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The Utility of the Novel Hematologic Parameters for Predicting in Hospital Mortality in Patients with Acute Mesenteric İschemia

Akut Mezenter İskemili Hastalarda Hastane İçi Mortaliteyi Öngörmede Yeni Hematolojik Parametrelerin Kullanımı

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ABSTRACT

Objective: Acute mesenteric ischemia (AMI) is recognized as a vascular emergency, having high mortality and requiring rapid and efficient and treatment. In this study, we aimed to assess the levels of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in patients with AMI and to search for a relationship between the NLR and PLR values and inhospital mortality of patients with AMI.

Methods: In total, one hundred and twenty three patients (67 AMI+ and 56 AMI-) were included in this retrospective study. Sixty seven patients diagnosed as having AMI following computed tomography angiography after presenting to the emergency room were included in AMI (+) group. "Receiver Operating Characteristic" analysis was done to determine the optimal NLR and PLR thresholds in diagnosis and inhospital mortality of AMI. Also, univariate and multivariate analyses were made to evaluate the complete blood count parameters affecting the outcomes of patients with AMI.

Results: It was found that AMI+ patients had higher neutrophil count than AMI- patients, while the lymphocyte count was significantly lower (p<0.001 p<0.001, respectively). The NLR and PLR values were significantly higher in AMI+patients than in AMI–patients (p<0.001, p<0.001, respectively). In the multiple logistic regression analysis, only NLR and red cell distribution width were identified as independent predictors of inhospital

ÖZ

Amaç: Akut mezenter iskemi, hızlı ve etkin olarak tedavi edilmesi gereken mortalitesi yüksek acil vasküler bir hastalık olarak bilinmektedir. Biz bu çalışmamızda, akut mezenterik iskemili (AMİ) hastalarda nötrofil/lenfosit oranını (NLO) ve platelet/lenfosit oranını (PLO) değerlendirmeyi ve AMI'lı hastaların hastane içi ölüm oranı ile NLO ve PLO değerlerini karşılaştırmayı amaçladık.

Yöntemler: Bu retrospektif çalışmaya toplam 123 hasta (67 AMİ+ ve 56 AMI-) alındı. Acil servise başvuran bilgisayarlı tomografi anjiyografi ile AMİ tanısı konulan 67 hasta AMİ (+) grubuna dahil edildi. AMİ'nın tanısı ve hastane içi ölüm oranını öngördüren optimal NLO ve PLO eşik değerlerini belirlemek için "Receiver Operating Characteristic" analizi yapıldı. Aynı zamanda, AMI'lı hastaların sonuçlarını etkileyen tam kan sayımı parametrelerini değerlendirmek için, univaryant ve multivaryant analizler yapıldı.

Bulgular: Lenfosit sayısı AMİ (+) hastalarda AMİ (-) hastalara göre anlamlı olarak daha düşükken, nötrofil sayısı AMİ (+) hastalarda daha yüksek bulundu (p<0,001, p<0,001, sırasıyla). NLO ve PLO değerleri AMİ (+) hastalarda AMİ (-) hastalara göre anlamlı olarak daha yüksekti (p<0,001, p<0,001, sırasıyla). Multivaryant lojistik regresyon anaIizinde, NLO ve RDW AMİ'lı hastaların hastane içi ölüm oranının bağımsız öngördürücüsü olarak saptandı. [Odds oranı (OR)=1,171, %95 güvenlik aralığı (GA)=1,020-1,345, p=0,026; OR=1,474, %95 GA=1,028-2,113, p=0,035,

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mortality of patients with AMI [Odds ratio (OR)=1.171, 95% confidence interval (CI)=1.020-1.345, p=0.026; OR=1.474, 95% CI=1.028-2.113, p=0.035, respectively]. Although PLR failed to predict inhospital mortality in AMI+ subjects (area under the curve (AUC=0.597, 95% CI=0.459-0.734, p<0.178), NLR level greater than 10.1, measured on admission, predicted inhospital mortality in AMI+ subjects (AUC=0.698, 95% CI=0.570-0.827, p<0.006).

Conclusion: Neutrophil-to-lymphocyte ratio is a reliable predictive marker in hospital mortality in patients with AMI.

