu, MD,* Fatih Mehmet Kayserili, MD,† Büşra Hayat, MD,† and Ihsan Ates, MD**

Objectives: There is no marker that can accurately predict the development of pancreatic necrosis in edematous acute pancreatitis (AP). This study aimed to investigate the factors associated with necrosis development in cases of edematous AP and to create an easy-to-use scoring system.

Methods: We retrospectively reviewed patients diagnosed with edematous AP between 2010 and 2021. Among the patients, those who were found to have developed necrosis during follow-up were categorized as the necrotizing group, whereas the others constituted the edematous group.

Results: With multivariate analysis, white blood cell, hematocrit, lactate dehydrogenase, and C-reactive protein levels at the 48th hour were revealed to be independent risk factors for necrosis. Using these 4 independent predictors, the Necrosis Development Score 48 (NDS-48) was derived. While the cutoff value was 2.5, the sensitivity and specificity of the NDS-48 for necrosis were 92.5% and 85.9%, respectively. The area under the curve value of the NDS-48 for necrosis was 0.949 (95% confidence interval, 0.920–0.977).

Conclusions: White blood cell, hematocrit, lactate dehydrogenase, and C-reactive protein levels at the 48th hour are independent predictors of necrosis development. The NDS-48, a new scoring system created with these 4 predictors, satisfactorily predicted the development of necrosis.

Key Words: acute edematous pancreatitis, acute necrotizing pancreatitis, contrast-enhanced computed tomography, necrosis development, scoring system

(*Pancreas* 2022;51: 1300–1307)

Acute pancreatitis (AP) is an inflammatory disease characterized by abdominal pain and elevated levels of pancreatic enzymes. Its severity may range from mild self-limited pancreatic edema to systemic inflammation that causes pancreatic necrosis, organ failure, and death.[1] Although recent studies have shown that the mortality rate has decreased to 2%, necrotizing pancreatitis may develop in 15% to 20% of patients, and such a condition is likely to increase the severity of the disease.

In patients with a decline in their clinical statuses during follow-up, contrast-enhanced computed tomography (CECT) scan is needed for the evaluation of pancreatic and extrapancreatic necrosis and local complications.[2] It is important to perform CECT for the right indications and the right patients because this modality has some unfavorable effects, such as renal toxic effects and radiation exposure. Therefore, CECT is planned only for patients who are thought to have severe pancreatitis.

From the *Department of Internal Medicine and; †Department of Radiology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey.
Received for publication March 20, 2022; accepted February 4, 2023.
Address correspondence to: Fatih Acehan, MD, Department of Internal Medicine, University of Health Sciences, Ankara City Hospital, Universiteler Neighborhood 1604, St No: 9 Çankaya, Ankara, Turkey (e-mail: acehanf@gmail.com).
The authors declare no conflict of interest.

DOI: 10.1097/MPA.0000000000002206

A great number of scoring systems have been developed for the early prediction of the severity of AP. The scoring systems commonly used in clinics include the Bedside Index for Severity in Acute Pancreatitis (BISAP), Acute Physiology and Chronic Health Examination (APACHE) II, the Glasgow criteria, Ranson score, and the Computed Tomography Severity Index (CTSI).[3–7] However, none of these scoring systems provide the necessary balance between accuracy and simplicity in clinical practice.[8] In addition, these systems have no ability to specifically predict pancreatic necrosis. Therefore, clinicians do not often use the currently available scoring systems to predict necrosis. However, many studies have revealed that early CECT improves the prognosis in selected patients, although not in most patients.[9,10] Necrosis should be detected early in the appropriate cases, necessary treatment procedures should be performed, and necessary interventions should be made, whereas unnecessary radiation exposure, nephrotoxicity, and high costs are avoided. Therefore, there is a need for a simple and effective scoring system that can predict pancreatic necrosis early.

In this study, we aimed to identify the clinical and laboratory parameters needed for the early prediction of the development of pancreatic necrosis in patients presenting with edematous AP and to create an easy-to-use scoring system with these parameters.

MATERIAL AND METHODS

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Health Sciences University Ankara City Hospital with decision number E1-21-1858, dated June 9, 2021.

Study Design and Definition

In this study, patients 18 years or older diagnosed with AP between 2010 and 2021 were retrospectively reviewed. In the first 72 to 96 hours of their hospital stays, CECT scans were performed, and patients diagnosed with AP were evaluated for eligibility for inclusion in the study. We designed the study to include only patients who were diagnosed with edematous AP at admission by CECT. Because of our study design, patients who did not undergo CECT and who were found to have necrotizing AP on CECT at the time of admission were excluded from the sample. In addition, patients who did not accept hospitalization or were followed for a period of less than 48 hours and whose data were insufficient were excluded from the study (Fig. 1).

