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Novel markers for mortality in patients with acute pancreatitis: NLR and PLR at the 48th hour

Akut pankreatitli hastalarda mortalite göstergesi olarak yeni belirteçler: 48. saat NLR ve PLR

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Abstract

Aims: In recent years, simple, effective, and rapid laboratory markers have become important to predict acute pancreatitis prognosis. In this study, we aimed to demonstrate whether there was a difference in predicting AP-related mortality between current scores and indirect markers of systemic inflammation, namely, red cell distribution width (RDW), mean platelet volume (MPV), platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) obtained at the 48th hour.

Methods: We retrospectively reviewed files of AP patients admitted to Gastroenterology Department of two hospitals to include the acute phase reactant values of 667 patients obtained at the 48th hour. CRP_0 indicates CRP value at presentation while CRP, RDW, MPV, NLR and PLR indicate values at the 48th hour. In all patients, Ranson score, Atlanta score, NLR and PLR values were calculated.

Results: The patients were classified into 2 groups as survivors (n=641; 96.1%) and non-survivors (n=26; 3.9%). Both NLR and PLR were found to be significantly higher in the non-survivor group (P<0.001 and P=0.02). Both NLR and PLR were weakly and positively correlated to mortality.

Conclusion: Based on our results, MPV was not correlated with mortality, while RDW was weakly and positively correlated. However, we found that NLR and PLR values obtained at the 48th hour after presentation are effective parameters in predicting mortality in AP. These easily accessible and low-cost tests may be used for closer monitoring of these patients when necessary.

Keywords: Acute pancreatitis, NLR, PLR, Atlanta score

Öz

Amaç: Son yıllarda akut pankreatit prognozunu öngörmede basit, etkili ve hızlı laboratuvar belirteçleri önem kazanmıştır. Bu çalışmada, mevcut skorlarla sistemik inflamasyonun dolaylı belirteçleri arasında AP ile ilişkili mortalite tahmininde bir fark olup olmadığını ortaya koymak amaçlandı (48. saatte RDW, MPV, PLR ve NLR).

Yöntemler: Bu çalışmada, Gastroenteroloji Bölümü'ne başvuran Akut pankreatitli hastaların dosyaları geriye dönük olarak incelendi. Genel olarak, 667 hastanın verileri dahil edildi. 48. saatte akut faz reaktan değerleri çalışmaya alındı. CRPo başvuru sırasındaki CRP'yi gösterirken CRP, RDW, MPV, NLR ve PLR 48. saatte değerleri gösterir. Tüm hastalarda Ranson skoru, Atlanta skoru, NLR ve PLR değerleri hesaplandı.

Bulgular: Hastalar sağ kalanlar (n=641; %96,1) ve ölenler (n=26; %3,9) olarak 2 gruba ayrıldı. Hem NLR hem de PLR, hayatta kalan grupta anlamlı olarak yüksek bulundu (sırasıyla P<0,001 ve P=0,02). NLR ile mortalite arasında zayıf, pozitif bir korelasyon vardı. Yine PLR ile mortalite arasında zayıf ve pozitif bir korelasyon vardı.

Sonuç: Çalışmamızda MPV değeri ile mortalite arasında ilişki saptanmazken, RDW ile mortalite arasında zayıf-pozitif bir ilişki olduğu görüldü. Başvurunun 48. Saatinde elde edilen NLR ve PLR değerlerinin mortaliteyi gösteren etkili parametreler olduğunu saptadık. Bu ulaşılması kolay ve düşük maliyetli testler, gerektiğinde hastaları daha yakından takip etmek amacıyla kullanılabilir.

Anahtar kelimeler: Akut pankreatit, NLR, PLR, Atlanta skoru

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Introduction

One of the most common disorders of gastrointestinal system, acute pancreatitis (AP) is an acute, inflammatory process of the pancreas with significant variability in clinical presentation and severity. The inflammation may cause local damage within the pancreas, release several cytokines, result in systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). In most cases, the disease has a mild course and good prognosis; however, 15 - 20% of patients present with severe AP with high morbidity and mortality rates [1]. Despite advances in the diagnosis and management, AP remains to be an important cause of in-hospital mortality and increased overall costs [2]. The AP-related early mortality generally occurs due to MODS caused by SIRS within the first 2 weeks while almost one-half of patients die due to peripancreatic necrosis, infection, or secondary MODS after 2 weeks [1]. Thus, it is crucial to identify patients with potentially severe AP and establish management plans accordingly. Today, several scoring systems have been proposed to assess and classify the severity of AP [3].

