Klinik Çalışma - Araştırma / *Original Article*

High C-Reactive Protein and Amylase Levels as Prognostic Markers in Non-Pancreatic Severe Sepsis Patients

Pankreatik Olmayan Ağır Sepsisli Hastalarda Belirleyici Faktörler Olarak Yüksek C-Reaktif Protein ve Amilaz Değerleri

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Objectives: Sepsis in critical illness is associated with the progressive failure of multiple organs. Additional biomarkers in severe sepsis are needed to tackle the challenges of determining a prognosis and optimizing the selection of high-risk patients for therapy. This paper evaluates serum C-reactive protein (CRP) and amylase as prognostic factors for survival in patients with severe sepsis.

Patients and Methods: Ninety-five patients (42 males, 53 females) meeting the criteria for severe sepsis were chosen for the study. APACHE II scores, serum levels of CRP and amylase were taken on admission to an intensive care unit, two days later, and on the day of discharge from the intensive care unit or on the day of death.

Results: Amylase levels, median CRP levels, and APACHE II scores were significantly higher in the non-survivors than in the surviving patients.

Conclusion: Serum amylase and CRP are predictors of survival in patients with severe sepsis. High amylase and CRP levels appear to be a valuable tool for individual risk assessment in severe sepsis patients and for stratification of high-risk patients in future intervention trials.

Key words: C-reactive protein; amylase; prognostic factor; severe sepsis.

Amaç: Kritik hastalarda sepsis ilerleyen multi organ yetmezliği ile ilişkilidir. Ağır sepsiste ilave biyogöstergeler, yüksek riskli hastaların etkili tedavi seçiminde ve prognozun belirlenmesi mücadelesinde başarılı olmak için gereklidir. Bu araştırmada ağır sepsisli hastalarda sağkalım için belirleyici faktörler olarak serumda C-reaktif protein (CRP) ve amilaz değerlendirildi.

Hastalar ve Yöntemler: Çalışmaya ağır sepsis kriterlerini sağlayan 95 hasta (42 erkek, 53 kadın) dahil edildi. APACHE II skorları, serum CRP ve amilaz düzeyleri hastaların yoğun bakım ünitesine kabul edildiğinde, iki gün sonra ve yoğun bakım ünitesinden taburcu edildiği gün veya kaybedildikleri gün alındı.

Bulgular: Amilaz ve ortalama CRP düzeyleri ile APACHE II skorları yaşamını kaybeden hastalarda, sağ kalan hastalardan anlamlı derecede yüksekti.

Sonuç: Serum amilaz ve CRP, ağır sepsisli hastalarda sağkalımı belirleyicidir. Yüksek amilaz ve CRP düzeyleri ağır sepsisli hastaların risk değerlendirmesinde ve gelecek çalışmalarda yüksek riskli hastaların sınıflandırılmasında değerli araçlar olarak görülebilir.

Anahtar sözcükler: C-reaktif protein; amilaz; prognostik faktör; ağır sepsis.

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Sepsis is a common cause of critical illness, often complicated by the development of multiple organ dysfunction syndrome. The dysfunction of organs such as lung, kidney, brain, liver, intestine, and hematopoietic and cardiovascular systems have been well characterized, and scoring systems have been developed to explain the relationship of organ dysfunction in sepsis with poor outcomes.[1]

Increases in serum amylase levels have been reported without clinical evidence of pancreatitis in patients with head injury, perforation of the duodenum, small intestinal obstruction, acute appendicitis, pneumonia, ovarian pathology, blunt trauma, and following cardiac surgery.[2] Little attention has been paid to the function of the exocrine pancreas in critical illness and sepsis.[3] Recently, Tribl et al.[4] described severe impairment of exocrine pancreatic function in critically ill patients with septic shock, which was not observed in nonseptic controls. These findings were consistent with animal studies. Several animal studies have shown a special vulnerability of pancreatic perfusion[5,6] at an early stage of the course of sepsis,[5] a finding that seems to be more pronounced than perfusion changes in other organs.[6,7] In addition, an in vitro lipopolysaccharide (LPS) challenge directly reduced amylase mRNA in acinar cells and in vivo protein output in rat pancreatic juice.[8,9] Takahashi et al.[10] hypothesized that shock and ischemia could lead to hypoperfusion and hypoxia of the pancreas and thus could alter the permeability of cell membranes, causing hyperamylasemia.

