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UTILIZING BIOMARKERS FOR RAPID ASSESSMENT OF HEADACHE IN THE EMERGENCY DEPARTMENT

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ABSTRACT

INTRODUCTION: Headache is a common presenting complaint in emergency departments (EDs), accounting for 2–5% of admissions. Although most headaches are benign, 4–5% are associated with life-threatening secondary pathologies. Accurate and rapid diagnosis is crucial, yet a standardized protocol for imaging and laboratory assessments is lacking. This study evaluates hematologic parameters as diagnostic tools for predicting acute pathologies in patients presenting with headaches.

MATERIAL AND METHODS: This retrospective study included 199 headache patients and 191 controls, aged 18 and above, who presented to the Ankara Etlik City Hospital between October 1 and December 15, 2022. Hematologic parameters, including neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-platelet ratio (NPR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), were analyzed, and compared with non-contrast brain computed tomography findings in patients with severe headaches.

RESULTS: NLR and NPR were significantly elevated in patients with acute pathologies on brain imaging. While platelet levels did not differ, indices like PLR and SII were elevated, indicating their diagnostic potential. Female patients were more prevalent; however, severe headaches and intracranial pathologies were more common in older male patients.

CONCLUSIONS: Hematologic parameters such as NLR, NPR, and SII serve as cost-effective, accessible biomarkers for stratifying headache patients in the ED. These markers can guide decisions on further imaging, particularly in high-risk populations. Future multicenter studies should validate these findings and explore their integration into clinical decision-making algorithms.

KEYWORDS: headache diagnosis; biomarkers; emergency department; hematologic parameters

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INTRODUCTION

Headache is the fifth most common symptom among emergency department (ED) visits, accounting for approximately 2–5% of all emergency admissions [1]. While it is a frequent presenting complaint, it also represents a significant cause of recurrent admissions [2]. Although the majority of headaches are attributed to benign causes, approximately 4–5% are associated with secondary pathologies that may be life-threatening, such as intracranial hemorrhage or mass lesions [3, 4]. Consequently, careful evaluation and early diagnosis of potentially serious conditions are critical for effective clinical management [3, 5]. Despite this, a clearly defined protocol for imaging and laboratory evaluation in headache management is lacking [6]. This ambiguity often shifts the focus to the patient's medical history and presenting

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complaints, resulting in increased reliance on neuroimaging and higher patient presentation rates.

In addition to clinical evaluation, numerous studies in the literature have highlighted the potential role of biomarkers in headache assessment [7, 8]. An ideal biomarker or biomarker panel could revolutionize the management and treatment of headaches by reducing unnecessary investigations and referrals [7]. Such biomarkers can accelerate the diagnostic process for secondary headaches, thereby contributing to reduced morbidity and mortality. Specifically, systemic inflammation indicators, such as increased levels of lymphocytes, neutrophils, and white blood cells (WBC), along with derived ratios including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-platelet ratio (NPR), and systemic immune-inflammation index (SII), have been implicated in the pathophysiology of headache [3–6].

This study aimed to evaluate the diagnostic value of hematologic parameters in predicting acute pathologies identified via brain tomography in patients presenting to the ED with headaches. Complete blood count, being a low-cost, rapid, and readily accessible test, offers significant potential for enhancing clinical practice. The authors propose that these parameters may facilitate the rapid assessment of patients with headaches in the ED and aid in the early identification of potentially serious underlying conditions.

MATERIAL AND METHODS

This retrospective study was conducted with patients aged 18 years and older who presented with headaches to the Emergency Medicine Clinic of Ankara Etlik City Hospital between October 1, 2022, and December 15, 2022. The study was approved by the Ankara Etlik City Hospital Ethics Committee (Approval number: AEŞH-BADEK-2025-0170). The primary aim was to evaluate the hematological parameters obtained at admission and compare these findings with the results of non-contrast brain computed tomography (CT) when clinically indicated. Patients whose clinical presentation warranted brain CT, as documented in physicians' notes, were categorized under the severe headache group. The hematological parameters of patients with and without pathologies on brain CT were analyzed alongside data from a control group for comparison.

Data collection

Patient demographic information, including age and gender, was recorded. Hematological parameters analyzed consisted of white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MON), eosinophil count (EO), red blood cell count (RBC), hemoglobin level (HGB), hematocrit (HCT), red cell distribution width (RDW), mean red cell volume (MCV), platelet count (PLT), mean platelet volume (MPV), and platelet distribution width (PDW). In addition, the following ratios were calculated to assess systemic inflammation and immune response: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-platelet ratio (NPR), and systemic immune-inflammation index (SII).

