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ORIGINAL RESEARCH

A Case-Control Study of Neutrophil-Lymphocyte Ratio as a Biomarker of Inflammation in Adults with Epilepsy

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Abstract

Background: There is growing evidence that inflammation plays a specific role in the pathogenesis of epilepsy and seizures also induce inflammation. The Neutrophil/Lymphocyte ratio (NLR) is an emerging inflammatory biomarker of epilepsy.

Objectives: To determine the association between epilepsy and Neutrophil /Lymphocyte Ratio among adults.

Methods: Adults with epilepsies the attending outpatient neurology clinics at two Nigerian tertiary health facilities, were recruited. One hundred cases and one hundred age-matched, healthy controls were recruited. The total white blood cell (WBC) and its differential counts were extracted from Full Blood Count (FBC) results and NLR was calculated. The predictors of the association between WBC parameters and epilepsy were established using a linear regression model derived from WBC parameters associated with epilepsy.

Results: Out of 100 cases and controls, there was no gender-related statistical difference between the cases and controls ($p = 0.777$). There was no difference between the mean ages of cases and control ($p = 0.058$). The total mean white blood cell count among the cases was $8.80\pm9.84\times10^9$ cells/L compared to was $6.30\pm1.90\times10^9$ cells/L in the controls, ($p = 0.013$). The mean neutrophil count in the cases was $59.00\pm17.89\times10^9$ cells/L compared to $49.50\pm15.44\times10^9$ cells/L among the controls ($p < 0.001$). The mean NLR for the cases was 4.24 ± 10.44 compared to 1.84 ± 2.26 in the controls ($p = 0.026$). The Neutrophil/Lymphocyte Ratio ($p = 0.013$) and Basophil ($p < 0.001$) predicted epilepsy on linear regression analysis.

Conclusion: This study shows a clear difference in the TWBC and NLR with between adults with epilepsies and health controls.

Key words: Adults, Biomarker, Epilepsy, Inflammation, Neurological disease, Neutrophil/Lymphocyte Ratio.

Introduction

Epilepsy is the most common non-communicable disease of neurological origin that affects approximately 70 million people worldwide, with more than 80% in sub-Saharan Africa. [1] There is growing evidence that inflammation plays specific role in pathogenesis of epilepsy and that epilepsy in turn induces inflammation. Disruption of Blood Brain Barrier (BBB), release of Interluekin-1β (IL-1 β), Tumour Necrosis Factor (TNF), Interleukin-6 (IL-6), activation and upregulation of microglia cells, induction

of cyclooxygenase (COX) enzyme, infiltration of hippocampus by leucocytes synaptic reorganization, apoptosis and component of compliment system, infiltration of hippocampus and temporal lobe by leucocytes are part of the inflammatory bases of epilepsy. [2–5] It has been proposed that epileptogenesis can be modulated by inflammatory response due to increased level of cytokines and chemokine expressions in the cerebrospinal fluid and peripheral blood of patients with epilepsy. Neutrophil/Lymphocyte Ratio (NLR) in peripheral blood reflects the balance between systemic inflammation and immunity and is emerging as a cheap prognostic biomarker in many diseases. [2]

Consistently, high levels of NLR were linked to poor prognosis and reduced survival in chronic conditions.[2,4,5] Several studies have indicated that increased NLR levels are associated with a worse prognosis or shorter survival in various malignancies, including brain glioma and brain metastases, and are associated with disease development in inflammatory brain diseases. [2,4,5] TNF*a* and neutrophils regulate neuronal hyper-excitability. Apart from releasing neuroexcitatory cytokines, neutrophils may indirectly affect neuronal hyper-excitability by releasing chemokine that attract other inflammatory agents. [2,3,6] There are no sufficient data on NLR in Nigerian patients with epilepsy. Therefore, this study is aimed at determining the association between epilepsy and NLR.

Methods

In this case-control study, adults attending the Outpatient Neurology Clinics at the Olabisi Onabanjo University Teaching Hospital, Sagamu and the Federal Medical Centre, Abeokuta, were recruited. The cases and the age-matched healthy controls were recruited from the registered patients in the clinics after obtaining their consent. The participants used as cases had epilepsy with the diagnosis and classification of the epilepsy done according to the International League Against Epilepsy (ILAE) criteria. The participants used as controls were those without history of seizure and normal electroencephalogram (EEG). Electroencephalography (EEG) was performed for the controls to exclude electroencephalographic features of seizure, although abnormal EEG does not imply seizure disorder. Epileptiform pattern and other EEG findings were defined according to standard international criteria. [7–9] One hundred cases and one hundred age match healthy controls were selected by convenient sampling method.