Keywords: Neutrophil to lymphocyte ratio, acute mesenteric ischemia, mortality

sırasıyla]. AMİ (+) olgularda hastane içi ölüm oranını öngörmede PLO yetersiz olmasına rağmen (eğri altı alan (EAA=0,597, %95 GA=0,459-0,734, p<0,178), hastaneye kabulde ölçülen 10,1 ve üzerindeki NLO değerleri AMİ (+) olgularda hastane içi ölüm oranını öngörmeyi başardı (EAA 0,698, %95 GA=0,570-0,827, p<0,006).

Sonuç: Nötrofil lenfosit oranı, AMİ'lı hastaların hastane içi ölüm oranını saptamada güvenilir öngördürücü bir belirteçdir.

Anahtar Sözcükler: Nötrofil lenfosit oranı, akut mezenterik iskemi, ölüm oranı

Introduction

Although acute mesenteric ischemia (AMI) accounts only 1% of all hospitalizations with acute abdomen, this rate may increase up to 10% in patients over 70 years of age (1). Primary AMI is a vascular disease and can be classified by etiologies as follows: Mesenteric arterial embolism, mesenteric arterial thrombosis, mesenteric venous thrombosis, and non-occlusive mesenteric arterial ischemia (2). Predisposing risk factors are as follows: Atrial fibrillation, heart failure, coronary heart disease, arterial hypertension, severe valvular cardiac disease and peripheral arterial occlusion (3). In contrast with its low incidence, mesenteric ischemia may be associated with very high mortality rates up to 40-70% (4). Major factors responsible for high mortality include late presentation, absence of simple and reliable biochemical parameters and experienced radiologists, and late diagnosis (5). In contrast with other conditions with abdominal pain of acute onset, AMI is more likely to result in the development of irreversible complications (6). Early diagnosis is of utmost importance for reducing the mortality rate in AMI. Although computed tomography (CT) angiography is considered the gold standard imaging modality in early diagnosis, currently no standard biochemical parameters exist that can be used for routine diagnosis of this condition. Laboratory investigations frequently demonstrate leukocytosis, metabolic acidosis, an elevated D-dimer and elevated serum lactate (7-9). Laboratory studies are non-specific; while abnormal laboratory values may be helpful in bolstering suspicion for AMI, normal laboratory values do not exclude AMI.

Detection of embolic or thrombotic arterial occlusion of the superior mesenteric artery (SMA) in 70 to 80% of patients diagnosed as having AMI after presentation at emergency room has fueled an interest in the use of novel hematological parameters in complete blood count (CBC) including NLR and PLR that indicate the inflammatory and thrombotic status (4,10-13). Although several studies suggested that high NLR and platelet to lymphocyte (PLR) may represent significant markers for early diagnosis of AMI, currently no data exists on the use of NLR and PLR in predicting inhospital mortality in AMI. The aim of this article is to search: (i) whether there exists an association between novel hematologic parameters (NLR, PLR) and AMI; (ii) whether elevated NLR and PLR counts are associated with mortality following AMI.

Methods

Study Design and Setting

In this retrospective study investigating novel CBC parameters that may have a predictive value in AMI mortality, a total of 67 patients diagnosed as having AMI following CT angiography after presenting to the emergency unit of our institute between 2010 and 2014 were included in AMI (+) group . The study was approved by the Local Ethics Committee.

Selection of Participants

A total of 56 age- and gender-matched individuals presenting with abdominal pain but without detection of AMI in CT angiography comprised the AMI (-) group. Patients with active infection, systemic inflammatory conditions, malignancy, advanced hepatic failure, renal failure, thyroid disease, use of corticosteroid or anti-inflammatory medications, and hematological conditions were excluded.

Baseline Measurements

Prior to the initiation of any medical treatments, venous blood samples were drawn from the antecubital vein and were collected in ethylene diamine tetraacetic acid containing tubes. Automatic blood counter (CELL-DYN Ruby, Abbott Diagnostics, Abbott Park, IL, USA) was used for whole blood count. NLR and PLR were calculated as the ratio of the neutrophils and platelets to lymphocytes, respectively, both obtained from the same automated blood samples that were taken at the time of admission to the study. CRP was measured using Cobas c501 analyzer (Roche Diagnostics, Indianapolis, IN).

