ORIGINAL ARTICLE

Diagnostic utility of the neutrophil-lymphocyte ratio in patients with acute mesenteric ischemia: A retrospective cohort study

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ABSTRACT

BACKGROUND: Acute mesenteric ischemia (AMI) remains fatal in 50–70% of cases. AMI is recognized as a vascular emergency, requiring rapid and efficient clinical evaluation and treatment. In the present retrospective study, the possible utility of the neutrophil-lymphocyte ratio (NLR) in the early diagnosis of AMI was explored. The potential use of this ratio to distinguish AMI from non-vascular bowel necrosis (NVBN) was investigated.

METHODS: A total of 58 AMI, 62 NVBN, and 62 control patients were enrolled between May 1, 2010 and April 30, 2015. Patients who underwent laparotomies and/or bowel resections to treat AMI were included, as were NVBN patients who underwent segmental bowel resection to treat incarcerated and strangulated hernias. Controls were patients who presented to the emergency room with non-specific abdominal pain.

RESULTS: Mortality rate was 51.7% in the AMI and 4.8% in the NVBN groups. White blood cell (WBC) count, C-reactive protein (CRP) level, and red cell distribution width (RDW) were highest in the AMI group. NLR was higher in the AMI and NVBN groups than in the control group ($p<0.001$), though no difference in NLR was found between the AMI and NVBN groups. In addition, WBC count, CRP level, and NLR were higher in the NVBN group than in the controls ($p<0.001$).

CONCLUSION: We suggest that preoperative NLR aids in the diagnosis of AMI, and can be used to distinguish this condition from NVBN. NLR should be calculated, in addition to clinical examination.

Keywords: Acute mesenteric ischemia; diagnosis; NLR; serum markers.

INTRODUCTION

Acute mesenteric ischemia (AMI), an abdominal emergency, is observed in 1 of every 1000 patients presenting to emergency rooms. Mortality from AMI remains high (40–70%), although diagnostic methods have advanced in recent years. An important contributor to mortality is the failure of timely diagnosis, as duration of ischemia affects AMI outcome.[1,2] A 24-hour delay reduces survival rate by 20%; early diagnosis is critical.[3] However, early AMI signs and symptoms on physical examination are vague, laboratory data are non-specific, and imaging methods including duplex ultrasonography and computerized tomographic angiography are not sufficiently sensitive when used to explore distal vascular pathologies.[4,5] Therefore, the development of new diagnostic methods is essential. An ideal biochemical marker should be highly specific and sensitive, measurable in a non-invasive manner, released from the intestinal mucosa, and should preferably be detectable in peripheral blood.

AMI is an acute inflammatory process; absorption of bacte-

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Qucik Response Code

Ulus Travma Acil Cerrahi Derg
2016;22(4):344–349
doi: 10.5505/tjtes.2015.28235

rial materials (including endotoxin) triggers inflammation that increases in extent as ischemia is prolonged, causing bacterial infiltration, sepsis, acidosis, septic shock, and, ultimately, death. During this process, inflammatory substances measurable in peripheral blood are released from necrotic cells of the gut wall.[2,6] Recent studies have focused on such materials because early and accurate detection of inflammation is essential in order to optimize treatment and prognosis of those with medical emergencies.[7] Several biomarkers, such as C-reactive protein (CRP), procalcitonin, and mean platelet volume (MPV) have been used as indicators of inflammation. Neutrophilia develops during inflammation, triggered by release of arachidonic acid metabolites and platelet activation. Such stress induces relative lymphopenia. Therefore, the neutrophil-lymphocyte ratio (NLR) accurately reflects underlying inflammatory processes.[8] Although several studies have explored the utility of NLR in the diagnosis and prognosis of inflammatory and malignant diseases, very rarely has NLR been used in the diagnosis of AMI.[9–11] In the present study, the diagnostic capacity of NLR was evaluated and compared to traditional parameters in such patients.

MATERIALS AND METHODS

Study Groups and Study Design

The present retrospective, cross-sectional, multi-center study was approved by the local ethics committee. A total of 58 AMI patients, 62 non-vascular bowel necrosis (NVBN) patients, and 62 control patients were enrolled. Each patient was treated in 1 of 3 hospitals: the Zonguldak Atatürk State Hospital, a 450-bed, 12-section, government-approved general hospital with high direct admission and referral rates, the Süleyman Demirel University Faculty of Medicine Hospital, a 400-bed, 14-section, government-approved general hospital with a high direct admission rate, or the Erzurum Regional Training and Research Hospital, a 700-bed, 18-section, government-approved general hospital with high direct admission and referral rates. Patients were enrolled between May 1, 2010 and April 30, 2015. Archived and electronically stored records were accessed.