Sample size determination

The sample size for this study was calculated using the formula:

$N = (Z_{\alpha/2} + Z_{\beta})^2 \times p(1-p)/d^2$

Where:

N=Minimum sample size required for the study.

$Z_{\alpha/2}$ = the normal deviates for the Type I error at 5%: 1.96.

Z_{β} = the normal deviates for Type II error at 10%: 1.28.

p = Prevalence of epilepsy was set at 5.6/1000 based on a previous study done at Igboora.

d = Margin of precision which was set at 3% since the interested prevalence was less than 5%.

$N = (1.96 + 1.28)^2 \times 0.0056(1-0.0056)/0.032$

N = 64.97.

To account for non-response, an increase of 20% was made which brought the sample size to 80 cases. The minimum required sample size for cases was 80.

Ethical considerations

This was obtained from Ethical Committees of the Olabisi Onabanjo University Teaching Hospital (OOUTHHREC/275/2019AP) and Federal Medical Centre, Abeokuta (FMCA/243/HREC/03/2016).

The participants were fully informed on the research protocol detailing the purpose, methods, risks, and benefits of the research. Each of the participants, thereafter, voluntarily

gave a written and well understood informed consent.

Data collection

A pre-established questionnaire was used to obtain the socio-demographic parameters of the participants. An auto-analyser (Sysmex®, Haematology analyzer) was used to analyse the venous blood samples obtained. The venous blood samples were drawn from the cases at least, one month from the last seizure. White blood cell counts derived from the full blood count was used to calculate NLR by dividing the Neutrophil count by Lymphocyte count.

Data analysis

The IBM Version 23 of the Statistical Package for Social Science (SPSS) was used to analyse the data. Pearson Chi-squared test was used to compare the categorical variables of cases and control, while independent sample t-test was used for continuous variables. Independent sample t-test or one-way ANOVA (where appropriate) was used to compare the mean values of WBC parameters. A linear logistic regression model was used to examine the predictors of the association between epilepsy and WBC parameters. Statistical significance was determined at $p<0.05$.

Results

Out of the 100 cases, there were 49 (49.0%) males and 51 (51.0%) females whereas the control group was made up of 47 (47.0%) males and 53 (53.0%) females. The difference in gender distributions lacked statistical significance ($p = 0.777$). The mean age of the cases was 40.11±19.87years and 34.55±20.58 years the for the control group ($p = 0.058$). Table I shows comparison between the sociodemographic characteristics of the cases and control.

The mean total white cell count for the cases was 8.80±9.84 $\times10^9$ cells/L compared to 6.30±1.90 $\times10^9$ cells/L for the controls ($p = 0.013$). The mean neutrophil counts were 59.00±17.89 $\times10^9$ cells/L and 49.50±15.44 $\times10^9$ cells/L for the cases and controls respectively ($p < 0.001$). The mean lymphocyte count in cases was 35.29± 42.78 $\times10^9$ cells/L and 39.78 ±13.90 $\times10^9$ cells/L for the cases and controls respectively ($p = 0.319$). Also, the mean NLR for the cases and controls were 4.24±10.44 and 1.84±2.26 respectively ($p = 0.026$) as depicted in Table II.

Among the cases, the mean total WBC for the males was 7.57 ± 3.38 $\times10^9$ cells/L and 9.95±13.27 $\times10^9$ cells/L for the females. The mean neutrophil count in the males was 58.96±18.78 $\times10^9$ cells/L compared to 59.03±17.18 $\times10^9$ cells/L in the females. Overall, the mean lymphocyte count was 59.03±17.18 $\times10^9$ cells/L; 30.13±14.94 $\times10^9$ cells/L for the males and 40.24±17.18 $\times10^9$ cells/L for the females. The mean monocyte count was significantly higher at 7.66±4.9 $\times10^9$ cells/L in the males compared to 5.52±3.45 $\times10^9$ cells/L in the females ($p = 0.014$). The NLR in males and females were 7.63±26.85 and 4.71±17.93 respectively ($p = 0.494$) as shown in Table III.