Statistical Analysis

Descriptive statistics included mean, standard deviation, minimum, maximum, and median, while categorical variables were expressed as number and percent. Independent group comparisons were performed using Student t-test for variables with normal distribution and using Mann-Whitney U test in the

absence of normal distribution. Percent comparisons between independent groups were performed with chi-square analysis. Risk factors were analyzed using the logistic regression analysis. ROC curve analysis was used to detect the predictive value of PLR and NLR for AMI mortality. The sensitivity, specificity, and positive and negative predictive value (PPV and NPV) were calculated using different cut-off values. P values less than 0.05 were considered significant, and the confidence interval (CI) was 95%. The statistical analyses were performed using SPSS, version 17 (SPSS, Chicago, Illinois, USA).

Results

Our study included a total of 123 subjects, 67 AMI (+) and 56 AMI (-) patients. All participants presented to the emergency room with abdominal pain. The baseline demographic characteristics and laboratory parameters of patients are shown in Table 1. There were no significant differences between the two groups in terms of age, gender, hemoglobin, platelet, and red cell distribution width (RDW). AMI+ patients had higher neutrophil count than AMI- patients, while the lymphocyte count was significantly lower (p<0.001 ve p<0.001, respectively). NLR was significantly higher in AMI+ patients than in AMI- patients (p<0.001) (Figure 1a). Platelet levels were not found to be significantly different between the groups (p=0.111). However, PLR was statistically higher in AMI+ subjects than in AMI- subjects (p<0.001) (Figure 1b). There was positive correlation between NLR and CRP (r=0.544, p<0.001), and between PLR and CRP (r=0.525, p<0.001).

Of AMI+ patients, 43% had atrial fibrilation (AF) rhythm. A lesion with ≥70% narrowing was present in superior mesenteric artery (SMA) and inferior mesenteric artery (IMA) in 88% and 12% of the patients, respectively. The inhospital mortality rate was 48%. Atrial fibrillation and mortality rates did not differ significantly between patients with SMA or IMA. Univariate logistic regression analysis showed significantly higher mean PLT and PLR values in patients with AF than in patients with sinus rhythm among those with AMI+ (p<0.001, p=0.010, respectively). In the multivariate logistic regression model NLR and RDW emerged as the most significant factors [Odds ratio (OR)=1.171, 95% confidence interval (CI)=0.020-1.345, p=0.026, OR=1.474, 95% CI=1.028-2.113, p=0.035, respectively) that predict mortality.

For determination of the best "cut-off" values of NLR and PLR in predicting the inhospital mortality among AMI+ patients, a receiver operating curve (ROC) characteristics analysis was performed. The analysis of PLR failed to determine such cut-off values for predicting inhospital mortality (AUC value of 0.597,

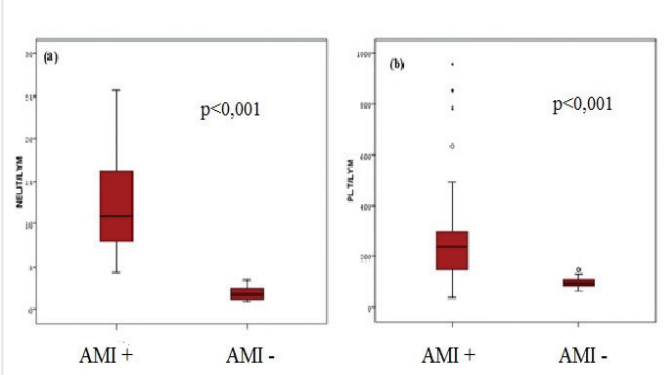


Figure 1. NLR and PLR values in diagnosis of AMI. NLR values in AMI + and AMI - groups (a), PLR values in AMI + and AMI - group (b), AMI; acute mesenteric ischemia, NLR; neutrophil/lymphocyte ratio, PLR; platelet/lymphocyte ratio