A number of inflammatory cells and mediators involved in the inflammatory response have been assessed for their roles as potential markers of the presence and severity of inflammatory response and organ failure.[11,12] Serum levels of C-reactive protein (CRP), an acute-phase protein synthesized by the liver following stimulus by various cytokines including tumor necrosis factor- and interleukin (IL)-6, markedly increase within hours of infection or inflammation.[13] Numerous studies have demonstrated increased CRP levels in patients with sepsis,[14,15] but their relation to multiple organ dysfunction and failure has not been well evaluated. Some studies have suggested that CRP may be an indicator of organ failure.[16]

In this study, we aimed to evaluate the prognostic value of amylase levels in a well-defined cohort of patients with severe sepsis but without pancreatitis, as compared with those of other biomarkers, C-reactive protein, and a physiological score (Acute Physiology and Chronic Health Evaluation [APACHE] II) in a heterogeneous group of intensive care unit (ICU) patients.

PATIENTS AND METHODS

This study was approved by the Committee for Ethics in Human Research. Informed consent was obtained from the next of kin of each patient. We studied critically ill patients at the medical–surgical ICU of the university hospital. Ninety-five patients (42 males, 53 females) in whom severe sepsis was diagnosed within four hours of clinical onset were consecutively enrolled. Critically ill patients with bacteriologically documented infections were included in the study as soon as they were known to have met at least two of the following criteria of sepsis, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee:[17] temperature of >38°C or <36°C; heart rate of >90 beats/min^{-1}; respiration of >20 breaths/min^{-1} or $PaCO_2$ of <32 mmHg; and leukocyte count of >12x10^9 cells L^{-1} or <4x10^9 cells L^{-1}. In addition, at least one of following conditions was required: hypoxemia (PaO_2/FiO_2 of <250 mmHg); oliguria (urine output of <0.5 mL.kg^{-1} body weight for two hours); lactic acidosis (lactate concentration of >2 mmol.L^{-1}); thrombocytopenia (platelet count of <100x10^9 L^{-1}), or a recent change in mental status without sedation. Although all patients admitted to the ICU and meeting the above criteria were eligible for enrollment, those with burns, under coronary care, admitted for alcohol abuse, with diseases of the liver, patients with insulin-dependent diabetes mellitus and patients with a history of pancreatitis were excluded. Patients who developed sepsis during their stay in the ICU, and thus did not have sepsis on admission, and who were in an immunosuppressed state

[undergoing steroid treatment, bone marrow or organ transplant recipients, with leukopenia (white blood cell count <1000/μL) or neutropenia (polymorphonuclear granulocyte count <500/μL), with hematological malignancy, and with AIDS], and with a medical condition considered to be irreversible or lethal within 24 hours of admission were also excluded. Patients with serum amylase and serum-lipase values higher than 300 U L^{-1} were performed abdominal ultrasonography and patients with a diagnosis of pancreatitis were excluded from the study.[4]

All patients had arterial catheters, central venous catheters and the subclavian vein in place, and, if required, were mechanically ventilated in volume- or pressure-controlled modes during continuous sedation with midazolam and fentanyl. All patients received routine resuscitation therapy for severe sepsis, including fluid administration with crystalloids and colloids. After blood and various biological specimens were collected for microbiological analysis, all patients initially received broad-spectrum antibiotics consisting of a combination of an aminoglycoside with either a fourth-generation cephalosporin or ciprofloxacin. Antibiotic treatment was adjusted based on culture results.