The mean total WBC was higher among epileptics with structural aetiology (10.98±15.59 $\times10^9$ cells/L) in contrast to others as shown in Table IV. The mean NLR among epileptics with structural aetiology was 3.44±3.22 compared to 6.42±24.29 for those with idiopathic disease. Similarly, the mean values of monocyte count, eosinophil count and basophil count were higher among epileptics with idiopathic disease as shown in Table IV. The majority (89; 89%) of the cases had primarily generalized seizure, 5 (5.0%) had focal seizures, 4 (4.0%) had combined types while 2 (2.0%) were unclassified. Comparing the WBC parameters among the seizure subtypes the mean total WBC and mean NLR were higher among those with primarily generalized seizures (9.00±10.34 $\times10^9$ cells/L) and 6.71±22.4 respectively).

Table I: Sociodemographic characteristics of adults with epilepsy and the controls

Characteristics		*Cases (n = 100)*	*Controls (n = 100)*	*Chi-Squared*	*p-value*
Gender	Male	49 (49.0)	47 (47.0)	0.08	0.777
	Female	51 (51.0)	53 (53.0)		
Marital status	Never married	51 (51.0)	62 (62.0)	6.928	0.140
	Married	44 (44.0)	33 (33.0)		
	Separated	2 (2.0)	0 (0.0)		
	Widow/ Widower	2 (2.0)	5 (5.0)		
	Divorced	1 (1.0)	0 (0.0)		
Education	Primary	3 (3.0)	2 (2.0)	19.134	<0.001
	Secondary	44 (44.0)	19 (19.0)		
	Tertiary	49 (49.0)	79 (79.0)		
	Postgraduate	2 (2.0)	0 (0.0)		
Ethnic group	Yoruba	88 (88.0)	95 (95.0)	3.518	0.172
	Igbo	11 (11.0)	5 (5.0)		
	Others	1 (1.0)	0 (0.0)		

Table II: Comparison of the mean values of WBC parameter between the cases and the controls

Groups	*TWBC (× 10⁹/l)*	*Neutro (× 10⁹/l)*	*Lympho (× 10⁹/l)*	*NLR*	*Mono (× 10⁹/l)*	*Eosin (× 10⁹/l)*	*Baso (× 10⁹/l)*
Cases (n = 100)	8.80±9.84	59.0±17.89	35.29±42.78	4.24±10.44	6.57±4.33	2.25±3.58	0.59±1.02
Controls (n = 100)	6.30±1.90	49.50±15.44	39.78±13.90	1.84±2.26	5.98±2.81	3.67±9.24	1.99±2.17
t-test	2.496	4.001	-0.998	2.247	1.135	-1.427	-5.759
p-value	0.013	<0.001	0.319	0.026	0.258	0.155	<0.001

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; Lymph-Lymphocyte count; NLR-Neutrophils/Lymphocytes Ratio; Mono-Monocyte count; Eosin-Eosinophil count; Baso-Basophil count; t-Student's t-test.

Table III: Comparison of the mean values of WBC parameter in relation to gender of the cases

Gender	*TWBC (× 10⁹/l)*	*Neutro (× 10⁹/l)*	*Lympho (× 10⁹/l)*	*NLR*	*Mono (× 10⁹/l)*	*Eosin (× 10⁹/l)*	*Baso (× 10⁹/l)*
Male (n = 49)	7.57±3.38	58.96±18.78	30.13±14.94	7.63±26.85	7.66±4.90	2.42±4.12	0.47±0.47
Female (n = 51)	9.95±13.27	59.03±17.18	40.24±57.95	4.71±13.93	5.52±3.45	2.07±3.01	0.71±1.34
t-test	-1.206	-0.021	-1.172	0.679	2.511	0.494	-1.202
p-value	0.231	0.983	0.244	0.494	0.014	0.622	0.232

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; Lymph-Lymphocyte count; Eosin-Eosinophil count; NLR-Neutrophils/Lymphocytes Ratio; Mono-Monocyte count; Baso-Basophil count; t-Student's t-test.

