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Hematologic Differences Between Migraineurs and Tension-Type Headache Patients

Khairul Putra Surbakti¹, Chairil Amin Batubara¹, Eka Mahendrayana²

ABSTRACT

Background: Headaches are among the most common complaints observed in neurology and medicine, notably migraines and tension-type headaches (TTH). **Objective:** The purpose of this study was to compare hematologic parameters comprised hemoglobin, hematocrit, platelets, leukocytes, neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) between migraineurs and tension-type headache patients. **Methods:** This cross-sectional study included 23 migraineurs and 23 TTH-diagnosed patients, in accordance with the International Classification of Headache Disorders-3 beta version (ICHD-3-beta). The patients underwent hematological laboratory testing, which included assessments of their serum levels of hemoglobin, hematocrit, platelets, leukocytes as well as neutrophils, lymphocytes and monocytes. **Results:** There were significant differences in the mean platelets serum levels between migraineurs and TTH patients, with migraineurs having $355.3 \times 103/\mu\text{l}$ ($SD \pm 47.4 \times 103/\mu\text{l}$) and TTH patients having $282.0 \times 103/\mu\text{l}$ ($SD \pm 44.2 \times 103/\mu\text{l}$), respectively ($p = 0.001$). However, there were no differences in the mean level of hemoglobin, hematocrit and leukocytes between the two groups. There was also a significant difference in PLR between migraineurs and TTH patients, with a ratio of 138.1 ($SD \pm 36.0$) in migraineurs and 110.2 ($SD \pm 21.9$) in TTH patients ($p = 0.003$), but no differences in NLR or LMR. **Conclusion:** The mean serum levels of platelets and platelets-to-lymphocyte ratio of migraineurs were significantly higher than TTH patients. However, there were no differences in the mean levels of hemoglobin, hematocrit, leukocytes, NLR and LMR between the two groups.

Keywords: hematologic parameters, migraineurs, tension-type headache.

1. BACKGROUND

Headache is a common symptom with a heterogeneous set of causes. The International Classification of Headache Disorders third edition beta (ICHD-3-beta) divides all headache entities into primary and secondary disorders and approximately 90% of headaches seen in general practice are of the primary variety, such as migraine, tension-type headache, or cluster headache [1]. The most prevalent types of primary headaches are migraine and tension-type headaches (TTH) [2]. Migraine affects 15% of the population, with TTH accounting for 60-80% of the cases [3].

Several studies have shown that there is a relationship between hematological parameters and headache [4]. Hematological parameters that are often used are hemoglobin (Hb), hematocrit (Ht), and leukocytes. The relationship between hematological parameters and headaches is generally related to anemia, increased blood viscosity and other factors. In a study conducted by Evrin and Katipoglu (2019) reported there were significant differences in the Hb and Ht of migraineurs patients compared to the control group and no significant differences were found in the levels of platelets and mean platelet volume [5, 6]. Meanwhile, in the study conducted by Gul et al. (2021) showed that platelets levels were significantly higher in migraineurs than controls but no significant differences were found in other hematological parameters [7]. Increased platelets levels are associated with the pathophysiology of migraine as an inflammatory process and platelets release many mediators such as thromboxane which can cause increased inflammation [7]. In a study conducted by Karabulut et al. (2016) found a significant difference in the number of platelets in migraineurs compared to the control group and this was associated with inflammation of cerebral neurovascular and extracerebral blood

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vessels in migraineurs. This inflammatory response is characterized by an increase in the number of circulating platelets [8].

There are several hypotheses in the pathophysiology of TTH, such as anemia conditions that can affect oxygen supply due to reduced oxygen-carrying red blood cells. In a study conducted by Ozdemir and Donder (2021) found leukocyte and platelets levels increased significantly in the Chronic Tension Type Headache (CTTH) group compared to the control group. This increased leukocyte level may be due to the inflammatory process that occurs. In addition, platelets levels were also found to increase significantly, increased platelets levels are also an indicator of the inflammatory process [9]. Research on hematological parameters in TTH has not been done much. However, it is said that anemia is a risk factor for the occurrence of TTH [8]. In a study conducted by Demirel et al. (2008) found a significant difference in the platelets levels of migraineurs patients with TTH and this is different from the study conducted by Arikan et al. (2021) which found no there is a significant difference to the patient's hematological parameters migraine and TTH [4, 10].

