

Role of increased immature granulocyte percentage in the early prediction of acute necrotizing pancreatitis

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ABSTRACT

BACKGROUND: Acute necrotizing pancreatitis (ANP) is the most severe form of acute pancreatitis (AP), and it has high mortality rates. Therefore, early diagnosis and treatment are of critical importance for the prognosis. The aim of this study was to investigate the effectiveness of immature granulocyte percentage (IG%) in the early prediction of ANP.

METHODS: This retrospective study included 96 adult patients hospitalized with a diagnosis of AP. Demographic data of the patients were recorded. The white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), IG%, C-reactive protein (CRP), and amylase levels were determined. Furthermore, computed abdominal tomography was applied to the patients, and the length of hospital stay was recorded. Patients were divided into two groups as those with acute edematous pancreatitis and ANP, according to the tomography results. The differences between the groups were analyzed statistically.

RESULTS: The WBC count, NLR, CRP, and IG% were significant markers in the prediction of ANP. However, IG% had higher values with regard to the sensitivity, specificity, AUROC, and negative and positive predictive values (100%, 95%, 0.982, 78.9%, and 100%, respectively).

CONCLUSION: An increased IG% is a simple, fast, and effective marker in the early prediction of ANP.

Keywords: Acute necrotizing pancreatitis; early prediction; immature granulocyte percentage.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease with a wide spectrum, ranging from self-limiting edematous pancreatitis to life-threatening necrotizing pancreatitis.^[1] Acute necrotizing pancreatitis (ANP) occurs in approximately 9%–20% of patients.^[2] Despite the improvements in its diagnosis and treatment in recent years, a mortality rate of 20%–30% is still observed in ANP.^[3] There is a need for aggressive supportive treatment in intensive care units for this disease. In addition, surgical treatment might be necessary in patients with a proper indication. Any delay in diagnosis and treatment leads to an increase in morbidity and mortality rates.^[4] There is need for a fast and reliable biomarker in the early diagnosis of ANP. Although various inflammation markers (C-reactive protein [CRP], procalcitonin, neutrophil-to-lymphocyte ratio [NLR])

and complex scoring systems (Ranson, Glasgow, APACHE II, and Balthazar) have been developed for this purpose, as yet there is no ideal method used in clinical routine.^[5–11]

The immature granulocyte percentage (IG%) is a new inflammation marker that is not adequately known by most clinicians.^[12] The detection of immature granulocytes in peripheral blood, which do not normally occur in healthy people, is an indicator of a bone marrow activation and severe infection.^[12,13] Due to technological advances in automated hematological analyzers, IG% can be easily and rapidly measured through a routine complete blood count (CBC).^[14] Recent studies have shown that IG% is a more effective marker in predicting the severity of infection than traditional markers such as the white blood cell (WBC) count, CRP, and NLR.^[12–16] The aim of this study was to demonstrate the role of IG%, which is

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a simple and reproducible inflammation marker, in the early prediction of ANP.

MATERIALS AND METHODS

This retrospective study was conducted on 96 adult patients hospitalized with a diagnosis of (AP) in the General Surgery Clinic of Ankara Training and Research Hospital between June 2017 and November 2018. Patients younger than 18 years and patients with a diagnosis of ANP who were referred from peripheral hospitals for the intensive care treatment were excluded from the study. Furthermore, patients who were not able to undergo contrast-enhanced abdominal computed tomography (CECT) due to a renal function disorder or other reasons were not included in the study.

Within the first 3 hours of admission to the hospital, laboratory tests of 96 patients were performed in the Emergency Department. These tests included CBC (WBC count, neutrophil count, lymphocyte count, and IG%) obtained with automated hematological analyzers and routine biochemical tests (CRP, amylase, BUN, and creatine). The NLR was calculated using the data in the CBC analysis.

