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ORIGINAL ARTICLE

Predictors of Seizure Severity using Neutrophil-to-Lymphocyte Ratio and C-Reactive Protein in Patients with Idiopathic Epilepsy

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ABSTRACT

Background: Many researchers studying epilepsy have focused on the immune system in the past ten years. As a result, the body of knowledge regarding the role of several immunological variables in the incidence of seizures and epileptogenesis is expanding quickly. This study aimed at improving epilepsy prognosis via identification of inflammatory biomarkers as predictors of seizure severity in patients with idiopathic Epilepsy. Methods: This Case-control study was done in Intensive Care Unit and Epilepsy Outpatient Clinic at Neurology Department, Zagazig University Hospitals, during the period between February 2022 and March 2025. This study was conducted on 90 subjects; 45 patients (25 Females and 20 Males) with ages ranging from 19-75 years with mean age (39.27±13.07 years) and 45 age and sex matched controls (26 Females and 19 Males), with ages ranging from 19-74 years with mean age 40.67±16.33 years]. All patients were assessed within 72 hours of the seizure onset. Seizure severity was assessed by National Hospital Seizure Severity Scale, electroencephalogram, brain MRI and routine laboratory tests including CBC and CRP. Results: Neutrophil-to-Lymphocyte ratio (≥2.75) significantly independently increases the risk of severe epilepsy by 20.885 folds, while CRP (≥62.77) non-significantly independently increases the risk of severe epilepsy by 1.8 folds. Conclusion: Neutrophil-to-Lymphocyte ratio and C-Reactive Protein can be used as independent inflammatory predictors for seizure severity in patients with idiopathic epilepsy.

Keywords: Idiopathic epilepsy; seizure severity; neutrophil-to lymphocyte ratio; C-reactive protein.

INTRODUCTION

A seizure is a transient clinical event caused by hypersynchronous neuronal firing, whereas epilepsy denotes a brain disorder in which unprovoked seizures recur (≥ 2 > 24 hours apart, or one seizure with ≥ 60 % 10-year recurrence risk, or a defined epilepsy syndrome) [1, 2]. Pooled global incidence is 61.4 /100 000 person-years and lifetime prevalence is 7.6 /1000, both higher in low-/middle-income countries owing to perinatal injury, infection and trauma [3]. According to Egyptian data, the yearly incidence of epilepsy was 48 per 100,000, and the lifetime prevalence was 5.5 per 1000 [4].

Neuroinflammation exists in a state of fine-tuned equilibrium. It starts as a protective measure for the Central Nervous System (CNS), acting as an immune defense. In the early stages of brain injury, it helps in preventing neuronal damage, however, if this balance is disrupted and inflammation becomes chronic, overactive glial cells and excessive cytokine production can lead to harmful neurodegeneration [5].

Whether triggered by brain injury or inflammation throughout the body, neuroinflammation disrupts communication within the brain and affects all CNS cells, including neurons and glial cells. This

imbalance of signaling molecules and increased inflammation can cause neurons to become overactive, increasing the brain's susceptibility to seizures and the development of epilepsy [6].

It was observed that the neutrophils and lymphocytes counts were higher in patients with epileptic seizures in comparison to patients with psychogenic nonepileptic seizures [7]. Additionally, because the neutrophil count increased and the lymphocyte count decreased during the acute phase of generalized tonic clonic seizures, it was found that the neutrophil/lymphocyte ratio (NLR) was higher than in the control group [8]. Additionally, it was discovered that epileptic patients had much higher peripheral blood levels of C-reactive protein than healthy controls, suggesting a strong link between inflammation and epilepsy [9].