There is currently a view that migraine is closely related to the inflammatory process with the release of inflammatory agents in the activation and sensitization of peripheral nociceptors. Elevated levels of inflammatory markers can provoke nerve activation trigeminal and vasoactive neuropeptide releases that contribute to inflammation [11]. Inflammatory markers that are often and easily studied include C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) and D-dimer. A study carried out by Saricam (2020) found that there was a significant increase in inflammatory markers such as CRP, NLR, PLR and LMR in migraineurs compared to controls. However, no significant results were obtained on other hematological parameters such as hemoglobin, platelets and platelets [12]. A study conducted by Yucel et al. (2014) found an increase in inflammatory markers such as CRP and D-dimer in migraineurs [13]. A study conducted by Yildiz and Koca (2019) it was found that CRP increased significantly in the migraine group compared to healthy individuals as the control group [14].

In the pathophysiology of TTH, there is also a hypothesis about central and peripheral sensitization which is characterized by repeated pain and stress that will cause a decrease in the pain threshold. The effects of systemic or local inflammation on TTH are still not fully understood. Research conducted by Ozdemir and Donder (2021) showed that there were significant differences in NLR and PLR in TTH patients compared to the control group. Another marker of inflammation found to be increased, namely CRP [8]. In Arikan et al. (2021) found there were differences in NLR in migraineurs and TTH patients but not significant, other parameters were not examined [3].

The purpose of this study was to compare hematologic parameters comprised hemoglobin, hemato-

crit, platelets, neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) between migraineurs and tension-type headache patients.

2. OBJECTIVE

The purpose of this study was to compare hematologic parameters comprised hemoglobin, hematocrit, platelets, leukocytes, neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) between migraineurs and tension-type headache patients.

3. MATERIAL AND METHODS

Ethical Approval

This study had an approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara, with the ethical number: 116/KEPK/USU/2022.

Study Design

The cross-sectional study was carried out over a period of 5 months, from February to June 2022, in the outpatient clinic at Adam Malik General Hospital Medan and Universitas Sumatera Utara Hospital. The International Classification of Headache Disorders, Third Edition Beta (ICHD-3 beta) was used to diagnose 23 migraineurs and 23 TTH patients aged 18 or older in our study [1].

After obtaining a thorough description of the study procedures and aims, all subjects voluntarily agreed to participate and gave informed consent. Patients with a history of cancer, renal failure, liver illness, infection and inflammation, autoimmune disease, or diabetes mellitus were excluded.

Blood Analysis

All patients in the present study had their venous blood samples drawn under strict aseptic circumstances. Using the SYSMEC XN-1000 analyzer, a fresh blood serum sample from each patient was utilized to determine the levels of hemoglobin, hematocrit, platelets, leucocytes, and differential telling, which included neutrophils, lymphocytes, and monocytes. Migraine without aura is characterized as a recurring headache with at least 5 attacks lasting 4-72 hours and at least two of the following symptoms: unilateral site, pulsating quality, moderate to severe pain intensity, condition increased by daily physical activity, accompanied by one or more of the following: and/or photophobia and phonophobia. Tension-type headache is defined as at least 10 episodes of attacks lasting at least 1 day per month or 12 days per year. The headache lasts 30 minutes to 7 days and has at least two typical headache symptoms: usually bilateral, mild to moderate pressure or tightness and pain that does not worsen with daily activity, and no nausea but photophobia or phonophobia may be present [15].

