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Can neutrophil gelatinase-associated lipocalin be a novel and efficient marker to predict the clinical course of acute pancreatitis?

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Abstract. – OBJECTIVE: This study aimed to determine the value of serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels to predict the severity of the disease and to identify its correlation with White Blood Cell (WBC), C-reactive protein (CRP), and high-sensitivity C-reactive protein (hs-CRP) levels in acute pancreatitis (AP).

PATIENTS AND METHODS: The study sample included 86 AP-diagnosed patients in the study group and 77 age- and gender-matched healthy volunteers with no comorbidity in the control group. The WBC, CRP, hs-CRP, and NGAL levels were examined at the time and 24 hours after diagnosis.

RESULTS: Between the control group and the study group, a significant difference with and without necrosis in terms of NGAL averages (p=0.003) at the time of admission was observed. The mean level of the 24th-hour NGAL in the study group with necrosis (132.7±11.7 ng/ml) was found to be higher than the mean of the 24th-hour NGAL (117.5±22.6 ng/ml) in the study group without necrosis (p=0.032). Additionally, a significant difference was observed between the control group and the study group with and without necrosis in terms of CRP averages evaluated at admission. When the correlation of NGAL levels with WBC, CRP, and hs-CRP levels at the admission (r=0.224, p=0.038) and at the 24th h (r=0.389, p<0.001) are evaluated, weak correlations between NGAL and WBC levels were identified, but no correlation between NGAL and CRP and hs-CRP levels were observed.

CONCLUSIONS: The usability of serum NGAL levels to predict the development of necrotizing pancreatitis in the early period was evaluated. Serum NGAL levels were found to be higher in the study group than in the control group, but there was no statistically significant difference between the mean values of 0th and 24th h NGAL values in any of the groups with/without pancreatic necrosis and the total study group was observed. More research is needed on the subject, with larger sampling sizes.

Key Words:
Pancreatitis, NGAL, Necrotizing pancreatitis, Marker, Inflammation, Severe.

Introduction

It is of great importance that the severity and clinical course of acute pancreatitis (AP) are predicted in the early period. Acknowledging the severity of the disease in the early period allows healthcare workers to place the patients in the intensive care unit, if necessary, to facilitate more intensive monitoring for the signs of multiorgan failure, achieve more effective hydration, and correct electrolyte abnormalities[1]. The clinical course of the disease and the mortality risk are higher in patients whose cases are accompanied by necrotizing pancreatitis. Therefore, it is important to predict the development of necrotizing pancreatitis at an early stage[2]. Some markers were used by various research groups to determine the severity and prognosis of the disease, and some criteria and scoring methods were developed. Unfortunately, neither is ideal[3,4].

Neutrophil gelatinase-associated lipocalin (NGAL) is a proinflammatory molecule. There is an accumulation of granulocytes in the inflamed area. After the apoptosis of granulocytes, secretory granules containing NGAL are exposed and mediate local tissue damage. After intraperitoneal injection of *Escherichia coli*, serum, and liver, NGAL levels increased within 4 h, and spleen NGAL levels increased within 6 h. This demonstrates the importance of NGAL as an acute-phase protein[5].

NGAL is synthesized from cells under stress. NGAL expression was proven to increase in tissues and body fluids in acute kidney injury, and

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a significant increase in NGAL expression was observed in the kidneys. Urine and serum NGAL measurement has become a standard biomarker for the early diagnosis of kidney injury and for predicting prognosis[6,7].

Studies[8] have shown that Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels are useful in predicting the severity of AP in the early period. In this study, the aim was to determine the value of serum NGAL levels in predicting the severity of the disease and its correlation with White Blood Cell (WBC), C-reactive protein (CRP), and high-sensitivity C-reactive protein (hs-CRP) levels in AP.

Patients and Methods

This is a single-center, prospective, and cross-sectional study conducted at Suleyman Demirel University Hospital, Isparta, Türkiye. The study protocol was reviewed and approved by the local ethics committee (Suleyman Demirel University Ethics Committee 21.05.2015/29) in accordance with the ethical principles for human investigations, as outlined by the Second Declaration of Helsinki. Written informed consent was obtained from all the patients.