Patients who underwent laparotomies and/or bowel resections to treat AMI were included, as were NVBN patients who underwent segmental bowel excision to treat incarcerated and strangulated hernias. The control group included patients who presented to the emergency department with non-specific abdominal pain. Pre-study power analysis showed that the chosen sample size afforded a power of 0.9 for achievement of 95% confidence interval.

Complete Blood Count and Biochemical Analysis

Biochemical tests and complete blood count (CBC) (on venous blood) were automated. CBC data from all 3 hospitals were similar to recognized international norms. White blood cell (WBC) count, MPV, and red cell distribution width (RDW) were evaluated, and NLRs were calculated. Normal values of all parameters were reference figures accepted by hematology laboratories nationwide.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). Data distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±SD and categorical variables as frequencies (percentages). Significance of each difference among continuous variables was explored using independent samples t-test or Mann-Whitney U test. Significance of each difference between categorical variables was compared using Pearson chi-squared test. Receiver operating characteristic (ROC) curve analysis was used to define optimal cut-offs of NLR and RDW, for which specificities, sensitivities, positive and negative predictive values (PPV, NPV), and overall accuracies were calculated. Youden index was used to optimize accuracies of all calculations. A p value of less than 0.05 was considered to reflect statistical significance.

RESULTS

A total of 58 AMI, 62 NVBN, and 62 control patients were enrolled. Mean patient age did not differ significantly among groups, being 68.43, 66.43, and 63.38 years, respectively. Of the AMI patients, 31 (36.2%) were female and 37 (63.8%) male, 26 (41.9%) NVBN patients were female and 36 (58.1%) male, and 28 (45.2%) control patients were female and 34 (54.8%) male. Patient profiles differed somewhat among the 3 hospitals, reflecting local population densities and hospital capacities.

Regarding affected bowels, segmental involvement was evident in 39 (67.2%) AMI patients, with complete involvement in 19 (32.8%). Forty-two (72.4%) patients exhibited only small bowel involvement, but 16 (27.6%) exhibited both small intestinal and colonic involvement. Segmental involvement was evident in all NVBN patients. Mortality rates were 51.7% in the AMI group and 4.8% in the NVBN group.

WBC counts, CRP levels, RDWs, MPVs, and NLRs are shown in Figures 1–4, as well as in Table 1. WBC counts and CRP levels were significantly higher in the AMI group than in the other groups (p=0.028 vs the NVBN group; p<0.001 vs controls in terms of WBC count; p<0.001 vs the NVBN and control groups in terms of CRP). RDW was significantly higher in the AMI group (p=0.002). MPV did not differ among groups (p=0.181). NLR was significantly higher in the AMI group than in the control group (p<0.001). WBC, CRP level, and NLR (but not RDW, p=1.000) were significantly higher in the NVBN group than in the controls (p<0.001 for all).

Sensitivities and specificities of CRP levels and CBC data used to distinguish controls from AMI patients, and ROC

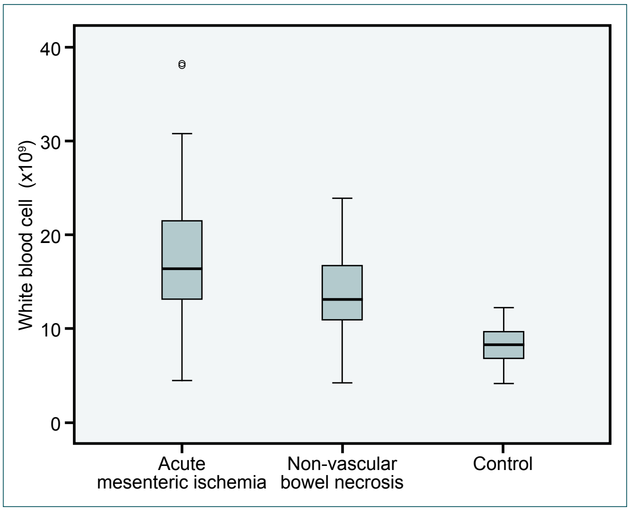

Figure 1. Distribution among groups of WBC counts.

