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The Importance of Blood Parameters for Prognosis Prediction in Status

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Abstract

Aim: To compare blood parameters between patients with status epilepticus (SE) and those with non-SE epileptic seizures at presentation to the emergency department, and to evaluate the prognostic value of immature granulocytes (IG).

Materials and Methods: This retrospective study included adult patients presenting with seizures. Hematological and biochemical parameters, including C-reactive protein (CRP), white blood cell count (WBC), blood gas parameters, IG, and IG% were analyzed.

Results: A total of 634 patients were screened; 68 hospitalized patients who met the inclusion criteria were analyzed (SE: n=37; non-SE: n=31). Significant differences between groups were observed for WBC, lactate, pH, bicarbonate (HCO_3^-), base deficit, CRP, IG, and IG% ($p<0.05$ for all). An IG cut-off value of 0.045 predicted clinical outcomes with 95.8% sensitivity and 97.7% specificity.

Conclusion: IG and IG% are promising, rapid, and cost-effective inflammatory biomarkers with high diagnostic accuracy in SE. Their use may support early risk stratification, guide clinical decision-making, and improve timely intervention in emergency settings.

Keywords: Status epilepticus, immature granulocyte, prognosis

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures and affects approximately 1% of the global population (1). Status epilepticus (SE) is a life-threatening neurological emergency defined as a prolonged seizure or recurrent seizures without recovery of consciousness between episodes. Although traditionally defined as seizures lasting more than 30 minutes, current clinical practice considers seizures lasting longer than 5 minutes as SE, given the low likelihood of spontaneous termination and the increased risk of neuronal injury (2-4). Early recognition and timely intervention are critical, as delays in treatment are associated with increased morbidity and mortality.

The pathophysiology of SE involves complex mechanisms, including sustained neuronal hyperexcitability, metabolic derangements, hypoxia, and systemic inflammatory responses. Several laboratory parameters such as lactate, leukocyte count, and acid–base disturbances have been investigated as potential biomarkers reflecting disease severity and clinical outcomes (5-7). However, these markers are often nonspecific and may not adequately support early risk stratification in emergency settings.

Immature granulocytes (IG), which represent early-stage granulocytic precursors released from the bone marrow, have recently emerged as markers of systemic inflammation. IG levels can be rapidly and reliably measured using automated hematology analyzers as part of routine complete blood count

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testing. Previous studies have demonstrated the prognostic value of IG in various clinical conditions, including sepsis, acute pancreatitis, and intracerebral hemorrhage (8-10). Despite these findings, the role of IG in neurological emergencies, particularly in SE, remains poorly understood.

We hypothesized that elevated IG and IG% on admission to the emergency department may serve as early predictive biomarkers of disease severity and need for urgent intervention in patients with SE.

To the best of our knowledge, no previous study has specifically evaluated the diagnostic and prognostic utility of IG in differentiating SE from non-SE epileptic seizures. Therefore, this study aims to compare hematological and biochemical parameters between these patient groups and investigate the potential role of IG and IG% as accessible, rapid, and clinically useful biomarkers in the early assessment of SE.

Materials and Methods

This retrospective, single-center observational study was conducted after approval by the Niğde Ömer Halisdemir Ethics Committee. The study included patients admitted to the Emergency Department of Niğde Ömer Halisdemir Training and Research Hospital between 01.12.2021 and 01.12.2023 with a diagnosis of SE (ICD-10 code G41.9), and patients admitted with epileptic seizures without an SE diagnosis (ICD-10 code G40.9). Demographic characteristics of the patients, including age and sex, were recorded. In addition, seizure type and changes in seizure-related blood parameters were analyzed. The study was conducted in accordance with ethical protocols. Our study began after approval by the Niğde Ömer Halisdemir Ethics Committee (protocol number: 2023/129, date: 04.01.2024).

The blood and biochemical parameters included: C-reactive protein (CRP), white blood cell count (WBC), blood gas parameters (lactate, pH, bicarbonate, base excess), and IG count and percentage. IG and IG% values were measured using the Sysmex XN-1000 automated hematology analyzer, which uses fluorescence flow cytometry, to ensure standardized and reproducible measurements.

Inclusion Criteria

All patients aged ≥18 years who presented to the adult emergency department of Niğde Ömer Halisdemir Training and Research Hospital between 01.12.2021 and 01.12.2023 with a diagnosis of SE or epileptic seizure and whose clinical and laboratory data were fully accessible were included in the study.