The patients underwent CECT on admission. A control CECT was implemented after 48–72 hours in patients whose clinical condition deteriorated during their medical treatment. The total length of hospital stay (LHS) and length of stay in the Intensive Care Unit (ICU) was determined. All the patient data were obtained from the hospital database. The study was approved by the Local Ethics Committee of Ankara Training and Research Hospital.

The patients received a diagnosis of AP when at least two of the following three criteria were present: (1) abdominal pain specific to AP; (2) serum amylase levels at least three times higher than the normal levels; (3) characteristic findings of AP on CECT.

The patients were divided into two groups as those with acute edematous pancreatitis (AEP) and ANP according to the CECT results (in some patients, no necrosis was detected on the first CECT, but necrosis was observed on the CECT performed after 48–72 hours. These patients were included in the ANP group). Demographic data and inflammation markers (WBC, IG%, NLR, and CRP) were analyzed statistically, and the two groups were compared.

Statistical Analysis

Data were assessed using the IBM SPSS Statistics 22.0 package software (IBM Corp., Armonk, New York, USA). Descriptive statistics were stated as the number of units (n), percentage (%), mean \pm standard deviation, and median (IQR) values. The Pearson chi-squared and Fischer's exact test were used to assess categorical variables. The normal distribution

of the data belonging to numerical variables was assessed with the normality test and Q–Q graphs. In the comparison of two groups, the independent sample t-test was used for variables with normal distribution, whereas variables without normal distribution were assessed using the Mann–Whitney U test. The cases were grouped as edematous and necrotizing pancreatitis according to the CECT findings. The receiver operating characteristic (ROC) analysis was performed to determine the success of the inflammation markers (WBC, NLR, CRP, and IG%) in predicting ANP. Threshold levels were detected using the Youden index. The specificity and sensitivity values with the positive predictive and negative predictive values were calculated based on the obtained threshold levels. A p-value <0.05 was accepted as statistically significant.

RESULTS

The present study included 96 patients diagnosed with AP, comprising 55 females (57.3%) and 41 males (42.7%) with a median age 54.2 ± 16.6 years (range, 19–95 years).

The patients were divided into two groups as AEP and ANP according to the CECT results. AEP was detected in 81 of 96 patients (84.4%) and ANP in 15 (15.6%) (Table 1). Necrosis was observed on the first CECT in nine patients, and in six patients on the control CECT in the ANP group.

There was no significant difference between the AEP and ANP groups in terms of gender ($p=0.736$). The median age of the patients was statistically significantly higher in the ANP group than the AEP group ($p=0.012$) (Table 1).

Etiologically, 90 of the AP cases (93.7%) were biliary, and six cases (6.3%) were non-biliary (3 chronic alcoholism, two hyperlipidemia, and one complication of endoscopic retrograde cholangiopancreatography). Of the ANP cases, five underwent surgical treatment (necrosectomy, debridement, lavage, drainage). One patient from the ANP group died (mortality rate 6.6%), while no patients died in the AEP group.

One patient (1.2%) in the AEP group and 14 patients (93.3%) in the ANP group underwent treatment in the ICU. This difference between the two groups was statistically significant ($p<0.001$). When the two groups were compared in terms of LHS, the average LHS was 5 days in the AEP group and 18 days in the ANP group, which was statistically significant ($p<0.001$). The demographic data, etiological characteristics, and the LHS of the patients are presented in Table 1.

The mean levels of WBC, NLR, CRP, and IG% were found to be significantly higher in the ANP group than in the AEP group ($p<0.05$ for all the markers). No significant difference was detected between the AEP and ANP groups ($p=0.348$) in the serum amylase levels. The comparison of inflammation markers and amylase between the AEP and ANP groups is presented in Table 2.

