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Seizure Severity Prediction using Neutrophil-to-Lymphocyte and Plateletto-Lymphocyte Ratios Together with C-Reactive Protein in Idiopathic Epilepsy

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Abstract

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and C-reactive protein (CRP) are inflammatory biomarkers which may play a role in the activity and prognosis of many different diseases including epileptic seizures.

Seizure is a transient abnormal excessive hyper-synchronous neuronal activity in the brain which can present as a paroxysmal alteration of neurological functions, disturbance of consciousness, behavioral changes, cognition, emotion, motor or sensory dysfunction. The inflammation is a biological response of the immune system that can be triggered by various factors, including pathogens, damaged cells, and toxic compounds. Inflammation is a conserved evolutionary process characterized by the activation of immune and non-immune cells that protect the host from bacteria, viruses, toxins, and infections by eliminating pathogens and promoting tissue repair and restoration. The aim of the present study was to identify the inflammatory biomarkers: NLR, PLR and CRP as predictors of seizure severity in patients with idiopathic Epilepsy

Key words: Idiopathic epilepsy; seizure severity; neutrophil-to-lymphocyte ratio; platelet-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 h apart, or one seizure with ≥ 60 % 10-year recurrence risk, or a defined epilepsy syndrome) **[1, 2]**. Acute symptomatic (provoked) seizures follow a recent systemic or cerebral insult and carry a lower long-term recurrence risk**[3,4]**.

Epidemiology

Pooled global incidence is 61.4 /100 000 person-years and lifetime prevalence is 7.6 /1000, both are higher in low-/middle-income countries owing to perinatal injury, infection and trauma **[5]**. Egyptian data showed that the lifetime prevalence is 5.5 /1000 and annual incidence is 48 /100 000 **[6]**.

Etiological Spectrum

The 2011 Shorvon scheme classified epilepsy into *idiopathic* (largely genetic), *symptomatic* (acquired or developmental structural lesions) and *provoked* or *reflex* forms, while about 40 % remaining as cryptogenic **[7]**.

Pathophysiology of Seizures

Seizures may be due to mitochondrial adenosine triphosphate (ATP) loss, oxidative stress and cytokine-driven neuro-inflammation converge on neuronal hyper-excitability via glutamate elevation, gamma-aminobutyric acid (GABA) depletion, ion-channel dysfunction and blood-brain-barrier leakage **[8]**.

