

RAPID COMMUNICATION

## Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis

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### Abstract

**AIM:** To determine factors related to disease severity, mortality and morbidity in acute pancreatitis.

**METHODS:** One hundred and ninety-nine consecutive patients were admitted with the diagnosis of acute pancreatitis (AP) in a 5-year period (1998-2002). In a prospective design, demographic data, etiology, mean hospital admission time, clinical, radiological, biochemical findings, treatment modalities, mortality and morbidity were recorded. Endocrine insufficiency was investigated with oral glucose tolerance test. The relations between these parameters, scoring systems (Ranson, Imrie and APACHE II) and patients' outcome were determined by using invariable tests and the receiver operating characteristics curve.

**RESULTS:** One hundred patients were men and 99 were women; the mean age was 55 years. Biliary pancreatitis was the most common form, followed by idiopathic pancreatitis (53% and 26%, respectively). Sixty-three patients had severe pancreatitis and 136 had mild disease. Respiratory rate > 20/min, pulse rate > 90/min, increased C-reactive protein (CRP), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) levels, organ necrosis > 30% on computed tomography (CT) and leukocytosis were associated with severe disease. The rate of glucose intolerance, morbidity and mortality were 24.1%, 24.8% and 13.6%, respectively. CRP > 142 mg/L, BUN > 22 mg/dL, LDH > 667 U/L, base excess > -5, CT severity index > 3 and APACHE score > 8 were related to morbidity and mortality.

**CONCLUSION:** APACHE II score, LDH, base excess and CT severity index have prognostic value and CRP is a reliable marker for predicting both mortality and morbidity.

### INTRODUCTION

Although acute pancreatitis (AP) has been recognized for more than a century, no definitive treatment has been developed. The recent improvements in outcome are brought about by the progress in intensive care and supportive treatment. Although the incidence varies between countries, it is on the rise<sup>[1-4]</sup>.

Improvements in diagnostic techniques and standardization in diagnosis and treatment have provided better understanding of the disease and many centers reported successful results<sup>[4-8]</sup>. The etiology of AP is heterogeneous and determined by local and social factors. Gallstones are the leading causes in many centers. Idiopathic cases comprise 10%-20% of the cases but this ratio varies with respect to the diagnostic capabilities of the center<sup>[3,4]</sup>.

Although the majority of the patients are successfully managed by medical treatment, complications develop in 15%-20% of the cases and cause significant risk of mortality. Reliable scoring systems, radiological evaluation and laboratory markers are required for identifying high-risk patients at an early stage in order to take prophylactic measures. Numerous scoring systems and laboratory parameters have been used to predict the severity and mortality: Ranson, Imrie (Glasgow), Goris and APACHE II scores, contrast-enhanced abdominal computed tomography (CET), C-reactive protein<sup>[4,8,9]</sup>. The APACHE II score and the CRP level have been reported to be useful markers. Although there is a general consensus on the value of CRP, conflicting opinions have been expressed on the APACHE II score<sup>[10]</sup>.

In this study from a tertiary referral center, we aimed to present the characteristics of the AP cases and to identify clinical, radiological and laboratory parameters as

well as scoring systems that are associated with treatment outcome.