Table 1. The comparison of demographic data, etiology, and the length of hospital stay between the groups

	Acute edematous pancreatitis	Acute necrotizing pancreatitis	p
Number of patients	81 (84.4%)	15 (15.6%)	
Gender			
Female	47 (85.5%)	8 (14.5%)	
Male	34 (82.9%)	7 (17.1%)	0.736
Median age (years)	52.2±15.7	63.8±18.5	0.012
Length of hospital stay (day)	5 (3)	18 (9)	<0.001
Intensive care unit (n)	1 (6.7%)	14 (93.3%)	<0.001
Etiology			
Biliary	77 (85.6%)	13 (14.4%)	0.085
Hyperlipidemia	1	1	
Alcohol	3	–	
ERCP	–	1	

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2. The comparison of inflammation markers and amylase between the groups

	Acute edematous pancreatitis	Acute necrotizing pancreatitis	p
White blood cell (µL)	11.200 (4700)	16.900 (9200)	0.001
Neutrophil-to-lymphocyte ratio	5.5 (4.3)	9.6 (20.2)	0.002
C-reactive protein (mg/L)	16 (52)	98 (150)	<0.001
Immature granulocyte percentage	0.4 (0.2)	1.6 (1.4)	<0.001
Amylase (U/L)	1194 (1421)	963 (1069)	0.348

The ROC curve was drawn to calculate the effectiveness of the inflammation markers (WBC, NLR, CRP, and IG%) in the discrimination between AEP and ANP (Fig. 1). The effective-

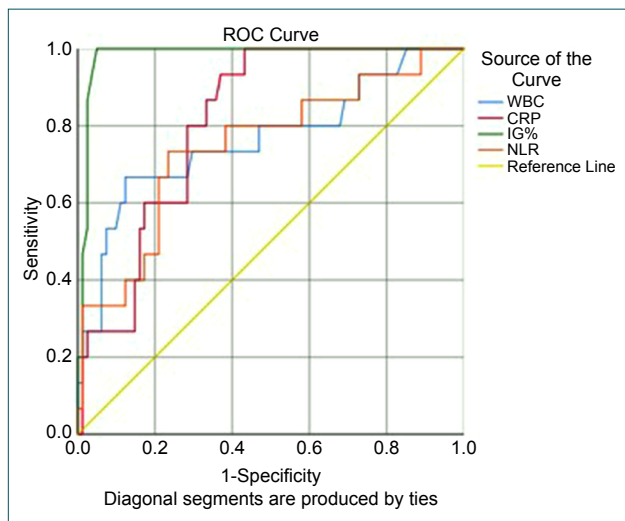


Figure 1. Receiver operating characteristic curve analysis of inflammation markers in the discrimination between acute edematous and acute necrotizing pancreatitis.

ness of all the markers in predicting ANP was statistically significant ($p < 0.05$ for all markers). However, the strength of IG% in predicting ANP was considerably higher than the others (for IG% AUROC: 0.982; sensitivity: 100%; specificity: 95%; positive predictive value [PPV]: 78.9%; negative predictive value [NPV]: 100%). The results of the ROC curve analysis are presented in Table 3.

DISCUSSION

ANP is a disease that requires long-term intensive care with a difficult and costly treatment process and a high mortality rate (20%–30%).^[1] This disease is observed in approximately 9%–20% of all AP cases.^[2] While the rate of ANP was 15.6% in this study, the mortality rate was 6.6%. The reason for such a low mortality rate may be the diagnosis using CECT and that it was possible to start the intensive care treatment early.

As the amount of necrosis increases in ANP, the rates of multiple organ failure and accordingly mortality rates also increase.^[10–17] Therefore, an early diagnosis and treatment are extremely important in this disease with respect to reducing the mortality rates and medical expenses.^[4]

Table 3. ROC analysis of Inflammation markers in the prediction of necrotizing pancreatitis

	AUROC	95%CI	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p
WBC	0.765	0.614–0.916	>15200 (µL)	66.6	87.6	50	93.4	0.001
NLR	0.747	0.603–0.892	>7.94	73.3	76.5	36.7	93.9	0.002
CRP	0.811	0.719–0.903	>19 (mg/L)	100	56.7	30	100	<0.001
IG%	0.982	0.958–1	>0.8	100	95	78.9	100	<0.001

WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; IG%: Immature granulocyte percentage; PPV: Positive predictive value; NPV: Negative predictive value; ROC: Receiver operating characteristic; AUROC: Area under ROC; CI: Confidence interval.

