

Use of the neutrophil to lymphocyte ratio compare CRP for the early prediction of acute pancreatitis severity?

Edip Erdal Yilmaz¹, Zübeyir Bozdag², Ahmet Turkoglu², Burak Veli Ulger², Zulfu Arikanoglu², Omer Uslukaya², Yilmaz Zengin³, Enver Ay⁴, Metehan Gumus¹

¹Gazi Yasargil Education and Research Hospital Department of General Surgery, Diyarbakir, Turkey

²Dicle University, Faculty of Medicine, Department of General Surgery, Diyarbakir, Turkey

³Dicle University, Faculty of Medicine, Department of Emergency Medicine, Diyarbakir, Turkey

⁴Mardin State Hospital, General Surgery, Mardin, Turkey

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Abstract

Aim: To determine the usefulness of the neutrophil to lymphocyte ratio (NLR) as a diagnostic tool for the early detection and prediction of acute pancreatitis (AP) severity compared with that of C-reactive protein (CRP).

Material and Methods: The medical records of 464 patients hospitalized with AP between 2006 and 2014 were reviewed. The patients were classified into two groups: severe AP (SAP) and mild/moderate AP groups. Lymphocyte and neutrophil counts and CRP levels at the time of admission were noted.

Results: Out of the total number of patients (n = 464), 67 had severe AP. The median NLR was significantly higher in the SAP group (median of 11.1) than in the mild/moderate AP group (median of 6.9) (p < 0.0001). The sensitivity and specificity of NLR were 83.6% and 49.4%, respectively, with a cut-off value of 6.8 and an AUC of 0.68. CRP levels were also significantly higher in the SAP group (median of 189 mg/L) than in the mild/moderate AP group (median of 53.5 mg/L) (p < 0.0001). The sensitivity and specificity of the CRP values were 83.6% and 74.9%, respectively, with a cut-off value of 113 mg/L and an AUC of 0.83.

Conclusion: The NLR was significantly higher in patients with severe AP. However, CRP measurement was superior to NLR as an early predictor of severe disease.

Keywords: Neutrophil; Lymphocyte Count; Pancreatitis.

INTRODUCTION

Despite being a reversible inflammatory disease, acute pancreatitis (AP) can range in severity from a mild, self-limiting clinical course to a severe and life threatening condition. Although patients with mild AP have a low mortality rate, mortality in patients with severe acute pancreatitis (SAP) can be as high as 30%. Prediction of SAP early in the course of the disease is important for allowing the timely transfer of these patients to intensive care and the initiation of prompt aggressive treatment (1).

Several multifactorial scoring systems, such as APACHE II, SOFA, and Ranson parameters, have been commonly used to predict AP severity (2,3). However, the complexity of these tests and the time needed to perform them are discouraging. Thus, attempts have been made in the literature to identify simpler single predictors of AP severity (4).

C-reactive protein (CRP) and procalcitonin (PCT) are two acute-phase reaction proteins of the inflammatory process. Some studies have underscored the predictive value of PCT for identifying infectious processes, characterizing the severity of the underlying illness, and guiding therapy and risk stratification in various clinical conditions. However, there are conflicting results regarding the prognostic value of PCT (5). CRP level correlates with disease severity and has been useful in the prediction of complications in AP (6).

White blood cell (WBC) count is a well-known indicator of inflammation. The neutrophil to lymphocyte ratio (NLR), an inexpensive and readily accessible marker, has recently been proposed as a predictive marker for a number of diseases and has been investigated as an indicator of inflammatory processes in these diseases (7,8). Furthermore, NLR may also associate with AP severity.

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Corresponding Author: Edip Erdal Yilmaz, Gazi Yasargil Education and Research Hospital Department of General Surgery, Diyarbakir, Turkey, E-mail: drediperdalylimaz@gmail.com

Specifically, an increased neutrophil count together with a concomitant decrease in lymphocyte count, previously associated with severe sepsis, might also be an indicator of SAP (9-11).

The aim of this study was to examine the usefulness of NLR in predicting AP severity and to compare its diagnostic value with that of CRP for the prediction of disease severity.