A total sample of 86 patients, consisting of 56 females and 34 males were included in the study; all patients were over 18 years of age and were diagnosed with AP between March 2015 and May 2016. Patients with comorbidities that could cause NGAL elevation were excluded (acute and chronic renal failure, history of myocardial infarction within the last 3 months, active infection, malignancy history, chronic obstructive pulmonary disease, acute ischemic event, acute exacerbation of chronic inflammatory disease). Patients in whom two of the following three parameters were positive were considered to have AP: sudden onset of upper abdominal pain, elevation of serum amylase and/or lipase levels exceeding three times the upper limit of normal, and detection of AP-specific findings by ultrasonography or computed tomography (CT). As the control group, 77 age- and gender-matched healthy volunteers with no comorbidity were included in the study. Further, patients with AP were grouped into two: group 1a consisted of patients with acute necrotizing pancreatitis, and group 1b consisted of patients with acute non-necrotizing pancreatitis. Ranson criteria and APACHE II scoring were used to determine disease severity. Patients with a Ranson score >3 and APACHE II score >8 at admission were considered severe AP.

Complete blood count (CBC), CRP, glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gama glutamine transferase (GGT), lactate dehydrogenase (LDH), total and direct bilirubin, amylase, lipase, triglyceride, calcium, and blood gases tests were performed at admission and repeated in the 24th h.

Contrast-enhanced CT was performed on all patients upon admission as an imaging method. For patients with clinically suspected necrotizing pancreatitis at their follow-up, contrast-enhanced CT was performed again 72 h after admission.

Hs-CRP and NGAL levels were examined at the time of diagnosis and at the 24th h after diagnosis. Blood samples taken for the determination of hs-CRP and serum NGAL levels were centrifuged at 4,000 rpm for 10 min, then serum was stored in dry tubes without anticoagulant at -80° until the day the serums were examined. Samples stored at -80°C were thawed at room temperature on the study day. Washing was performed using the Bio Tek Instruments, Inc. The ELx50 device was evaluated using the micro-ELISA method with a Human Lipocalin-2/NGAL ELISA kit (Santa Clara, CA, USA). Serum NGAL levels were measured as ng/ml using themicro-ELISA method. Samples reserved for hs-CRP were thawed again at room temperature on the study day and examined in a Siemens BN Prospec device (Labexchange-Die Laborgerätebörse Burladingen/Germany) using the ELISA method.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). The Chi-square test was used to compare the categorical variables between the groups. One-way ANOVA with post-hoc Bonferroni and Kruskal-Wallis tests were used, respectively, in normally and non-normally distributed continuous data. An independent sample *t*-test was used for the comparison of continuous variables between the two groups. A two-sided $p<0.05$ was considered statistically significant.

Results

The study group consisted of 86 patients, and the control group consisted of 77 healthy vol-

Table I. Laboratory parameters.

Laboratory parameters	Study group (total) (n=86) Ort±SS¹	Study group: necrotizing pancreatitis (n=7) Ort±SS¹	Study Group: non-necrotizing pancreatitis (n=79) Ort±SS¹	p*
WBC (admission)	11,886.05 ± 4,501.04	17,500.00 ± 4,762.70	11,388.61 ± 4,153.74	**0.003**
WBC (24th h)	10,159.30 ± 4,630.78	15,814.29 ± 3,403.15	9,658.23 ± 4,399.26	**0.001**
Creatinine (admission)	0.91 ± 0.17	1.04 ± 0.27	0.89 ± 0.16	0.137
Creatinine (24th h)	0.87 ± 0.19	0.97 ± 0.20	0.86 ± 0.19	0.116
GFR (admission)	77.50 ± 14.77	72.57 ± 15.80	77.94 ± 14.70	0.335
GFR (24th h)	82.22 ± 17.66	77.14 ± 15.57	82.67 ± 17.86	0.411
AST (admission)	231.92 ± 238.27	173.00 ± 189.46	237.14 ± 242.42	0.482
AST (24th h)	125.22 ± 155.11	63.86 ± 91.08	130.66 ± 158.79	0.105
ALT (admission)	208.66 ± 199.07	100.57 ± 116.45	218.24 ± 202.48	0.157
ALT (24th h)	169.05 ± 170.09	71.57 ± 102.46	177.68 ± 172.60	0.099
Amylase (admission)	1,697.83 ± 4,709.88	1,327.00 ± 945.34	1,730.68 ± 4,908.31	0.602
Amylase (24th h)	552.74 ± 551.08	642.14 ± 345.31	544.82 ± 566.56	0.221
Lipase (admission)	2,526.90 ± 2,196.42	3,027.14 ± 2,170.98	2,482.58 ± 2,206.85	0.407
Lipase (24th h)	900.63 ± 1,063.89	940.43 ± 516.73	897.10 ± 1,101.25	0.182
Total bilirubin (admission)	2.56 ± 2.86	0.75 ± 0.57	2.71 ± 2.93	**0.028**
Total bilirubin (24th h)	2.22 ± 2.83	1.05 ± 0.50	2.32 ± 2.92	0.221
Direct bilirubin (admission)	1.36 ± 1.79	0.24 ± 0.35	1.46 ± 1.83	**0.008**
Direct bilirubin (24th h)	1.09 ± 1.79	0.24 ± 0.24	1.17 ± 1.85	0.053
Calcium (admission)	8.99 ± 0.59	8.90 ± 0.66	9.00 ± 0.59	0.943
Triglyceride (24th h)	168.26 ± 265.57	503.86 ± 733.70	138.52 ± 156.34	0.591
CRP (admission)	28.41 ± 45.88	14.44 ± 16.06	29.65 ± 47.49	0.389
CRP (24th h)	60.56 ± 59.17	71.30 ± 65.79	59.61 ± 58.92	0.575