Serum amylase used in the diagnosis of AP increases in a few hours following the onset of symptoms and returns to the normal level in 3–5 days. Amylase levels are important for the diagnosis, but they are not effective in predicting the AP severity.^[18] There were no significant differences between the AEP and ANP groups in terms of serum amylase levels in the present study ($p=0.348$), which was consistent with previous findings in the literature.

To date, researchers have studied the inflammation markers such as NLR, procalcitonin, CRP, and CRP/albumin and scoring systems such as Ranson, Glasgow, APACHE II, and Balthazar to predict the severity and prognosis of AP.^[5–11,19,20] The Balthazar score is valuable in predicting the extent of pancreatic necrosis, while the Ranson and APACHE II scores are better at predicting multiple organ failure and other adverse outcomes.^[5,6,21] However, most of these scoring systems can only be implemented 48 hours after the first admission, and this is not early enough.

The effectiveness of traditional inflammation markers in predicting the severity of AP has also been investigated.^[5,6] The marker most frequently used for this purpose is CRP, an acute phase reactant.^[5,6] CRP is synthesized by hepatocytes as a reaction to the release of pro-inflammatory cytokines in acute inflammation and tissue damage.^[22] In a study by Schütte et al.^[5] it was reported that CRP reached a cut-off value of 150 mg/dL, the sensitivity and specificity rates of 80%, and an accuracy rate of 86% in the first 48 hours in predicting necrotizing pancreatitis. Moreover, previous studies suggested that of the markers used to predict the severity of AP and pancreatic necrosis, CRP was the reference marker.^[5,6,23,24] The present study found a cut-off value >19 mg/L, sensitivity of 100%, and specificity of 56.7% for CRP in the prediction of necrotizing pancreatitis.

The total WBC count is important in predicting the severity of AP and pancreatic necrosis, but it does not have any diagnostic value. While the number of neutrophils increases as a physiological response to inflammatory reactions in the organism, the number of lymphocytes decreases. Therefore, rather than total WBC, the ratio of these two subgroups to one another (NLR) is suggested as an inflammation marker.

^[25] In a study conducted by Azab et al.,^[26] NLR was shown to be superior to a total WBC count in predicting the severity of AP, with a cut-off value of NLR >4.7 as an indicator of severe AP. In another study, Jeon et al.^[27] showed that increasing levels of NLR indicated the severity of AP and the existence of organ failure, and subsequent changes in the NLR levels reflected therapeutic response and prognosis in severe AP. The present study found a cut-off value of NLR >7.9, sensitivity of 73.3%, and specificity of 76.5% in the prediction of pancreatic necrosis.

CECT (particularly thin-section multidetector CT scan) is the most effective method in discriminating between edematous and necrotizing pancreatitis and in the accurate diagnosis of necrosis.^[1,10,28] Necrotic pancreatic tissue is displayed as non-contrast-enhanced areas on CECT.^[28] In a study by Balthazar et al.^[10] and another study by Balthazar,^[28] it was reported that as the amount of necrosis in pancreatic tissue increased, the rates of organ failure and mortality also increased. Those studies also showed a strong correlation between morphological changes in the pancreas identified through CECT and the clinical results of patients.

In similar studies designed by Casas et al.^[29] and Taydas et al.,^[30] it was stated that CECT performed in the first 72 hours after the onset of symptoms had an important role in the management of AP and the detection of pancreatic necrosis and other complications. In another study on this topic, CECT was proposed for control purposes to patients with AP on admission and also to patients who did not have clinical recovery 48–72 hours after the admission for control.^[31] In the present study, CECT scanning was applied to all the patients on admission and to patients whose clinical condition did not improve 48–72 hours after admission. The patients were divided into two groups as the AEP and ANP according to the CT results.