## MATERIALS AND METHODS

### Patients

The data of the patients who were treated for AP at the Ondokuz Mayıs University Medical School, Department of General Surgery, between 1998 and 2002 (5-year period) were recorded prospectively in prepared forms. AP was diagnosed by history, physical examination, laboratory and radiological findings (ultrasonography and contrast-enhanced computed tomography (CECT) which was taken in the first week after admission in some cases but not all). Amylase and lipase levels higher than three times the upper level of the normal range were considered significant. In patients with findings of acute abdomen, the diagnosis was made by laparotomy. The CECT findings were graded according to the Balthazar-Ranson classification and a CT-severity index was determined<sup>[6]</sup>. Patients with gallstones on ultrasonography were accepted as cases of biliary pancreatitis; patients consuming large amounts of alcohol were considered as having alcoholic pancreatitis; in patients with hyperlipidemia (triglyceride level more than 1000 mg/dL), this was accepted as the etiological factor. Patients with undetermined etiology were considered to be idiopathic cases. Patients with APACHE II scores  $\geq 8$  were diagnosed as having severe AP. If the patients were getting worse clinically and CECT findings demonstrated infected necrosis they were accepted as severe. Treatment algorithm was illustrated in Figure 1. Cholecystectomy and/or ERCP were performed before discharge in patients with biliary pancreatitis. Surgery was performed in patients with clinical deterioration and those with infected necrosis, which was diagnosed by fine needle aspiration under CT guidance. Antibiotic prophylaxis was conducted in patients with severe AP (carbapenems or a quinolone). The antibiotics were changed according to culture results. Oral glucose tolerance test (OGTT) was performed to evaluate endocrine function at one year after the onset of AP in patients with no history of diabetes mellitus.

Demographic data, etiology, time of admission after onset of symptoms, disease severity, clinical and laboratory findings including blood urea nitrogen (BUN), creatinine, glucose, calcium, alkaline phosphatase (ALP), bilirubin, aspartate amino transferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), albumin, base excess (BE), CRP,  $\alpha$ -1 antitrypsin, and treatment methods were recorded and their associations with mortality and morbidity were investigated. Also, the associations of clinical, laboratory and radiological findings with disease severity were analyzed

### Statistical analysis

Statistical evaluation was performed with SPSS 13.0 for Windows. The associations of clinical, radiological and laboratory findings with disease severity were investigated by univariate analysis (chi-square, Mann-Whitney-U and Fisher's exact test). After identification of radiologic findings, laboratory findings and disease scores (Ranson,

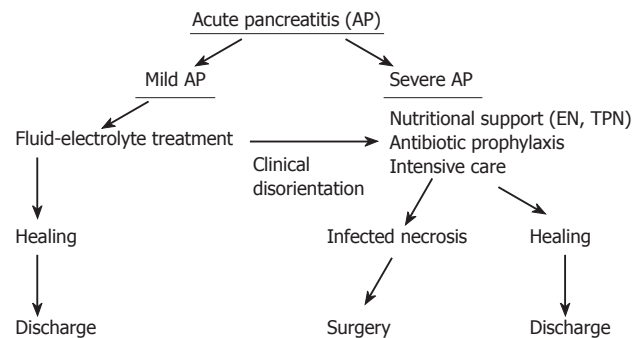


Figure 1 Treatment algorithm of the patients.

Table 1 Etiology and disease severity of the patients

Etiology	Disease severity		
	Mild (n)	Severe (n)	Total (n, %)
Biliary	71	34	105 (52.7)
Idiopathic	37	14	51 (25.6)
Alcohol	14	-	14 (7)
Hyperlipidemia	4	5	9 (4.5)
Miscellaneous	10	10	20 (10)
Drug			7
Infection			5
Trauma			5
Hypercalcemia			2
Others			1

There was no significant correlation between the etiology and disease severity.

Imrie and APACHE II) significantly associated with mortality and morbidity, their diagnostic or predictive values were determined by ROC (Receiver Operating Characteristic) analysis.

## RESULTS

### Epidemiology

During the study period of 5 years, 199 patients with AP were hospitalized; 99 were women and 100 were men; the mean age was  $55.1 \pm 1.1$  years (range: 16-92). Overall, 136 patients (68%) had mild AP and 63 (32%) had severe AP. Mean interval between onset of symptoms and admission was  $48 \pm 3$  h (range: 1-300) and it had no association with mortality or morbidity.