In the recent years, simple, effective, and rapid laboratory markers have become important to predict AP prognosis. These markers rely on inexpensive laboratory tests such as neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW), mean platelet volume (MPV) and platelet-lymphocyte ratio (PLR), which are direct or combined markers of systemic inflammation. The elevation of NLR within the first 48 hours of admission is considered a negative prognostic marker and associated with severe AP [4]. Previous studies have shown that NLR may predict AP severity in patients with hypertriglyceridemia and biliary pancreatitis [5]. In a recent study, it was found that NLR and PLR were effective in predicting both AP severity and mortality [1].

In this study, it was aimed to demonstrate whether there was a difference in predicting AP-related mortality between current scores (e.g. Atlanta score, Ranson score, CRP at presentation, CRP at the 48th hour) and indirect markers of systemic inflammation (PLT, MPV, PLR and NLR at the 48th hour).

Materials and methods

In this study, we retrospectively reviewed files of AP patients admitted to the Gastroenterology Clinic of Mersin City Hospital between March 2016 and August 2019 and the Gastroenterology Clinic of Aksaray Teaching and Research Hospital between June 2017 and September 2019. Among 824 patients, 157 patients were excluded due to incomplete data. Overall, data from 667 patients were included.

AP diagnosis was made in the presence of two of following three criteria: i) abdominal pain compatible with disease; ii) serum amylase and/or lipase levels greater than three times the upper limit of normal range, and iii) characteristic findings in abdominal imaging studies [6]. Demographic characteristics were examined in all included patients. Clinical (blood pressure, respiration rate, heart rate) and laboratory parameters (white blood cell count, neutrophil count, lymphocyte count, hemoglobin level, platelet count, RDW, MPV, hematocrit, liver and kidney function tests, electrolyte, arterial blood gases) were assessed and recorded in all patients. As CRP values obtained at the 48th hour were found to be correlated with disease severity in previous studies, we included acute phase reactant values at the 48th hour [7]. CRP_0 indicates CRP at presentation while CRP, RDW, MPV, NLR and PLR indicate values obtained at the 48th hour of presentation. In all patients, Ranson score, Atlanta score, NLR and PLR values were calculated [8, 9].

The revised Atlanta score is a parameter that indicates the severity of the disease, according to which the patients were classified into 3 groups as mild AP (MAP), moderate AP (MSAP) and severe AP (SAP). MAP was defined as disease with no-organ failure and no local or systemic complications. MSAP was defined with the presence of local or systemic complications and/or temporary organ failure which resolved within 48 hours. SAP was defined as disease with persistent organ failure (>48 hours) [9].

We evaluated whether there were significant differences between Ranson score, Atlanta score, RDW, MPV, CRP, NLR and PLR values of survivors and non-survivors. Correlation and ROC curve analyses were performed upon detection of a significant difference.

Statistical analysis

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows version 20 (IBM SPSS Inc., Chicago, USA). The data distribution was assessed by Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation while continuous variables with skewed distribution were presented as median (min-max). The categorical variables were presented as percentages. For inter-group comparisons, categorical variables were assessed using Chi-square test while continuous variables with normal distribution were assessed with the t test. Continuous variables with abnormal distribution were evaluated with the Mann Whitney test. Spearman's correlation analysis was used to assess correlation among data. The Receiver Operator Characteristics (ROC) analysis was performed and Area under Curve (AUC) was compared to determine the predictive values of NLR, PLR, RDW, CRP and AP severity scores. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated based on cut-off values. A two-sided p value was used. A p-value <0.05 was considered as statistically significant.

Ethical approval

This study was approved by the Local Ethics Committee and conducted in accordance with the Helsinki Declaration.

Results

Overall, 667 patients were included to the study, and classified into 2 groups as survivors (n=641; 96.1%) and non-survivors (n=26; 3.9%). Table 1 presents the demographic characteristics of the two groups. Among 641 survivors, 211 (32.9%) were male and 430 (67.1%) were female, with an overall mean age of 54.64 years. 26 non-survivors comprised 10 (38.4%) males and 16 (61.6%) females with an overall mean age of 77.88 years. There was no significant difference in gender distribution between groups (P=0.55). Mean age was significantly higher among non-survivors when compared to

survivors (*P*<0.001). A weak positive correlation was detected between age and mortality (rs=0.23; *P*<0.001).

In the etiology of AP, biliary causes were most common reason detected in 473 patients (70.9%), followed by idiopathic AP in 102 patients (15.2%) (Table 2).

Table 2 presents the distribution of AP severity scores according to groups. Atlanta score determined that mortality increased with the severity of the disease (*P*<0.001). There was a significant difference in Ranson scores between survivor and non-survivor groups (1.37 vs. 2.65; *P*<0.001). Both Atlanta and Ranson scores were significantly higher in the non-survivor group. A weak, positive correlation was detected between Ranson scores and mortality (rs=0.20; *P*<0.001).

