



Resistin: New serum marker for predicting severity of acute pancreatitis

Yunus İ Kibar¹, Fatih Albayrak²,
Mahmut Arabul¹, Hakan Dursun²,
Yavuz Albayrak³ and Yasin Ozturk¹

Abstract

Objective: To assess the effectiveness of resistin in predicting the severity of acute pancreatitis.

Methods: Patients with acute pancreatitis who presented at the Gastroenterology Clinic, Erzurum Education and Research Hospital, Turkey were enrolled in this prospective study. White blood cell (WBC), C-reactive protein (CRP) and resistin levels were measured on admission and at 24 h, day 3 and day 7 following admission, along with other blood parameters. Patients were divided into two groups: mild acute pancreatitis and moderate/severe acute pancreatitis.

Results: Of 59 patients with acute pancreatitis (mild, $n = 37$; moderate/severe, $n = 22$), significant between-group differences were found in terms of resistin and CRP levels. Receiver operating curve analysis showed that resistin levels were better for predicting severe cases of acute pancreatitis than CRP or WBC levels on day 3 (area under the curve [AUC], 0.88 versus 0.81 and 0.63, respectively). Resistin levels on day 3 were better than CRP levels for predicting necrosis development (AUC, 0.70 versus 0.69, respectively).

Conclusions: Resistin may represent a new, effective indicator to predict the severity of acute pancreatitis and presence of necrosis in patients with acute pancreatitis.

Keywords

Resistin, acute pancreatitis, predictive factor, C-reactive protein (CRP)

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Introduction

Acute pancreatitis is a common disease with a highly variable clinical course. Most cases of acute pancreatitis are mild and resolve spontaneously (or following supporting treatments) without complications. The clinical outlook is less favourable, however, in the 10–20% of cases that are associated with organ failure and heightened morbidity.^{1–3}

¹Department of Internal Medicine, Education and Research Hospital, Erzurum, Turkey

²Department of Internal Medicine, Section of Gastroenterology, Ataturk University Faculty of Medicine, Erzurum, Turkey

³Department of Surgery, Education and Research Hospital, Erzurum, Turkey

Corresponding author:

Hakan Dursun, Department of Internal Medicine, Section of Gastroenterology, Ataturk University, Faculty of Medicine, Erzurum 25240, Turkey.

Email: hadursun@hotmail.com



Rating systems and serum markers are used in conjunction with clinical, laboratory and radiological findings in order to predict the severity of clinical progression in cases of acute pancreatitis.⁴⁻⁶ One acute-phase reactant, C-reactive protein (CRP), is a commonly used marker for distinguishing between a mild and severe acute pancreatitis attack. Damage to the pancreas in acute pancreatitis and the intensity of the organism response (i.e., the acute-phase response) is accompanied by a substantial increase in the serum CRP level, which is the most significant reactant in this response, as a result of hepatocyte stimulation by cytokines. In acute inflammation, CRP levels often reach their peak at 48 h.^{7,8}

Improved knowledge of the roles of cytokines has increased understanding of the pathogenesis of acute pancreatitis. White adipose tissue is a multifunctional organ that releases protein signals and factors such as leptin, adiponectin, resistin, ghrelin and apelin on a vast scale.⁹ Changes in the function and quantity of these proteins plays a role in the pathogenesis and progress of inflammation, inflammatory response, insulin resistance and metabolic syndrome.¹⁰ Resistin is a newly identified peptide hormone, secreted specifically by adipocytes,¹¹ that can cause obesity and hypertriglyceridaemia, due to its association with insulin resistance.^{12,13} Studies have revealed that resistin is also an important cytokine in inflammatory reactions, and in the regulation of other cytokines.¹⁴⁻¹⁶

The aim of the present study was to assess the effectiveness of resistin in predicting the severity of acute pancreatitis, and to compare resistin with CRP in predicting the severity of acute pancreatitis.