Aim of the work:

This study aimed at improving epilepsy prognosis via identification of inflammatory biomarkers that predict seizure severity in patients with idiopathic Epilepsy

METHODS

This case-control study was carried out in Zagazig University Hospitals' Intensive Care Unit and Epilepsy Outpatient Clinic during period between February 2022 and March 2025. The study included 45 patients with idiopathic epilepsy and 45 age- and sex-matched healthy controls. Patients' ages ranged from 19 to 75 years (mean ± SD: 39.3 ± 13.1), while ages of control subjects ranged from 19 to 74 years (mean ± SD: 40.7 ± 16.3). Participants were classified into three age groups according to Horng et al. [10]: Middle-aged adults (40–59 years), senior people (≥60 years), and young adults (18–39 years) [10]. Approval was taken from the research ethical committee and the institutional review board (IRB# 9380-13-4-2022) of Zagazig University's Faculty of Medicine. Every patient gave their consent to participate in the study. The work was carried out in accordance with the 1964 Declaration of Helsinki, the World Medical Association's Code of Ethics, and its later unifications for research involving human people.

Inclusion criteria included patients who were above eighteen years old and had been diagnosed with idiopathic epilepsy according to the International League Against Epilepsy's (ILAE) classification and those who presented within 72 hours postictally. Exclusion criteria included history of recent trauma, cardiac ischemia or infection, metabolic or endocrine disorders, malignancy, active systemic infections, menstruation, pregnancy, or use of medications known to affect leukocyte counts e.g. cytotoxic drugs.

All patients underwent a thorough clinical assessment within 72 hours of seizure onset, including detailed medical history and neurological examination. The National Hospital Seizure Severity Scale (NHSSS), which has a range of 1 to 27, was used to classify and assess the seizures. Seizures with a score of ≥15 were considered severe. [2,3,11]. Complete blood count (for calculating the neutrophil-to-lymphocyte ratio), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), renal and liver function tests, fasting glucose, lipid profile, and serum electrolytes were done routinely to patients and control group.

Neurophysiological assessment was performed using a 22-channel digital electroencephalography (EEG) system (Neurofax, NIHON KOHDEN) in the Neurology Department, Zagazig University. The international 10–20 system was followed when placing the scalp electrodes. While the patients were awake, EEG recordings were made for 20 to 40 minutes using activation techniques such photic stimulation and hyperventilation. EEG results were interpreted as normal or abnormal; depending on the epileptiform patterns seen, abnormal findings were further divided into focal, generalized, or focal discharges with secondary generalization.

All patients underwent cerebral magnetic resonance imaging (MRI) using a Philips ACHEVIA 1.5 Tesla equipment, both with and without contrast. at the Radiology

Department of Zagazig University Hospitals, to exclude secondary causes of epilepsy

Statistical analysis:

Data were analyzed using IBM SPSS Statistics, version 26 (IBM Corp., 2019). The chi-square test or Fisher's exact test was used to compare categorical variables, and the chi-square test for trend was used to evaluate ordinal data. Using the Shapiro-Wilk test, continuous variables were first evaluated for normality. Depending on the findings, either independent-samples t-tests or Mann-Whitney U tests were used for comparison. Tukey's or Dunn's tests, as appropriate, were used for post-hoc analyses after one-way analysis of variance (ANOVA) or Kruskal-Wallis tests were completed for multiple group comparisons. To find the best diagnostic cut-offs, receiver operating characteristic (ROC) curves were utilized, and independent predictors were found using logistic regression analysis. Results were deemed very significant if $p \leq 0.001$, and statistical significance was defined at $p < 0.05$. Pearson correlation (for regularly distributed data) and Spearman rank correlation coefficients (for non-normally distributed data) were used to evaluate the direction and degree of correlations between two variables.

RESULTS

Table (1) showed that the age of seizure onset ranged from 2 to 55 years with median age 17 years. Most of patients had abnormal EEG. Most of patients were on polytherapy of anti-seizure medications. Most patients had GTC type followed by focal seizures with secondary generalization, lastly focal type of seizure.

Table (2) demonstrated that the two groups under study differed in terms of neutrophils in a statistically meaningful way, lymphocyte counts and N/L ratio (all were significantly higher among case group except for lymphocytes which were significantly lower in that group).

Table (3) showed that there was a statistically significant difference between the two studied groups regarding to C reactive protein (significantly higher among case group).

Table (4) showed that in the patient group, NHS3 scores ranged from 3 to 27 with mean 15.09. Taking point of 16 (median) to differentiate patients into non-severe (48.9%) and severe (51.1%) groups.