Inclusion criteria

1. Patients who presented to the emergency department with headaches between October 1, 2022, and December 15, 2022.
2. Individuals aged 18 years and older.
3. Availability of hematologic parameters from blood samples at the time of application.

Exclusion criteria

1. Patients under 18 years of age.
2. Patients with missing hematologic data on admission.

Study groups

- **Headache group:** 199 patients who met the inclusion criteria and presented with headaches. If non-contrast brain CT imaging was performed at the time of presentation, the findings (*e.g.*, ischemic cerebrovascular events, hemorrhagic cerebrovascular events, arteriovenous fistulas, aneurysms) were recorded.
- **Control group:** 191 patients aged 18 years and older with hematologic data available, who presented with non-headache conditions during the same period.

Statistical analysis

Statistical analysis was performed using the SPSS 26.0 (Statistics for Social Sciences Version 26) program. The compatibility of the variables with normal distribution was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics were presented as number (n) and percentage (%)

Table 1. **Hematological parameters of patients and controls**

Parameter	Patient group (n = 199)	Control group (n = 191)	p value
WBC	8.47 (3.02, 22.48)	8.29 (4.03, 23.96)	0.248
NEU	5.66 (1.47, 18.26)	4.84 (1.76, 18.98)	**0.005**
LYM	2.09 (0.26, 6.48)	2.39 (0.53, 5.48)	**< 0.001**
EO	0.09 (0, 0.93)	0.14 (0, 0.75)	**0.004**
PLT	276 ± 73.3	279.7 ± 77.5	0.448
MPV	10.2 (8.4, 13.4)	10.5 (8.8, 13.4)	0.054
PDW	11.6 (6.2, 18.7)	12.1 (8.7, 19.3)	0.168
HCT	41.3 (28.9, 55.3)	43.8 (20.4, 57.8)	**< 0.001**
HGB	13.5 (8.1, 18.3)	14.3 (6.2, 18.7)	**0.001**
NLR	2.75 (0.55, 22.96)	1.91 (0.6, 18.6)	**< 0.001**
PLR	125.47 (14.2, 774.19)	111.97 (31.41, 415.07)	**< 0.001**
NPR	0.021 (0.01, 0.08)	0.018 (0.01, 0.05)	**0.004**
SII	652.3 (50.7, 4560.3)	524.7 (125.7, 5636.6)	**< 0.001**

EO — eosinophil count; HCT — hematocrit; HGB — hemoglobin level; LYM — lymphocyte count; MPV — mean platelet volume; NEU — neutrophil count; NLR — neutrophil-to-lymphocyte ratio; NPR — neutrophil-to-platelet ratio; PLT — platelet count; PDW — platelet distribution width; PLR — platelet-to-lymphocyte ratio; SII — systemic immune-inflammation index; WBC — white blood cell count

for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median (min, max) for non-normally distributed parameters.

For the comparison of normally distributed continuous data, the independent samples t-test was applied, while the Mann–Whitney U test was used for non-normally distributed data. The Pearson chi-square test was utilized to analyze categorical data. Multivariate logistic regression analysis was conducted to identify risk factors predicting acute pathology on brain tomography. The diagnostic performance of hematologic parameters in detecting acute pathology was assessed using the area under the receiver operating characteristic (ROC) curve (AUC), and optimal cut-off values were determined using the Youden index.

The AUC was interpreted as follows: 0.90–1.0, excellent discriminator; 0.80–0.90, very good; 0.70––0.80, good; 0.60–0.70, fair; 0.50–0.60, poor; and 0.50, random guess. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 199 patients and 191 controls with similar age and gender distributions were included in the study. The demographic characteristics of the study groups are as follows: The median age of the patient group was 42 years (range: 18–80), while the control group had a median age of 42 years (range: 29–83). The proportion of females was 58.8% (n = 117) in the patient group and 54.5% (n = 104) in the control group. No significant differences were observed in terms of age ($p = 0.083$) or gender distribution ($p = 0.414$) between the groups.

Table 1 compares the hematological parameters of the patient and control groups. Significant differences were identified for several parameters. NEU, NLR, PLR, NPR, and SII were significantly elevated in the patient group compared to the control group ($p < 0.05$). Conversely, LYM, EO, HCT, and HGB were significantly lower in the patient group ($p < 0.05$). No significant differences were observed in WBC, PLT, MPV, or PDW. Conversely, LYM, EO, HCT, and HBG levels were significantly lower in the patient group ($p < 0.05$). No significant differences were observed in WBC, PLT, MPV, or PDW. Conversely, LYM, EO, HCT, and HBG were significantly lower in the patient group ($p < 0.05$). No significant differences were observed in WBC, PLT, MPV, or PDW.