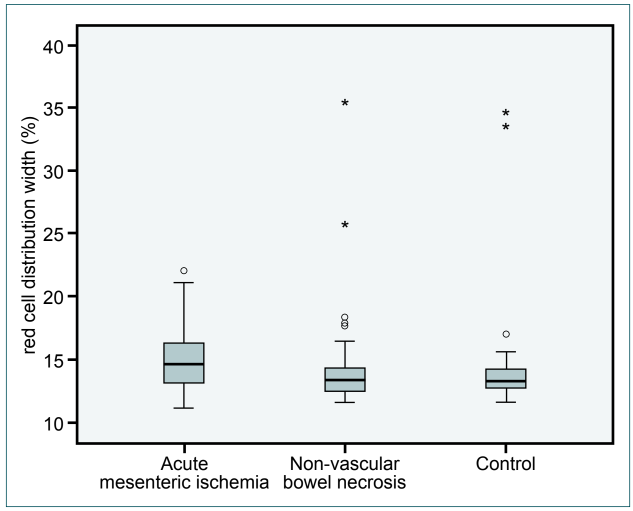

Figure 3. Distribution among groups of RDWs.

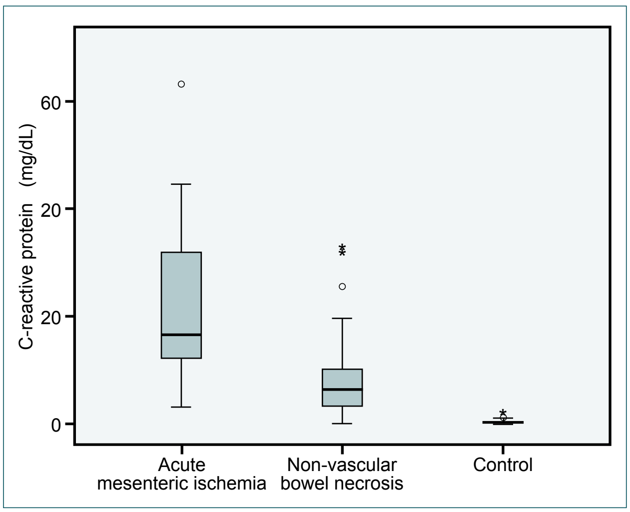

Figure 2. Distribution among groups of CRP levels.

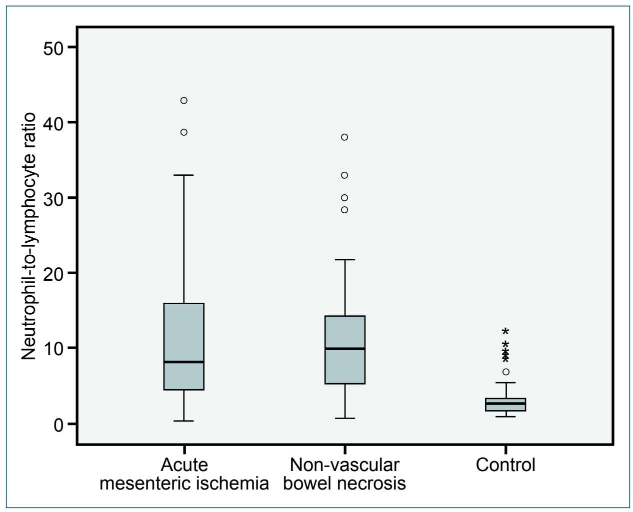

Figure 4. Distribution among groups of NLR ratios.

curve analysis data on WBC counts, RDWs, and NLRs are shown in Table 2 and Figure 5. Sensitivities, specificities, PPVs, and NPVs of WBC counts (>10×10^9/L) and CRP levels (>0.5 mg/dL) were 86.21%, 95.16%, 94.30%, and 88.10%, and 100%, 100%, 100%, and 100%, respectively. Sensitivities, specificities, PPVs, and NPVs of NLRs were 74.14%, 88.71%, 86%, and 78.60%. The same figures for RDWs were 48.28%, 88.71%, 80%, and 64.70%, respectively. Youden index values for WBC count, CRP, RDW, and NLR were 0.814, 1.000, 0.369, and 0.628, respectively. ROC analysis showed that WBC count, CRP level, RDW, and NLR cut-off values that afforded optimal sensitivities and specificities were 10.99×10^9/L (86–95%), 2.10 mg/dL (100–100%), 14.70% (48–89%), and 5.21 (74–89%), respectively. Areas under the