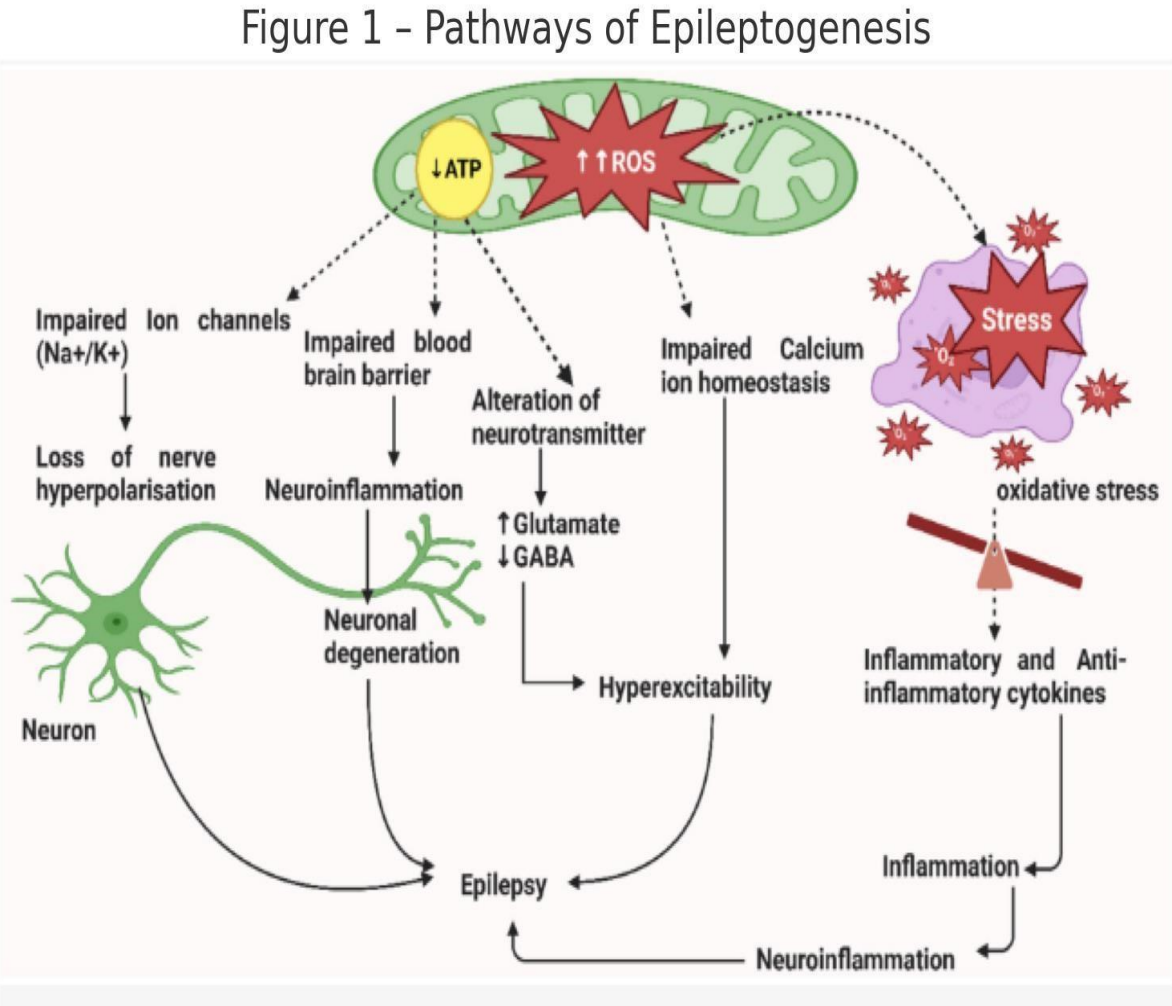

Figure 1 - Pathways of epileptogenesis adapted [8].

Focal seizures originate from paroxysmal depolarisation shifts in cortical microcircuits; when millions of neurons discharge synchronously, an interictal spike becomes detectable on scalp EEG **[9, 10]**. Generalised absence seizures reflect disturbed thalamo-cortical oscillations modulated by T-type Ca^{2+} channels and GABA-B activity **[11, 12]**. Generalised convulsive seizures involve rapid subcortical spread, autonomic activation and subsequent inhibitory exhaustion, producing tonic-to-clonic evolution and post-ictal deficits **[13–15]**.

Seizure Classification

In the recent classification published in **2025**, the International League Against Epilepsy (ILAE) has updated the operational classification of epileptic seizures, building upon the framework established in 2017 **[16]**.