Among the patients diagnosed with edematous AP at the time of admission, those who were found by CECT to have developed necrosis during follow-up were categorized as the necrotizing group, whereas the others who did not have necrosis in the control CECT or were discharged without a control CECT constituted the edematous group. It was aimed to identify the predictors associated with necrosis development and to use those predictors to develop a scoring system that predicts necrosis development. The predictive role of this newly developed scoring system in necrosis detection was then investigated.

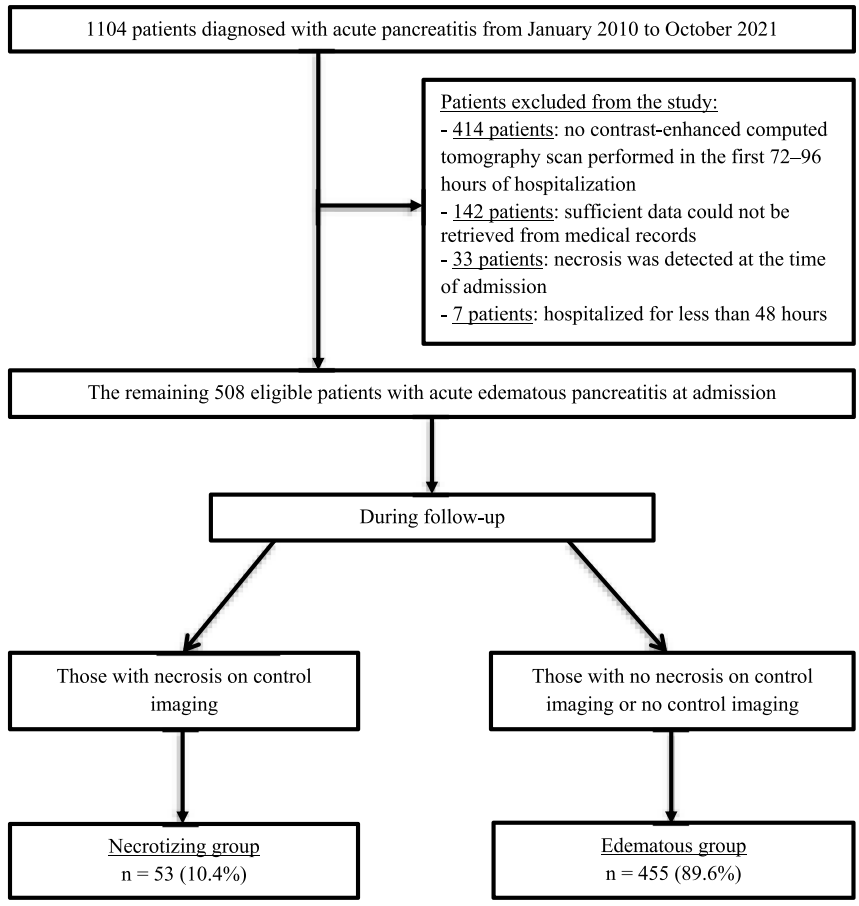


FIGURE 1. A flow chart showing patient selection and study design.

For all clinical conditions related to AP, the 2012 revised Atlanta classification was taken as a basis. For the diagnosis of AP, at least 2 of the following 3 criteria needed to be met: (1) epigastric pain radiating to the back, (2) amylase and/or lipase values at least 3 times higher than the upper limit, and (3) radiological appearance compatible with AP.[11] The absence of contrast enhancement in the pancreatic parenchyma and/or peripancreatic area after intravenous contrast agent administration in CECT scan was taken as evidence of necrotizing pancreatitis. The time that elapsed from hospital admission to the moment when necrosis was detected by CECT was taken as the time of necrosis development. Local complications were entered into the record-keeping system as acute peripancreatic fluid collection, pseudocyst, acute necrotic collection, and walled-off necrosis; systemic complications as exacerbation of an underlying comorbid disease; and vascular complications related to AP as splanchnic venous thrombosis.[11] Organ failure was defined with a minimum score of 2 according to the modified Marshall scoring system.[11]

Clinical, Laboratory, and Radiological Parameters

Data including age, sex, etiology, length of hospital stay, intensive care unit (ICU) admission, organ failure, severity, and mortality were collected clinically from the electronic patient files.

Many biochemical parameters were recorded at admission. In addition, white blood cell (WBC), hematocrit (HTC), blood urea nitrogen, creatinine, lactate dehydrogenase (LDH), C-reactive protein (CRP), calcium, and albumin levels at the 48th hour were also collected.