The comparison of hematological parameters between patients with severe headache (n = 104) and those with non-severe headache (n = 95) is presented in Table 2. Patients with severe headaches were older ($p < 0.001$) and more likely to be male ($p = 0.019$) compared to those with non-severe headaches. No significant differences were observed in other hematological parameters between these two subgroups.

Table 2. **Comparison of hematological parameters by headache severity**

Parameter	Severe headache (n = 104)	Non-severe headache (n = 95)	p value
Age	46 (18, 80)	36 (19, 69)	**< 0.001**
Male	51 (49)	31 (32.6)	**0.019**
WBC	8.68 (3.02, 22.48)	8.33 (4.1, 15.15)	0.827
NEU	5.63 (1.47, 18.26)	5.66 (2.28, 12.53)	0.690
EO	0.11 (0.01, 0.93)	0.09 (0, 0.47)	0.205
LYM	2.06 ± 0.97	2.17 ± 0.86	0.966
PLT	272.5 ± 79.1	272.8 ± 69.3	0.851
MPV	10.3 ± 0.7	10.3 ± 0.9	0.810
PDW	11.7 (8.1, 16.4)	11.5 (8.2, 19.5)	0.778
HCT	41.8 ± 5.5	40.9 ± 4.2	0.181
HBG	13.6 ± 2.1	13.4 ± 1.7	0.375
NLR	2.56 (0.55, 22.96)	2.86 (0.86, 17.62)	0.638
PLR	127.8 (14.2, 774.2)	125.4 (27.4, 605.9)	0.554
NPR	0.02 (0.01, 0.08)	0.02 (0.01, 0.05)	0.788
SII	645.3 (50.3, 4560.3)	666.1 (111.4, 4196.2)	0.752

EO — eosinophil count; HCT — hematocrit; HGB — hemoglobin level; LYM — lymphocyte count; MPV — mean platelet volume; NEU — neutrophil count; NLR — neutrophil-to-lymphocyte ratio; NPR — neutrophil-to-platelet ratio; PLT — platelet count; PDW — platelet distribution width; PLR — platelet-to-lymphocyte ratio; SII — systemic immune-inflammation index; WBC — white blood cell count

Table 3. **Hematological parameters by acute pathology on brain CT**

Parameter	Pathology present (n = 30)	Pathology absent (n = 74)	p value
Age	51.9 ± 15.3	43.9 ± 10	**0.012**
Male	19	32	0.063
WBC	9.2 (4.73, 16.58)	8.25 (3.02, 22.48)	0.447
NEU	6.1 (2.68, 14.6)	4.92 (1.47, 18.26)	0.081
EO	0.07 (0.01, 0.93)	0.11 (0.01, 0.67)	0.181
LYM	1.85 ± 0.88	2.29 ± 0.98	**0.034**
PLT	251.8 ± 55.3	284.1 ± 85.5	0.059
MPV	10.34 ± 0.84	10.28 ± 0.69	0.698
PDW	12.04 ± 1.94	11.86 ± 1.53	0.606
HCT	42.93 ± 5.99	41.34 ± 5.19	0.179
HBG	14.02 ± 2.24	13.49 ± 2.05	0.246
NLR	3.24 (1.2, 22.96)	2.25 (0.55, 17.34)	**0.014**
PLR	137.85 (64.25, 774.19)	125.71 (14.2, 503.45)	0.312
NPR	0.024 (0.01, 0.06)	0.019 (0.01, 0.08)	**0.018**
SII	731.5 (304.1, 4343.23)	620.5 (50.26, 4560.33)	0.068

CT — computed tomography; EO — eosinophil count; HCT — hematocrit; HGB — hemoglobin level; LYM — lymphocyte count; MPV — mean platelet volume; NEU — neutrophil count; NLR — neutrophil-to-lymphocyte ratio; NPR — neutrophil-to-platelet ratio; PLT — platelet count; PDW — platelet distribution width; PLR — platelet-to-lymphocyte ratio; SII — systemic immune-inflammation index; WBC — white blood cell count

Brain imaging findings

Among the patients who underwent brain computed tomography (CT), acute pathological findings were observed in 30 cases. The distribution of pathologies included cerebral edema (n = 3), hemorrhage (n = 18), ischemia (n = 3), and space-occupying lesions (n = 6). Among the space-occupying lesions, four were newly diagnosed arachnoid cysts and two were metastases.