Clinical and functional investigations

The study was designed to evaluate the predictive value of amylase and CRP levels on the mortality of patients with severe sepsis. During the course of 27 months, 95 patients who met the diagnostic criteria for severe sepsis were enrolled in the study. Patient characteristics are shown in Table 1. Normal levels of bilirubin (0.4-2 $mgdl^{-1}$), creatinine (0.6-1.1 $mgdl^{-1}$), amylase (normal level 36-128 UL^{-1}) and CRP (normal level 0-1 $mgdl^{-1}$) levels (Beckman Coulter CX9, Florida, USA) were collected on admission (i.e., during the first 24 hours), on day 2, and on the day of discharge from the ICU or on the day of death. Vital signs, clinical status, and severity of disease parameters (APACHE II score)[18] were assessed daily. The APACHE II score was calculated by means of maximal daily deviations of 12 physiological variables from normal, plus correction for age and for various chronic illnesses.

The duration of mechanical ventilation was recorded. Survival was defined as being alive at the time of ICU discharge.

Results of routine blood analyses (i.e., complete blood count and serum chemistry including CRP and amylase) were recorded.

Statistical methods

Results are expressed as mean±SD, or median and interquartile range in the case of parametric or nonparametric variables, respectively. The Kolmogorov-Smirnov test was used to assess the normality of continuous data. A comparison between any two groups was by the Student's t test for normally distributed data or by the Mann-Whitney U test for non-normally distributed data. Correlation analyses were performed with the Pearson and Spearman rank correlation. In order to remove the effect of confounding factors (age, CRP, and APACHE II score), the Analysis of Covariance (ANCOVA) test was used to compare amylase levels between groups; the Bonferroni post-hoc test was used for multiple comparisons when a significant result was obtained. The survival time was determined using the Kaplan–Meier survival analysis with a log rank test for amylase on the first and last days.

Table 1. Patient characteristics at admission

	Median	Min-Max
Heart rate (bpm)	115	100-135
Systolic blood pressure (mmHg)	88	79-100
Temperature (°C)	37.9	37.1-38.9
FiO_2 (%)	0.6	0.5-0.8
PaO_2 (mmHg)	110	54-135
Leukocyte count (10^9/L)	13	7-28
Bilirubin level ($mgdl^{-1}$)	0,8	0.1-1.9
Albumin ($mgdl^{-1}$)	2.9	2.1-3.9
Prothrombin time	12	11-15
Alanine aminotransferase ($IU.L^{-1}$)	41	35-55
Urinary output (l/day)	2.9	2.1-3.9
Creatinine ($mgdl^{-1}$)	0.9	0.5-1.7
Serum potassium (mmol/l)	4.0	3.3-4.3
Serum sodium (mmol/l)	139	134-145
Serum bicarbonate (mmol/l)	22	18-27

Table 2. Origin of severe sepsis and microbiological findings

Septic shock	Survivors (n=45)	Nonsurvivors (n=50)
Type of infection		
Pneumonia[1]	25 (55.6)	37 (74.0)
Peritonitis[2]	6 (13.3)	4 (8.0)
Urosepsis[3]	10 (22.2)	6 (12.0)
Wound infection[4]	4 (8.9)	3 (6.0)
Type of pathogen		
Gram-negative (*Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae*)[3]	21 (46.7)	34 (68.0)
Gram-positive (*Streptococcus pneumoniae, S. aureus, other Streptococcus* spp.)[1,3]	8 (17.8)	8 (16.0)
Mixed (≥1 type of gram-negative) (As above)[1,2,3]	11 (24.4)	6 (12.0)
Anaerobe (Bacteroides fragilis)[2,3]	5 (11.1)	2 (4.0)

[1]The diagnosis of pneumonia was based on clinical and chest x-ray findings in all patients. 62 patients grew pathogens on quantitative culturing of endobronchial secretions obtained by bronchoalveolar lavage or protected specimen brush; 11 patients had similar microorganisms in bronchial aspirate and blood cultures. [2]Peritonitis was diagnosed preoperatively in all patients, who also had positive blood cultures. [3]Blood cultures were positive in patients with catheter sepsis and urosepsis. [4]The diagnosis of wound infection was made clinically.