WBC: White Blood Cell, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein; *Mann-Whitney U.

unteers. Necrotizing pancreatitis developed in 7 (8.1%) patients in the study group. The clinical, laboratory, and demographic characteristics and laboratory results of the controls and AP data are presented in Table I.

At admission, there was a significant difference between the control group and the study groups with and without necrosis in terms of hs-CRP averages (p<0.001), and there was a significant difference between the control group and the study groups with and without necrosis in terms of NGAL averages (p=0.003). The mean level of the 24th h NGAL in the study group with necrosis (132.7±11.7 ng/ml) was higher than the mean of the 24th h NGAL (117.5±22.6 ng/ml) in the study group without necrosis (p=0.032). There was also a significant difference between the control group and the study groups with and without necrosis, in terms of the CRP averages evaluated at admission (Table II).

The mean level of the study group's hs-CRP in 24 h (9.1±3.0 mg/dL) was higher than the mean hs-CRP at admission (8.0±3.4 mg/dL) (p<0.001). The mean of hs-CRP at 24 h (9.52±2.85) in the group with necrotizing pancreatitis was higher than the mean of hs-CRP (8.01±2.79) at admis-

Table II. Distribution of control group and study group by means of sNGAL, WBC, CRP, and hs-CRP.

Laboratory parameters	Control group (n = 77) Ort ± SS¹	Study Group (n = 86) Ort ± SS¹	p
Hs-CRP	1.76 ± 2.33	7.99 ± 3.41	**< 0.001***
NGAL	107.90 ± 18.90	116.99 ± 2.29	**0.001***
CRP	3.82 ± 2.57	28.41 ± 45.88	**< 0.001***
WBC	6,618.18 ± 1,766.93	11,886.04 ± 4,501.03	**< 0.001***

WBC: White Blood Cell, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein; *Mann-Whitney U.

Table III. Distribution of necrotizing and non-necrotizing pancreatitis groups NGAL, WBC, CRP, and hs-CRP averages.

Laboratory parameters	Study group: necrotizing pancreatitis (n = 7) mean ± SD¹	Study group: non-necrotizing pancreatitis (n = 79) Ort ± SS¹	p
hsCRP (admission)	8.01 ± 2.79	8.00 ± 3.48	0.536
hsCRP (24th h)	9.52 ± 2.85	9.05 ± 2.96	0.543
NGAL (admission)	121.85 ± 12.38	116.56 ± 21.92	0.776
NGAL (24th h)	132.67 ± 11.66	117.52 ± 22.54	**0.032****
CRP (admission)	14.44 ± 16.06	29.65 ± 47.49	0.389
CRP (24th h)	71.30 ± 65.79	59.61 ± 58.92	0.575
WBC (admission)	17,500.00 ± 4,762.70	11,388.61 ± 4,153.74	**< 0.001***
WBC (24th h)	15,814.29 ± 3,403.15	9,658.23 ± 4,399.26	**0.001****

WBC: White Blood Cell, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein; *Mann-Whitney U.

sion. In the necrotizing pancreatitis group, the mean level of hs-CRP was higher than the levels at admission, but there was no statistically significant difference. The 24th h CRP levels of the study group and the necrotizing pancreatitis group were statistically significantly higher than the CRP levels at the time of admission (p<0.001). The 24th h WBC levels of the study group and the necrotizing pancreatitis group were lower than the WBC levels at the time of admission. When we evaluated NGAL levels, the necrotizing pancreatitis group was higher, but it was not statistically significant (Table III).