Data analysis

To determine the differences of the mean serum levels of hemoglobin, hematocrit, platelets and PLR between migraineurs and TTH patients unpaired T-test was used, since the samples data were normally distributed,

whereas for leukocytes, NLR, and LMR, Mann-Whitney test was used due to samples data were not normally distributed. Tests of Normality Kolmogorov-Smirnov were used to determine whether data distributions were normally distributed. Descriptive analysis was used to determine the demographic characteristics of migraineurs and TTH patients at Adam Malik General Hospital Medan and Universitas Sumatera Utara Hospital. All data were presented as mean ± SD. P values <0.05 were considered statistically significant.

4. RESULTS

Characteristics of migraineurs and TTH patients as the subjects in this study based on sociodemographic that included gender, age, education, occupation, ethnicity and VAS score. The mean age of migraine sufferers was (39.1±15.1) years while in TTH patients the mean age was (43.6±15.5) years. In migraineurs and TTH patients, the maximum age range is 26-45 years as many as 14 patients (60.9%) in migraineurs while in TTH patients 10 patients (43.5%) as shown in following Table 1.

On examination of hematological parameters, the average hemoglobin level of migraineurs patients was 13.2 g/dl (SD±1.2 g/dl) while in TTH patients it was found to be 13.6 g/dl (SD±1.4 g/dl). Assessment of the mean difference using an unpaired T-test did not reveal a difference in the mean hemoglobin level in migraineurs and TTH patients (p = 0.243).

On the hematocrit parameter, the mean was 39.3% (SD±3.1%) in migraineurs and 40.8% (SD± 3.8%) in TTH patients. Unpaired T-test was used to assess the difference in the mean hematocrit in the two groups and there was no difference in the mean hematocrit (p = 0.169).

In leukocyte parameters, the mean was 8.2 x 10³/µl (SD±2.3 x 10³/µl) in migraineurs and 7.3 x 10³/µl (SD±1.7 x 10³/µl) in TTH patients. The assessment of the mean difference used the Mann-Whitney test to see if there was a difference in the mean between the two groups, there was no difference in mean (p = 0.102).

In the platelets parameter, it was found that 355.3 x 10³/µl (SD = 47.4 x 10³/µl) in migraineurs patients and 282.0 x 10³/l in TTH patients (SD = 44.2 x 10³/µl). By using the unpaired T-test, the mean difference in platelets levels was found in the two groups (p = 0.001).

Inflammatory marker parameters assessed in this study were values of platelets, platelets, NLR, PLR and LMR. On examination of hematological parameters, the average hemoglobin level of migraineurs patients was 13.2 g/dl (SD±1.2 g/dl) while in TTH patients it was found to be 13.6 g/dl (SD±1.4 g/dl). Assessment of the mean difference using an unpaired T-test did not reveal a difference in the mean hemoglobin level in migraineurs and TTH patients (p = 0.243).

On examination of hematological parameters in leukocyte parameters, the mean was 8.2 x 10³/µl (SD±2.3 x 10³/µl) in migraineurs and 7.3 x 10³/µl (SD±1.7 x 10³/µl) in TTH patients. The assessment of the mean difference used the Mann-Whitney test to see if there was a

Characteristics	Migraine n = 23 n (%)	TTH n = 23 n(%)
Age (year), Mean (SD)	39.1(15.1)	43.6(15.5)
≤ 25 years	3(13.0)	4(17.4)
26 - 45 years	14(60.9)	10(43.5)
46 - 65 years	4(17.4)	8(34.8)
> 65 years	2(8.7)	1(4.3)
Gender		
Male	21(91.3)	16(69.6)
Female	2(8.7)	7(30.4)
Education		
Bachelors	9(39.1)	5(21.7)
Senior High School	11(47.8)	10(43.5)
Middle school	3(13.0)	8(34.8)
Occupation		
Civil servants	5(21.8)	3(13.0)
Private employee	4(17.4)	5(21.7)
Self employee	1(4.3)	1(4.3)
Housewife	9(39.1)	9(39.1)
Farmer	1(4.3)	1(4.3)
Student	3(13.0)	4(17.4)
Ethnic group		
Bataknese	10(43.5)	10(43.5)
Malay	6(26.1)	7(30.4)
Javanese	5(21.7)	3(13.0)
Acehnese	2(8.7)	3(13.0)
VAS, Median (min-max)	4(3-6)	4(3-4)