Exclusion Criteria

Patients younger than 18 years and those with comorbid conditions such as diabetes mellitus, hypertension, pregnancy, renal failure, oncologic diseases, and chronic liver disease were excluded. In addition, patients without a confirmed diagnosis of epileptic seizure or SE and those with incomplete data were excluded from the analysis.

Statistics Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median and interquartile range (IQR: 25^{th}-75^{th} percentile). Categorical variables were expressed as frequencies and percentages.

Comparisons between categorical variables were performed using Pearson's chi-square test or Fisher's exact test. Continuous variables were compared using Student's t-test or Mann–Whitney U test, as appropriate. Correlation analyses between continuous variables were conducted, and correlation coefficients with corresponding significance levels were reported. ROC curve analysis was performed to evaluate the diagnostic performance of IG and IG% in distinguishing SE from non-SE epilepsy.

A p-value <0.05 was considered statistically significant.

Results

A total of 634 patients were evaluated. A total of 68 patients who met the criteria for evaluation were hospitalized. 36 of these patients had convulsive SE, and 1 had the non-convulsive SE subtype. 37 patients were diagnosed with SE. In addition, the number of patients admitted with epileptic seizures was 31.

There was no statistically significant difference between the SE group and epilepsy according to gender as a result of the χ^2 test ($p=0.641$). The mean age of the patients was 42.25±20.11 years and the median age (IQR: 25-75) was 37 (22.25-59.75). Of the patients, 48.5% were female and 51.5% were male.

Statistically significant differences between SE and non-SE epilepsy groups were found in WBC count and percentage, lactate, pH, bicarbonate (HCO_3^-), base deficit, CRP, and IG. This relationship is given in Table 1.

In the correlation analysis, statistically significant positive correlations of moderate to strong magnitude were found between IG and WBC ($r=0.537$, $p<0.001$) and between IG and neutrophils ($r=0.475$, $p<0.001$), and between IG% and WBC

(r=0.368, p=0.002) and between IG% and neutrophils (r=0.319, p=0.008) (Table 2).

ROC analysis was performed for the number and percentage of IGs with respect to clinical outcome (intubated vs non-intubated patients), and the area under the curve was reported (Figure 1). Optimal cut-off values for IG number and percentage were determined using the Youden index (sensitivity + specificity-1). A cut-off value of 0.045 for IG count provides 95.8% sensitivity and 97.7% specificity. For the IG percentage, a cut-off value of 0.45 yields 95.8% sensitivity and 96.8% specificity. This relationship is presented in Table 3.

Discussion

Epilepsy is a neurological disorder characterized by recurrent seizures. SE is a medical emergency characterized by prolonged epileptic seizures. The biochemical differences between these two conditions often involve changes during and after seizures. However, the information on this issue remains incomplete, and research is ongoing. In a study on IG, which is the subject of research in the diagnosis and treatment of neurological diseases, it was reported that the number of IG effectively showed 30-day mortality in ischemic stroke patients (10). In another study, it was reported that IG number affected the course of poor prognosis in spontaneous intracerebral hemorrhage (11). In addition, a recent study reported that IG count was an effective predictor of hospital mortality in spontaneous intracerebral hemorrhage (12). In our study, IG associated with the immune response provided important data, especially for differentiating SE from epileptic seizures.

In this study, IG count, IG%, neutrophil count, neutrophil % levels differed significantly between groups. Our correlation analysis showed that these inflammatory markers were positively correlated, suggesting a potential link between inflammation severity and disease progression.

Table 1. Comparison of hematological and biochemical parameters between SE and non-SE groups

Variables	Group	N	Mean	SD	Mean rank	p*
WBC	SE	37	13.04	6.48	41.62	<0.001
	Non-SE epilepsy	31	8.57	2.93	26.02	
Lactate	SE	37	5.64	6.10	40.05	0.011
	Non-SE epilepsy	31	2.10	1.70	27.82	
pH	SE	37	7.30	0.14	29.42	0.02
	Non-SE epilepsy	31	7.39	0.04	40.56	
Bicarbonate	SE	37	19.55	5.02	28.01	0.003
	Non-SE epilepsy	31	22.95	1.96	42.24	
Base excess	SE	37	-3.30	7.55	29.07	0.013
	Non-SE epilepsy	31	0.15	2.82	40.98	
CRP	SE	37	23.02	20.56	44.45	0.027
	Non-SE epilepsy	31	14.67	13.01	28.34	
IG	SE	37	0.07	0.05	42.50	<0.001
	Non-SE epilepsy	31	0.02	0.008	24.95	
IG%	SE	37	0.56	0.24	42.39	<0.001
	Non-SE epilepsy	31	0.25	0.006	25.08	

