

PAPER DETAILS

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Identification of Neutrophil/Lymphocyte Ratio as a Unique Biomarker for Migraine Follow-up

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Abstract

Aim: As in many chronic pain syndromes, self-reported pain is the main criterion used by clinicians assessing patients with migraine. However, it is subjective, and there is no reliable marker for follow-up, and it hinders adequate follow-up and treatment. Therefore, in this study, we aimed to investigate the correlation of the NLR (neutrophil-lymphocyte ratio) level, which is increased due to the neuroinflammatory process and oxidative stress, with the clinical and demographic characteristics of the patients, and to investigate its feasibility as an objective marker during follow-ups.

Materials and Methods: Our study included one hundred migraine patients without aura who met the "The International Classification of Headache Disorders 3rd edition" (ICHD-3) criteria. The demographic characteristics of all patients and the clinical features of migraine pain were obtained. In addition, blood NLR level and its correlation to these features were examined.

Results: There was a significant and positive correlation between NLR level with disease duration and pain severity ($r=0.43$ $p<0.001$, $r=0.76$ $p<0.001$, respectively), however, it was independent of age, gender, and migraine subtypes (episodic/chronic) ($p=0.48$, $p=0.14$, $p=0.13$, respectively).

Conclusions: Our study found a significant correlation between the NLR level and the clinical features of migraine patients, indicating that this easily accessible parameter may be a promising marker that can be used during the follow-up period.

Keywords: Biomarker, migraine, neutrophil lymphocyte ratio

INTRODUCTION

Migraine is one of the most common diseases in the world, and if the attacks are not controlled, it seriously affects the quality of life (1-3). Although there are many alternative therapies for migraine currently, it is still insufficient for many patients. In many chronic pain syndromes, self-reported pain by the patients is the primary criterion used by clinicians assessing pain. However, it is subjective, and multiple intrinsic and extrinsic factors can affect pain levels, and this prevents effective treatment and follow-up. Therefore, it is essential to investigate a reliable and objective marker for better treatments.

The neuroinflammatory process, vasomotor changes, some cytokines, neuropeptides, and inflammation due to increased oxidative stress and the pathophysiological process in the vessels have been suggested as responsible for the underlying mechanism (4,5). In systemic inflammation and oxidative stress, even if

the total white blood cell count is within normal limits, increased neutrophil and decreased lymphocyte counts occur. Thus, neutrophil/lymphocyte ratio (NLR) becomes a more reliable marker in this case (6,7). Studies have shown that NLR can predict prognosis and mortality in many conditions such as coronary artery disease, malignancies, and rheumatological and neurological diseases (8-11). In addition, since it is an easily accessible and inexpensive parameter, we hypothesized that NLR can be used as a useful and practical biomarker to show the inflammation and oxidative processes, and follow up the patients.

In previous studies, NLR was found to be significantly higher in migraine patients compared to the control group during the attack, but there was no difference between them in the attack-free period (12,13). While these studies have concluded that NLR is an increasing parameter during the attack period, it is still unknown whether it can be used as biomarker in the patient's follow-up period.

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In this study, we aimed to investigate the NLR level in migraine patients and its correlation with clinical and demographic characteristics, thereby its usability as a reliable and objective biomarker in the follow-up of patients.

MATERIAL AND METHOD

Study Design

We conducted a cross-sectional study with 100 subjects with migraine without aura examined at our Neurology Outpatient Clinic. Diagnosis of all patients was made by a neurologist according to International Headache Disorders Classification-III (beta version) (ICHD-III) (14). This study was approved by the X Ethics Committee (Date: 16.6.2022, Decision No: 12/14) and was conducted following the principles of the Declaration of Helsinki.

Participants

Inclusion Criteria: Adult patients who were between 18–65 years old and have certain diagnosis of migraine without aura.