Patients and methods

Study population

This prospective observational study included patients with acute pancreatitis

who presented to the Gastroenterology Clinic of Erzurum Education and Research Hospital, Erzurum, Turkey, between November 2012 and December 2013. Patients whose diagnoses were verified through clinic and laboratory findings, and who met the criteria for study inclusion, were sequentially enrolled.

Inclusion criteria for the study comprised the presence of clinical findings, typical history, body mass index (BMI) between 20 and 25, a more than three-fold increase in serum amylase and lipase values, and verification of the monitoring methods. Exclusion criteria included iron deficiency anaemia, renal failure, liver disease, chronic pancreatitis, a second or later pancreatitis attack, symptoms lasting >3 days prior to admission, and a diagnosis that was not verified through monitoring methods.

Upper abdominal ultrasonography was conducted on admission, and computed tomography (CT) was performed on day 4 or 5 following admission. Biochemical parameters were assessed using two different blood samples taken within the first 2 h following presentation and at a time between the first 2 and 72 h, based on when the patient was admitted to hospital. Each patient's age, sex and reason for hospital admission were recorded.

Each patient was evaluated by monitoring with the Balthazar CT rating system and CT severity index, and pancreatic necrosis assessment. The patients were divided into two groups based on the Atlanta classification.¹⁷ The first group included patients without complications (mild acute pancreatitis); the second group included patients with one or several organ failures (moderate or severe acute pancreatitis).

Approval for the study was obtained from the Ethical Committee of Erzurum Regional Education and Research Hospital. All patients participating in the study provided written informed consent.

Blood samples and tests

Blood samples were collected from each patient a total of four times: on admission (0 h), day 1 (24 h), day 3 (72 h) and day 7 (168 h) following admission. Blood (10 ml) was drawn into heparin-treated tubes by venepuncture and, within 1.5 h following collection, a 5-ml portion of the sample was centrifuged for 10 min at 1700 *g* at 25°C. The plasma was then collected and stored at -80°C prior to analysis. All plasma samples were analysed within 12 months. For routine blood parameter measurements, blood samples were collected into tubes containing ethylenediaminetetra-acetic acid to prevent clotting. Complete blood counts (white blood cell [WBC] and haematocrit), CRP and resistin levels, and routine examination results for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ -glutamyltransferase (γ -GT), lactate dehydrogenase (LDH), bilirubin, amylase, blood urea nitrogen, creatinine, Na, K, calcium and glucose were obtained.

White blood cell and thrombocyte counts were measured automatically using standard methods with a Coulter® LH 780 analyser (Beckman Coulter, Brea, CA, USA). Amylase, lipase, albumin, creatinine, LDH, AST, ALT, glucose, ALP, γ -GT, and bilirubin values were determined using photometric methods with a Roche PP800 autoanalyser (Roche Diagnostics, Indianapolis, IN, USA) in the routine biochemistry laboratory of Erzurum Education and Research Hospital. CRP levels were measured nephelometrically using a Beckman Coulter IMAGE® 800 system.

Plasma resistin levels were measured using a human resistin ELISA (Catalogue number: RD191016100; BioVendor-Laboratori Medicina a.s., Bmo, Czech Republic), according to the manufacturer's instructions.

Statistical analyses

Data were presented as *n* patient incidence, mean (range) or mean \pm SD. Kolmogorov–Smirnov test was used to assess normality of the data. Between-group comparisons of serum resistin values were performed using Mann–Whitney *U*-test, as the serum resistin values did not show normal distribution. The association between categorical variables was assessed using χ^2 -test or Fisher's exact test. Receiver operating curves (ROC) were drawn in order to determine the optimum cut-off points to reach high sensitivity and specificity values. The area under the curve (AUC) was calculated using the 95% confidence interval (CI). All analyses were two-tailed and performed using SPSS® software, version 17.0 (SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