Table 1. Laboratory data from all groups

	Acute mesenteric ischemia (n=58)	Non-vascular bowel necrosis (n=62)	Control (n=62)
White blood cell ($\times10^9$/L)	16.38 (4.48–38.20)$^{\#,*}$	13.10 (4.20–23.90)*	8.28 (4.15–12.23)
C-reactive protein (mg/dL)	16.60 (3.20–63.20)$^{*,£}$	6.40 (0.10–33.00)*	0.20 (0–2.10)
Red cell distribution width (%)	14.55 (11.10–22.10)$^{¥}$	13.35 (11.60–35.40)	13.30 (11.60–34.60)
Mean platelet volume (fL)	8.67±1.47	8.50±1.37	8.93±1.03
Neutrophil-to-lymphocyte ratio	8.16 (0.36–42.87)*	9.92 (0.75–38.00)*	2.68 (0.96–12.28)

$^{\#}$p=0.028 vs. non-vascular bowel necrosis, *p<0.001 vs. control, $^{£}$p<0.001 vs. non-vascular bowel necrosis, $^{¥}$p=0.002 vs. non-vascular bowel necrosis and control.

Table 2. Overall accuracies afforded by laboratory parameters used to distinguish AMI patients from controls (%)

	Sensitivity	Specificity	PPD	NPD	Cut-off	Youden's Index
White blood cell	86.21	95.16	94.30	88.10	10.99	0.814
C-reactive protein	100	100	100	100	2.10	1.000
Red cell distribution width	48.28	88.71	80	64.70	14.70	0.369
Mean platelet volume	46.55	70.97	60	58.70	8.30	0.175
Neutrophil-to-lymphocyte ratio	74.14	88.71	86	78.60	5.21	0.628

NPV: Negative predictive value; PPD: Positive predictive value.

Table 3. Overall accuracies afforded by laboratory parameters used to distinguish AMI patients from NVBN patients (%)

	Sensitivity	Specificity	PPD	NPD	Cut-off	Youden's Index
White blood cell	67.24	66.13	65	68.30	14.50	0.334
C-reactive protein	89.66	72.58	75.40	88.20	8.50	0.622
Red cell distribution width	65.52	66.13	64.40	67.20	13.90	0.317
Mean platelet volume	81.03	24.72	51.10	60.70	7.40	0.057
Neutrophil-to-lymphocyte ratio	50.00	66.13	58	58.60	7.85	0.161

NPV: Negative predictive value; PPD: Positive predictive value.

curves (AUCs) for WBC count, RDW, and NLR were 93.4%, 69.7%, and 81.9%, respectively.

Sensitivities and specificities of CRP levels and CBC data used to distinguish NVBN and AMI patients, and ROC data on WBC counts, RDWs, and NLRs, are shown in Table 3 and Figure 6. Sensitivities, specificities, PPVs, and NPVs of WBC counts (>10x10^9/L) and CRP levels (>0.5 mg/dL) were 67.24%, 66.13%, 65%, and 68.30%, and 89.66%, 72.58%, 75.40%, and 88.20%, respectively. Sensitivities, specificities, PPVs, and NPVs of NLRs were 50%, 66.13%, 58%, and 58.60%, respectively. Those of RDWs were 65.52%, 66.13%, 64.40%, and 67.20%, respectively. Youden index values for WBC count, CRP level, RDW, and NLR were 0.334, 0.622, 0.317, and 0.161, respectively. ROC analysis showed that WBC count, CRP level, RDW, and NLR cut-off values affording the best sensitivities and specificities were 14.50x10^9/L (67–66%), 8.50 mg/dL (90–73%), 13.90% (66–66%), and 7.85% (50–66%),

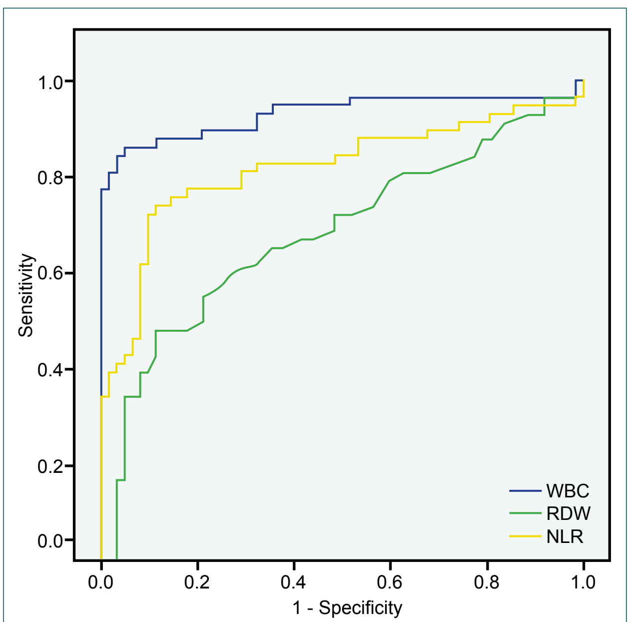

Figure 5. ROC curve used to distinguish AMI patients from controls.