Table 1. Characteristics of migraineurs and tension-type headache patients

Parameter	Migraine, Mean (SD)	TTH, Mean (SD)	p
Hemoglobin (gr/dl)	13.2 (1.2)	13.6 (1.4)	0.243 ^a
Hematocrit (%)	39.3 (3.1)	40.8 (3.8)	0.169 ^a
Leukocyte (10 ³ /µl)	8.2 (2.3)	7.3 (1.7)	0.102 ^b
Platelets (10 ³ /µl)	355.3 (4.4)	282.0 (44.2)	0.001 ^a

Table 2. Comparison of Hematological Parameters between Migraineurs and Tension-type headache Patients. ^aUnpaired T-test; ^bMann-Whitney test; significant p <0.05; SD, standard deviation TTH, tension-type headache; gr/dl, Gram per deciliters; µl, Microliters

difference in the mean between the two groups, there was no difference in mean (p = 0.102).

In the platelets parameter, it was found that 355.3 x 10³/µl (SD±47.4 x 10³/µl) in migraineurs patients and 282.0 x 10³/µl in TTH patients (SD±44.2 x 10³/µl). By using the unpaired T-test, the mean difference in platelets levels was found in the two groups (p = 0.001). Table 2 shows the comparison of hematological parameters in migraineurs and TTH patients.

In the NLR parameter, the mean of migraine patients was 1.9 (SD±0.6) and 1.6 (SD± 0.5) in TTH patients. The mean difference was assessed using the Mann-Whitney test and there was no difference in mean between the two groups (p = 0.072). The PLR parameter for migraineurs was 138.1 (SD±36.0) and in TTH patients it

Parameter	Migraine, Mean (SD)	TTH, Mean (SD)	p
NLR	1.9 (0.6)	1.6 (0.5)	0.072 ^b
PLR	138.1 (36.0)	110.2 (21.9)	0.003 ^a
LMR	5.3 (1.5)	4.9 (1.5)	0.328 ^b

Table 3 Comparison of NLR, PLR and LMR between Migraineurs and Tension Type Headache Patients. ^aUnpaired T-test; ^bMann-Whitney test; significant $p < 0.05$; SD, standard deviation; TTH, tension-type headache; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

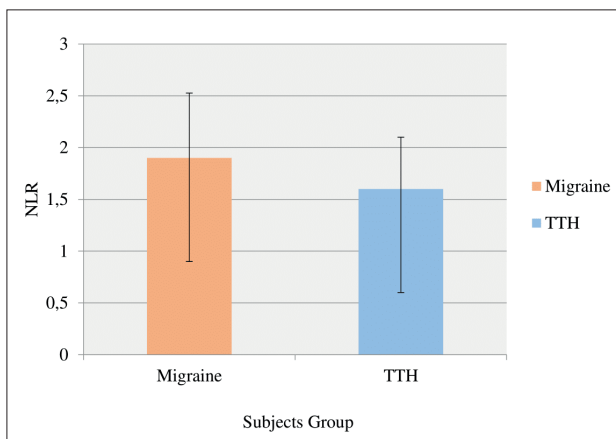


Figure 1. Comparison of neutrophil-to-lymphocyte ratio (NLR) between migraineurs and TTH patients. Mann-Whitney test showed no significant difference of NLR values ($p=0.072$).

was 110.2 (SD±21.9). In the assessment of the mean difference using the paired T-test, it was found that there was a difference in the mean PLR in the two groups ($p = 0.003$).