In the light of the mentioned studies, it can be said that there is a need for an ideal biomarker that could be used independently in clinical practice in the early diagnosis of ANP. This ideal biomarker should be early, fast, simple, easily measurable, highly accurate, and cost-efficient. Including all these characteristics, IG% has been presented by researchers as a

new and promising inflammation marker.^[12,16] The IG% has been shown to increase even if a total WBC count and the number of absolute neutrophils are normal in the early period of severe acute infections.^[32] Moreover, the IG% also reflects the therapeutic effectiveness of treatment implemented in severe infection cases.^[12]

Lipiński et al.^[33] suggested that IG% was a better and independent biomarker in the early diagnosis of severe AP than systemic inflammatory response syndrome and the WBC count, with a cut-off value of IG% >0.6, sensitivity of 100%, specificity of 96.2%, PPV of 85.7%, and NPV of 100%.

The present study found a statistically significant difference in all the inflammation markers (WBC, NLR, CRP, and IG%) between the AEP and ANP groups (p -value 0.001, 0.002, <0.001, <0.001, respectively). However, the prediction ability of IG% in ANP was far superior to that of the other markers (for IG% AUROC: 0.982; cut-off value >0.8; sensitivity: 100%; specificity: 95%; PPV: 78.9%; NPV: 100%).

Conclusion

According to the results of this study, IG%, which can be easily measured without the need for additional time and expenses, is a more effective and reliable marker than traditional inflammation markers such as WBC, NLR, and CRP in the early prediction of ANP. An IG% value of >0.8 in routine CBC in a patient diagnosed with AP is an important and early indicator of pancreatic necrosis. This result is more important in cases in which CECT cannot be performed for any reason. It is necessary to be prepared for an aggressive supportive treatment in ICUs in such patients.

Conflict of interest: None declared.

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ORJİNAL ÇALIŞMA - ÖZET

Akut nekrotizan pankreatitin erken tahmininde artmış immatür granülosit yüzdesinin rolü

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AMAÇ: Akut nekrotizan pankreatit akut pankreatitin en şiddetli formudur ve yüksek mortalite oranlarına sahiptir. Bu yüzden bu hastalıkta erken tanı ve tedavi prognoz açısından kritik önem taşımaktadır. Bu çalışmanın amacı immatür granülosit yüzdesinin (IG%), akut nekrotizan pankreatitin erken tahminindeki etkinliğini araştırmaktır.

GEREÇ VE YÖNTEM: Bu geriye dönük çalışma akut pankreatit tanısıyla hastaneye yatırılan 96 erişkin hasta üzerinde gerçekleştirildi. Hastaların demografik verileri kaydedildi. Beyaz küre sayısı, nötrofil/lenfosit oranı, IG%, C-reaktif protein ve amilaz düzeyleri tespit edildi. Ayrıca hastalara kontrastlı bilgisayarlı abdominal tomografi incelemesi yapıldı ve hastanede kalış süreleri kaydedildi. Hastalar tomografi sonuçlarına göre akut ödematöz pankreatit ve akut nekrotizan pankreatit olarak iki gruba ayrıldı. Gruplar arasındaki farklılıklar istatistiksel olarak analiz edildi.

BULGULAR: Beyaz küre sayısı, nötrofil/lenfosit oranı, C-reaktif protein ve IG% akut nekrotizan pankreatit tahmininde anlamlı belirteçlerdi. Ancak IG%'nin duyarlılık, özgüllük, AUROC, negatif ve pozitif tahmin edici değerleri diğerlerinden daha yüksek idi (sırasıyla, %100, %95, 0.982, %78.9, %100).

TARTIŞMA: Artmış IG% akut nekrotizan pankreatitin erken tahmininde basit, hızlı ve etkili bir belirteçtir.

Anahtar sözcükler: Akut nekrotizan pankreatit; erken tahmin; immatür granülosit yüzdesi.

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