For the BISAP and APACHE II scoring systems, scores were calculated based on the clinical and laboratory findings in the first 24 hours of hospital stay, whereas, for the Ranson and Glasgow scoring systems, they were calculated based on the clinical and laboratory findings in the first 48 hours of hospital stay.[3–6] The CTSI scores were calculated according to a total possible score of 10 comprising an inflammation score of 0 to 4 based on noncontrast tomography findings and a necrosis score of 0 to 6 based on the CECT findings.[7] The CTSI scores were calculated by 2 radiologists, who were blinded to the patient outcomes, based on CECT imaging performed in the first 72 to 96 hours in the edematous group and the most severe CECT imaging results during follow-up in the necrotizing group. In addition, peripancreatic local and vascular complications were reviewed by CECT scan. The presence of pleural effusion in the first 48 hours was investigated based on CECT or x-ray images.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics version 26.0 for Windows (IBM Corp, Armonk, NY). The data were evaluated for normality by performing the Shapiro-Wilk test. Comparisons of continuous variables with normal distribution were made with Student *t* tests, whereas comparisons of those with nonnormal distribution were made with Mann-Whitney *U* tests, and categorical variables were compared with Pearson χ^2 tests. Univariate logistic regression analysis was performed for the development of necrosis; parameters found to be significant ($P < 0.05$) in the univariate analysis were subsequently included in multivariate

stepwise logistic regression analysis, and independent predictors of necrosis development were identified. In the univariate and multivariate analyses, the odds ratio was calculated with 95% confidence intervals (CIs) for these parameters. Appropriate cutoff values for independent predictors were identified by receiver operating characteristic curve analysis based on Youden index method. At different cutoff values, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the new scoring system created with independent predictors were calculated, and risk analysis was performed. The area under the curve (AUC) values were calculated by receiver operating characteristic curve analysis with 95% CIs to evaluate their performances in distinguishing necrosis. Values of $P < 0.05$ were considered to be significant in the statistical analyses.

RESULTS

Comparative Baseline Clinical and Laboratory Findings

The mean age of the overall population was 57.64 years (SD, 17.40 years). Of the patients, 55.2% were men, and 44.8% were women. Of the total of 508 patients, 53 (10.4%) were in the necrotizing group, whereas 455 (89.6%) were in the edematous group. Systemic complication, ICU admission, persistent organ failure, and mortality rates were 26.4%, 49.1%, 41.5%, and 18.9%, respectively, in the necrotizing group, whereas they were 7.5%, 11.0%, 6.2%, and 3.3%, respectively, in the edematous group ($P < 0.001$ for all). The comparative clinical and imaging findings of the patients are shown in Table 1.

Independent Risk Factors for Necrosis

Univariate logistic regression analysis was performed for the development of necrosis, and parameters found to be significant ($P < 0.05$) in the univariate analysis were subsequently included in multivariate stepwise logistic regression analysis. Among the parameters included in the stepwise multivariate logistic regression model, WBC, HTC, LDH, and CRP levels at the 48th hour were found to be independent risk factors for necrosis development (Table 2). The appropriate cutoff values for WBC, HTC, LDH, and CRP levels, which are the 4 independent predictors of necrosis development, were 169.5 mg/L, 366 U/L, 15.25 × 10^9/L, and 39.35%, respectively. Using these 4 parameters, dichotomous