Exclusion Criteria: Presence of any additional disease or condition that may lead to elevated inflammation markers; presence of any infection (sinusitis, otitis, urinary tract infection, etc.), concomitant chronic inflammatory disease, cardiovascular or pulmonary disease, smoking, alcohol use >20g/day, hypertension, diabetes, obesity (BMI ≥30), corticosteroid or use of immunosuppressant medication, and migraine treatment in the last six months or currently having a migraine attack.

Demographic and Clinical Characteristics

As a primary outcome, we investigated the correlation between demographic and clinical characteristics (age, gender, disease duration, number and severity of attacks) and NLR level. Headache severity was scored with VAS (visual analog scale). NLR level which is calculated by dividing the neutrophil count by the lymphocyte count was evaluated with blood samples obtained during morning fasting.

Pain Assessment

VAS was used for evaluation of pain. VAS is a validated, unidimensional scale for acute and chronic pain (15). It is commonly used in clinics related to pain. Pain severity is rated with a simple 10- point scale (0 = “no pain”, 10 = “pain as bad as you can imagine”). Pain severity is considered mild if it was less than 3.5, moderate if it was between 3.5 and 6.5, and severe if it was above 6.5 (16).

Laboratory Assessment

Blood samples were obtained after an overnight fasting period. Blood lipid profiles, including total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), high-density lipoprotein (HDL) were measured in mg/dl units. TC, TG, and HDL concentrations were measured using an enzymatic method. LDL concentrations were calculated using Friedewald’s formula (17).

Statistical Analysis

Statistical Package for the Social Sciences package program version 28.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Descriptive analysis of assessment results was evaluated with mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Histogram and Shapiro-Wilk tests were used for normality distribution. Unpaired t-test and Mann-Whitney U tests were used for continuous variables according to normality distribution, and Fisher Exact test was used for categorical variables in comparing groups. Pearson or Spearman tests were used for correlation analysis according to normality distribution. The significance value was accepted as $p<0.05$.

RESULTS

A total of 100 migraine patients without aura were included in the study. None of the patients were using anti-migraine treatment during the attack or prophylactically. Further clinical data and the laboratory parameters were provided in Table 1.

Table 1. Descriptive and clinical characteristics of patients	
	Patients
Age (years)	34.9 (±11.4)
Gender (F/M)	86/14
Disease duration (month)	28.4 (±33.7)
Episodic/Chronic	58/42
Average of pain severity (0-10)	5.35 (±2.16)
Average of NLO level	1.89(±0.77)
* F: Female, M: Male, NLO: Neutrophil-lymphocyte ratio, Mean± SD; n (%)	

The mean pain intensity was 5.35 (±2.16) out of 10 which is considered as the moderate severity. There was a significant and positive correlation between the duration of the disease, and the severity of the pain with the NLR level ($r=0.43$ $p<0.001$, $r=0.76$ $p<0.001$, respectively) (Figures 1 and 2).

Also, NLR level was found to be independent of age, gender, and migraine subtypes (episodic/chronic) ($p=0.48$, $p=0.14$, $p=0.13$, respectively).