Results

The present study included 59 patients with acute pancreatitis (37 with mild acute pancreatitis; 22 with moderate or severe acute pancreatitis, based on the Atlanta classification¹⁷). Patient's clinical and biochemical characteristics are shown in Table 1. A statistically significant difference in terms of age was observed between patients with mild acute pancreatitis (mean, 63.7 years [range, 18–94]) and those with moderate or severe acute pancreatitis (mean, 54.8 years [range, 43–82]; *P* = 0.007). No statistically significant between-group differences were observed in terms of BMI (data not shown) or in biliary factors. In patients with severe pancreatitis, there were three deaths caused by systemic inflammatory response syndrome and multiorgan deficiency. There were no statistically significant between-group differences in terms of sex, aetiology, or lipase, albumin, creatinine and WBC values on admission, however, admission AST, LDH and glucose values were

Table 1. Demographic, laboratory and clinical characteristics of patients with mild and moderate or severe acute pancreatitis.

Characteristic	Study group		Statistical significance
	Mild acute pancreatitis <i>n</i> = 37	Moderate or severe acute pancreatitis <i>n</i> = 22	
Age, years	63.7 (18–94)	54.8 (43–82)	<i>P</i> = 0.007
Sex, male/female	12/25	9/13	NS
Aetiology, biliary/nonbiliary	34/3	19/3	NS
Amylase, U/l	1755 (146–4084)	1720 (767–2312)	NS
Lipase, U/l	2651 (149–8751)	2809 (1010–6990)	NS
Albumin, g/dl	3.82 ± 0.43	3.70 ± 0.31	NS
Creatinine, mg/dl	0.95 ± 0.45	0.90 ± 0.13	NS
AST, U/l	291 ± 229	112 ± 57	<i>P</i> < 0.001
LDH, U/l	273 ± 79	494 ± 104	<i>P</i> = 0.001
Glucose, mg/dl	143 ± 45	159 ± 29	<i>P</i> = 0.029
WBC, /mm ³	13740 ± 6840	14350 ± 4777	NS
Resistin _a , ng/ml	18.3 ± 6.95	28.9 ± 5.22	<i>P</i> = 0.001
Resistin ₁ , ng/ml	15.0 ± 5.35	33.7 ± 5.49	<i>P</i> < 0.001
Resistin ₃ , ng/ml	19.8 ± 8.70	33.6 ± 8.19	<i>P</i> = 0.002
Resistin ₇ , ng/ml	16.8 ± 6.57	48.8 ± 4.83	<i>P</i> < 0.001
CRP _a , mg/dl	6.18 ± 7.41	10.7 ± 10.0	NS
CRP ₁ , mg/dl	13.26 ± 8.98	23.4 ± 6.18	<i>P</i> = 0.001
CRP ₃ , mg/dl	13.05 ± 9.48	25.1 ± 10.8	<i>P</i> < 0.001
CRP ₇ , mg/dl	9.05 ± 9.07	18.7 ± 10.2	<i>P</i> = 0.002
Hospital stay, days	8.5 ± 4.4	16.3 ± 7.7	<i>P</i> < 0.001
Balthazar score	1.0 (0–4)	3.6 (3–4)	<i>P</i> < 0.001
CT severity index	0.9 (0–4)	5.6 (3–10)	<i>P</i> < 0.001
Mortality	0	3	<i>P</i> < 0.001

Data presented as *n* patient incidence, mean (range) or mean ± SD.

Table shows admission levels of amylase, lipase, albumin, creatinine, AST, LDH, glucose and WBC.

AST, aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, white blood cell count; Resistin_a, resistin measured at admission; Resistin₁, resistin measured 24 h following admission; Resistin₃, resistin measured 72 h following admission; Resistin₇, resistin measured 168 h following admission; CRP_a, C-reactive protein measured at admission; CRP₁, C-reactive protein measured 24 h following admission; CRP₃, C-reactive protein measured 72 h following admission; CRP₇, C-reactive protein measured 7 days (168 h) following admission; CT, computed tomography.