The leukocyte-to-monocyte ratio parameter for migraineurs patients was 5.3 (SD±1.5) and TTH patients were 4.9 (SD±1.5). By using the Mann-Whitney test to assess the difference in the mean of the two groups, it was found that there was no difference in the mean of the LMR parameters ($p = 0.328$). Comparison of NLR, PLR and LMR between Migraineurs and Tension Type Headache Patients are presented in Table 3.

Neutrophil-to-lymphocytes ratio between migraineurs and TTH patients was not significantly different, PLR was significantly higher, LMR was not significant different compared to TTH patients as shown in Figure 1, 2 and 3 respectively.

5. DISCUSSION

This research is descriptive analytic with cross sectional data collection method using primary data sources obtained from all migraineurs and TTH patients with the aim of knowing differences in hematological parameters, migraineurs and TTH patients.

In terms of age characteristics, migraineurs in this study had a mean of (39.1±15.1) years, while TTH sufferers had a mean of (43.6±15.5) years. The highest age range for migraineurs and TTH sufferers was at the age of (26-45) year range with 14 sufferers (60.9%) in migraineurs and 10 sufferers (43.5%) in TTH. This is in line with previous research which showed that the age

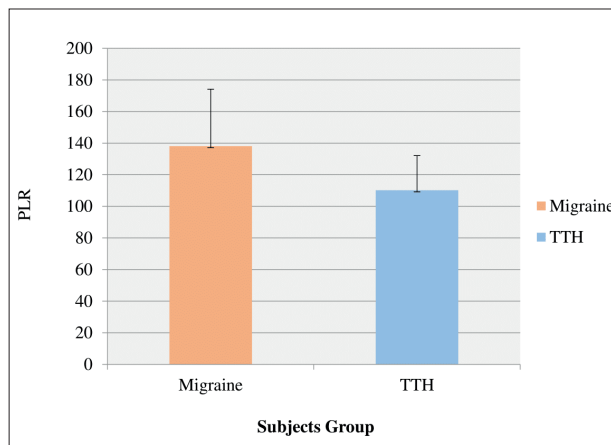


Figure 2. Comparison of platelet-to-lymphocyte ratio (PLR) between migraineurs and TTH patients. Unpaired T-test showed significantly higher values of PLR in migraineurs ($p=0.003$).

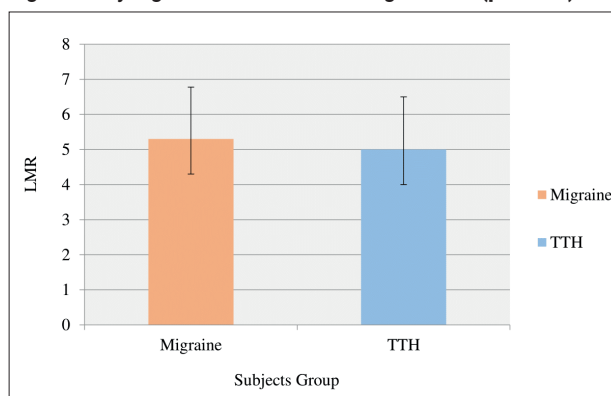


Figure 3. Comparison of lymphocyte-to-monocyte ratio (LMR) between migraineurs and TTH patients. Mann-Whitney test showed no significant difference of LMR values ($p=0.378$).

of most migraine sufferers was in the (25-55) year range [15]. Migraine can appear from adolescence, young adulthood to pre-elderly age [16].

In terms of gender characteristics, the most sufferers were found in women, both in migraineurs and TTH sufferers. This is in line with previous research conducted by Yilmaz et al. (2021) and Arikan et al. (2020) which showed that women suffer from migraines and TTH more compared to men [4, 17]. Epidemiologically, both migraine and TTH are more common in women than men with a ratio of 3: 1. In a study conducted by Neumeir et al.(2021) which highlighted the high prevalence of migraine and TTH in women, several things were found which can underlie such as the presence of comorbid diseases, response to treatment, response to pain and problems faced, anxiety and depression and hormonal factors [18].