Biliary pancreatitis was the most common form, followed by idiopathic pancreatitis (53% and 26%, respectively) (Table 1). Seven patients were using thiazide diuretics. The infectious agents were leptospirosis in 2 patients and various viruses in 3. Traumatic AP was due to blunt trauma in 3 patients and coronary bypass operation in 2. One patient had obstruction of the afferent loop after Billroth II gastrectomy. Biliary pancreatitis was more frequent in women than in men (59.59% and 45.45%,  $P < 0.002$ ). With the introduction of endoscopic retrograde cholangiopancreatography (ERCP), the frequency of idiopathic pancreatitis decreased from 31.5% at the beginning of the study to 20% at the end of the study.

**Table 2** Relations between clinical, radiological and laboratory findings and disease severity

Parameters	MAP	SAP	P
RR > 20	21.7%	48.1%	< 0.001
PR > 90	36%	65%	< 0.001
Necrosis ratio in CT > 30%	4.1%	27.1%	< 0.001
CRP (mg/L)	116 ± 8	171 ± 15	< 0.002
LDH (U/L)	570 ± 31	959 ± 104	< 0.05
AST (U/L) × N	4.7 ± 1.3	4.75 ± 0.7	< 0.05
Leukocytosis (× 10 <sup>3</sup> /mm <sup>3</sup> )	13 ± 0.4	16 ± 0.7	< 0.05

RR: Respiratory rate; PR: pulse rate; CRP: Serum C-reactive protein; LDH: lactate dehydrogenase; AST: Aspartate aminotransferase; CT: Contrast-enhanced abdominal computed tomography.

**Table 3** Disease severity and CECT findings in 172 radiologically examined patients *n* (%)

CECT findings	Disease severity	
	MAP	SAP
Normal (non-diagnostic)	20 (16.4)	3 (6.3)
Edema in pancreas	62 (50.8)	18 (37.5)
Pancreatic necrosis < 30%	33 (27)	14 (27.1)
30% < Pancreatic necrosis > 50%	5 (4.1)	13 (27.1) <sup>b</sup>
Pancreatic necrosis > 50%	2 (1.6)	0

<sup>b</sup>*P* < 0.001 vs patients with mild AP. CECT: Contrast-enhanced abdominal computerized tomography; MAP: Mild acute pancreatitis; SAP: Severe acute pancreatitis.

### Factors related to disease severity

Tachypnea (respiratory rate > 20 at the initial examination), a heart rate > 90 and pancreatic necrosis more than 30% were found to be associated with disease severity. CRP, LDH, AST and leukocyte levels were significantly higher in severe AP (Table 2). The bilirubin level was higher in biliary pancreatitis in comparison with other forms (*P* < 0.05, *Z*-test). In 13 patients, although the amylase level was 3 times higher than the upper limit of the normal range, the lipase level was normal. Disease severity and etiology showed no statistically significant association with amylase, pancreatic amylase and lipase levels.

### Factors associated with morbidity

CT showed varying degrees of necrosis in 56.3% of the patients with severe AP (Table 3). CT findings were unremarkable (non-diagnostic) in 16% of the mild pancreatitis cases and 6% of the severe cases. Extensive necrosis more than 30% was significantly associated with disease severity, early complication and mortality rates (*P* < 0.001, *P* < 0.05 and *P* < 0.004, respectively, Table 2). The early complication rate was significantly higher in the severe AP group in comparison with mild AP (67% vs 8%, *P* < 0.001). The overall early complication rate was 26%: abscess in 11 patients, multiorgan dysfunction syndrome (MODS) in 9, pseudocysts in 8, ARDS in 3 patients and upper gastrointestinal bleeding in 2 (33 patients in total). Fourteen of these patients died. Factors associated with morbidity are shown in Table 4.