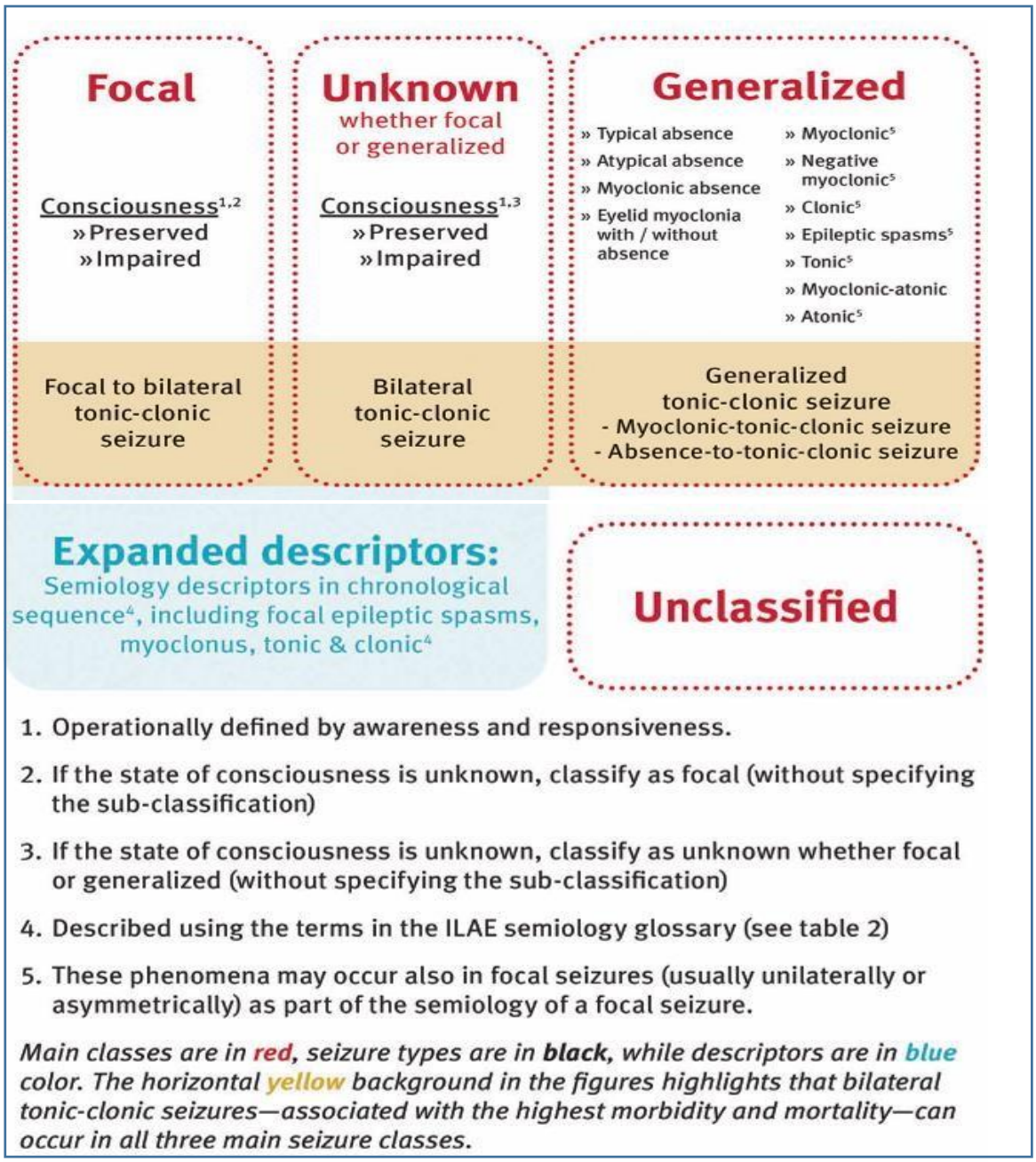

Figure 2 - Expanded version of the updated seizure classification [16]

Status epilepticus (SE)

Status epilepticus (SE) is a failure of termination mechanisms after 5 min (operational t_1), with neuronal injury risk after 30 min (t_2) **[17]**; non-convulsive SE is a common, treatable source of acute confusion **[18]**.

Epileptogenesis and Neuro-inflammation

After cerebral insult, a cascade of microglial activation, cytokine release and blood brain barrier disruption transforms an acutely damaged brain into one primed for spontaneous seizures **[19–21]**. Both hippocampal and extrahippocampal gliosis contribute to epileptogenesis **[22–24]**. Multiple sclerosis exemplifies cortical inflammation

predisposing to epilepsy **[25]**. Central nervous system (CNS) infection is one of the leading causes in the developing countries **[26]**.

Cell-count–derived ratios

The simplest and most clinically mature peripheral markers come directly from the automated full-blood count. Neutrophil-to-lymphocyte ratio (NLR) distinguishes epileptic seizures from psychogenic nonepileptic events and rises acutely together with neutrophil-to-eosinophil ratio (NER) after generalized tonic-clonic attacks, with one-unit increments for NLR nearly doubling seizure risk. Platelet-to-lymphocyte ratio (PLR) as well behaves in parallel and, together with NLR, outperforms either measure alone in children with febrile convulsions **[27]**.

Acute-phase reactants

C-reactive protein levels in peripheral blood were significantly increased in epileptic patients compared to healthy controls, indicating a significant association between inflammation and epilepsy. **[28]**.