TABLE 1. Comparative Baseline Clinical and Imaging Findings

Parameter	Overall N = 508	Necrotizing Group n = 53	Edematous Group n = 455	*P*
Clinical findings				
Age, mean (SD), y	57.64 (17.40)	55.36 (15.05)	57.90 (17.65)	0.257
Sex, male, n (%)	255 (55.2)	33 (62.3)	222 (48.8)	0.063
Length of hospital stay, median (range), d	7 (2–112)	29 (7–112)	7 (2–105)	<0.001
Etiology, n (%)				
Idiopathic	93 (18.3)	9 (17)	84 (18.5)	0.792
Biliary (including microlithiasis)	328 (64.6)	35 (66.0)	293 (64.4)	0.813
Alcohol	30 (5.9)	6 (11.3)	24 (5.3)	0.113
Hypertriglyceridemia	22 (4.3)	1 (1.9)	21 (4.6)	0.717
Other	35 (6.9)	2 (3.8)	33 (7.3)	0.564
Necrosis development time, median (range), d	3 (1–15)	3 (1–15)	—	—
Area of necrosis, n (%)				
Pancreatic	20 (3.9)	20 (37.7)	—	—
Peripancreatic	5 (1.0)	5 (9.4)	—	—
Pancreatic and peripancreatic	28 (5.5)	28 (52.8)	—	—
Infected pancreatic necrosis/peripancreatic abscess, n (%)	20 (3.9)	16 (30.2)	4 (0.9)	<0.001
Serious clinical events, n (%)				
Systemic complication	48 (9.4)	14 (26.4)	34 (7.5)	<0.001
ICU admission	76 (15.0)	26 (49.1)	50 (11.0)	<0.001
Persistent organ failure (>48 h)	50 (9.8)	22 (41.5)	28 (6.2)	<0.001
Mortality	25 (4.9)	10 (18.9)	15 (3.3)	<0.001
Imaging findings (during follow-up)				
CTSI, mean (SD)	2.61 (2.26)	7.72 (1.95)	2.02 (1.37)	<0.001
Inflammation score	2.21 (1.42)	3.87 (0.39)	2.02 (1.37)	<0.001
Necrosis score	0.4 (1.31)	3.85 (1.79)	—	—
Pleural effusion, n (%)	132 (26.0)	31 (58.5)	101 (22.2)	<0.001
Local complications, n (%)				
None	177 (34.8)	1 (1.9)	176 (38.7)	<0.001
Acute peripancreatic fluid collection	259 (51.0)	—	259 (56.9)	—
Acute necrotic collection	20 (3.9)	20 (37.7)	—	—
Pseudocyst	20 (3.9)	—	20 (4.4)	—
Walled-off necrosis	32 (6.3)	32 (60.4)	—	—
Splanchnic venous thrombosis	13 (2.6)	13 (24.5)	0 (0.0)	<0.001

TABLE 2. Laboratory Parameters Predicting the Development of Necrosis

	Univariate Analysis		Multivariate Analysis	
Parameter	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
At admission				
WBC	1.142 (1.086–1.202)	<0.001		
HTC	1.164 (1.100–1.231)	<0.001		
Platelet	1.002 (0.999–1.005)	0.167		
Blood glucose	1.007 (1.003–1.010)	<0.001		
Blood urea nitrogen	1.034 (1.006–1.063)	0.018		
Creatinine	1.110 (0.785–1.568)	0.555		
Alanine aminotransferase	0.999 (0.998–1.001)	0.362		
Aspartate aminotransferase	0.999 (0.998–1.000)	0.166		
Alkaline phosphatase	0.996 (0.992–1.000)	0.035		
γ-Glutamyl transpeptidase	1.000 (0.998–1.001)	0.371		
LDH	1.000 (0.999–1.001)	0.534		
Total bilirubin	0.914 (0.776–1.077)	0.283		
Amylase	1.000 (1.000–1.000)	0.011		
Albumin	1.775 (0.919–3.429)	0.087		
Calcium	0.789 (0.542–1.149)	0.216		
48th hour				
WBC	1.247 (1.177–1.321)	<0.001	1.146 (1.062–1.235)	<0.001
HTC	1.213 (1.144–1.286)	<0.001	1.087 (1.006–1.174)	0.035
Blood urea nitrogen	1.081 (1.056–1.106)	<0.001		
Creatinine	1.367 (1.061–1.760)	0.015		
LDH	1.004 (1.003–1.006)	<0.001	1.001 (1.000–1.003)	0.023
Albumin	0.361 (0.198–0.655)	0.001		
Calcium	0.354 (0.244–0.513)	<0.001		
CRP	1.013 (1.010–1.016)	<0.001	1.010 (1.007–1.014)	<0.001

OR indicates odds ratio.

variables were created according to the appropriate cutoff values, and multivariate regression analysis was repeated (Table 3).

Stages of Derivation of the New Scoring System

White blood cell, HTC, LDH, and CRP levels as independent predictors of necrosis development were included in the scoring system. In the scoring model, the integer part of the B coefficient in the multivariate analysis performed with dichotomous variables was assigned as the score of the variable (Table 4), based on some studies in which scoring systems were derived.[12,13] Because the scoring system included values of parameters at the 48th hour, it was named Necrosis Development Score 48 (NDS-48).

Predictive Values of the NDS-48 Score at Different Cutoffs

The predictive values of the NDS-48 score at different cutoffs were evaluated (Table 5). Accordingly, when the Youden index method was taken as a basis, the most appropriate cutoff was 2.5, and the sensitivity, specificity, PPV, and NPV of the NDS-48 scoring system at this cutoff were 92.5%, 85.9%, 43.4%, and 99.0%, respectively. Patients with an NDS-48 score of ≥3 were at 74.8 times higher risk of developing necrosis than others (odds ratio, 74.8; 95% CI, 26.1–214.5). None of the patients with an NDS-48 score of 0 developed necrosis (NPV 100% for NDS-48 of <1).