SE: Status epilepticus, SD: Standard deviation, WBC: White blood count, CRP: C-reactive protein, IG: Immature gyranolocyte, *Mann-Whitney U test

Table 2. Correlation analysis of WBC, neutrophil count, IG, and IG%

Correlations (total n= 68)		Correlation coefficient	p*
IG	WBC	0.537**	<0.001
	Neutrophil	0.475**	<0.001
IG%	WBC	0.368**	0.002
	Neutrophil	0.319**	0.008

WBC: White blood count, IG: Immature gyranolocyte, *Pearson, ** Correlation is significant at the 0.01 level (2-tailed)

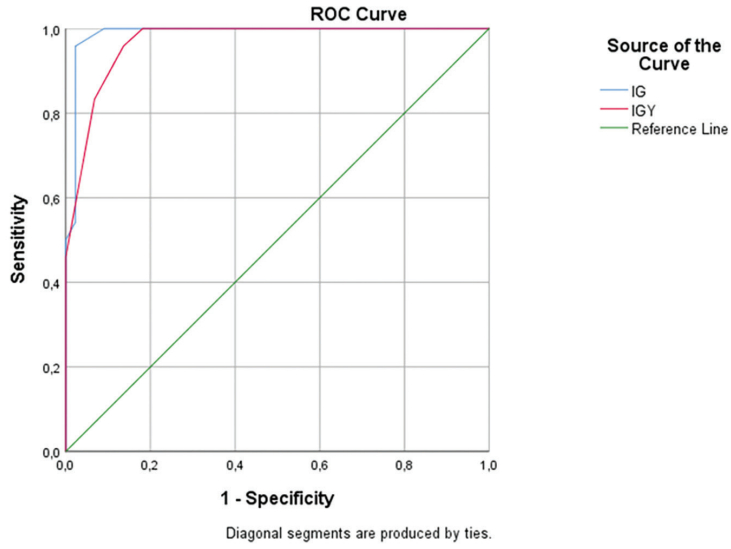

Figure 1. ROC curve graph for IG count and IG%
IG: Immature granulocytes, IGY: Immunoglobulin Y

Table 3. AUC, sensitivity, and specificity of IG count and IG% at optimal cut-off values

Factor	AUC	95% CI (lower-upper)	Sensitivity	Specificity	Youden index	cut-off
IG	IG	0.965-1.000	0.958	0.977	0.936	0.045
IG%	0.968	0.933-1.000	0.958	0.968	0.864	0.4500

AUC: Area under the curve, IG: Immature gyranolocyte, CI: Confidence interval

The elevation of IG during SE may be explained by several underlying pathophysiological mechanisms. Prolonged neuronal hyperactivity can trigger a systemic inflammatory response, leading to cytokine release and activation of the immune system. In addition, seizure-related hypoxia and metabolic stress may stimulate bone marrow activity, resulting in the premature release of granulocytic precursors into the peripheral circulation. Furthermore, increased catecholamine levels during seizures may contribute to leukocyte mobilization. Oxidative stress and neuronal injury may further amplify inflammatory pathways, leading to elevated levels of IG and IG%. These mechanisms provide a plausible biological explanation for the association between IG levels and disease severity observed in our study (13,14).

In the literature, there are findings indicating that inflammatory mediators are released by peripheral immune and brain cells in epileptic seizure processes (15). The significant difference in CRP levels observed in this study suggests that CRP may be used in the differential diagnosis between SE and epilepsy. In one study, the potential use of leukocytosis to differentiate non-epileptic from epileptic seizures was evaluated, and leukocytosis was found to begin approximately 2 hours after the seizure. It was reported that there was a significant difference between epileptic and non-epileptic seizures (16).

A positive correlation was found between IG count and intubated patients in acute respiratory distress syndrome due to coronavirus disease 2019 (COVID-19) (17). In our study, IG in and IG% were determined to be biomarkers with high sensitivity and specificity in intubated patients. Oxidative stress increases during seizures, resulting in neuronal damage and inflammation; consequently, the number and rates of IG, which is an indicator of inflammation, increase. IG, which physicians can measure easily and early, may serve as an early biomarker to guide the decision to intubate. A hemogram is a rapid, low-cost test. Therefore, IG count, other hemogram parameters, and immune response-related markers that can be easily calculated from these parameters will contribute to the differential diagnosis. However, to generalize the findings of this study to large populations, prospective, well-designed studies with large sample sizes that account for time of seizure onset should be conducted. The biggest limitation of this study is that blood tests analyzed immediately after admission to the emergency department were performed only once.