According to the APACHE II criteria, 8.1%, and according to the Ranson criteria, 15.1% of the patients were evaluated as having severe pancreatitis. The mean NGAL values of patients with severe pancreatitis at admission were higher than those with mild pancreatitis. The mean NGAL value of patients with severe pancreatitis, according to APACHE II, was (119.43±18.30). The mean NGAL value of patients with mild pancreatitis was (116.78±21.64), but it was not statistically significant. The mean NGAL value of patients with severe pancreatitis, according to Ranson, was (122.35±19.74). The mean NGAL value of patients with mild pancreatitis was (116.04±21.56), but it was not statistically significant.

When we evaluated the correlation of NGAL levels with WBC, CRP, and hs-CRP levels at the admission (r=0.224, p=0.038) and in the 24th h (r=0.389, p<0.001), there were weak correlations between NGAL and WBC levels, but none were detected between NGAL and CRP, hs-CRP levels (Tables IV and V).

Discussion

It is of great importance that the severity and clinical course of AP are predicted in the early period. Acknowledging the severity of the disease in the early period allows health workers to place the patients in the intensive care unit, if necessary, to facilitate more intensive monitoring of the signs of multiorgan failure and to accomplish more effective treatment modalities[9]. Criteria and scoring methods were developed to

Table IV. Correlations of study group NGAL value with hs-CRP, CRP, and WBC at admission.

Laboratory parameters	NGAL (r*)	p**
Hs-CRP	0.066	0.547
CRP	0.015	0.893
WBC	0.224	**0.038**

WBC: White Blood Cell, CRP: C-reactive protein, hs-CRP: Highly sensitive-CRP, *Pearson Correlation Coefficient, **Pearson Correlation test.

Table V. Correlations of study group's 24th h NGAL value with 24th h hs-CRP, CRP, and WBC levels..

Laboratory parameters	NGAL (r*)	p**
hs-CRP	0.155	0.154
CRP	0.136	0.210
WBC	0.389	**< 0.001**

WBC: White Blood Cell, CRP: C-reactive protein, hs-CRP: Highly sensitive-CRP; *Pearson Correlation Coefficient, **Pearson Correlation test.

determine the severity and prognosis of the disease. Unfortunately, neither is ideal. The revised Atlanta classification system divides AP into two main groups[10]:

1) Acute interstitial edematous pancreatitis, characterized by acute inflammation of the pancreatic parenchyma and peripancreatic tissues, without distinguishable tissue necrosis.
2) Necrotizing AP characterized by pancreatic parenchymal necrosis and/or peripancreatic necrosis. Morbidity and mortality rates are much higher in necrotizing pancreatitis. In our study, we classified the study group as necrotizing and non-necrotizing AP. We sought a marker that would enable us to detect the development of necrotizing pancreatitis at an early stage. In our study, the number of patients with a Ranson score ≥3 at admission was 13 (15.1%), and the number of patients with an APACHE II score ≥8 was 7 (8.1%), and none of these patients had necrotizing pancreatitis. In summary, according to our study, Ranson and APACHE II scores made no significant contribution to predicting the development of necrotizing pancreatitis in the early period. This result supports the view that the Ranson score has some disadvantages and inadequacies: it needs a period of 48 h for evaluation, this scoring does not make a clear distinction between acute edematous interstitial pancreatitis and necrotizing pancreatitis, and its sensitivity is low[11,12].

In recent years, much effort has been devoted to identifying an objective marker that can predict AP severity at hospitalization. The only useful marker is CRP. In acute inflammations, the CRP level usually peaks at the 48th h. It has been shown that the CRP value measured at 48 h from the onset of symptoms is more beneficial than the value measured in the early period[13]. This limits the use of CRP in predicting AP's severity and pancreatic necrosis in the early stages. Thus, a marker is needed to predict the severity of AP early and accurately. There are very few publications regarding the relationship between NGAL and AP. Therefore, we aimed to determine whether serum NGAL levels are a guide in predicting the development of acute necrotizing pancreatitis. We also evaluated its correlation with other inflammatory markers, such as CRP and hs-CRP.