TABLE 3. Multivariate Regression Analysis for Necrosis With Dichotomous Variables of Independent Predictors

Parameter	**Cutoff Value**	**β Coefficient**	**Standard Error**	**OR (95% CI)**	***P***
WBC, 48th h	>15.25 10^9/L	1.252	0.434	3.499 (1.496–8.184)	0.004
HTC, 48th h	>39.35%	1.002	0.443	2.725 (1.143–6.496)	0.024
LDH, 48th h	>366 U/L	2.422	0.443	11.265 (4.729–26.837)	<0.001
CRP, 48th h	>169.5 mg/L	2.580	0.533	13.198 (4.646–37.493)	<0.001

OR indicates odds ratio.

TABLE 4. Components of the NDS-48 Score

Parameter	Score		
	0 Points	1 Point	2 Points
WBC, 48th h	<15.25 10^9/L	>15.25 10^9/L	
HTC, 48th h	<39.35%	>39.35%	
LDH, 48th h	<366 U/L		>366 U/L
CRP, 48th h	<169.5 mg/L		>169.5 mg/L

Minimum score, 0; maximum score, 6.

Comparison of Necrosis Discrimination Abilities of the NDS-48 and Other Scoring Systems

The diagnostic ability of the NDS-48 score in predicting necrosis development was identified and compared with those of the 4 conventional scoring systems. The AUC value of the NDS-48 for necrosis was 0.949 (95% CI, 0.920–0.977), and this scoring system had a significantly better ability to distinguish necrosis compared with other scoring systems. Figure 2 illustrates the ability of scoring systems to distinguish necrosis.

DISCUSSION

In this study, our main aim was to create a scoring system that could predict or exclude the development of pancreatic necrosis at an early stage in patients presenting with edematous AP, which would primarily help to avoid the harmful effects and high cost of CECT. Therefore, patients diagnosed with necrotizing AP at admission were excluded from the study, whereas patients diagnosed with edematous AP at admission were included to determine the factors associated with pancreatic necrosis developing in the days after admission. Accordingly, WBC, HTC, LDH, and CRP at 48 hours were identified as independent predictors for the development of pancreatic necrosis. Based on these findings, a simple and usable scoring system was derived from these routinely checked laboratory parameters, namely, NDS-48. The NDS-48 score had high NPVs but relatively low PPVs associated with a low incidence of necrosis. When the NDS-48 score was 2 or less, the probability of developing necrosis was ruled out as high as 99%. Furthermore, the NDS-48 had an AUC of 0.949 for development of necrosis, and it distinguished the development of pancreatic necrosis significantly better than existing scoring systems, which are complex and time-consuming.

Many systemic complications causing mortality and morbidity can develop during the course of AP. Such systemic complications are rare, and they are observed in cases of necrotizing AP rather than edematous AP. Studies have proved that the mortality rate of necrotizing AP is significantly higher than that of edematous AP.[14,15] Tenner et al[16] suggested an increase of up to 50% in mortality rate among patients with necrotizing AP. Likewise, in our study, 18.9% of patients with necrotizing AP died compared with just 3.3% of patients with edematous AP. In addition, the rates of systemic complications, ICU admission, and persistent organ failure were significantly higher in patients with necrotizing AP.

Acute pancreatitis is characterized by noninfected inflammation of the pancreatic tissue. In general, there is a close relationship between the extent of inflammation and the severity of the disease and necrosis development.[17,18] Because the inflammatory response is expected to be more severe in necrotizing pancreatitis, higher values of markers indicating inflammation are expected, as well. White blood cell and CRP levels are 2 of the parameters indicating systemic inflammation. In the study conducted by Khanna et al,[19] the sensitivity and specificity for necrosis development were 100% and 81.4%, respectively, when the CRP cutoff was considered as 150 mg/L. In another study, WBC and CRP levels were found to be independent predictors for pancreatic necrosis development.[20] We identified WBC and CRP levels as independent predictors of necrosis development. White blood cell count of >15.25 $\times$ 10^9/L and CRP level of >169.5 mg/L at the 48th hour were associated with 3.5 and 13.1 times higher risks of developing necrosis, respectively.