MATERIAL and METHODS

Patients and collection of data

Ethics committee approval was received for this study from Institutional Ethics committee of Dicle University. Extensive demographic, clinical, laboratory, and radiologic data from consecutive AP patients admitted to our hospital from July 2006 to April 2014 were retrospectively collected. Lymphocyte and neutrophil absolute counts obtained from the complete blood count and CRP levels studied during first admission to the emergency room were noted. The period between the onset of patient complaints and admission to the hospital was also noted. Exclusion criteria included incomplete clinical or laboratory data and presence of chronic pancreatitis or cancer. We also excluded the patients who had symptoms more than 48 h before admission to hospital, in order to produce a homogeneous patient group. Of the 513 cases analyzed, 464 patients were eligible for inclusion in the study. Total and differential leukocyte counts were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). Absolute values, calculated by multiplying the total WBC count by the percentage of each type of WBC, were used in the analyses.

Diagnosis of AP

The diagnosis of AP was based on the presence of two of the following three features: characteristic acute pain (a severe, persistent abdominal pain often radiating to the back), blood amylase level at least three times higher than normal, and characteristic findings of AP on computerized tomography or transabdominal ultrasonography (13).

AP Severity

We classified patients into two groups according to the revised Atlanta Symposium Criteria: patients with SAP and those with either mild or moderate AP. SAP is based on single or multiple persistent organ failure, lasting for more than 48 h (13). Organ failure was defined as cardiovascular (systolic pressure, <90 mmHg), renal (serum creatinine, >2 mg/dL after rehydration), pulmonary insufficiency (arterial PO₂, <60 mmHg), or gastrointestinal bleeding (>500 cc/24 h) (13,14).

Statistical analysis

Statistical analysis was performed using SPSS (Version 18.0; SPSS Inc, Chicago IL). Categorical data were evaluated using the Chi-square test, and continuous and ordinal variables were evaluated with the Mann-Whitney U-test (after checking for normality using the Kolmogorov-Smirnov test). To evaluate NLR as a

predictor of SAP, receiver operating characteristic (ROC) curves were used. A P value of <0.05 was considered to be statistically significant.

RESULTS

Patients and General Characteristics

Of the 464 patients included in the study, 32 had necrosis, 23 had a pseudocyst, and 67 had organ failure (some patients had more than one pathology). Therefore, the 67 who met the criteria of organ failure were considered to have SAP. Median patient ages were similar between patients with SAP (median age, 63; range, 16–86) and those with mild/moderate AP (median age, 58; range, 16–85) ($p = 0.0841$). The etiologies of AP were biliary disorders (56.2%), idiopathy (11.4%), endoscopic retrograde cholangiopancreatographic (10.6%), alcohol (5.6%), and others (17.2%) (hyperlipidemia, drugs, postcholecystectomy, hydatid cyst, etc.). There were no differences between the two groups for the period between the onset of patient complaints and admission to the hospital ($p = 0.542$). The length of hospital stay was significantly longer for patients with SAP than for those with mild/moderate AP. The characteristics of the patients are shown in Table 1.

Table 1. Characteristics of Patients

	SAP*	Others**	p
Sex (Male/Female)	25/42	136/261	0.7283
Median Age(intervals)	63(16-86)	58(16-85)	0.0841
Etiology (n)			0.6254
Gallstones	37 (55.2%)	219(72.2%)	
Idiopathy	6 (8.9%)	47(15.5%)	
ERCP	7(10.4%)	42(13.8%)	
Alcohol	3(4.4%)	23(7.5%)	
Others	14(20.8%)	66(21.7%)	
Hospital stay (days)	15(10-124)	9(2-21)	<0.0001
Pain-to admission time	22 hours (3-48)	25 hours (8-48)	0.543

*Severe Acute Pancreatitis

**Mild and Moderate Acute Pancreatitis

NLR

Median NLR was significantly higher in SAP patients (median, 11.1; range, 1.8–47) than in mild/moderate AP patients (median, 6.9; range, 0.2–56.2) ($p < 0.0001$) (Table 2). The sensitivity and specificity of the NLR were 83.6% and 49.4%, respectively, with a cut-off value of 6.8 and an AUC of 0.68 (Figure 1).

CRP

CRP levels were also significantly higher in SAP patients (median, 189 mg/L; range, 7–327 mg/L) than in mild/moderate AP patients (median, 53.5 mg/L; range, 1–302 mg/L) ($p < 0,0001$) (Table 2). The sensitivity and specificity of the CRP were 83.6% and 74.9%, respectively, with a cut-off value of 113 mg/L and an AUC of 0.83 (Figure 1).