Table 1. Demographic and clinical characteristics of study population

Variable	AMI (n=67)	Control (n=56)	p value
Age (mean ± SD)	67±16	62±9	0.61
Men, n (%)	28(42)	24 (43)	0.92
Atrial fibrillation, n (%)	29 (43)	22 (40)	0.86
Diabetes mellitus, n (%)	39 (58)	31 (56)	0.27
Hypertension, n (%)	55 (82)	45 (80)	0.21
Coronary artery disease, n(%)	40 (59)	34 (60)	0.56
Cerebrovascular disease, n (%)	12 (18)	9 (16)	0.8
White blood cell count, ×10⁹/L	16.3±3.5	7.7±1.9	<0.001
Neutrophils, ×10⁹/L	13.8±3.4	4.7±1.5	<0.001
Lymphocytes (ч L)	2.8±1.2	2.6±0.6	<0.001
Hemoglobin (g/dL)	12.9±2.4	13.2±2.4	0.82
Platelet count, ×10³ µL	300±110	259±61	0.111
Red cell distribution width (%)	17.2±16.5	16±14.3	0.415
Mean platelet volume (fL)	8.9±1.7	7.5±1.9	<0.001
Neutrophil/lymphocyte ratio	12.5±5.8	1.9±0.8	<0.001
Platelet/lymphocyte ratio	269±189	99±20.6	<0.001

AMI: Acute mesenteric ischemia, SD: Standard deviasion

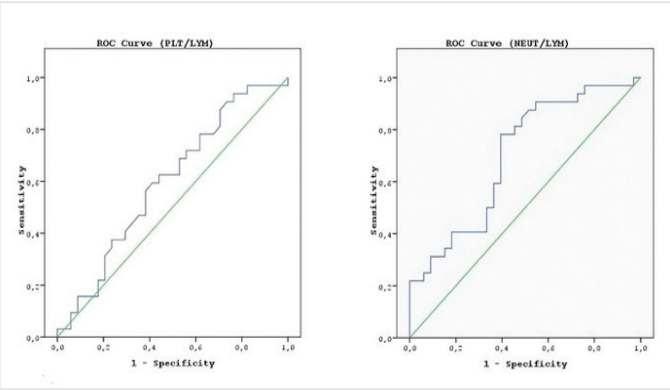


Figure 2. Comparison of receiver-operating characteristic analysis of NLR and PLR in prediction of AMI mortality. AMI; acute mesenteric ischemia, NLR; neutrophil/lymphocyte ratio, PLR; platelet/lymphocyte ratio

95% CI=0.459-0.734, p<0.178). A NLR level greater than 10.1, measured on admission, yielded an area under the curve (AUC) value of 0.698 (95% CI=0.570-0.827, sensitivity 78%, specificity 61%, p<0.006) (Figure 2a, 2b).

Discussion

Our study showed that NLR and PLR levels increased in AMI+ patients. In addition, increased NLR levels, not PLR, predicted inhospital mortality in patients with AMI.

Despite the advances in diagnostic and imaging modalities, mortality rates in AMI remain high, partly due to the failure to consider AMI in differential diagnosis, use of unnecessary diagnostic procedures leading to diagnostic delay, as well as due to the fact that at the time AMI is diagnosed, it is generally too late to administer appropriate treatment (14). Etiology of AMI includes embolic or thrombotic arterial occlusion in 60 to 70% of the cases, non-occlusive ischemia or infarction in 20 to 30%, and mesenteric venous thrombosis in 5 to 10%. SMA is involved in 85% of the cases with embolic or thrombotic arterial occlusion (10). Acute and complete cessation of intestinal blood flow leads to perfusion abnormality in the intestinal wall, resulting in the initiation of a process with high mortality in the absence of urgent treatment due to gangrene, ileus, sepsis, and multi-organ failure following bacterial translocation and infiltration after the collapse of mucosal barrier and bacterial translocation (15). Mortality rate with acute treatment after symptom onset is between 0 and 10%, while this figure rises quickly to 50-60% and 80-100% with delays of 6-12 hours and >24 hours, respectively (16). Despite these high mortality figures, the average delay between symptom onset and establishment of a diagnosis of AMI and initiation of treatment is around 11 hours, showing the need for improved diagnostic performance (10,17). Until now many serum parameters have been tested with regard to their ability to diagnose AMI accurately, and none of these markers have proven sensitive and specific enough to facilitate early diagnosis and to predict early mortality. Similarly, although elevated serum lactate and D-dimer levels are associated with increased mortality in AMI, they are not specific for predicting this increase (9,18).

