An evaluation of the neutrophil-to-lymphocyte ratio as a prognostic and predictive marker in thromboangiitis obliterans

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Abstract

Aim: The aim of this study was to investigate whether the neutrophil/lymphocyte ratio is an independent predictor of poor prognosis, mortality, co-morbidities, critical limb ischmemia, amputation, or a potential prognostic biomarker predicting pathological and survival outcomes in thromboangiitis obliterans. We also investigated whether there was any relation between an increased neutrophil/lymphocyte ratio in patients with Buerger's disease and amputation, the ultimate outcome of poor prognosis.

Material and Methods: The hospital records of patients treated, followed-up and diagnosed with thromboangiitis obliterans were analyzed retrospectively. Surgical procedures performed and medical treatments applied were recorded from patients' clinical data. Extremities exposed to the disease during its course were identified. Amputations were recorded as minor and major. Neutrophil and lymphocyte values were recorded from peripheral blood samples at time of first presentation to hospital, with the neutrophil/lymphocyte ratio being calculated from these. One hundred ten subjects were finally enrolled as the patient group (TAO; n=110). A control group (n=49) was established consisting of smoker volunteers with no health problems. Statistical changes in neutrophil/lymphocyte ratio values between the groups were investigated.

Results: No statistically significant difference was observed between the two groups' basic characteristics. In terms of neutrophil/lymphocyte ratio values, a statistically significant increase was observed in the patient group compared to the control group. We observed no statistical correlation between amputations and neutrophil/lymphocyte ratio values.

Conclusions: We think that the neutrophil / lymphocyte ratio, obtained easily and cheaply from routine peripheral blood samples, may be of clinical benefit in thromboangiitis obliterans.

Keywords: Thromboangiitis Obliterans; Neutrophil-To-Lymphocyte Ratio; Predictive Marker; Prognostic Marker.

INTRODUCTION

Thromboangiitis obliterans (TAO) is a non-atherosclerotic inflammatory disease. Although the etiological causes are not known for certain, there is a powerful correlation with smoking. The disease exhibits segmental occlusion of the small or medium arteries, veins and nerves of the extremities (1-5). In contrast to other forms of vasculitis, there are no laboratory tests that can assist in the diagnosis or prognosis of the disease (6). TAO is typically more commonly seen in middle-aged males of low socioeconomic status. In epidemiological terms it is more widespread in the peoples of the Middle and Far East compared to North America and Europe (1,2,4).

Patients experience severe ischemic extremity pains with walking in the early stage, but also at rest as the disease progresses. In the more advanced stages of the disease, acral ulceration and gangrene are seen together with analgesic-resistant pain. Tissue hypoxia is the main source of the pain and symptoms. The course may conclude with amputation in untreated cases (1-6). Numerous recent papers have described the neutrophil/lymphocyte ratio (NLR) as a potential early marker of morbidity and mortality in cases with accompanying ischemic and inflammatory events (7-9). In this study we compared the NLR values of patients diagnosed with TAO with those of healthy individuals. Our purpose was to investigate the practicability of the NLR as a predictive prognostic marker, easily and economically obtained from routine peripheral blood sample tests, in TAO, an

inflammatory disease. Our study is the first performed for this purpose in the literature.

MATERIAL and METHODS

Study population: This research, planned as a retrospective cohort study, was performed with the approval of the local ethical committee and in agreement with the principles of the Helsinki Declaration. The hospital records of patients treated, followed-up and diagnosed with TAO at the Karadeniz Technical University and Kanuni Training and Research Hospital, Turkey, in 2000-2016, were examined. We identified 194 patients diagnosed with TAO through the assessment of clinical and angiographic findings. Any of these patients who had recently undergone major operations, with hematological disorder, diagnosed with renal and hepatic failure or cancer, with autoimmune connective tissue disease or other chronic disease and using non-steroid anti-inflammatory and corticosteroid drugs were excluded from the study. One hundred ten subjects were finally enrolled as the patient group (TAO; n=110). A control group (n=49) was established consisting of smoker volunteers with no health problems in the young or middle-aged populations and providing consent forms.