P < 0.05 considered statistically significant (Kolmogorov–Smirnov test, Mann–Whitney *U*-test, χ^2 -test or Fisher's exact test). NS, no statistically significant between-group difference (*P* > 0.05).

significantly different (*P* < 0.001, *P* = 0.001, and *P* = 0.029 respectively). Strongly significant between-group differences were also found in terms of resistin levels (day 1 [24 h], day 3 and day 7) and CRP levels (day 1 [24 h], day 3 and day 7; Table 1), with lower levels in the mild acute pancreatitis groups versus moderate/severe acute pancreatitis group. Duration of hospital stay was

significantly lower in the mild acute pancreatitis patient group (8.5 ± 4.4 days) compared with the moderate/severe patient group (16.3 ± 7.7 days, *P* < 0.001). A significant between-group difference was also found in terms of Balthazar score and CT severity index (1[0–4] versus 3.6 [3–4], *P* < 0.001 and 0.9 [0–4] versus 5.6 [3–10], *P* < 0.001, respectively).

Table 2. Correlation between resistin and C-reactive protein (CRP) levels or white blood cell (WBC) counts in patients with acute pancreatitis.

	CRP _a	WBC _a	CRP ₂₄	WBC ₂₄	CRP ₇₂	WBC ₇₂	CRP ₁₆₈	WBC ₁₆₈	
Resistin*	0.56	0.70	0.84	0.75	0.74	0.55	0.71	0.77	<i>r</i>
	<i>P</i> = 0.014	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> = 0.013	<i>P</i> < 0.001	<i>P</i> < 0.001	Statistical significance

*Resistin values corresponded to same timepoints as CRP and WBC values.

CRP_a, CRP measured at admission; CRP₁, CRP measured 24 h following admission; CRP₃, CRP measured 72 h following admission; CRP₇, CRP measured 7 days (168 h) following admission; WBC_a, WBC count at admission; WBC₁, WBC count 24 h following admission; WBC₃, WBC count 72 h following admission; WBC₇, WBC count at 7 days (168 h) following admission.

A strong correlation was observed between resistin and CRP, and resistin and WBC in the first 24 h, day 3 and day 7 (Table 2). In patients with mild acute pancreatitis, resistin levels remained relatively stable during the 7-day study period, whereas in the moderate or severe acute pancreatitis group, resistin levels gradually increased.

The ROC analysis (applied to predict cases of severe acute pancreatitis) showed that the predictive value was significantly higher for resistin levels than for CRP and WBC levels on day 3 (AUC, 0.88, 0.81 and 0.63, respectively; Figure 1). Resistin levels on day 3 were also revealed to be significantly better than CRP levels in predicting necrosis development (AUC, 0.70 and 0.69, respectively; Figure 2). The cut-off value was determined to be 19.5 ng/ml (93% sensitivity, 70% specificity) for severe pancreatitis

Discussion

Acute pancreatitis is a frequently seen disease with a wide clinical spectrum ranging from mild to severe. Most acute pancreatitis progresses mildly and is self-limiting, however, 10–20% of the cases progress severely and 29–43% of severe cases progress fatally.^{2,3,18,19} Mortality rates associated with systemic inflammatory responses in the earlier periods of severe pancreatitis

have decreased, but the death rate due to infected necrosis and septic complications in the latter period remains relatively high.²

C-reactive protein is an easily detectable marker that is frequently used to predict the clinical severity of acute pancreatitis, necrosis and mortality. CRP is able to differentiate between mild and severe acute pancreatitis with high precision, and to predict the development of severe acute pancreatitis even at 24 h following hospital admission.^{20–22} However, very few studies have examined the power of CRP for predicting pancreatic necrosis.²³ Patients with CRP levels > 150 mg/l on admission to the emergency unit and on transfer to the intensive care unit have been shown to have significantly and independently worse outcomes than those with lower CRP levels.²⁴ Although there is a 24–48-h latency period before CRP levels increase, which limits its utility as an early predictor of severity, CRP remains a useful predictor when levels have risen.^{20,23,24}

The main problem in managing acute pancreatitis is the lack of availability of convenient indicators or scoring systems for predicting severity and necrosis in the first hours of the disease, although many indicators have been researched in this regard.^{1,4–8,19–24} The adipokine family, which contains adiponectin, leptin, resistin and visfatin, may help to resolve this