Hematological parameters studied in this study consisted of hemoglobin (Hb), hematocrit (Ht), leukocyte and platelets levels. On examination of hematological parameters, the average hemoglobin level of migraineurs patients was 13.2 g/dl (SD±1.2 g/dl) while in TTH patients it was found to be 13.6 g/dl (SD±1.4 g/dl). There was no significant difference in hemoglobin levels in migraineurs and TTH patients ($p = 0.243$). The results of this study are relevant to the previous study conducted by Arikan et al. (2020) which found no differ-

ence in hemoglobin parameters between the two groups with the same mean value as this study, namely 13.56 g/dl in migraine and 13.43 g/dl in TTH. Routine hematology reference values are generally in adults for Hb 13.5 – 16.5 g/dl (in men) and 12.0 – 15.0 g/dl (in women) this is still within the normal range. Theoretically, high hemoglobin can cause headaches by increasing blood viscosity. Hyperviscosity is thought to cause pain by damaging the microcirculation, causing cerebral hypoxia, reactive vasodilation and neurogenic inflammation. [5, 8]. While low hemoglobin will cause the oxygen supply to the brain to decrease, resulting in ischemia in the muscles. Hypoxic conditions in turn will cause vasodilation and the formation of NO and inflammatory mediators [4].

On the hematocrit parameter, the mean was 39.3% (SD±3.1%) in migraineurs and 40.8% (SD±3.8%) in TTH patients. There was no significant difference in the mean hematocrit in the two groups ($p = 0.169$). The results of this study are relevant to previous research conducted by Arikan et al. (2020) which found no difference in hematocrit parameters between the two groups with a mean value of 40.22% in migraineurs and 43.65 % in TTH [4]. Likewise in a study conducted by Yilmaz et al. (2021) which did not find a significant difference in the hematocrit value of the two groups with a hematocrit value of 40.3% in migraineurs and 41.6% in TTH patients. Normal hematocrit reference values are 41 – 50% (in men) and 30 – 44% (in women) [5]. In this study, the hematocrit values for both groups were still in the normal range. Theoretically, a high hematocrit can cause headaches by increasing blood viscosity. Hyperviscosity is thought to cause pain by impairing microcirculation resulting in cerebral hypoxia, reactive vasodilation and neurogenic inflammation [4].

In leukocyte parameters, the mean was $8.2 \times 10^3/\mu\text{l}$ (SD±2.3 $\times 10^3/\mu\text{l}$) in migraineurs and $7.3 \times 10^3/\mu\text{l}$ (SD±1.7 $\times 10^3/\mu\text{l}$) in TTH patients. There was no difference in mean between migraineurs and TTH patients ($p = 0.102$). This study is relevant to study conducted by Arikan et al. (2020) which found no significant difference in leukocyte levels in migraineurs and TTH patients with the mean leukocyte levels in migraineurs $7.67 \times 10^3/\mu\text{l}$ (SD±1.94 $\times 10^3/\mu\text{l}$) and in TTH patients $8.41 \times 10^3/\mu\text{l}$ (SD±8.47 $\times 10^3/\mu\text{l}$). In addition, it is the same as the research that conducted by Yilmaz et al. (2021) who found that there was no significant difference in leukocyte levels between migraineurs and TTH patients with a mean leukocyte level of migraineurs $7.67 \times 10^3/\mu\text{l}$ (SD±8.94 $\times 10^3/\mu\text{l}$). The reference value for platelets is 4.5 – 11 $\times 10^3/\mu\text{l}$ for both men and women [5]. Leukocyte values in this study were still in the normal range. Platelets play the most important role in phagocytosis and immunity to protect the body against infection or foreign bodies [5]. Migraine headaches and TTH attacks are the result of inflammation of the cerebral neurovascular and extracerebral blood vessels, this inflammatory response with an increase in the number of circulating platelets. Another study comparing leukocyte levels in migraineurs patients with healthy subjects found significant differences such as a study conducted

by Karabulut et al.(2016) found a significant difference in the number of platelets in migraineurs compared to the control group with a value of (7.95 ± 2.210) ($p = 0.008$) compared to (7.11 ± 1.71) [8]. Likewise in TTH patients in a study conducted by Ozdemir and Donder (2021) found leukocyte levels increased significantly in the CTTH group compared to the control group with (8.38 ± 0.69) ($p = 0.028$) and (7.94 ± 0.82) . However, if we observe the leukocyte values in both the migraineur and TTH groups, the two studies above are still within the normal range but significantly different from the leukocyte levels in the control group [9].