Ultimately, reduced mortality rate in AMI requires early diagnosis and treatment. Recent studies showed that NLR may represent an important marker for cardiac and non-cardiac conditions, and particularly in detecting the inflammation in malignancies, gastrointestinal conditions, and chronic renal failure (19-22). Toptas et al. (23) reported significantly higher NLR and PLR in patients with AMI as compared to controls where a NLR greater than 4.5 had 77% sensitivity and 72% specificity for a diagnosis of AMI and a PLR greater than 157 had 59% and 65% sensitivity and specificity, respectively. Aktimur et al. (24) found a sensitivity and specificity of 74.3% and 82.9%, respectively for a NLR of ≥9.9 in the diagnosis of AMI and they reported even higher diagnostic yield when NLR and RDW were combined. In another study, a NLR level of greater than 4.68 as a marker of inflammation was associated with acute appendicitis, while higher values (≥5.74) were indicative of complicated appendicitis (25). In the current study comparing NLR and PLR for diagnosis of AMI, it was found that AMI+ patients had significantly higher values than AMI- patients (p<0.001, p<0.001, respectively). In contrast with the above-mentioned studies, although ROC analysis on the predictive value of NLR and PLR for inhospital mortality in patients with AMI identified a best cut-off value of >10.1 for NLR, no such values could be identified for PLR. In other words, NLR exhibited a significantly higher "area under curve" value. In our participants, the overall inhospital mortality rate was 48% versus 66% in those with a NLR of greater than 10.1, suggesting that NLR, as a strong marker of inflammation, could represent a more valuable indicator of inhospital mortality in patients with AMI as compared to PLR. A significantly increased release of neutrophils into circulation occurs in response to inflammation and neutrophils play a significant role in tissue destruction and injury. In contrast with neutrophils, number of circulatory lymphocytes decreases during inflammation due to increased steroid release due to stress and increased apoptotic cell death (26). In our study, patients who died had statistically insignificant increase in their neutrophil count as compared to patients who survived. (13.9±3.3, 11.6±4.4, p=0.07, respectively). However, patients, who died had significantly lower lymphocyte count (1.3±0.3, 3.0±1.3, p=0,015, respectively). Also, no significant differences in platelet counts were observed between those patients who did and did not survive (302.2±115.4, 279.5±53.7, p=0.890, respectively). Interestingly, despite there was a significant initial difference in neutrophil counts between AMI+ and AMI- patients, no such differences could be identified in platelet counts. Among AMI+ patients who died, there was an insignificant increase in neutrophil counts in conjunction with a significant decrease in lymphocytes. Although the cause of the decrease in lymphocyte counts could not be fully elucidated, it may be associated with the increased release of cortisol secondary to the concurrent occurrence of thrombus and ischemia in the mesenteric artery. Based on our observations, we believe that the increase in NLR in our study is associated with the delay in diagnosis, extent of the intestinal segment with high risk of necrosis, and increased neutrophil count and decreased lymphocyte count secondary to the infection and inflammation. While a lower cut-off value for

NLR may represent an important parameter for AMI diagnosis, NLR may predict inhospital mortality at higher cut-off levels. Further prospective studies with larger sample size are warranted for defining the role of these novel hematological parameters in the diagnosis of AMI and in predicting its mortality.

Our study has several limitations. Firstly, it is a single-center and retrospective study. Also, the time from presentation to diagnosis and the type of treatment administered were not assessed. Thirdly, the increase in CRP, a non-specific marker of inflammation, in AMI+ patients led to the consideration of increased NLR and PLR values in AMI patients as a strong marker of inflammation. Although it is interesting to note a significant increase of NLR in both patients with diagnosis of AMI and inhospital mortality of AMI+ patients, its association with clinical course could not be fully understood. Finally, thrombus formation causing AMI was not confirmed histopathologically.

Conclusion

In this study, high NLR and PLR were found to have significant value in the diagnosis of AMI, while only elevated NLR was significant for predicting inhospital mortality. We believe that as compared with other inflammatory markers, NLR represents a practical, economical, accessible, and useful parameter that can be utilized particularly in the absence of advanced imaging modalities and experienced radiologist assessment. However, further prospective studies are warranted to ascertain the role of NLR as a reliable marker for predicting inhospital mortality in AMI.

Ethics

Ethics Committee Approval: (Şişli Hamidiye Etfal Training and Research Hospital 07.08.2018/2066).

Informed Consent: It was not taken due to a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.S.Y., M.A., G.A., Design: G.E., H.K., S.S., S.S.Y, Data Collection or Processing: G.E., S.S.Y., H.K., M.A., Analysis or Interpretation: H.K., G.A., M.A., S.S., Literature Search: S.S.Y., G.A., H.K., M.A., Writing: G.A., S.S.Y., H.K., S.S., G.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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