Demographic data such as age, sex and smoking addiction were recorded. Surgical procedures performed (sympathectomy and peripheral revascularization) and medical treatments applied (antiaggregant, antiplatelet and anticoagulant medications) were recorded from patients' clinical data. Patients' clinical status at time of first presentation was assessed according to the Fontaine classification. Extremities exposed to the disease during its course were identified. Amputations, if applicable, were recorded as minor (distal tip amputations such as to leave a functional foot permitting the patient to stand and walk with no prosthesis) or major (extremity amputations severe enough to require prostheses). Leukocyte, neutrophil and lymphocyte values were recorded from peripheral blood samples at time of first presentation to hospital, with the NLR being calculated from these. Peripheral blood samples were also taken from the control group, and data were recorded from these. This study focused on routine peripheral blood sample values obtained through the retrospective scanning of patients' records. We particularly evaluated the NLR, which can be calculated from neutrophil and lymphocyte numbers. Statistical changes in NLR values between the groups were investigated.

Statistical analysis: Data analysis was performed on SPSS 23.0 (IBM, New York, USA) software. Descriptive statistics were expressed as number for categoric variables and mean, standard deviation, minimum and maximum for numerical variables. Normal distribution of numerical data was tested using the One Sample Kolmogorov Smirnov test. Comparisons of numerical variables between two independent groups were performed with the Mann Whitney U test since normal distribution conditions were not established. The chi square test was used for the analysis of categoric variable ratios in independent groups. $p<0.05$ was regarded as statistically significant.

RESULTS

Baseline characteristics of the TAO group are given in Table 1.

Table 1. Baseline characteristics of the TAO group (n = 110)	
Gender, n (% of males)	108 (98.2%)
Age, years (mean±SD)	48±13.6
Smokers on admission, n (%)	93 (84.5%)
Previous sympathectomy, n (%)	36 (32.7%)
Previous revascularization, n (%)	19 (17.3%)
Extremity involvement	
Upper extremity, n (%)	2 (1.8%)
Lower extremity, n (%)	97 (88.2%)
Upper and lower extremities, n (%)	11 (10%)
Fontaine classification	
Fontaine Stage 2B, n (%)	5 (4.5%)
Fontaine Stage 3, n (%)	21 (19.1%)
Fontaine Stage 4, n (%)	84 (76.4%)
TAO: Thromboangiitis Obliterans, SD: Standard Deviation	

Age, gender and smoking addiction data were determined, and no statistically significant difference was observed between the groups (Table 2).

Table 2. Age, gender and smoking addiction data from the two groups			
	TAO Group (n=110)	Control Group (n=49)	p
Age, years (mean±SD)	48±13.6	44.6±11.3	0.286
Gender, % of males	98.2%	98%	1.000
Smoking addiction, %	84.5%	81.6%	0.821
TAO: Thromboangiitis Obliterans, SD: Standard Deviation			

In terms of medical treatment, 86.4% of patients in the TAO group had used pentoxifylline, 97.3% acetyl salicylic acid, 16.4% clopidogrel, 77.3% cilostazol, and 47.3% iloprost. Amputation was performed on 64 (58.2%) patients. Minor amputation was performed on 25 (22.7%) of these patients and major amputation on 39 (35.5%).Peripheral blood sample values in the TAO and control groups were subjected to statistical analysis. A significant increase in neutrophil values and a significant decrease in lymphocyte values were observed in the TAO patients compared to the control group ($p < 0.0001$). In terms of NLR values, a statistically significant increase was observed in the TAO group compared to the control group ($p < 0.0001$) (Table 3).

Table 3. Comparison of the groups' neutrophil, lymphocyte and NLR values			
	TAO Group (n=110)	Control Group (n=49)	p
Neutrophil, (mean±SD)	6.29±2.46	4.48±1.39	<0.0001
Lymphocyte, (mean±SD)	2.16±0.84	2.73±0.88	< 0.0001
NLR, (mean±SD)	3.16±1.41	1.63±0.12	<0.0001
NLR: Neutrophil/Lymphocyte ratio, SD: Standard Deviation			

We investigated the relation between the NLR and amputation, the final outcome of poor prognosis in the clinical course of TAO. We observed no statistical significance between minor amputation (p=0.169) or major amputation (p=0.117) and the NLR. The median NLR value was 2.76. We then investigated patient levels above and below this value. Nine (36%) patients who had undergone minor amputation had NLR values below 2.76, while 16 (64%) patients had NLR values above 2.76. No statistical significance was observed between these two groups (p=0.142). Fifteen (38.5%) patients undergoing major amputation had NLR values below 2.76 and 24 (61.5%) had NLR values above 2.76. No statistical significance was observed between the two major amputation groups (p=0.083). However, NLR values were above 2.76 in 40 (62.5%) of the patients undergoing amputation during the clinical course of the disease (Table 4).