Table 3 presents the distribution of laboratory parameters according to groups. No significant difference was detected in CRP_0 values (*P*=0.631) while there was significant difference in CRP values obtained at the 48^{th} hour between groups (*P*<0.001). A weak, positive correlation was detected between CRP and mortality (rs=0.16; *P*<0.001).

There were no significant differences in PLT and MPV values between the survivor and non-survivor groups (*P=0.054* and *P=0.126*, respectively). A significant difference was detected in RDW values between groups (*P*=0.006). A weak, positive correlation was found between RDW and mortality (rs=0.11; *P*=0.01).

Both NLR and PLR were found to be significantly higher in the non-survivor group (*P*<0.001; and *P*=0.02, respectively), and weakly but positively correlated with mortality (rs=0.19, 0.19; *P*<0.001, *P*<0.001, respectively).

The ROC analysis was performed and AUCs were compared to assess the predictive values of NLR, PLR, RDW, CRP and AP severity scores (Figure 1). The AUC values for NLR, Atlanta score, Ranson score, CRP, RDW and PLR were found as 0.79, 0.88, 0.80, 0.72, 0.68 and 0.68, respectively. The Atlanta and Ranson scores had the highest predictive values for mortality (AUC: 88% and 80%, respectively). The cut-off value for NLR was calculated as 12 with a sensitivity of 64% and a specificity of 80% (AUC: 0.79; *P*<0.001). The cut-off value for PLR was 352 with a sensitivity of 52% and a specificity of 87% (AUC: 0.68; *P*=0.002).

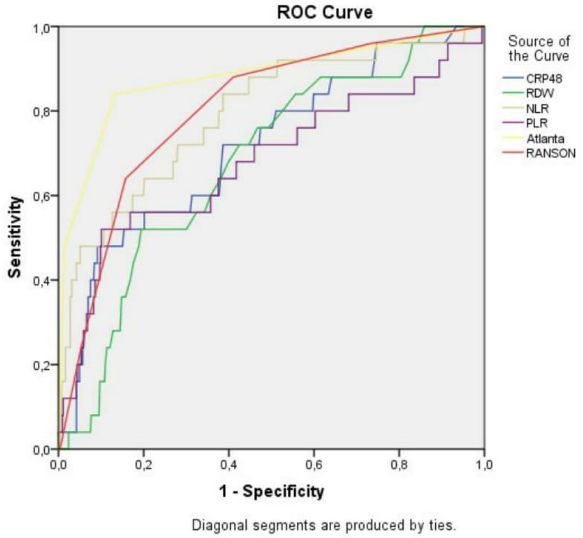

Figure 1: ROC analyse for NLR, Ranson score, Atlanta score, CRP48, PLR and RDW. NLR AUC: 0.79, Ranson Score AUC: 0.80, Atlanta Score AUC: 0.88, CRP48 AUC: 0.71, PLR AUC: 0.68, RDW AUC: 0.67

Table 1: Demographic findings of groups

Groups	Survivors (n=641)	Non-survivors (n=26)	*P*-value
Age (year)	54.64	77.88	<0.05
Gender (M/F)	211/430	10/16	>0.05

M: Male, F: Female

Table 2: Etiology of acute pancreatitis and distribution of severity scores by groups

Etiology	Survivors (n=641)	Non-survivors (n=26)	*P*-value *
Biliary	451	22	N/A
Hypertriglyceridemia	37	0	
Alcohol	32	0	
İdiopathic	99	3	
Others	48	1	
Severity scores			
Atlanta score			
MAP	502	0	<0.001
MSAP	91	3	
SAP	48	23	
Ranson score			
0-3	473	0	<0.001
4-6	101	5	
≥7	67	21	

N/A: Not applicable, * Mann-Whitney u test

Table 3: Laboratory values of groups

	Survivors (n=641)	Non-survivors (n=26)	*P*-value *
Glucose (mg/dl)	151.4	155.2	0.759
Creatinine (mg/dl)	0.88	1.42	0.007
ALT (U/L)	171.4	116.8	0.24
AST (U/L)	188.14	349.5	0.001
LDH	379.3	515.4	0.006
WBC (µL)	12143	16411	<0.001
Hgb	13.0	12.7	0.567
Platelet (µL)	257730	233720	0.138
CRPo (mg/L)	4.14	6.28	0.631
CRP (mg/L)	16.8	44.4	<0.001*
MPV (fl)	8.5	9.0	0.226*
RDW (%)	15.6	16.3	0.006
Neutrophile (µL)	9514	13991	<0.001
Lymphocyte (µL)	1700	1194	0.006
NLR	8.0	19.7	<0.001*
PLR	196.8	342.3	0.02
ALP (u/L)	156	157	0.983
GGT (u/L)	264	209	0.337
Albumin (g/L)	4.5	3.6	0.733
T. bilirubin (mg/dL)	2.1	3.2	0.675
Calcium (mg/dL)	9.0	8.8	0.361
Ranson score	1.37	2.65	<0.001*