Table 2. Neutrophil lymphocyte ratio and C reactive protein levels in patients with SAP and others

	SAP*	Others**	p
Neutrophil lymphocyte ratio median (ranges)	11.1(1.8-47)	6.9(0.2-56.2)	<0.0001
C reactive protein (mg/L) median (ranges)	189mg/L(7-327 mg/L)	53.5 mg/L(1-302 mg/L)	<0.0001

*Severe Acute Pancreatitis
**Mild and Moderate Acute Pancreatitis

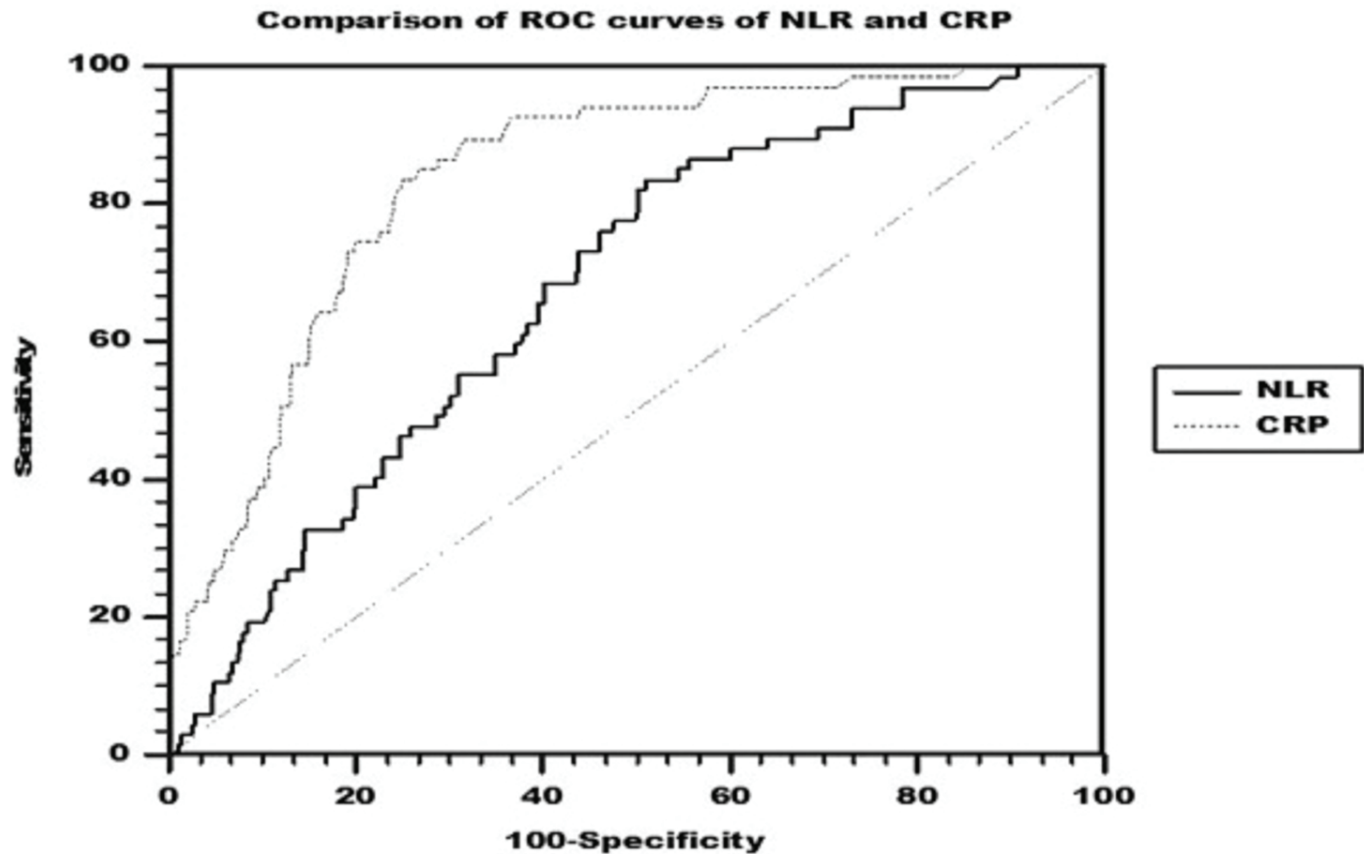


Figure 1. ROC curve of NLR versus CRP in predicting severe for acute pancreatitis