Table IV: Comparison of the mean values of WBC parameter in relation to aetiologies of seizure

Aetiology	*TWBC (× 10⁹/l)*	*Neutro (× 10⁹/l)*	*Lympho (× 10⁹/l)*	*NLR*	*Mono (× 10⁹/l)*	*Eosin (× 10⁹/l)*	*Baso (× 10⁹/l)*
Structural (n = 36)	10.89±15.59	62.88±17.50	30.30±14.98	3.44±3.22	4.79±4.85	1.23±1.90	0.38±0.48
Metabolic (n = 1)	9.09	88.50	0.89	99.44	0.30	0.01	9.09
Genetic (n = 2)	5.62±0.15	44.90±9.90	43.15±9.69	1.10±0.47	9.55±0.92	1.55±0.21	1.35±0.21
Idiopathic (n = 60)	7.59±3.48	57.05±17.61	38.51±53.66	6.42±24.29	7.41±3.32	2.88±4.26	0.53±0.53
Infectious (n = 1)	7.53	36.50	38.00	0.96	19.70	4.20	1.60
F-test	0.712	2.059	0.372	6.082	6.181	1.375	72.812
p1 value	0.586	0.092	0.828	<0.001	<0.001	0.249	<0.001
p2 value	0.096	0.109	0.393	0.350	0.002	0.003	0.131

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; Lymph-Lymphocyte count; NLR-Neutrophils/Lymphocytes Ratio; Mono-Monocyte count; Eosin-Eosinophil count; Baso-Basophil count; F–One Way ANOVA test; p1-comparing all the aetiologies; p2-comparing the structural aetiologies with the others.

Table V: Comparison of the mean values of WBC parameter in relation to the types of seizure

Epilepsy type	*TWBC (× 10⁹/l)*	*Neutro (× 10⁹/l)*	*Lympho (× 10⁹/l)*	*NLR*	*Mono (× 10⁹/l)*	*Eosin (× 10⁹/l)*	*Baso (× 10⁹/l)*
Focal (n = 5)	7.74±3.20	50.68±12.41	42.06±11.81	1.37±0.76	5.51±3.27	1.02±1.47	0.70±0.57
Generalized (n = 89)	6.93±3.26	59.76±45.25	34.79±45.25	6.71±22.45	6.68±4.49	2.32±3.74	0.61±1.07
Combined (n = 4)	11.58±19.58	39.08±5.04	39.08±5.04	1.34±0.42	6.35±2.11	3.35±1.80	0.45±0.37
Unclassified (n = 2)	10.17±5.71	26.65±18.03	32.35±22.27	2.79±2.47	0.10±1.00	0.10±0.00	0.10±1.00
F-test	1.16	0.710	0.058	0.185	0.223	0.564	0.201
p-value	0.32	0.548	0.982	0.906	0.880	0.640	0.896

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; Lymph-Lymphocyte count; Eosin-Eosinophil count; NLR-Neutrophils/Lymphocytes Ratio; Mono-Monocyte count; Baso-Basophil count; F-One Way ANOVA test.

However, both differences lacked statistical significance (p = 0.926 and p = 0.906 respectively) as shown in Table V. The cases aged 41-60 years at the onset of seizure had higher mean values of total WBC, NLR and neutrophils: 11.58±19.58 ×10⁹ cells/L, 9.81±20.74 and 70.08±17.18 ×10⁹ cells/L. The mean neutrophil count was significantly different (p = 0.001). The mean monocyte count was higher among the cases aged less than 20years of age and was statistically significant as shown in Table VI.

Table VI: Comparison of the mean values of WBC parameter in relation to the age at the onset of seizure

Groups	*TWBC (× 10⁹/l)*	*Neutro (× 10⁹/l)*	*Lympho (× 10⁹/l)*	*NLR*	*Mono (× 10⁹/l)*	*Eosin (× 10⁹/l)*	*Baso (× 10⁹/l)*
< 20 years (n = 35)	7.47±3.20	52.81±14.88	49.91±68.38	7.38±31.78	8.23±3.94	2.77±3.88	0.63±0.63
20-40 years (n = 22)	6.93±3.26	53.62±18.44	34.58±15.27	2.84±3.93	7.89±4.53	3.29±4.60	0.56±0.49
41-60 years (n = 22)	11.58±19.58	70.08±17.18	23.72±16.15	9.81±20.74	4.05±3.48	1.33±2.59	0.68±1.90
> 60 years (n = 21)	10.17±5.71	63.05±16.39	29.53±15.46	3.48±3.25	4.88±3.86	0.82±0.87	0.35±0.37
F-test	1.16	5.950	1.440	0.508	6.588	2.209	0.329
p-value	0.32	0.001	0.236	0.678	<0.001	0.092	0.804

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; Lymph-Lymphocyte count; Eosin-Eosinophil count; NLR-Neutrophils/Lymphocytes Ratio; Mono-Monocyte count; Baso-Basophil count.