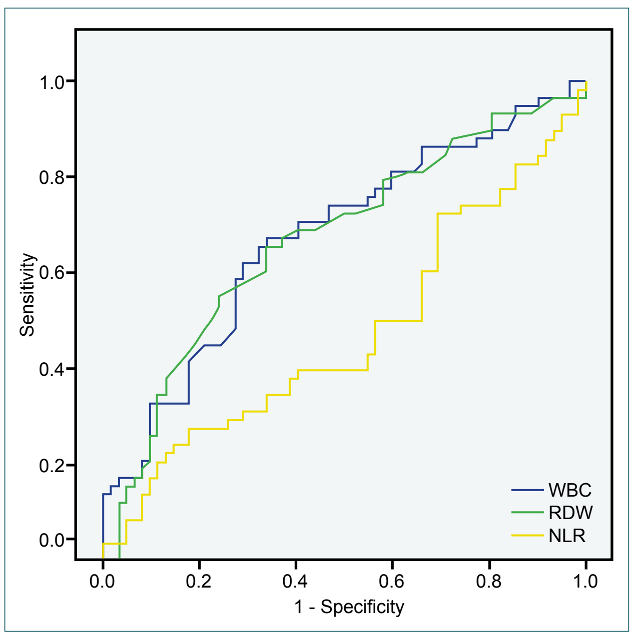

Figure 6. ROC curve used to distinguish AMI from NVBN patients.

respectively. AUCs for WBC count, RDW, and NLR were 67.4%, 67%, and 47.4%, respectively.

DISCUSSION

It was presently determined that NLR was highly sensitive and specific when used to identify patients with AMI (an abdominal emergency with a high mortality rate). Differential diagnosis of AMI must be urgently performed. Mean age of AMI patients exceeds 65 years.[12] Kougias et al.[13] reported a mean age of 71 years; the mean age of our AMI group was 68.43 years.

Early diagnosis and treatment of AMI are essential in the prevention of irreversible damage to the bowel wall.[14,15] Any diagnosis that begins with a suspicion raised by clinical findings should be confirmed by laboratory and imaging methods. Clinical presentation of AMI is highly varied. Classically, the condition is associated with dramatic-onset severe abdominal pain, disproportionate to findings on physical examination. However, early correct diagnosis is often difficult, as many AMI signs and symptoms are shared by other emergency intra-abdominal pathologies, including appendicitis, pancreatitis, small intestine obstruction, and acute diverticulitis.[1,16] Such problems have encouraged researchers to devise new laboratory and imaging methods. As AMI is an inflammatory process, intense effort has been devoted to the definition of specific early biochemical and serological markers of such inflammation.[17] However, useful markers are few.

Classically, AMI patients exhibit leukocytosis, metabolic acidosis, and elevated levels of serum D-dimer and lactate.[18] Although the leukocytosis is significant, it has been reported as unhelpful in differential diagnosis.[1] However, in the retrospective study of Paladino et al.,[19] leukocytosis was a significant diagnostic and prognostic factor. In the present study, profound leukocytosis was evident in AMI patients ($p<0.001$). Other useful parameters are D-dimer and serum lactate levels.[1] These levels were not measured in the present patients.

NLR is a simple biomarker of inflammation. Total leukocyte and neutrophil counts have traditionally been considered markers of infection. Associations are evident between monocyte and lymphocyte counts, as well as between these counts and infection.[7,20] During inflammation, neutrophil counts increase as lymphocyte counts decrease, controlled by neurohormonal mechanisms. Therefore, NLR accurately reflects underlying inflammatory processes.[8]