At the end of 1 year, OGTT was performed in 112

**Table 4** Factors related to morbidity and mortality

Factors	Morbidity			Mortality		
	Cut-off level	Positive LR	AUC	Cut-off level	Positive LR	AUC
APACHE-II	8.5	5	0.72	8.5	5	0.88
BE	-5	3.36	0.69	-5	4.63	0.84
CT-INDEX	2	2.04	0.67	3	4.3	0.68
BUN (mg/dL)	22	2.23	0.70	23	2.85	0.70
CRP (mg/L)	142	2.03	0.72	160	2.03	0.82
LDH (U/L)	667	4.07	0.82	667	2.79	0.82

The AUC (Area Under Curve) value near to 1.00 means having high prediction rate of the morbidity and mortality. Positive LR (likelihood ratio) is also correlated with high prediction rate of the morbidity and mortality. CRP: Serum C-reactive protein; LDH: Lactate dehydrogenase; BE: Base excess.

patients. Twenty-seven of these patients (24%) had impaired glucose tolerance. In 13 (12%) of these patients, diabetes developed. The impaired glucose tolerance was not associated with necrosis or disease severity.

Suspicion of necrosis led to fine needle aspiration and culture in 20 patients; cultures grew bacteria in 13; *E. coli* (*n* = 6) was the most common bacterium. Eighty-two per cent of the cases (163 patients) were treated conservatively and 18% (36 patients) underwent surgery. Seven underwent laparotomy for acute abdomen and AP was diagnosed by operative findings. Necrosectomy + closed lavage techniques were performed in 23 patients and "open abdomen" and planned re-laparotomy in 6. Nutritional support was not significantly associated with mortality or morbidity.

### Factors associated with mortality

Mortality was 37.5% in severe AP, 2.3% in mild AP and 13.6% (27 cases) overall. The mean base excess was -7.6 in patients who died and -1.9 in those who survived (*P* < 0.05). Among Ranson, Imrie and APACHE II scores, the APACHE II score was the best predictor of mortality. Mean APACHE II score was 5.7 ± 0.3 in patients who survived and 15 ± 1.7 in those who died (*P* < 0.05). CT severity index, LDH, BUN, CRP and base excess were the other parameters associated with mortality (Table 4).

## DISCUSSION

Although the mortality due to AP has decreased markedly in recent years, it is still a life-threatening disease. The demographic characteristics of AP are similar in many series; most patients are in the 50-60 year age group. In most series published in the English literature, gallstones are the leading cause, followed by alcohol. Although the reported figures vary, the frequencies of metabolic and infectious causes in the present series are higher than those reported<sup>[4,8,11,12]</sup>. Idiopathic AP includes cases with unelucidated etiology. The frequency is lower in centers that perform extensive investigations and usually biliary causes are revealed. Accordingly, with the introduction of ERCP, the frequency has decreased from 30% to 20% in our center.



The increased frequencies of tachypnea, tachycardia and leukocytosis which are components of the systemic inflammatory response syndrome (SIRS) are expected findings. Also, AST level was significantly higher in severe AP than in mild AP. AST, which is a component of various scoring systems, is a marker of serious liver damage<sup>[6,10]</sup>. Higher levels of bilirubin in biliary AP in comparison with other forms are not surprising. Although many studies include ALT and ALP elevations with hyperbilirubinemia<sup>[2,6,13]</sup>, our results are not in accordance. It was reported that, lipase was more specific and sensitive than amylase<sup>[5,6]</sup>. Thirteen patients with AP in the present study had higher than 3 times normal amylase level but normal lipase levels. Our view is that lipase measurement does not contribute to the diagnosis. Conversely, the diagnosis of AP should be approached with caution in patients with increased lipase but normal amylase<sup>[14]</sup>.

Contrast-enhanced CT has been used for a long time for diagnosis and prediction of severity of the disease<sup>[2,5,6]</sup>. In some series, the frequency of organ failure increases with more extensive necrosis<sup>[15]</sup>. In the present study, extensive necrosis more than 30% was associated with increased severity and mortality. Mertele and Balthazar reported similar results in their series<sup>[16,17]</sup>. The restricted power in our study prohibited the detailed evaluation of these findings. CT was non-diagnostic in 6% of the severe AP patients and only 63% of the severe AP patients had necrosis on CECT in our study. The majority of the patients with necrosis had mild AP according to scoring systems. This may be explained by the possibility that radiological findings do not always reflect disease severity. Because AP is a mediator disease, pancreas necrosis is not mandatory for cytokine effects.