Table 4. Comparison of NLR values in terms of amputation			
	Median NLR value below 2.76	Median NLR value above 2.76	p
Minor Amputation, n (%)	9 (36%)	16 (64%)	0.142
Major Amputation, n (%)	15 (38.5%)	24 (61.5%)	0.083
NLR: Neutrophil/Lymphocyte ratio			

DISCUSSION

TAO began being described as Buerger's disease following a paper that appeared in 1908 in which Leo Buerger announced his pathophysiological findings (2). It is a non-atherosclerotic, segmental disease characterized by vasculitis, generally involving the ends of the extremities, in which smoking has an adverse impact on prognosis. The great majority of patients are young, male smokers.

The lack of any clinical or laboratory finding specific to the disease is one of the main difficulties in the diagnosis and follow-up of TAO (6). Ischemic symptoms caused by occlusion and stenosis constitute the clinical manifestation (1-6). Despite being classified as a vasculitic disease, in contrast to the majority of other vasculitic diseases, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), acute phase reactants and antibody levels such as rheumatoid factor, antinuclear antibody and immune complexes in the circulation are normal or negative (6). At angiography, the proximal arteries are normal, while segmental occlusive lesions are seen in the distal vascular bed. Corkscrew-shaped collaterals known as Martorelli's sign can be useful for diagnosis (1-3). However, this finding is also not specific for TAO, and may also be seen in systemic lupus erythematosis, mixed connective tissue disease, scleroderma, CREST syndrome or any other obstructive disease with small vessel occlusion (10). Use can frequently be made in clinical diagnosis of the criteria published by Shionoya in 1998 (smoking history, onset before the age of 50 years, infrapopliteal arterial occlusions, either arm involvement or phlebitis migrans,

and absence of atherosclerotic risk factors other than smoking) (6).

The main element in treatment is smoking cessation and patient education. Antiaggregant and peripheral vasodilators are the essential components of medical treatment. Acetylsalicylic acid, clopidogrel, pentoxifylline, cilostazol, calcium channel blockers and prostacyclin (PGI2) analogs are used in this context. The outcomes of surgical revascularization are not promising, although this can be tried in selected cases. Growth factor application, sympathectomy, omentopexy and spinal cord stimulation and hyperbaric oxygen therapy are other additional therapeutic options (1-6).

NLR is a novel inflammatory marker. A growing number of publications suggest that it is even more valuable that the total leukocyte number in systemic inflammation. Since it is easily obtained and calculated from routine peripheral blood sample it involves no additional costs (11). Neutrophils cause reactive oxygen radicals, myeloperoxidase and proteolytic enzymes to be released in inflammatory events. They thus also lead to tissue injury. Lymphocytes play a relatively protective role in inflammatory events by regulating the immune system (8). For these reasons, the ratio between these two leukocyte subgroups is used as a predictive and prognostic marker in inflammatory events (12,13), cardiovascular diseases (7-9,11,14-17) and cancer cases (18-21).

This study examined the value of the NLR, an inflammatory marker, in TAO, in which inflammatory processes and smoking are known to play a key role. In the light of the data obtained, we think that the NLR obtained easily and inexpensively from routine peripheral blood samples can be of clinical importance in the diagnosis and monitoring of TAO. NLR values are confirmed as a predictive marker in TAO, as in other inflammatory conditions. We also think that the NLR can represent grounds for suspicion of a worsening clinical course in TAO. A statistically significant increase was observed in neutrophil values in our TAO group, while there was a significant decrease in lymphocyte values. This confirms previous findings to the effect that a decrease in lymphocytes is at least as important as an increase in neutrophils in the pathology at the cellular level in TAO.

CONCLISION

There is no prognostic and predictive marker for clinicians to use in the evaluation of patients' clinical condition and prognostic course. In the light of the findings from this study, we think that in addition to being easily and inexpensively obtained from peripheral blood samples, the NLR can be of clinical importance in Buerger's disease, for which there are currently no specific methods capable of use in diagnosis and follow-up. Our study confirms that high NLR values can be a predictive factor of mortality, poor prognosis and amputation in Buerger's disease, as in other inflammatory diseases. While the use of NLR values as a prognostic factor in Buerger's disease is not

statistically significant, we still think that it can raise suspicions regarding a poor clinical course.

Its retrospective nature and the small study population are two limitations of this study. The prognostic and predictive relation between the NLR and TAO might be revealed more powerfully through future studies involving wider patient populations. In addition, examination of NLR values during periods when the disease exhibits progression and observation of responses to treatment can also serve as a guide to medical or surgical treatment.

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