The area under the curve (AUC) of the receiver operating characteristic (ROC) curves was used to assess the predictive power of CRP, amylase, and APACHE-II for days. The sensitivity, specificity, and predictive rate of CRP, amylase, and APACHE II for days were estimated by cut-off points. Statistical analysis was carried out using a software package (SPSS for Windows 9.0) and a two-tailed test was used with the significance level (α) set at 0.05.

RESULTS

Of 97 patients who were recruited, two of them had evidence of pancreatitis. We therefore followed 95 patients with severe sepsis. None of the 95 patients had clinical evidence of acute pancreatitis at any time during the study. Pneumonia was the most frequent underlying cause, followed by peritonitis, urosepsis, and wound infection (Table 2). Those patients who met the above criteria for severe sepsis were enrolled in the study within four hours of ICU admission. In 88 patients (82%), one or more pathogenic infectious agents could be isolated or identified (Table 2). In the remaining seven patients, no microorganisms could be cultured, but in all of them the infectious focus was confirmed clinically. Survivors (n=45) and non-survivors (n=50) did not differ in terms of the underlying etiology of severe sepsis (Table 2). The majority of patients who died (66%) suffered from multiple organ failure, defined as the failure of two or more vital organs. Survivors (n=45) and non-survivors (n=50) did not differ in terms of a history of tobacco (24 and 22 patients, respectively) or alcohol use (14 and 18 patients, respectively).

Table 3. Age, ICU and ventilation days, CRP ($mgdl^{-1}$) levels, APACHE II scores of patients

Characteristic	Survivors (n=45) [median (IQR)]	Nonsurvivors (n=50) [median (IQR)]	*p*
Age	50 (22-68)	55.5 (28-69)	0.032
ICU days	12 (8-19)	14.5 (9-22)	0.015
Ventilation days	10 (6-17)	14 (9-22)	<0.001
CRP 1.day	10 (5-17)	25 (5.1-45)	<0.001
CRP 2.day	8.0(4-15)	28 (4-72)	<0.001
CRP last day	7 (1.8-10)	27 (6-65)	<0.001
APACHE II 1.day	15 (14-18)	20 (18-23)	<0.001
APACHE II 2.day	12 (10-16)	22 (18-26)	<0.001
APACHE II last day	9 (8-10)	25 (21-26)	<0.001

IQR: Interquartile range; SD: Standard deviation; APACHE II: Acute physiology and chronic health evaluation; CRP: C-reactive protein.

Table 4. ANCOVA results for amylase levels adjusted by age, CRP, and APACHE II scores

	Survivors (n=45) (mean±SD)	Nonsurvivors (n=50) (mean±SD)	*p*
Amylase 1.day	118.5±49.4	234.8±39.3	<0.001
Amylase 2.day	113.3±49.5	282.3±56.8	<0.001
Amylase last day	101.2±37.0	288.2±61.9	<0.001

CRP: C-reactive protein; APACHE II: Acute physiology and chronic health evaluation; ANCOVA: Analysis of Covariance Test.

Arterial blood analysis, hemodynamic parameters, and biochemical parameters at ICU admission were shown in Table 1, and there was no significant difference between the groups (all p>0.05).

Age, ICU and ventilation days, CRP ($mgdl^{-1}$) levels and the APACHE II scores of patients are shown in Table 3. Between survivors and non-survivors, there were significant differences in age (p=0.032), ICU days (p=0.015), ventilation days (p<0.001), and CRP and APACHE II values on the first, second, and last days (all p<0.001).

Non-survivors were significantly older than survivors and tended to have higher CRP and APACHE II scores. Therefore, they could be confounding factors in terms of amylase levels. In order to remove this effect, the ANCOVA test was used (Table 4). ANCOVA results for amylase levels, adjusted by age and by CRP and APACHE II scores, showed that amylase levels in non-survivors were significantly higher than those in survivors on the first, second, and last study days (all p<0.001).