Cytokines and chemokines

Peripheral interleukins; IL-1β, IL-2 and IL-6 surge after convulsive seizures and remain chronically elevated in drug-resistant epilepsy **[29,30]**. Tumor necrosis factor alpha (TNF-α) amplifies glutamatergic currents and internalises Gamma Aminobutyric Acid Type A (GABA-A) receptors, directly lowering the seizure threshold **[31]**. The chemokine axis Chemokine (C-C motif) ligand 2 (CCL2)/ CC chemokine receptor 2 (CCR2) drives monocyte ingress and delayed neuronal loss following status epilepticus, implicating leukocyte trafficking in secondary damage **[32]**. Elevated serum C-X-C motif chemokine ligand 13 (CXCL13) mirrors intrathecal production in intractable temporal-lobe epilepsy, suggesting peripheral sampling can reflect compartmentalised CNS inflammation **[33].**

Platelet-derived mediators

Activated platelets release platelet-activating factor (PAF), which enhances presynaptic glutamate release; PAF-receptor antagonists attenuate kindled seizures in rodents **[34, 35]**. Mean platelet volume (MPV) and platelet distribution width surrogates of platelet reactivity track with seizure frequency and, when combined with NLR, improve differentiation of status epilepticus from prolonged psychogenic events **[36]**.

Endothelial and matrix markers

Circulating matrix-metalloproteinase-9 (MMP-9) and its regulator S100 calcium binding protein B (S100B) rises in mesial-temporal lobe epilepsy with hippocampal sclerosis and correlate with MRI-defined hippocampal volume loss **[37]**. Cluster of Differentiation 44 (CD44) up-regulation alters dendritic morphology, while higher soluble CD44 in serum has been proposed as a surrogate of active dendritic remodelling **[38]**.

Neuro-injury markers

Serum neuron-specific enolase (NSE) peaks within 24 h of status epilepticus and identifies hippocampal injury on diffusion-weighted MRI **[39]**. Total tau concentrations in CSF and in ultra-sensitive blood assays predict cognitive decline after prolonged seizures**[40]**.

Seizure Severity, Biomarkers and Prognosis

Severity integrates duration, semiology and spread. The **National Hospital Seizure Severity Scale** (NHS3, scores 1–27) is quick, reliable and correlates with patient perception **[41, 42]**. High inter-ictal cytokine panels, serum albumin < 35 g L^{-1}, low uric acid, elevated CSF tau or NSE, and acute increases in NLR, MPV or CRP each predict refractory status epilepticus, higher seizure frequency or worse outcomes **[43–51]**. Large prospective cohort studies are warranted to validate cut-offs and clarify temporal dynamics.

Machine-learning studies that combine NLR, CRP, IL-6 and MMP-9 achieve AUCs > 0.90 for distinguishing refractory epilepsy from controlled disease but still await external validation**[52]**. Confounders—age, obesity, infection, medication, venepuncture timing—limit generalisability, and most datasets are hospital-based convenience samples.

Large, phenotype-stratified cohorts with serial sampling are essential to establish normative trajectories, unify cut-offs and test whether anti-inflammatory interventions guided by biomarker profiles can meaningfully alter seizure outcomes.

Anti-inflammatory Therapeutics

Conventional anti-seizure medicines such as valproate and levetiracetam suppress circulating IL-6 and CRP **[53]**; steroids, IVIG, the ketogenic diet, and vagus-nerve stimulation provide additional immune modulation **[54–57]**. Nonsteroidal anti-inflammatory drugs—including low-dose aspirin in Sturge– Weber syndrome and high-frequency ibuprofen use—show seizure-attenuating effects, while experimental agents such as 2-deoxy-glucose and Cyclindependent kinase 5 (CDK5) inhibitors target microglial pathways **[58–61]**. Selective IL-1β antagonists and caspase-1 inhibitors are under clinical investigation **[62]**.

Conclusion:

NLR, PLR and CRP were independant inflammatory predictors for severity of idiopathic seizures making them a reliable prognostic biomarkers of seizure severity.

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