Table 3 summarizes the comparison of demographic and hematological parameters between

Table 4. **Predictive value of hematological parameters for acute pathologies**

Parameter	AUC	CI 95%	Sensitivity	Specificity	Cut-off value	p value
LYM	0.629	0.508–0.750	0.667	0.581	2.06	**0.041**
NLR	0.655	0.540–0.769	0.63	0.64	2.92	**0.014**
NPR	0.649	0.537–0.760	0.67	0.65	0.023	**0.018**

AUC — area under the curve; CI — confidence interval; LYM — lymphocyte count; NLR — neutrophil-to-lymphocyte ratio; NPR — neutrophil-to-platelet ratio

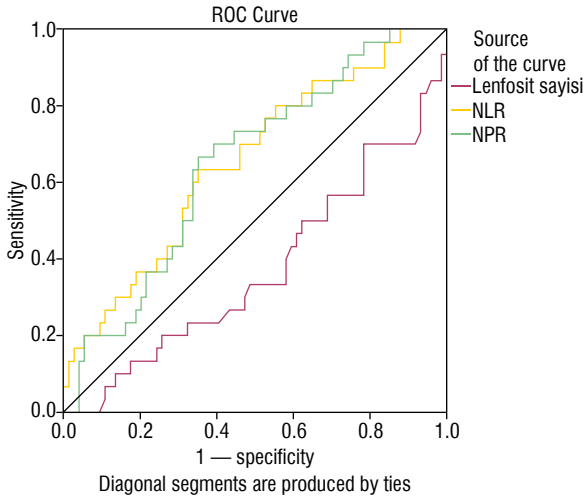

FIGURE 1. Diagnostic value of lymphocyte count, NLR, and NPR in detecting acute pathology on brain tomography

patients with and without acute pathologies identified on brain CT. Patients with acute pathologies (n = 30) were significantly older (p = 0.012) and had lower lymphocyte levels (p = 0.034). Additionally, NLR (p = 0.014) and NPR (p = 0.018) were significantly elevated in this group. No significant differences were noted for other hematological parameters.

The diagnostic utility of hematological parameters in predicting acute pathologies on brain CT was evaluated using receiver operating characteristic (ROC) analysis, as shown in Table 4 and Figure 1. Lymphocyte count, NLR, and NPR demonstrated moderate predictive value, with area under the curve (AUC) values of 0.629, 0.655, and 0.649, respectively (p < 0.05). The optimal cut-off values for predicting acute pathologies were determined as follows: lymphocyte count, 2.06; NLR, 2.92; and NPR, 0.023.

Multivariate analysis of risk factors for acute pathologies is summarized in Table 5. Age was identified as a significant risk factor, with each additional year increasing the likelihood of acute pathology by 5.9% (p = 0.004, OR: 1.059, 95% CI: 1.018––1.102). Lymphocyte count, NLR, and NPR did not reach statistical significance in multivariate analysis (p > 0.05).

DISCUSSION

Headache is one of the serious complaints of patients in the emergency department. Accurate and rapid diagnosis is important in patients with headaches due to the presence of vital conditions such as bleeding and masses in the differential diagnosis. The correlation of hematologic parameters with headaches for diagnosis in the emergency department has been evaluated in various studies in the literature. However, emergency department studies based on the severity and pathologic results of headaches are limited. The present study evaluated the hematologic differences between patients admitted to the emergency department with headaches compared to patients without headaches. The use of hematologic parameters was evaluated as a predictive factor in patients with severe headaches who underwent brain tomography.

Neutrophils, lymphocytes, and other white blood cells are the primary sources of proinflammatory and anti-inflammatory cells [9]. The response

Table 5. **Multivariate analysis of risk factors for acute pathologies**

Parameter	B	SE	Wald	p value	OR	CI 95%
Age	0.058	0.02	8.173	**0.004**	1.059	1.018–1.102
Lymphocyte	−0.210	0.367	0.326	0.568	0.811	0.395–1.665
NLR	0.104	0.087	1.441	0.230	1.109	0.936–1.315
NPR	1.083	1.496	6.103	0.958	2.952	–

B — beta; CI — confidence interval; NLR — neutrophil-to-lymphocyte ratio; NPR — neutrophil-to-platelet ratio; OR — odds ratio; SE — standard error

of circulating leukocytes to stress leads to an increase in the number of neutrophils and platelets and a decrease in the number of lymphocytes. Therefore, the ratio of these values to each other is used as an indicator of inflammation [9]. In the literature, PLR, NLR, and NPR values are frequently used as systemic inflammation and prognostic indicators [10]. The present study found an increase in neutrophil count, NLR, PLR, and SII levels and a decrease in lymphocyte and eosinophil levels. This is consistent with inflammatory processes and previous literature [10–12]. Yazar et al. [11] and Evrin et al. [12] showed that inflammatory markers including NLR and PLR were significantly higher in migraine patients compared to healthy controls and supported the hypothesis that systemic inflammation plays a role in the pathophysiology of headache.