To define an optimal decision threshold for CRP, amylase, and APACHE II values in patients, we performed an ROC curve analysis. Table 5 shows the AUC for all parameters, including the 95% confidence intervals and the cut-off point. The CRP, amylase, and APACHE II scores for all days had an area under the ROC curve in the 0.852-1.0 range (Figs. 1, 2, and 3). The AUC indicates that CRP, amylase, and APACHE II have good diagnosis values for all days (p<0.001).

The optimal cut-off points for CRP, amylase, and APACHE II were >17, >179, and >17, respectively, for the first day. At these cut-off points, the sensitivity rates for correct prediction of non-survival were 68%, 92%, and 100%, respectively, while the specificity rates were

Table 5. AUCs and predictive values of CRP, amylase, and APACHE II

Time	Variables	Sensitivity	Specificity	ROC Curve		
		(%)	(%)	Cut-off	AUC (95% CI)	*p*
1. Day	CRP	68.0	100.0	>17	0.852 (0.771-0.932)	<0.001
	Amylase	92.0	88.9	>179	0.966 (0.934-0.997)	<0.001
	APACHE II	100.0	91.1	>17	0.995 (0.987-1.003)	<0.001
2. Day	CRP	70.0	100.0	>15	0.888 (0.822-0.954)	<0.001
	Amylase	98.0	100.0	>200	1.000 (0.999-1.001)	<0.001
	APACHE II	100.0	100.0	>16	1.000 (1.000-1.000)	<0.001
Last Day	CRP	90.0	97.8	>9	0.950 (0.905-0.995)	<0.001
	Amylase	96.0	100.0	>171	0.980 (0.950-1.011)	<0.001
	APACHE II	100.0	100.0	>10	1.000 (1.000-1.000)	<0.001

AUC: Area under the curve; ROC: Receiver operating characteristic; APACHE II: Acute physiology and chronic health evaluation; CRP: C-reactive protein.

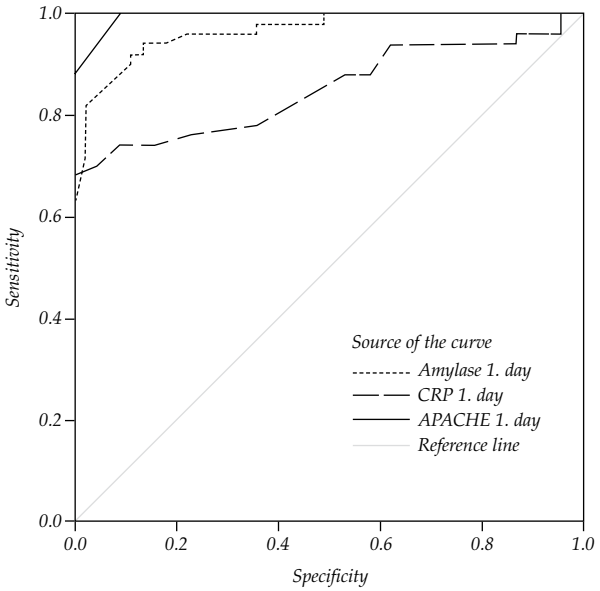

Fig. 1. *Receiver operating characteristic curves for CRP, amylase, and APACHE II on the first day. APACHE II: acute physiology and chronic health evaluation; CRP: C-reactive protein.*