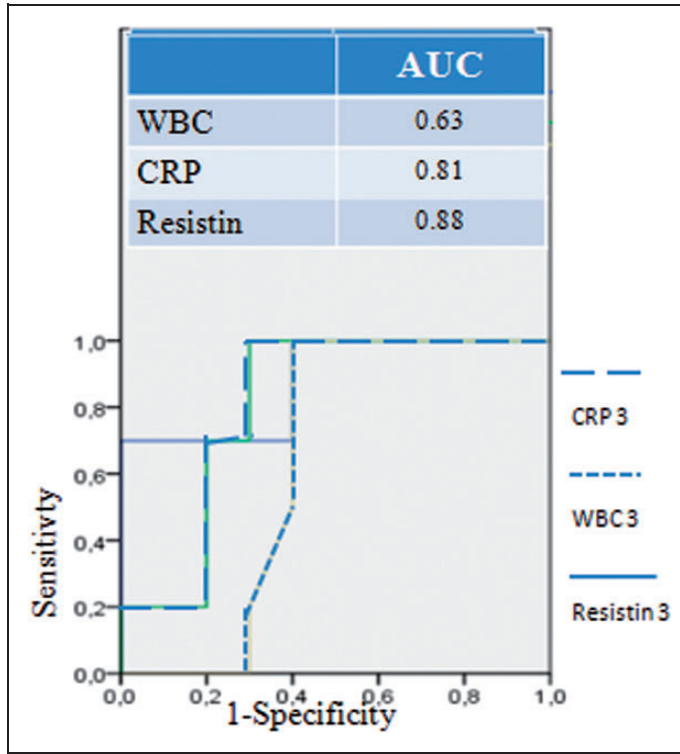


Figure 1. Receiver operating curve analysis of resistin, CRP and WBC levels on day 3 following hospital admission for predicting severe acute pancreatitis (AP) in patients with mild or moderate/severe acute pancreatitis. CRP, C-reactive protein; WBC, white blood cell count.

problem. Resistin and visfatin are hormones that are synthesized in neutrophils, macrophages, bone marrow, and fat tissue and can increase proinflammatory cytokine release.^{16,25,26}

Adipose tissue is thought to be part of the endocrine system, and to play a role in the pathogenesis of acute pancreatitis. Peripancreatic adipose tissue necrosis can lead to intense cytokine release (interleukin [IL]-1, IL-6, tumour necrosis factor- α) and adipokines can play a role in multiorgan failure and systemic changes.^{27,28} The early increase in adipocyte-induced indicators can be an important predictor of the clinical progress of acute pancreatitis.²⁹ Obesity is considered an independent risk factor for the development of severe acute

pancreatitis.^{30,31} Resistin may be a causative factor of obesity and hypertriglyceridemia, due to its association with insulin resistance.^{13,30}

A relationship between acute pancreatitis and adipokines was shown by a study reporting significantly higher serum leptin levels in patients with acute pancreatitis and an animal model of acute pancreatitis, compared with control groups.³² A study that investigated resistin levels in the pancreatic tissue of rats with acute pancreatitis revealed a correlation between the resistin level and disease-related tissue damage,³⁰ and also showed that the CRP level was associated with disease severity.³⁰ Another study revealed that resistin levels were significantly higher in patients with acute