The present findings underline the role of inflammation, especially in patients with acute pathologic findings on brain imaging where NLR and NPR are significantly elevated. When secondary headaches were examined, Eryiğit et al. [13] found that NLR was significantly higher in patients with subarachnoid hemorrhage (SAH) compared to patients with primary headaches. Oliveira et al. [14] found that NLR was significantly associated with recurrent bleeding and surgery in patients with chronic subdural hematoma. Sun et al. [15] found that NLR was a poor prognostic factor in cerebral venous sinus thrombosis. The present study found that pathologic results in brain tomography were significantly associated with NLR and NPR. Investigations are not planned in emergency departments for every patient with a headache. A decision is made with the combination of the patient's age, history, current complaints, and physical examination findings. Especially elevated NLR should play a warning role for clinicians and should suggest planning further investigations in these patients.

Given its cost-effectiveness and wide availability, NLR is widely utilized in diverse clinical settings. A meta-analysis conducted in 2024 highlighted that NLR was significantly elevated in patients with acute myocardial infarction and serves as a reliable predictor of MACE risk, particularly in STEMI patients [16]. These findings underscore the critical role of NLR in clinical decision-making, particularly in emergency departments, to inform further diagnostic investigations.

Platelets also play a complex role in headache mechanisms as supported by Danese et al. [17]. In the present study, while there was no significant difference in platelet levels between the groups, inflammatory indices including platelets such as PLR and SII were elevated, indicating their potential as diagnostic markers.

SII has been studied in the literature on headache. It was reported that SII and other oxidative stress markers were elevated in acute pain and there was a link between oxidative imbalance and headache severity [18]. Sadri et al. [19] reported that complaints regressed and SII tended to decrease significantly with nerve block applied to patients with headaches. The present study found significantly higher SII levels compared to the control group. However, no significant difference was found in pathologic diagnoses. This may be explained by the presence of different pathophysiologies due to different organic causes that trigger headaches.

Studies have shown that the highest prevalence of headache in adults is observed in the 40s and women have higher rates of headache than men at any age [4, 9, 12]. In the present study, the female population was higher in accordance with the literature [12, 20]. Despite this, more severe headache was observed in the male population. It was found that male patients were more likely to present with severe headaches or acute intracranial pathology with increasing age. Delaruelle et al. [21] reported that headache was more common in women than in men at all ages, even among the elderly. Marcus [22] reported that men showed more underlying pathologic conditions associated with headaches. Sundström et al. in their epidemiologic study in which they evaluated patients with SAH epidemiologically, stated that the frequency and severity were higher in women. Lindbohm et al. [23] stated that female gender was not an independent risk factor, but more SAH was observed in the female population. Although there are studies specific to certain diseases in the literature, studies examining secondary headaches, severity and poor outcome in the general population are limited. It is noteworthy that the present study evaluated this and emphasized the male population. The authors think that it will be a basis to prevent the prejudice of female dominance in the literature.

Limitations

Despite the promising findings, this study has several limitations. First, the retrospective design may

introduce selection bias and limit the ability to establish causal relationships. Second, the study was conducted at a single center, which may affect the generalizability of the results. Third, while hematologic parameters provide valuable information, their specificity for different headache etiologies remains limited. Future multicenter, prospective studies are needed to confirm these findings and to investigate the role of these markers in larger headache populations.

CONCLUSIONS

The findings of this study highlight the utility of hematologic parameters as cost-effective and accessible biomarkers in the emergency department setting. Parameters such as NLR, NPR, and SII may help rapidly identify patients at risk for serious intracranial pathologies, allowing timely intervention and potentially reducing the reliance on advanced imaging modalities in low-risk cases. Furthermore, the significant association between age and acute pathology observed in this study is consistent with previous reports suggesting that elderly patients presenting with headaches should be carefully evaluated for underlying pathologies. Furthermore, integrating these parameters into routine practice may help stratify patients and optimize resource utilization in busy EDs. Further research should focus on integrating hematologic markers into clinical decision-making algorithms for headache assessment in the ED. Combining these markers with advanced imaging techniques or clinical scoring systems may improve diagnostic accuracy.

Article information and declarations

Data availability statement

Data and materials used or analyzed during the present study are available from the corresponding author upon reasonable request.

Ethics statement

The study was approved by the Ankara Etlik City Hospital Ethics Committee (Approval number: AEŞH-BADEK-2025-0170).

Author contributions

This study did not include specific contributions from individual authors. All work was collectively conducted by the research team.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

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