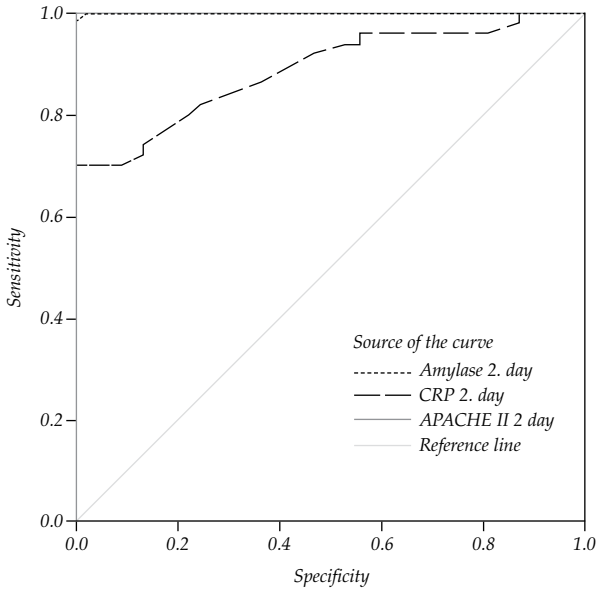

Fig. 2. *Receiver operating characteristic curves for CRP, amylase, and APACHE II on the second day. APACHE II: Acute physiology and chronic health evaluation; CRP: C-reactive protein.*

100%, 88.9%, and 91.1%. The optimal cut-off points for CRP, amylase, and APACHE II were >15, >200, and >16, respectively, for the second day. At these cut-off points, the sensitivity rates for correct prediction of non-survival were 70%, 98%, and 100%, respectively, while the specificity rates were 100%, 100%, and 100%. The optimal cut-off points for CRP, amylase, and APACHE II were >9, >171, and >10, respectively, for the last day. At these cut-off points, the sensitivity rates for correct prediction of non-survival were 90%, 96%, and 100%, respectively, while the specificity rates were 97.8%, 100%, and 100% (Table 5).

DISCUSSION

Elevated serum amylase levels are frequently encountered in critically ill patients. The results of this study show that severe sepsis influences amylase and CRP levels. Our study used elevated serum amylase levels as a prognostic marker in severe sepsis. The amylase and CRP levels and APACHE II scores were significantly higher in non-survivors than in survivors.

Elevations in serum amylase are frequently observed in patients admitted to an ICU without a primary diagnosis of pancreatitis. The incidence of hyperamylasemia ranges from 30% to 80% in groups of patients with traumatic injury, head injury, and following cardiac surgery.[10,19] In many of these previous reports, the elevations in serum amylase have been found to be of non-pancreatic origin; however, when coupled with increases in serum lipase, the hyperamylasemia was usually of pancreatic origin.[20,21]

Nonpancreatic amylase, also known as salivary amylase, arises from the prostate, breast, lung, liver, fallopian tubes, ovaries, and endometrium in addition to the salivary gland. The pancreatic isoenzyme originates only from the pancreas.[22] Clinically, the total serum amylase has been used in recent years as an indicator of pancreatic disease or injury with the well-accepted understanding that it is a nonspecificity test. The total amylase may be elevated in biliary tract disease, alcoholism, perforated peptic ulcer, intestinal obstruction, mesenteric thrombosis, ectopic pregnancy, mumps, and after narcotic administration.[23] Isoamylase determination can identify a pancreatic source of the amylase but is not a sensitive predictor of true pancreatic pathology in the critically ill patients.[19,24]

Studies with animal models of sepsis show an impairment of the regional perfusion of the pancreas, which may be a crucial factor in the development of exocrine pancreatic dysfunction. Reduction in pancreatic blood flow in rat sepsis was found to occur before[5] and without[25] changes in systemic perfusion pressures. In hyperdynamic sepsis in sheep, increased blood flow to the heart, spleen, adrenal, and small intestine was accompanied by decreased organ blood flow to the stomach, muscles, and pancreas.[26] Other work supports findings that blood flow is preferentially redistributed away from the pancreas in sepsis.[6,7] Laser flowmetry has been used in a pig model of sepsis and showed impaired pancreatic flow (–56%) during hypodynamic shock. When a hyperdynamic state of septic shock was induced by fluid infusion, the systemic flow increased threefold, but the flow to the pancreas remained 26% under baseline.[6] These data clearly suggest a disproportional impairment of pancreatic perfusion in states associated with circulatory dysfunction.[1]