Adequate fluid resuscitation in the initial period of AP is associated with decreased mortality and morbidity.[21] If any fluid leakage into the extravascular space is not compensated by adequate hydration, it is likely to cause hypovolemia and, subsequently, hypotension. Necrotizing pancreatitis results in vascular leak syndrome, which leads to increased third-space fluid losses and worsens pancreatic perfusion.[22] Hemoconcentration secondary to third-space fluid losses is an indirect indicator of hypovolemia in patients with AP. In a study investigating the role of hemoconcentration in predicting pancreatic necrosis, the HTC at admission and at 24 hours was found to be significantly higher in patients with necrotizing AP than in patients with interstitial AP.[23] Likewise, another study revealed that persistent hemoconcentration at 24 hours was associated with the development of necrotizing AP.[24] Lankisch et al[25] argued that CECT may be unnecessary in the absence of hemoconcentration at admission (NPV was 88%). Similarly, Gardner et al[26] showed that the absence of hemoconcentration at admission had a strong NPV for necrosis (NPV was more than 90%), whereas another study demonstrated that the presence of hemoconcentration was the most accurate compared with other parameters in predicting pancreatic necrosis.[27] If we make an inference from these studies, in which the HTC at the 48th hour

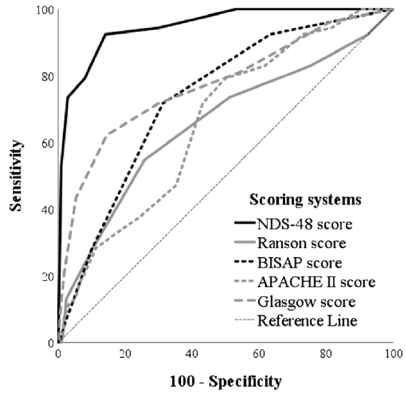
TABLE 5. The Ability of the NDS-48 Scoring System to Predict Necrosis at Different Cutoffs

Cutoff Value	No. Patients Over the Cutoff, n (%)	OR (95% CI)	Sensitivity, %	Specificity, %	PPV, %	NPV, %
0.5 Point	295 (58.1)	Noncalculated*	100.0	46.8	18.0	100.0
1.5 Points	186 (36.6)	39.1 (11.9–127.5)	94.3	70.1	26.9	99.1
2.5 Points†	113 (22.2)	74.8 (26.1–214.5)	92.5	85.9	43.4	99.0
3.5 Points	78 (15.3)	44.4 (21.1–93.7)	79.2	92.1	53.8	97.4
4.5 Points	52 (10.2)	94.7 (41.6–215.7)	73.6	97.1	75.0	96.9
5.5 Points	32 (6.3)	126.3 (41.1–387.9)	52.8	99.1	87.5	94.7

*When the NDS-48 score was below 1, OR could not be calculated because no patient developed necrosis.

†Optimal cutoff based on Youden index.

OR indicates odds ratio.



AUC Values of Scoring Systems	
Score	**AUC (95% CI)**
NDS-48 score	0.949 (0.920–0.977)
Ranson score	0.656 (0.570–0.742)
BISAP score	0.736 (0.671–0.802)
APACHE II score	0.661 (0.590–0.733)
Glasgow score	0.774 (0.699–0.850)

Pairwise Comparison of ROC Curves	
NDS-48 score ~ Ranson score	
Difference between areas	0.292
95% Confidence Interval	0.214-0.371
z statistic	7.304
P	<0.001
NDS-48 score ~ BISAP score	
Difference between areas	0.212
95% Confidence Interval	0.150-0.275
z statistic	6.655
P	<0.001
NDS-48 score ~ APACHE II score	
Difference between areas	0.287
95% Confidence Interval	0.216-0.358
z statistic	7.909
P	<0.001
NDS-48 score ~ Glasgow score	
Difference between areas	0.174
95% Confidence Interval	0.111-0.238
z statistic	5.377
P	<0.001

FIGURE 2. Ability of NDS-48 and other scoring systems to discriminate necrotizing AP from edematous AP. ROC, receiver operating characteristic.

was not evaluated, the HTC at the 48th hour is expected to be higher in patients with necrotizing AP than in patients with interstitial AP, similar to that at admission and at the 24th hour. Consistent with this expectation, we showed that high hemoconcentration at the 48th hour after the time of admission was associated with necrosis development in AP.

Lactate dehydrogenase is a marker associated with cell damage and subsequent cell death. Because necrosis development is associated with cell death, an increase in the LDH values of patients during follow-up may predict necrosis development. In a systematic review, LDH values higher than 290 U/L at the 5th day were found to have 87% sensitivity and 100% specificity for necrosis.[28] In another study, LDH values higher than 270 U/L were found to have high accuracy of 82% in detecting pancreatic necrosis.[29] In our study, LDH at the 48th hour after the time of hospital admission was an independent predictor of necrosis, and LDH increased the risk of necrosis development 11.2 times at values above 366 U/L.