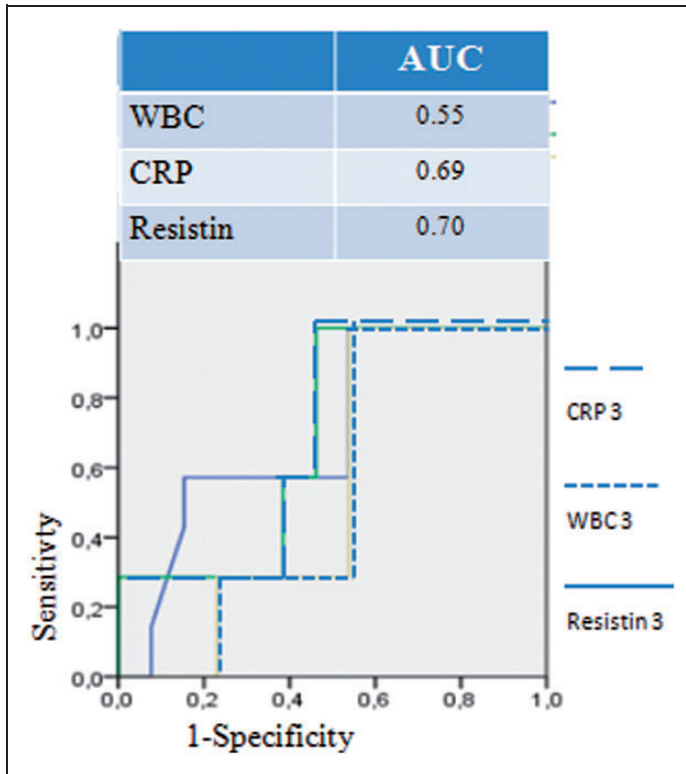


Figure 2. Receiver operating curve analysis of resistin, CRP and WBC levels on day 3 following hospital admission for predicting necrosis development in patients with mild or moderate/severe acute pancreatitis. CRP, C-reactive protein; WBC, white blood cell count.

pancreatitis compared with healthy controls.³³ Prompted by these published studies, the present study further investigated the relationship between resistin levels and the severity of acute pancreatitis.

In one study,³⁴ significantly elevated admission resistin levels was shown in patients with higher pancreatic and extra-pancreatic necrosis scores, and a resistin cut-off value of 11.9 ng/ml was found in the presence of peripancreatic necrosis. These results³⁴ suggest that there is a significant correlation between resistin levels and severity of disease, intervention requirements, morbidity and mortality; such findings concurred with another acute pancreatitis study,³⁵ in which resistin levels were significantly higher at hospital admission, and on

day 3 following admission, compared with controls. Resistin levels were increased on day 5 compared with day 3, and a significant correlation was found between the CRP and resistin levels.³⁵

In the present study, resistin levels were significantly different between patients with mild acute pancreatitis and those with moderate or severe acute pancreatitis at admission and on days 1, 3 and 7 following admission. Likewise, in patients with mild acute pancreatitis, resistin levels remained relatively stable during the 7-day study period, whereas in the moderate/severe acute pancreatitis group, resistin levels gradually increased. The present study revealed that day 3 resistin levels provided improved prediction for severe pancreatitis compared

with CRP and WBC values measured on day 3. In addition, day 3 resistin levels provided a better prediction of necrosis development compared with day 3 CRP levels. Published studies have shown that day 3 resistin levels were similar to CRP in predicting severe pancreatitis, in contrast to previous predictions of necrosis.^{34,35} One reason for this difference may be due to the large number of patients with severe pancreatitis in the previously published studies compared with the present study. In the present study, the cut-off value was determined to be 19.5 ng/ml (93% sensitivity, 70% specificity) for severe pancreatitis.

Increases in adipose tissue due to obesity increases the complexity of acute pancreatitis, for example, obesity can lead to an increase in local complications, organ failure and mortality risk.³⁶ Fat necrosis cannot be assessed with CT because fat tissue does not hold contrast. Therefore, there is a clear need for methods other than CT that are more effective, usable, economical, and have very few side-effects, for the early determination of peripancreatic fat necrosis in particular. Resistin may be a useful marker as an indirect indicator of adipose tissue necrosis and predictor for the severity of acute pancreatitis. However, the present study is limited by the relatively small sample size and further randomized, controlled studies that include a larger patient group are required to validate these results.

In conclusion, resistin may represent a new, inexpensive and effective indicator for predicting the severity of acute pancreatitis and presence of necrosis, and thus the hospitalization period, disease management, and early endoscopic, percutaneous or surgical intervention requirements in patients with acute pancreatitis.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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