In the platelets parameter, it was found that $355.3 \times 10^3/\mu\text{l}$ (SD±47.4 $\times 10^3/\mu\text{l}$) in migraineurs patients and $282.0 \times 10^3/\mu\text{l}$ in TTH patients (SD±44.2 $\times 10^3/\mu\text{l}$). By using the unpaired T-test, the mean difference in platelets levels was found in the two groups ($p = 0.001$). This research is relevant to a study conducted by Aksoy (2020) found differences in platelets levels between migraineurs and TTH patients with platelets levels of migraineurs $313.42 \times 10^3/\mu\text{l}$ (SD±73.95 $\times 10^3/\mu\text{l}$) and $292.10 \times 10^3/\mu\text{l}$ in TTH patients (SD±70.42 $\times 10^3/\mu\text{l}$) with $p = 0.025$ [19]. Likewise, a study conducted by Demirel et al. (2008) which found differences in platelets levels in migraineurs and TTH patients with the platelets levels of migraineurs at $280.1 \times 10^3/\mu\text{l}$ (SD±63 $\times 10^3/\mu\text{l}$) and in TTH patients (255×10^3) / μl (SD±69.9 $\times 10^3/\mu\text{l}$) with p value = 0.003 [10]. Platelets are nulliploid anuclear cells (no nucleus in their DNA) with irregular shape with a diameter of 2-3 μm which is fragmentation from megakaryocytes. Platelets circulate in the blood and are involved in cellular-level hemostasis mechanisms in the blood clotting process by forming blood clots. Platelets reference value is 150 – 450 $\times 10^3/\text{mm}^3$ in both sexes [4]. Platelets will increase in blood circulation within 24 hours after the occurrence inflammation or infection. This increase in platelets levels is related to the pathophysiology of migraine as an inflammatory process and platelets release many mediators such as thromboxane which can cause increased inflammation and describe the possible chronicity of the disease [7].

Inflammatory marker parameters assessed in this study were levels of platelets, platelets, NLR, PLR, and LMR. In the NLR parameter, the mean of migraine patients was 1.9 (SD±0.6) and 1.6 (SD± 0.5) in TTH patients. Not found the mean difference between the two groups ($p = 0.072$). In previous studies that compared the NLR of migraineurs to the control group or the NLR of TTH patients to the control group, there were differences [8, 9]. However, there were differences in the population of the study subjects with this study. In a previous study conducted on subjects with chronic headaches. On the other hand, in previous studies comparing the NLR of migraineurs and TTH patients, there were no differences as did Arikan et al. (2020) [4]. Normal NLR values in Indonesia have not been data, but in a study conducted in South Korea by Lee et al. (2018) it was found in the population adults are in the range 0.86 – 2 [20, 21]. Neutrophil-lymphocyte ratio is a biomarker that reflects the balance between two aspects of the im-

immune system, those are acute and chronic inflammation (as indicated by neutrophil count) and adaptive immunity (lymphocyte count). Neutrophils are responsible for the first line of host immune response against invading pathogens through different mechanisms, including chemotaxis, phagocytosis, releasing of Reactive Oxygen Species (ROS), granular proteins and cytokine production and release. Lymphocytes play a role in adaptive cells. Neutrophils can increase < 6 hours after infection or inflammation and if the infection process continues then neutrophil levels will continue to increase so that it can also be used as a predictor of prognosis in patients with severe infections [22, 23].