It has been reported in the literature that it is important to analyze lactate, anion gap and ammonia levels at the onset of epileptic seizures (18,19). However, these tests are more costly than a hemogram.

SE may increase lactate levels by affecting energy metabolism and may cause changes in base deficit, bicarbonate, and pH values. Changes in neurotransmitters, such as serotonin and dopamine, can be observed during seizures. These changes are associated with the frequency and severity of seizures. Furthermore, imbalances in neurotransmitters such as gamma-aminobutyric acid and glutamate are associated with epileptic seizures. These imbalances may be more pronounced during SE. During seizures, increased oxidative stress intercellular can be observed. This can lead to cell damage and inflammation. Inflammation and immune-system responses triggered by seizures may lead to changes at the biochemical level, and prolonged seizure duration may exacerbate hypoxia and explain differences in blood gas parameters. These changes may differ between individuals and between seizure types. It is important to remember that epilepsy and SE are complex conditions, and it is natural that the biochemical mechanisms are not yet fully understood. Further research is needed in this area. Treatment and intervention should generally be individualized depending on the type of seizure, the patient's condition and general health (19-21).

The ideal prognostic markers of SE are those that are easily accessible to clinicians at the bedside and provide high sensitivity and specificity in predicting SE-related outcomes. These will provide information on the likelihood of SE outcomes, including progression to refractoriness, functional outcomes, and mortality. Such prognostic markers are essential, as they enable individualization of treatment and aid decisions regarding treatment intensity. No ideal prognostic marker exists for SE, and we are currently limited to the SE markers mentioned above. Despite their good negative predictive value, the positive predictive value of these scores is poor, which prevents their use in decisions to discontinue life-sustaining treatment (20,21). The data obtained in our study will allow the inclusion of clinical, genetic, epigenetic, metabolic, inflammatory, and structural biomarkers in scoring systems that will provide more accurate prognoses.

Our findings show that IG count and % IG levels, in particular, are significant in differentiating SE and epileptic seizures, since they are markers related to the immune response. IG has also shown promising results in COVID-19 and other diseases (21,22). Therefore, we suggest that inflammation and elevated inflammatory markers may help physicians in the early prediction of patients' prognosis and overall condition. In our study, intubated patients with poor general condition had higher IG and IG%.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective and single-center design may limit the generalizability of the findings and introduce the potential for selection and information bias. Second, only hospitalized patients were included in the analysis, which may have resulted in a selection bias toward more severe clinical presentations.

Third, IG and IG% levels were measured only once on admission to the emergency department, and the lack of serial measurements precluded assessment of temporal changes in these parameters. In addition, IG levels may vary with the timing of blood sampling relative to seizure onset, which could not be standardized in this study.

Finally, multivariate analysis could not be performed because the limited number of outcome events (e.g., intubation) precluded assessment of IG and IG% as independent predictors. Therefore, the findings should be interpreted with caution, and prospective, multicenter studies with larger sample sizes and repeated measurements are needed to validate these findings.

Conclusion

We observed that inflammatory markers are elevated during epileptic seizures compared with normal reference ranges. Furthermore, we found IG and IG% in epileptic seizures are inflammatory markers with high sensitivity and specificity for predicting early intubation and may guide clinical management and early intervention.

Ethics

Ethics Committee Approval: The study was conducted in accordance with ethical protocols. Our study began after approval by the Niğde Ömer Halisdemir Ethics Committee (protocol number: 2023/129, date: 04.01.2024).

Informed Consent: This retrospective, single-center observational study was conducted after approval by the Niğde Ömer Halisdemir Ethics Committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.D., A.V., M.O.C., D.A., N.Ö.A., Concept: T.D., D.A., Design: T.D., A.V., Data Collection or Processing: D., A.V., M.O.C., D.A., N.Ö.A., Analysis or Interpretation: T.D., M.O.C., Ö.Y., G.Ç., Literature Search: T.D., Ö.Y., G.Ç., Writing: T.D., M.O.C., Ö.Y., G.Ç., D.A., N.Ö.A.

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