NLR is increasingly used to predict the survival of patients with malignancies, coronary artery disease, acute appendicitis, acute cholecystitis, acute pancreatitis, and community-acquired infections.[7] Lee et al.[21] found that preoperative NLR accurately predicted the development of severe cholecystitis. Yu et al.[22] found that preoperative NLR was prognostic for gastric cancer patients. Suppiah et al.[23] found that NLR elevation during the first 48 hours of admission was significantly associated with severe acute pancreatitis, and was an independent (negative) prognostic factor. Kahramanca et al.[24] found preoperative NLR useful in the diagnosis of acute appendicitis, as well as in the differentiation of patients with simple and complicated appendicitis. Aktimur et al.[11] found high NLR (<9.99) valuable in AMI diagnosis. In addition, RDW was higher in AMI patients than in those with acute appendicitis, and MPV was higher in AMI patients than in controls. In the present study, NLRs were higher in the AMI and NVBN groups than in the control group ($p<0.001$). However, no difference was found between the AMI and NVBN groups in this respect ($p=1.000$). Unlike the findings of Aktimur et al.,[11] the present MPVs were similar in all groups ($p=0.181$). RDWs were higher in the AMI group than in the other groups ($p=0.002$), but did not differ between the NVBN and control groups ($p=1.000$).

In terms of AMI diagnosis, sensitivity of 80% and specificity of 50% was afforded by WBC count; the same figures for the NLR were 69% and 71%.[2,11] In an earlier study[25] of RDW in the context of diagnosing AMI, cut-off value, sensitivity, and specificity were 15.04%, 40.8%, and 81.2%, respectively. Another study[26] found that the AUC for RDW was 0.713, and that the cut-off value was 14.85%. Sensitivities, specificities, PPVs, and NPVs for WBC count, RDW, and NLR were 86.21%, 95.14%, 94.30%, and 88.10%; 48.28%, 88.71%, 80%, and 64.70%; and 74.14%, 88.71%, 86%, and 78.60%, respectively. RDW and NLR data were consistent with published findings, but WBC count figures were higher. ROC analysis yielded cut-offs for WBC count, RDW, and NLR, as well as for optimal sensitivities and specificities. These were 14.50×10^9/L (67–66%), 13.90% (66–66%), and 7.85 (50–66%), respectively.

In conclusion, preoperative NLR aids in the diagnosis of AMI, differentiating the condition from NVBN, and can be used as an adjunct to clinical examination.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Akut mezenterik iskemili hastalarda nötrofil-lenfosit oranının tanısal yararı: Geriye dönük kohort çalışma

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AMAÇ: Akut mezenterik iskemi (AMI) olgularının %50–70'i ölümcül olup, hızlı ve etkili bir klinik değerlendirme ve tedavi gerektiren bir vasküler acil olarak kabul edilmektedir. Mevcut geriye dönük çalışmada, biz AMI erken tanısında nötrofil/lenfosit oranının (NLR) olası yararını ve bu oranın AMI ile non-vasküler bağırsak nekrozu (NVBN) ayırıcı tanısında etkili olup olmadığını araştırdık.
GEREÇ VE YÖNTEM: Bu çalışmada 1 Mayıs 2010–30 Nisan 2015 tarihleri arasında 58 AMI, 62 NVBN ve 62 kontrol hastası incelendi. Akut mezenterik iskemi tanısıyla laparotomi ve/veya bağırsak rezeksiyonu yapılan hastalar çalışma grubuna alındı. İnkarsere ve strangüle herni nedeniyle segmenter bağırsak rezeksiyonu yapılan hastalar NVBN grubuna alındı. Kontrol grubu hastaları non-spesifik karın ağrısı nedeniyle acil servise başvuran hastalarda oluşturuldu.
BULGULAR: Mortalite oranı AMI grubunda %51.7, NVBN grubunda %4.8 idi. Akut mezenterik iskemi grubunda lökosit (WBC) sayısı, C-reaktif protein (CRP) ve eritrosit dağılım aralığı diğer gruplardan daha yüksekti. Nötrofil/lenfosit oranı, AMI ve NVBN grubunda kontrol grubundan daha yüksekti ($p<0.001$), ancak AMI ve NVBN grupları arasında fark yoktu. Ayrıca, NVBN grubunda WBC sayısı ve CRP control grubundan daha yüksekti ($p<0.001$).
TARTIŞMA: Ameliyat öncesi NLR düzeyinin AMI tanısında yardımcı olacağını ve AMI ile bağırsak nekrozu ile seyreden NVBN gibi durumlarla ayırıcı tanıda kullanabileceğini düşünmekteyiz. Bundan dolayı, bu tür hastalarda NLR klinik muayeneye ek olarak hesaplanmalıdır.
Anahtar sözcükler: Akut mezenterik iskemi; NLR; serum belirteçleri; tanı.

Ulus Travma Acil Cerrahi Derg 2016;22(4):344–349 doi: 10.5505/tjtes.2015.28235