Disease severity was evaluated by APACHE II scoring system instead of other scoring systems like Ranson's and CT scan scoring in this study. The need of CECT was decided by clinical behavior of patients and not all patients underwent CECT. Atlanta criteria overlook the amount and location of necrosis on CECT<sup>[7]</sup>. However, Kempainen *et al*<sup>[18]</sup> showed that, the outcome was favorable for patients with necrosis restricted to the distal part of the pancreas. CECT may yield negative findings in 20%-30% of the mild AP patients. If the CT staging is required, the CT severity index, as prepared by Balthazar should be used<sup>[19]</sup>. The CT index that reflects the extent of necrosis as well as peripancreatic or extrapancreatic inflammation is valuable in predicting morbidity and mortality in this study and the literature<sup>[2,3,6,16]</sup>. One of the complications of AP, peripancreatic abscess, may develop in the absence of pancreatic necrosis. CT not only shows necrosis but also guides the fine-needle aspiration for culture (FNAC). As in the present series, the diagnostic value of FNAC varies between 60% and 90%<sup>[19,20]</sup>.

Surgical treatment was performed in 18% (36) of the cases. Necrosectomy and continuous closed lavage were the techniques we preferred mostly. Although this technique and planned relaparotomy do not appear to differ significantly with respect to mortality and morbidity, less invasive procedures are usually preferred<sup>[21-25]</sup>. The best strategy is probably the one with which the center feels most comfortable. Because there is a large difference

between the numbers of patients who underwent each treatment (necrosectomy + closed lavage versus planned re-laparotomy), comparison was not made. Nine of the 29 patients (31%) who underwent surgery for AP died; this is slightly higher than the 20%-25% rate in the literature<sup>[21-23]</sup>. Although favorable results with percutaneous drainage have been reported with a limited number of patients, this approach has not received general acceptance. The reason for the failure is recurrent obstruction of the catheter by the necrotic debris<sup>[26]</sup>.

Glucose intolerance was detected in 24% of the AP cases. In two series with a smaller number of patients, the frequency was 25%-35%<sup>[27,28]</sup>. All patients in those series were necrotizing pancreatitis, which may account for the higher value in those series. Diabetes mellitus may be due to inflammation and fibrosis that destroys parts of the gland.

The overall mortality rate (13.6%) was slightly higher than the previous series, and the mortality of severe AP was higher than the literature<sup>[8,9,25]</sup>. Fourteen of the 33 patients who had early complications died. Deaths were mostly due to MODS. We think that, the mortality rate was also dependent on the suitability of the hospitals' intensive care unit (ICU) for these kinds of cases. Although our center was a regional tertiary care center, the ICU bed availability might not be possible at that time. This factor might be the reason for our high mortality rate. The deterioration parameters such as base excess and BUN reflect that morbidity and mortality are due to distant organ injury and tissue perfusion impairment, that is to say, due to systemic damage. ROC analysis showed that these are useful parameters for predicting mortality (Table 4).

The CT index, in conjunction with the APACHE II score and the CRP value are important determinants of mortality and morbidity. CRP is a practical and inexpensive parameter that has been proved in other studies also<sup>[29]</sup>. Of the Ranson, Imrie and APACHE II scoring systems, APACHE II was the most reliable in the present study. The role of systemic complications in mortality and morbidity decreased the usefulness of pathology-specific scoring systems such as Ranson and Imrie scores. One potential weakness of the APACHE II is that patients older than 65 years have very high scores and there is a possibility of a false-positive score in that age group<sup>[30]</sup>. In the present study, age had no association with disease severity, morbidity or mortality. A multiorgan system score has been developed to supersede the APACHE II and Ranson scores, but the number of cases in that report is small<sup>[10]</sup>.

In conclusion, AP is a condition with high morbidity and mortality and may cause endocrine dysfunction in the long run. Base excess, CRP, CT index and the APACHE II score are useful in prediction of the course.

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