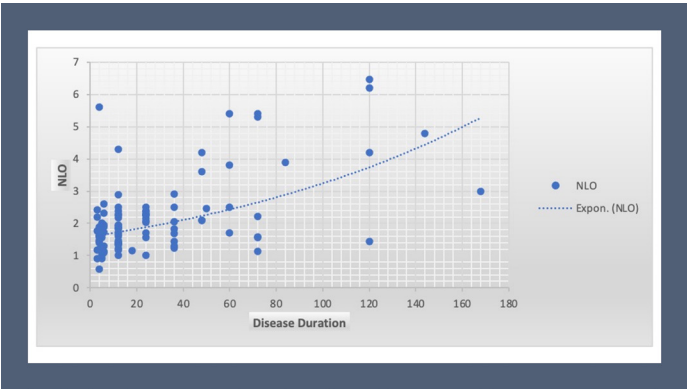


Figure 1. Positive correlation between NLO and disease duration

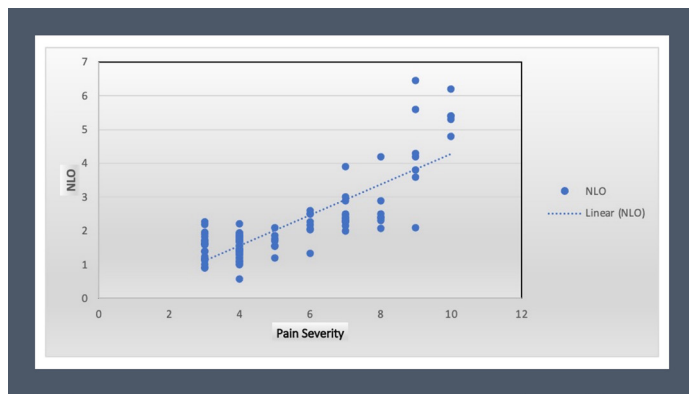


Figure 2. Positive correlation between pain severity and NLO level

DISCUSSION

Our study showed that NLR was positively correlated with the pain severity and disease duration, also independent of age and gender in migraine patients. This result supports our hypothesis that NLR is not only a parameter increasing during the migraine attack period but can also be used as a prognostic marker related with clinical features of the disease. Thus, we did not prefer to obtain only the level of NLR in migraine patients, so we searched the correlation between these parameters to find an easy applicable prognostic tool.

Recent studies have shown that the NLR level, as an indicator of systemic inflammation, is more reliable than the neutrophil or lymphocyte count alone or the total white blood cell count. Furthermore, this parameter is in parallel with the progression of the disease (18-20). Along with studies showing that increased NLR level can be an independent prognostic marker in cerebrovascular, cardiovascular diseases, vasculitis, and cancer. Promising results were also reported in a meta-analysis investigating its usability on sepsis progression, and it was suggested as a reliable marker in this direction (8,9,21-23).

To date, studies on NLR level in migraine patients have usually been conducted to investigate whether NLR level increases during the attack or not (12-24). For example, Karabulut et al. showed that the NLR level in migraine patients was higher during the attack than in healthy controls (24), and Ateş et al. showed that the NLR level in migraine patients with aura was higher during the attack than in the attack-free period, and the control group (13). In addition, Ocak et al. did not find any differences between migraine and other headaches for the NLR level. They suggested that it cannot play a role in the differential diagnosis (25).

In this study, we found a positive correlation between NLR level with migraine attack severity and disease duration. Since there is no reliable biomarker for follow-up of chronic pain diseases, an objective evaluation is often difficult. The fact that NLR is positively correlated with pain severity saves us from this difficulty and offers an objective evaluation opportunity. In addition, the

positive correlation between NLR level and the disease duration suggests that patients are constantly exposed to neurogenic inflammation even if they are not in the attack period. This increased exposure time may be related to the NLR level. However, Simsek et al. found that NLR level is not related to parameters such as age, disease duration, attack number and duration (12). This result is likely to be associated with the time of the NLR level evaluation, which is during the attack; the increased NLR level during the attack may not have provided objective information about the clinical features of the disease. Surprisingly, our study found no difference between episodic and chronic subtypes, suggesting that the NLR level may be independent of the number of attacks.

Our study has several limitations. First, only migraine patients without aura were evaluated, so future studies with larger numbers of patients, including migraine patients with aura, will help to understand the value of this parameter as a prognostic marker. Also, we conducted a cross-sectional study, which does not allow us to assess the direction of the association.

CONCLUSION

In conclusion, our study will help to individualize the follow-up and treatment of each patient, thanks to this objective biomarker. In addition, the fact that NLR is an easily accessible, inexpensive, and reliable parameter which is supposed to be a promising biomarker that may be used in the follow-up of chronic pain syndromes such as migraine.

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Conflict of Interest: The authors declare that they have no competing interest.

Ethical approval: This study was approved by the Antalya Kepez State Hospital Ethics Committee (Date: 16.6.2022, Decision No: 12/14) and was conducted following the principles of the Declaration of Helsinki.

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