Table (5) demonstrated that the NHS3 score and both CRP and NLR in the case group had a statistically significant positive connection.

Table (6) showed that in the case group, the NLR (≥2.75) was significantly independently increased the risk of severe seizure by 20.885 folds and the CRP (≥62.77) non-significantly independently increased the risk of severe seizure by 1.8 folds.

Table 1: The distribution of patients according to disease-specific data:

	N=45	**%**
Age of seizure onset (year): Median Range	 17 2-55	
EEG changes: Abnormal: Focal discharge Focal with 2ry generalization discharge Generalized discharge Normal	 39 7 4 28 6	 86.7% 18% 10.3 % 71.7% 13.3%

	N=45	%
ASM: Monotherapy Polytherapy	 19 26	 42.2% 57.8%
Semiology: Generalized Absence Myoclonic GTC Tonic Focal Focal (tonic) with preserved consciousness Focal (automatic) with impaired consciousness Focal with secondary generalization	 3 6 18 3 4 4 7	 6.7% 13.2% 40% 6.7% 8.9% 8.9% 15.6%

ASM; Anti-seizure medication GTC; Generalized Tonic-Clonic

Table 2: The comparison between the studied groups regarding to hematological findings:

	Case group	Control group	Z	p
	Median (IQR)	Median (IQR)		
Neutrophil	9.8(5.4 – 15.85)	4.1(3.05 – 5.5)	-5.056	<0.001**
Lymphocyte	3.2(1.7 – 4.55)	4.4(3.4 – 4.9)	-2.951	0.003*
NLR	3.0(1.29 – 9.97)	0.96(0.71 – 1.4)	-5.774	<0.001**

NLR; neutrophil-to-lymphocyte ratio Z; Mann Whitney test IQR; interquartile range *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table 3: The comparison between the two studied groups regarding to C reactive protein:

	Case group	Control group	z	p
	Median (IQR)	Median (IQR)		
CRP (mg/L)	19(12 – 78)	3.6(2.4 – 5.45)	-7.113	<0.001**

Z Mann Whitney test IQR interquartile range **p≤0.001 is statistically highly significant

Table 4: The severity of seizures assessed by NHS3 in the patient group:

	N = 45	%
Non-severe (<16) Severe (≥16)	22 23	48.9% 51.1%
NHS3 mean: Range:	 15.09 ± 6.64 3 – 27	

NHS3; The National Hospital Seizure Severity Scale

Table 5: The correlation between NH3S, NLR and CRP in the patient group:

	r	p
NLR	0.893	<0.001**
CRP	0.401	0.006*

**p≤0.001 is statistically highly significant r; Spearman rank correlation coefficient

Table 6: The binary regression analysis of factors associated with severe epilepsy:

	β	p	AOR	95% C.I.	
				Lower	Upper
NLR (≥2.75)	3.039	0.003*	20.885	2.812	155.12
CRP	0.008	0.34	1.008	0.991	1.026

AOR; adjusted odds ratio *p<0.05 is statistically significant CI Confidence interval

DISCUSSION

Epilepsy denotes a persistent tendency to seizures. The patient's and/or witnesses' statements of their symptoms are typically the basis for the clinical diagnosis. It might be challenging to distinguish whether a single or multiple seizures are indicative of a permanent seizure propensity or of temporary causes such acute brain injury or drug usage [12].

Other potential epilepsy biomarkers are inflammatory markers, as inflammation is thought to play a significant role in epileptogenesis. Blood can be used to measure several of them [13].

In our investigation, we found that in comparison to the healthy control, the case group's neutrophil count was significantly higher and the lymphocyte count was significantly lower thus N/L ratio were much greater. In agreement with this, Güneş and Büyükgöl who looked explored how NLR and generalized epileptic seizures in patients and healthy controls related to each other, showing that epilepsy patients had greater NLRs than healthy controls. Additionally, this study indicated that increasing NLR values were associated with a substantial increase in the likelihood of epileptic seizures [8].