The PLR parameter for migraineurs was 138.1 (SD±36.0) and in TTH patients it was 110.2 (SD±21.9). In the assessment of the mean difference using the unpaired T-test, it was found that there was a difference in the mean PLR between the two groups ($p = 0.003$). In a study conducted by Saricam (2020) found that there was a significant increase in the PLR of migraineurs patients compared to the control group with a mean of (133.97 ± 42.15) ($p = 0.006$) compared to (127.45 ± 69.4.11). Likewise, the PLR of TTH patients compared to the control group was found to be an average of (185.90 ± 58, 52) ($p = 0.001$) compared to (136.12 ± 50.31) significantly increased in chronic TTH patients compared to the control group [12]. However, in the study comparing the PLR values of migraineurs and TTH patients, there was no significant difference in the PLR of migraineurs and controls with $p = 2.70$ which is different from the results obtained in this study. Platelets-to-lymphocyte ratio (PLR) was calculated as the ratio of platelets to absolute lymphocyte count (obtained from the same blood sample). In this study also obtained an increase in platelets levels, the mean of which was significantly different between migraineurs and TTH patients. This increase in platelets levels is related to the pathophysiology of migraine as an inflammatory process and platelets release many mediators such as thromboxane which can cause increased inflammation [7].

The LMR parameter for migraineurs patients was 5.3 (SD±1.5) and TTH patients were 4.9 (SD± 1.5). By using the Mann-Whitney test to assess the difference in the mean of the two groups, it was found that there was no difference in the mean of the LMR parameters ($p = 0.328$). There are no studies assessing the differences in LMR between migraineurs and TTH patients, studies that previously assessed LMR in migraineurs compared to healthy subjects and found no mean differences. Lee et al. (2018) were found in the adult population in the range of 3.45 – 7.17 [20, 24]. Lymphocytes increased in normal conditions acute infection, smoking and the response to stress while monocytes will increase in inflammatory conditions or chronic infection. The ratio of lymphocytes and monocytes in other studies has been used as an indicator of the prognosis of malignancy as well as the prognosis of the severity of atherosclerosis and rheumatoid arthritis [12].

In this study, the inflammatory markers that showed the mean difference between migraineurs and TTH pa-

tients were PLR. The mean values of PLR were significantly higher in migraineurs compared to TTH patients. Migraine is associated with an increased risk of cardiovascular disease and a 2-fold increase in the risk of stroke [25]. Repeated migraine attacks are also associated with arteriopathies of blood vessels, especially cranial blood vessels so that migraine is said to be a neurovascular disease associated with the occurrence of Cortical Spreading Depression (CSD), inflammation neurogenic and cranial vascular contractility dysfunction [25].

The platelets-to-lymphocyte ratio can be a key factor to emphasize the interaction between the 2 main components of atherothrombosis, thrombosis and inflammation. Previous studies have shown that higher platelets and lower lymphocyte counts are associated with cardiovascular disease [26]. The results of this study support the neurovascular and inflammatory theory of migraine pathophysiology which is higher than TTH.

6. CONCLUSION

In the present study, there was found a significant difference of the mean serum levels of platelets and PLR between migraineurs and TTH patients. The results of this study support the theory of neurovascular and inflammation in the pathophysiology of migraine and TTH since the increase in platelets levels is related to the pathophysiology of migraine as an inflammatory response and the platelets release many mediators such as thromboxane and serotonin that can cause increase inflammation. Blood serotonin levels reflect intraplatelet serotonin because most blood serotonin is stored inside platelets. Also, increased platelet levels are an important indicator of an inflammatory response. Despite inflammation occurs in both migraine and TTH pathophysiology, the higher level of platelets as one of the inflammatory markers in migraineurs compared to TTH may indicate that the inflammatory process in migraineurs is greater than in TTH patients. We believe that more comprehensive and controlled studies are needed to evaluate in detail the factors involved in the pathogenesis of migraine and TTH.

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