When the effect of interval from the last episode of seizure was related to the mean WBC parameters, subjects with intervals from the last episode of seizure longer than 2 years had higher mean WBC (13.76±22.12×10⁹ cells/L), lower mean NLR (2.51±1.93) and higher mean neutrophil count (61.38±15.93 ×10⁹ cells/L) as shown in Table VII.

Table VIII shows that the mean values of total WBC (p = 0.013), NLR (p = 0.026), Neutrophil (p < 0.001) and basophils (p < 0.001) were significantly associated with epilepsy. However, only NLR (p = 0.013) and basophil count (p < 0.001) predicted epilepsy on linear regression analysis as shown in Table VIII.

Discussion

This study demonstrated higher mean total white blood cell count (TBWC) and its differential counts except for eosinophils among adults with epilepsy compared to the controls. Previous reports from clinical and basic research have established the supporting role of inflammation in epilepsies. [2, 4] The relationship between seizure and inflammation is best described as bi-directional [4] viz - disruption of blood brain barrier, production of interleukins-1β, Tumour Necrosis Factor (TNF), Interleukin-6, activation and upregulation of microglia cells, induction of

cyclooxygenase enzyme, synaptic reorganization, apoptosis and activation of the components of compliment system. [2, 4] The presence of pathological events leads to the activation of leucocytes, which in turn release inflammatory mediators that are capable of inducing hyper excitability of the neurones to generate seizure and further worsening the inflammation in a vicious cycle. [3,6,10,11]

Table VII: Comparison of the mean values of WBC parameter in relation to the interval from the last episode of seizure

Groups	*TWBC (× 10^9/l)*	*Neutro (× 10^9/l)*	*Lympho (× 10^9/l)*	*NLR*	*Mono (× 10^9/l)*	*Eosin (× 10^9/l)*	*Baso (× 10^9/l)*
< 2 years (n = 83)	7.73±3.77	58.53±18.30	35.74±46.45	6.85±23.12	7.17±3.85	2.42±3.79	0.64±1.09
≥ 2 years (n = 17)	13.76±22.12	61.38±15.93	32.98±13.45	2.51±1.93	3.53±5.44	1.37±2.11	0.38±0.41
t-test	-2.3333	-0.580	0.235	0.746	3.210	1.075	0.934
p-value	0.022	0.563	0.815	0.456	0.002	0.285	0.353

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; Lymph-Lymphocyte count; Eosin-Eosinophil count; NLR-Neutrophils/Lymphocytes Ratio; Mono-Monocyte count; Baso-Basophil count.

Table VIII: Linear regression of WBC parameters as predictors of epilepsy

Variables	*Standard Error*	*Beta*	*t*	*p-value*
TWBC	0.000	-0.076	-1.091	0.277
NLR	0.0005	-0.199	-2.496	0.013
Neutro	0.002	-0.022	-0.272	0.786
Baso	0.022	0.351	4.357	<0.001

TWBC-Total White Blood Cell counts; Neutro-Neutrophils count; NLR-Neutrophils/Lymphocytes Ratio; Baso-Basophil count; t-Student's t-test.