* Mann-Whitney u test, MPV: mean platelet volume, RDW: red cell distribution width, PLR: platelet to lymphocyte ratio, NLR: neutrophile to lymphocyte ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gama glutamyl transferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CRP: c-reactive protein, WBC: white blood cell

Discussion

Our study showed that mortality increased with increasing NLR, PLR, Atlanta and Ranson scores. Significant differences in CRP, NLR, PLR, Atlanta and Ranson scores were observed between patient groups. Atlanta and Ranson scores, NLR, PLR, CRP and RDW values all positively correlated with mortality. ROC analyses showed that the Atlanta scoring system had highest AUC value for prediction of mortality in AP, followed by the Ranson score. NLR, CRP, PLR and RDW values showed a weak, positive correlation with mortality while RDW had the lowest AUC value. Our findings were generally consistent with the previous studies in the literature; however, AUC for RDW was found to be lower than those in previous studies [1]. In the United States, acute pancreatitis is the most common diagnosis at discharge among gastrointestinal system disorders and associated with a major burden. It has an annual cost of about 2.6 billion dollars for healthcare system [10]. The mortality rate is about 1% among all AP cases while it may reach 20-30% in severe disease [11]. There is no single prognostic index for assessment of severity in AP; disease severity and mortality are generally evaluated using clinical data, imaging studies and biochemical parameters [12]. In AP, early mortality occurs due to SIRS, resulting in MODS, while delayed mortality is generally due to sepsis and its complications [13]. Therefore, it

is important to diagnose and treat the disease early, perform accurate risk assessment for stratification into high or low risk categories, and to admit patients with organ dysfunction to the intensive or intermediate care units [14].

It is well-known that inflammatory markers can be used for prognostication in many diseases including cancer [15, 16]. NLR was introduced as a simple parameter that can assess systemic inflammation and stress in critically ill patients. Wang et al. [17] showed that NLR has a high discrimination capacity for acute pancreatitis caused by severe hypertriglyceridemia. In a study by Jeon and Park, it was shown that elevated baseline NLR was associated with SAP and organ failure [18]. In a study on 359 patients, Li et al. [19] concluded that NLR had the highest AUC value when compared to RDW, CRP, lymphocyte-monocyte ratio and prognostic nutrition index. Ilhan et al. [20] compared 30 patients with pregnancy-induced AP with 30 healthy pregnant women to show that NLR was significantly increased in AP group but PLR did not change when compared to controls. Azab et al. [21] reported that NLR was superior than WBC in prediction of ICU presentation and longer hospital stay. They reported that the cut-off value was around 4.7.

A recent study proposed that NLR-PLR combination could be an effective marker for prediction of AP severity and prognosis [22]. In our study, it was found that both NLR and PLR were associated with mortality. This finding is compatible with studies indicating a correlation between AP severity, NLR and PLR. However, our findings are inconsistent with the study by İlhan et al. [20] regarding the correlation between PLR and mortality.

In ROC analysis, AUC value was calculated as 0.88 for Atlanta score, 0.78 for Ranson score, 0.77 for NLR and 0.68 for RDW. The sensitivity and specificity of the predictive value of NLR for mortality were calculated as 64% and 80%, respectively, at a cut-off value of >12. The cut-off value for PLR was calculated as 325 with 52% sensitivity and 87% specificity. In our study, it was concluded that NLR and PLR values at the 48th hour are significant markers for prediction of mortality in patients with AP.

CRP and Ranson scores were correlated with mortality in our study. This finding is consistent with the findings of one of the studies conducted by Başak et al. [23].

Limitations

Lack of comparison with NLR and PLR values obtained at the 24th hour may be the limitation of our study.

Conclusion

Morbidity and mortality are closely related with disease severity in AP. It is highly important to predict patients likely to develop severe disease. Thus, rather than complex scoring systems, simple markers can be helpful to determine disease severity in early periods. We believe that NLR and PLR values obtained at the 48th hour can be useful for predicting mortality in AP. Further and larger studies are needed to calculate standardized cut-off values. The addition of NLR and PLR values into hemogram results will facilitate use of these parameters by clinicians.

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