Similarly, Baran and his colleagues examined the effect of history of febrile seizures in patients with TLE on inflammatory biomarkers such as NLR, their results showed that epilepsy patients had a larger NLR than controls. Additionally, another study published by Güneş and Büyükgöl, In patients with generalized epilepsy, which was deemed the most severe form on the scale we employed in our study, it was found that the neutrophils count and NLR values were significantly higher in the acute phase compared to the subacute phase [8,14].

Özdemir and his colleagues Additionally, it was discovered that patients with status epilepticus had a considerably decreased lymphocyte count during the acute phase when compared to controls [15]. Another study carried out by Mete and his colleagues [16] verified that patients with temporal lobe epilepsy had a considerably lower lymphocyte count than controls [16], and another study that was published in2021 by Morkavuk and his colleagues found that the group with generalized epilepsy had significantly more neutrophils during the post seizure phase than during the pre-seizure phase [7].

In contrast to our study Eroglu and his colleagues evaluated the NLR levels of healthy controls and epileptic patients during seizure-free and seizure-related times; no statistically significant differences were found between the two groups.[17]. Moreover, Morkavuk and his colleagues sought to measure the NLR value in the pre- and post-seizure phase of epilepsy and psychogenic non-epileptic seizures (PNES) in order to distinguish between seizures and pseudo seizures. The findings showed that there was no discernible difference between the two groups' NLR values [7].

According to a study by Li and his colleagues, which supports our findings, an increase in NLR soon after an acute seizure may predict a propensity for recurrent seizures in the days that follow. This suggests that the inflammation reflected by NLR may be a causative factor in epileptogenesis [18]. According to the scale we employed in our study, recurrent seizures were deemed more severe.

Regarding C-reactive protein, there was a statistically significant difference between the groups in our study (the case groups was much higher).

A meta-analysis of 16 case-control studies, which included 1918 people, revealed that CRP blood levels "were significantly increased in epileptic patients compared to healthy controls, indicating a significant association between inflammation and epilepsy [10]," which is consistent with our findings. Later individual research conducted by Meguid and his colleagues, Simoes and his colleagues, Tao and his colleagues and Sangeetha and his colleagues have confirmed this [19-22].

In agreement with our study Ishikawa and his colleagues examined the levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) in children with epilepsy who experienced frequent, refractory generalized motor seizures. The findings indicated that patients with daily motor seizures had significantly higher levels of hs-CRP and IL-6, which may indicate a persistent inflammatory process as a possible pathophysiological cause of children's intractable epilepsy with frequent motor seizures [23].

Alapirtti and his colleagues focused on relationship between focal epileptic seizures and CRP. The results of this video-electroencephalographic study helped to clarify the function of inflammation in the pathogenesis of epilepsy by shedding light on the relationship between CRP and seizures in focal epilepsy. The correlation between inflammation and epilepsy is highlighted by the fact that CRP levels were greater in refractory epilepsy patients than in healthy controls [24].

According to our research, CRP (≥62.77) non significantly independently raises the chance of severe epilepsy by 1.8 times, while NLR (≥2.75) significantly increases the risk by 20.885 times.

Similarly, Güneş and Büyükgöl discovered that the likelihood of an epileptic seizure increased by 1.954 times and 1.731 times, respectively, for every unit increase in NLR throughout the acute and subacute phases [8].

In contrast to our study, Baran and his colleagues discovered that NLR was not significantly elevated in temporal lobe epilepsy patients and that it cannot be utilized to gauge the severity of the condition based on factors like seizure frequency and duration [14].

In agreement with our study, Madžar and his colleagues evaluated the importance of the initial CRP level measured during a status epilepticus (SE) episode for predicting SE outcomes. According to the study's findings, in-hospital mortality and poor functional outcome at discharge were independently linked to greater initial CRP concentrations in logistic regression models. The study emphasized how initial CRP levels may be used to predict the outcome of SE, a severe kind of seizures [25].

Conclusion:

We concluded that NLR and CRP were independent inflammatory predictors for severity of idiopathic seizures making them reliable prognostic biomarkers of seizure severity.

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Conflict of interest:

The authors declare that they have no conflicts of interest with respect to horshipaut or publication ofthis article .

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