Overall, between the cases and the controls, there were significance differences in the mean neutrophil levels. Comparing the WBC parameters among the seizure subtypes, the mean total WBC and mean NLR were higher among those with primarily generalized seizures. The neutrophils are the most abundant leucocytes involved in innate immunity, and the level of neutrophils increases in systemic inflammation. [2] A 2021 study reported that the number of neutrophils was considerably higher in the post-seizure phase than in the pre-seizure phase in the group with generalized epilepsy. [12] Another study found an association between status epilepticus and neutrophil-mediated inflammation. [13] Güneş and Büyükgöl detected that the number of neutrophil cells and NLR values were significantly higher in the acute period in comparison to the subacute period in patients with generalized epilepsy. [14] These studies proved the concept that epileptic seizures are linked to neutrophil-mediated systemic inflammation. A study published in 2021 also suggested that TNF*a* and neutrophils regulate neuronal hyperexcitability, which is associated with a variety of aetiologies. [15] Morkavuk *et al.* reported that increased excitability of neuronal cells might cause epilepsy disease. [12] Another nexus between elevated neutrophil numbers and epileptic disease is that, apart from releasing neuroexcitatory cytokines, neutrophils may indirectly affect neuronal hyperexcitability by releasing chemokines that attract other inflammatory cells. Both CCL3 and CCL2 (Chemokine Ligand), which were shown to be substantially elevated in epileptic brain tissue, are generated by neutrophils and help bone marrow-derived cells and monocytes to recruit these leucocytes. [15] Epilepsy often goes along with an increase in leucocytes, like neutrophils, in the hippocampus. The more these cells infiltrate the hippocampus, the more neurones degenerate. Blood brain barrier dysfunction and interactions between leucocytes and

endothelium may be the reasons behind the infiltration and leakage of neutrophils and leucocytes into the hippocampus. Therefore, one of the ways to prevent seizures is to inhibit vascular-leucocyte interactions. This idea is based on experimental studies. Studies have also shown that infiltration of neutrophils and leucocytes can cause a rise in inflammatory mediators, including COX-2, complements, and tumour necrosis factors, all of which can explain why seizures happen in epilepsies. [16]

In this study, lymphocyte counts were reduced in the cases compared to the control group, though without statistical significance. This is similar to a 2020 study which observed that lymphocyte counts were significantly lower in patients with epilepsies compared to the controls, and that lymphocytes were substantially lower in the acute phase in comparison to the subacute phase in patients with epilepsies. [14] However, other researchers reported that lymphocyte counts are significantly reduced in both the acute and subacute phases of epilepsy compared to the controls. [13] Another study confirmed that lymphocyte counts are significantly reduced in patients with temporal lobe epilepsy compared to the controls. [17]. So, this study found that neutrophil count increased and lymphocyte count decreased in epilepsy patients. This explains why the NLR ratio increases in these patients, hence the value of NLR as a potential biomarker for epilepsy as it is in other diseases such as cancers. [18]

This study demonstrated that mean NLR values were consistently higher among patients with epilepsies compared to the healthy controls, suggesting its possible inflammatory role in epilepsy. This observation is in concordance with previous findings that NLR values in patients in the acute or subacute phases of epilepsies were higher than that of healthy controls. [2, 19] A significant difference in NLR levels was also reported between patients in the acute and subacute phases. [2,19] It can be deduced that inflammation plays a role in epilepsy, and elevated NLR value can be a good biomarker for inflammation in epilepsies. [2,19,20] A study had established that every one-unit increase in NLR increased the incidence of epileptic seizures by 1.23. [21] Another study also reported that the probability of epileptic seizures increased 1.95 times for every unit rise in NLR. [14] Neutrophil- Lymphocyte Ratio is a simple ratio between proinflammatory cells, neutrophils, regulatory immune cells, and lymphocytes. Therefore, higher NLR values indicate a higher degree of inflammation, contributing to the development of epileptic seizures. [21]

Limitations

This findings in this study are restricted only to adults, thus it is difficult to extrapolate the findings to children. This study used a small sample size thus, the power may be inadequate to make a concrete conclusion regarding the values of WBC parameters in epilepsies among adults. Further studies with larger sample sizes will be needed to establish the relationship between NLR changes and epileptic diseases among Nigerian adults and possibly, children.

Conclusion

This study shows a clear difference in the TWBC between adults with epilepsies and the controls and suggests possible inflammatory role of WBC, NLR, and neutrophil count among adults with epilepsies. This may be used for evaluating prognostic and therapeutic factors in clinical management of epilepsies. It further shows that NLR increases in epilepsy hence May be a promising biomarker that can be easily obtained from a simple blood test such as full blood count.

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Authors contribution: OSB, OL and AA2 conceived the study while all the authors designed the study. OL, AA and OD did data analysis. All the authors interpreted the data. OSB, OL, AA1 and OBM

drafted the manuscript. All the authors revised the draft manuscript for sound intellectual contents and approved the final draft of the manuscript.

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