Many studies have shown that CECT scans performed without adequate patient selection do not change the prognosis in AP,[30,31] but many other studies have argued that computed tomography (CT) scans performed at the appropriate time and for selected patients improve mortality and clinical outcomes.[9,10] It is considered very important to predict pancreatic necrosis early and reveal it with abdominal CT in appropriate cases. Therefore, the predictive role of the existing conventional scoring systems in predicting necrosis development in AP has been investigated by many researchers. In a prospective study, the Ranson, BISAP, and APACHE II scoring systems predicted severity, organ failure, and mortality well, but they could not significantly predict necrosis development.[32] In another prospective study, the role of the Ranson, BISAP, APACHE II, and Glasgow scores in predicting necrosis was found to be considerably limited.[19] In a comparative study, the Ranson score was proven to predict pancreatic necrosis better than BISAP or APACHE II.[33] This may be related to the fact that the Ranson score is evaluated with parameters at the 48th hour, whereas BISAP and APACHE II are evaluated with parameters measured in the first 24 hours. Because pancreatic necrosis and peripancreatic necrosis usually appear not earlier than 72 hours after the onset of AP, there may be no clinical or laboratory findings indicating the development of necrosis in the first 24 hours.

The NDS-48, created with simple laboratory parameters measured at the 48th hour after admission to the hospital, predicted necrosis development significantly better than the other 4 scoring systems. Considering that necrosis and peripancreatic complications develop less often in the early stages of the disease, it would be appropriate to evaluate patients for necrosis development at the 48th hour after hospitalization. Necrosis development was predicted with considerably high accuracy by the NDS-48, a very simple and inexpensive method consisting of 4 laboratory parameters commonly used in routine procedures. When the cut-off value is 2.5, the sensitivity and specificity of the NDS-48 are 92.5% and 85.9%, respectively. Those with NDS-48 scores of ≥3 were seen to have approximately 75 times higher risk of developing necrosis compared with other patients. In addition, no patient developed necrosis when the NDS-48 score was <1 (NPV, 100%), and the probability of developing necrosis became 87.5% (PPV, 87.5%) when a maximum score of 6 was reached. Considering that necrotizing AP causes significantly higher mortality and morbidity rates than edematous AP, evaluations should be made by CECT scan to reveal necrosis, and more attention should be paid to possible complications, poor prognosis, and higher mortality in patients found to be at higher risk of developing necrosis according to the NDS-48 scoring system (NDS-48 score of ≥3). In contrary cases, because the probability of necrosis development is quite low when the NDS-48 score is 0, no CECT scans should be performed unnecessarily, and the patients can be discharged safely. Computed tomography scans performed at the appropriate time favorably affect prognosis,[9,10] whereas unnecessary scans lead to many problems. The first of such problems is the unnecessary exposure of patients to high doses of radiation and nephrotoxic ionized contrast media. A second problem is that abdominal CT is an expensive examination method. A third problem is that unnecessary advanced imaging tests create diagnostic confusion, far from providing benefits. For these reasons, the conditions of patients with complicated courses should be identified quickly by applying the simple and easy-to-use NDS-48 scoring

system, and necessary therapeutic interventions can be made earlier. Unnecessary further imaging tests can be avoided for patients not expected to follow a complicated course.

This study has some limitations. The first is that it was a single-center study conducted with a retrospective design. Second, control CECT scans were not performed for most of the patients who were considered not to have developed necrosis, and patients with possible necrosis were considered to be in the edematous patient group of the study. However, necrosis, a clinically significant condition, was taken into account in the design of this study. Because the current guidelines do not recommend control CECT scans unless clinical worsening occurs, patients for whom control scans were not performed and who were discharged after recovery were considered to have edematous AP. Finally, the fact that we excluded a large number of patients because they did not have CECT in the first 96 hours can be considered as another limitation. Many patients with a high probability of developing necrosis may not have undergone CECT because of conditions such as kidney failure and contrast allergy, or on the other hand, many patients with possible edematous AP may not have undergone CECT because of their mild course. For this reason, many patients from both groups may have been missing in a way that we do not know at what rate. This may have caused a selection bias and partially influenced the results. In this study, however, because we aimed to examine a specific group of patients who were initially diagnosed with edematous AP and turned into necrotizing AP during follow-up, we wanted clear findings rather than assumptions, and we designed the study in this way.

In this study, the parameters associated with necrosis development were evaluated in patients followed with the diagnosis of edematous AP with the goal of creating a simple, easy-to-use scoring system with appropriate parameters. White blood cell, HTC, LDH, and CRP levels at the 48th hour are independent predictors of necrosis development. The new scoring system presented here, NDS-48, was created using these 4 predictors, and it predicted the development of necrosis quite well in patients presenting with edematous AP. However, this scoring system needs to be validated in more comprehensive prospective and multicenter studies.