DISCUSSION

Our study found that NLR was significantly higher in patients with SAP. However, we also found that CRP was superior to NLR for predicting AP severity in ROC analysis. We found two observational studies in the literature that examined the relationship between NLR and AP severity. The first study, conducted by Azab et al., compared NLR with WBC count and reported that NLR was superior to WBC count in predicting adverse outcomes of AP (9). The primary outcomes examined in that study were the length of stay and the need for admission to the intensive care unit. They hypothesized that the predictive superiority of NLR could be attributed to alterations of the WBC count by various physiological and pathological conditions. The second study, conducted by Supiah et al., investigated the relationship between NLR and AP severity on days 0, 1, and 2 (10). They concluded that NLR could be determined as a component of the routine work-up for patients with

AP, and thus, would incur no additional costs. They also suggested that continuous NLR monitoring on each day of admission provided a dynamic reflection of the variable course of AP. However, continuous monitoring of CRP in patients with AP is also a common practice, and because CRP is a superior predictor AP severity, one must ask if NLR monitoring provides any extra advantage, particularly considering that the predictive value of CRP increases in days following admission (15,16). However, NLR monitoring may be useful in a secondary care hospital where CRP measurement is unavailable.

WBC and neutrophil counts are commonly used as primary indicators of the inflammatory response, and they both increase in AP correlating with disease severity (9). Neutrophil predominance is also observed in bacterial infections characterized by leukocytosis. Because neutrophil predominance is a sign of bacterial attack, it may be a precursor to severe disease (17). Bacterial infection

is a major determinant of organ failure in patients with acute necrotizing pancreatitis (18). Peripheral lymphocyte count has also been suggested to be a predictor of subsequent infection risk. Several possible mechanisms have been implicated in decreasing lymphocytes by apoptosis. One possible mechanism is the direct effect of endotoxins on T lymphocytes. Another hypothesis is that those lymphocytes that have undergone apoptosis are immediately removed from systemic circulation by the reticuloendothelial system (19).

CRP, an acute-phase protein known to be a non-specific sensitive indicator of an inflammatory response and bacterial infection, is useful in determining AP severity (20). Zrnic et al. found that CRP levels correlate with AP severity and were useful in preventing complications (21). CRP levels during the initial 48 h of symptom onset have a sensitivity and specificity of 80%–86% and 61%–84%, respectively (22).

Mäkelä et al. found that a CRP value over 150 mg/L was an independent predictor of admission to the intensive care unit and of mortality (23). They stated that although there was a 24 to 48 h delay before notable increases in CRP (limiting its utility as an early predictor), it was still a useful predictor of AP severity. In our study, the sensitivity and specificity of CRP were compatible with those reported in the literature. However, we found a cut-off value of >113 mg/L, which was less than that in the literature, likely because we considered the CRP levels at first admission (within 48 h of symptom onset).

Another important issue is how to determine the best cut-off value of NLR for the prediction of AP severity. Azab et al. suggested a cut-off value of >4.7 (9), whereas Supiah et al. found a cut-off value of >10.6 on day 0, >8.1 on day 1, and >4.8 on day 2 (10). Gürol et al. suggested a cut-off value of >5 in cases of bacteremia or sepsis (24). Xiao et al. reported that an NLR value of $\geq 3-5$ g/ml could be a useful predictor of the prognosis of patients with hepatocellular carcinoma after liver transplantation (25). We compared the NLR levels on admission and found an optimal cut-off value of 6.8 for the prediction of SAP.

LIMITATIONS

Despite having a large number of patients, our study was designed as a retrospective, cohort study. Although detailed records were kept over the last 7 years, we were compelled to eliminate some patients when we could not get all the necessary data. The values of NLR in the days following patient admission were not evaluated in our study. In addition, our patients were mostly inhabitants of southeast Turkey, in whom the most common cause of AP is gallstones.

CONCLUSION

NLR was significantly higher in patients with SAP. However, CRP was superior to NLR for the early prediction of severe disease. CRP is an easily accessible and useful parameter that is commonly employed in daily use.

Because calculating NLR requires slightly more effort than calculating CRP, NLR does not provide an advantage when CRP is available.

Competing interests: The authors declare that they have no competing interest.

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