Ischemic injury to the pancreas is one factor that is postulated to contribute to increases in serum lipase and amylase in critically ill patients. A direct correlation between increases in serum pancreatic amylase levels and aortic cross-clamping time has been reported in patients undergoing surgery for thoracoabdominal aneurysms.[27] In a small prospective series[28] of 13 patients with circulatory shock, each of the patients had increases in serum amylase and lipase in their subsequent course. Hypotension in the setting of traumatic injury has also been associated with the development of hyperamylasemia in some, but not all, studies.[19] Manjuck et al.[21] reported that increased lipase levels were associated with hypotension, and the highest lipase levels occurred in patients undergoing emergency surgery. Both of these observations are consistent with a role for ischemia in mediating these elevations.

C-reactive protein is a marker of inflammation that has been used to monitor the course of infection and inflammatory diseases.[12-14] Recently, CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. Increasing or persistently high levels, suggesting ongoing inflammatory activity, indicated a poor prognosis, while declining values, suggesting a diminishing inflammatory reaction, were associated with a more favorable prognosis. Hence, trends in CRP concentrations during the first 48 hours of ICU admission can be important in helping to decide whether or not further and more invasive diagnostic procedures are needed and whether therapeutic interventions should be maintained or modified.

C-reactive protein is thought to represent a measure of cytokine-induced protein synthesis. Its relatively short half-life of approximately 19 hours makes it a useful monitor for follow-up of inflammatory response, infection, and antibiotic treatment. In addition, laboratory tests for CRP are easily available and less costly than cytokine tests. In patients with sepsis, Presterl et al.[29] demonstrated a correlation between the plasma levels of CRP, IL-6 and tumor necrosis factor-sR, and the APACHE III and mortality probability model II scores. Both scoring systems, as well as CRP levels, were significantly higher in the nonsurvivors compared with the survivors. Nonsurvivors had significantly higher CRP levels.

The APACHE II score—a complex algorithm—was not originally developed for individual outcome prediction in sepsis patients.[18] Despite their limitations, outcome predictors such as the extensively evaluated APACHE II score are helpful in identifying those septic patients who are at high risk of death and who are more likely to benefit from intervention. In this study, the prognostic value of amylase and CRP levels were comparable to that of the APACHE II score. Our belief is that the simultaneous use of amylase and other variables may be needed to increase its prognostic value; these may include, for instance, severity of illness, age, and infection, variables already considered in currently available scoring systems. Tribl et al.[1] showed an impairment of exocrine pancreatic function in sepsis, which increases with the severity of the sepsis. Impaired exocrine function was significantly correlated with APACHE III and SOFA scores.

Lobo et al.[30] reported that study is the first to detail the relationship between CRP concentrations and the severity and pattern of multiple organ dysfunction in ICU patients. They conclude that CRP levels are a good early markers of morbidity and mortality in these patients. In addition, CRP concentrations may be a valuable addition to APACHE II scores to predict the risk of death.

Our study used elevated serum amylase as a prognostic marker in severe sepsis. The amylase levels were significantly higher in the non-survivors than in the surviving patients. The CRP levels were significantly higher in the non-survivors than in the survivors. The APACHE II scores were significantly higher in non-survivors than in survivors. None of the 95 severe sepsis patients had clinical evidence of pancreatitis. Elevated serum amylase levels are frequently encountered in critically ill patients. Hypoperfusion and inflammatory processes associated with multiple organ failure appear to contribute to these increases.

We can conclude that hyperamylasemia and increased CRP concentrations may be a valuable addition to APACHE II scores to predict the risk of death. Persistently high amylase and CRP concentrations are associated with a poor outcome. Serial measurements of amylase and CRP concentrations in critically ill patients may help to identify patients who may require more aggressive diagnostic and therapeutic interventions to avoid complications. Amylase and CRP concentrations may also be helpful in clinical trials to identify high-risk patients who would benefit from new therapeutic interventions.

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