REFERENCES

1. Kong L, Santiago N, Han TQ, et al. Clinical characteristics and prognostic factors of severe acute pancreatitis. *World J Gastroenterol*. 2004;10:3336–3338.
2. Block S, Maier W, Bittner R, et al. Identification of pancreas necrosis in severe acute pancreatitis: imaging procedures versus clinical staging. *Gut*. 1986;27:1035–1042.
3. Singh VK, Wu BU, Bollen TL, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. *Am J Gastroenterol*. 2009;104:966–971.
4. Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet*. 1989;2:201–205.
5. Blamey SL, Imrie CW, O'Neill J, et al. Prognostic factors in acute pancreatitis. *Gut*. 1984;25:1340–1346.
6. Ranson JH, Rifkind KM, Roses DF, et al. Objective early identification of severe acute pancreatitis. *Am J Gastroenterol*. 1974;61:443–451.
7. Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiology*. 1990;174:331–336.
8. Cho JH, Kim TN, Chung HH, et al. Comparison of scoring systems in predicting the severity of acute pancreatitis. *World J Gastroenterol*. 2015;21:2387–2394.
9. Choi HW, Park HJ, Choi SY, et al. Early prediction of the severity of acute pancreatitis using radiologic and clinical scoring systems with classification tree analysis. *AJR Am J Roentgenol*. 2018;211:1035–1043.
10. Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. *Radiology*. 2002;223:603–613.
11. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.
12. Campos GM, Bambha K, Vittinghoff E, et al. A clinical scoring system for predicting nonalcoholic steatohepatitis in morbidly obese patients. *Hepatology*. 2008;47:1916–1923.
13. Brueckmann B, Villa-Uribe JL, Bateman BT, et al. Development and validation of a score for prediction of postoperative respiratory complications. *Anesthesiology*. 2013;118:1276–1285.
14. Singh VK, Bollen TL, Wu BU, et al. An assessment of the severity of interstitial pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9:1098–1103.
15. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141:1254–1263.
16. Tenner S, Sica G, Hughes M, et al. Relationship of necrosis to organ failure in severe acute pancreatitis. *Gastroenterology*. 1997;113:899–903.
17. Mayer J, Rau B, Gansauge F, et al. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. *Gut*. 2000;47:546–552.
18. Pandol SJ, Saluja AK, Imrie CW, et al. Acute pancreatitis: bench to the bedside. *Gastroenterology*. 2007;132:1127–1151.
19. Khanna AK, Meher S, Prakash S, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. *HPB Surg*. 2013;2013:367581.
20. Leese T, Shaw D, Holliday M. Prognostic markers in acute pancreatitis: can pancreatic necrosis be predicted? *Ann R Coll Surg Engl*. 1988;70:227–232.
21. Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatology*. 2009;9:770–776.
22. Whitcomb DC, Muddana V, Langmead CJ, et al. Angiopoietin-2, a regulator of vascular permeability in inflammation, is associated with persistent organ failure in patients with acute pancreatitis from the United States and Germany. *Am J Gastroenterol*. 2010;105:2287–2292.
23. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas*. 2000;20:367–372.
24. Brown A, Baillargeon J-D, Hughes MD, et al. Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? *Pancreatology*. 2002;2:104–107.
25. Lankisch PG, Mahlke R, Blum T, et al. Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? A critical appraisal. *Am J Gastroenterol*. 2001;96:2081–2085.
26. Gardner TB, Olenec CA, Chertoff JD, et al. Hemoconcentration and pancreatic necrosis: further defining the relationship. *Pancreas*. 2006;33:169–173.
27. Koutroumpakis E, Wu BU, Bakker OJ, et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. *Am J Gastroenterol*. 2015;110:1707–1716.
28. Komolafe O, Pereira SP, Davidson BR, et al. Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis. *Cochrane Database Syst Rev*. 2017;4:CD012645.
29. Uhl W, Buchler M, Malfertheiner P, et al. PMN-elastase in comparison with CRP, antiproteases, and LDH as indicators of necrosis in human acute pancreatitis. *Pancreas*. 1991;6:253–259.

30. Spanier BW, Nio Y, van der Hulst RW, et al. Practice and yield of early CT scan in acute pancreatitis: a Dutch observational multicenter study. *Pancreatology*. 2010;10:222–228.

31. Dachs RJ, Sullivan L, Shanmugathasan P. Does early ED CT scanning of afebrile patients with first episodes of acute pancreatitis ever change management? *Emerg Radiol*. 2015;22:239–243.

32. Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis — a prospective observational study. *Int J Surg*. 2018;54:76–81.

33. Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol*. 2010;105:435–441 quiz 442.