NGAL is a proinflammatory marker. When tissue damage develops, it releases apoptosis of granulocytes and plays a role in local tissue damage, so NGAL levels can be used as an acute-phase reactant. NGAL is known to be the best early marker of acute and chronic kidney injury. However, NGAL has been reported to play a role in serious extrarenal diseases, including many malignancies such as abdominal aortic aneurysms, preeclampsia, rheumatoid arthritis, and breast, stomach, colon, and pancreatic adenocarcinomas, apart from renal diseases[14,15]. Serum NGAL levels were significantly higher in patients with heart failure and patients with acute coronary syndrome compared with healthy individuals[16]. In light of this information, we also have additional diseases, such as acute renal failure(ARF), chronic renal failure (CRF), heart failure (HF), and malignancy. We excluded patients with active infection, active rheumatic disease, or a history of myocard infarctus (MI) in the last three months.

In in an animal model study[8], NGAL levels were significantly elevated at 6 h with both mild and severe AP (compared with the control group). However, at 48th h, NGAL levels in mice with mild AP decreased to similar levels with the control group but remained significantly higher in those with severe necrotizing pancreatitis. Based on this information, we evaluated the NGAL levels of the patients in our study, both at the time of admission and after 24 hours. There was a significant difference between the control and study groups in terms of NGAL levels evaluated upon admission. When the AP group with and without necrosis was examined, there was no significant difference between the admission NGAL values. In the study group with necrotizing pancreatitis, the mean NGAL level in the 24th h was higher than in the group without necrosis, but it was not statistically significant. In our study group, only seven patients developed necrotizing pancreatitis. The lack of statistically significant results may be related to the low number of patients with necrotizing pancreatitis. In fact, the mean NGAL values of the necrotizing pancreatitis group were high. For these reasons, NGAL may still be a promising marker.

A study conducted by Moniaux et al[15] showed that NGAL levels increase in the early period in pancreatic adenocarcinoma and pancreatitis. In our study, NGAL levels were significantly higher in the study group compared with the healthy control group. Moniaux et al's study[15] and our study showed that NGAL levels are significantly increased in pancreatitis. Probably due to the low number of necrotizing pancreatitis cases, we were unable to obtain a significant result in the

differentiation of mild and severe pancreatitis. However, to determine whether NGAL levels can distinguish severe from mild pancreatitis in the early period, it is necessary to design further studies with larger patient groups. If meaningful results are obtained in these studies and a cut-off value can be obtained, NGAL can contribute greatly to the management of pancreatitis.

A study by Bhatia et al[17] showed that elevated NGAL levels in AP initially protected the pancreas from oxidative stress and stimulated regeneration, but persistently high NGAL levels increased endothelial permeability and increased the risk of multiorgan failure. NGAL may be a considerable marker of pancreatitis, as demonstrated in this study. As in acute renal failure, NGAL may be a diagnostic and prognostic marker in pancreatitis.

Conclusions

In our study, we evaluated the usability of serum NGAL levels in predicting the development of necrotizing pancreatitis in the early period. We investigated the correlation of WBC, CRP, and hs-CRP levels with serum NGAL levels. In our study, serum NGAL levels were found to be higher in the study group than in the control group, but there was no statistically significant difference between the mean values of the 0^{th} and 24^{th} h NGAL values in any of the groups with or without pancreatic necrosis and the total study group. More research with larger patient groups is needed on this subject.

All authors read and approved the final version of the manuscript.

Conflict of Interest
The authors declare that they have no conflict of interests.

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None.

Informed Consent
The authors declare that the patients included in the study signed an informed consent to use their medical information for this study.

Authors' Contribution
S.D. and A.S. conceived and designed the study. S.D. and B.O. collected the data and performed the statistical analysis. A.S. and C.K. analyzed data; A.S. and O.S. drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data Availability
The data used and analyzed during this research are available from the corresponding author upon reasonable request.

Ethics Approval
This study was conducted in accordance with the Principles of the Declaration of Helsinki and was approved by the Suleyman Demirel University Faculty of Medicine Scientific Ethics Committee (Ethics approval date: 21 January 2015, Issue No.: 29).

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