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The effects of systemic inflammatory indices, lactate, and blood gas parameters on drug-resistant and drug-nonresistant epilepsy

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Abstract

Epilepsy is one of the neurological diseases that affects a significant number of individuals in the world. In addition to having important effects on the social lives of the patients, this disease is a significant cause of disability. Neurological mechanisms underlying the disease are still being investigated. The patients' gender, age, hemogram parameters (white blood cells, hemoglobin, erythrocyte, neutrophil, lymphocyte, monocyte, eosinophil, platelet), blood gas values, drugs used, presence of drug-resistant epilepsy, and the duration of the disease were analyzed. The patients were divided into two groups of similar ages and genders as DRE (drug-resistant epilepsy) and DNRE (drug-nonresistant epilepsy) patients. This grouping was made according to the ILAE (International League Against Epilepsy) classification by considering the patients' anamnesis, clinical history, seizure frequency, and antiepileptic drugs currently used. Seventy-seven drug-resistant and 129 drug-nonresistant epilepsy patients, 206 in total, were included in the study. 64.9% of the drug-resistant epilepsy group were male, and the remaining 35.1% were female, while 65.9% of the drug-nonresistant epilepsy group were male and 34.1% were female. No significant difference was found between the groups in terms of systemic inflammatory indices. The disease duration of the patients in the drug-resistant epilepsy group was significantly higher than those in the drug-nonresistant epilepsy group. A negative and significant correlation was found between pH and pO2, pCO2, and lactate. In addition, a positive and significant correlation was determined between pO2 and lactate, and a negative and significant correlation was found between pO2 and pCO2. It was determined that there was no significant difference between drug-resistant epilepsy patients and drug-nonresistant epilepsy patients in terms of parameters used as a systemic inflammatory biomarker in epilepsy patients. New biomarkers that would significantly affect these patients should be investigated.

Keywords: epilepsy, drug-resistant epilepsy, NLR, PLR, MLR, lactate, blood gas

1. Introduction

Epilepsy is a neurological disease affecting nearly 50 million individuals worldwide with 16-53 new onset cases in 100,000 individuals yearly (1). Epilepsy is one the diseases that frequently leads to disability and can affect individuals of all ages, races, social classes, and geographical regions (2, 3). The WHO (World Health Organization) has reported that DRE (drug-resistant epilepsy) develops in approximately one-third of these patients (4-6).

DRE refers to situations in which a seizure-free period could not be achieved despite using two or more tolerable antiepileptic drugs (monotherapy or polytherapy) (7). These patients experience significant socioeconomic and psychological restrictions, such as decreased quality of life and increased mortality risk (8, 9).

Basic neuronal mechanisms that underly epileptogenicity have long been investigated. It has been argued that the blood-brain barrier (BBB) is disrupted, especially in epileptogenic foci, and neuroinflammation has a significant role in pathogenesis (2). Finding the biomarkers for epileptogenesis can offer important opportunities for diagnosing and treating the disease. It is known that systemic inflammatory indices (SII) [(Neutrophil/Lymphocyte ratio (NLR), Platelet/Lymphocyte ratio (PLR), Monocyte/Lymphocyte ratio (MLR)] can display differences in epilepsy patients similar to many systemic and neurological diseases (10-18). Hence, this study aimed to examine the changes in SII and blood gas parameters in patients grouped as drug-resistant epilepsy (DRE) and drug-nonresistant epilepsy (DNRE) according to their clinical history.

2. Materials and Methods

2.1. Data Collection

Ethical approval for the study was obtained from Malatya Turgut Ozal University Non-Interventional Clinical Research Ethics Committee with the decision numbered 2022/92 and dated 10.05.2022. The study had a retrospective design. The patients' gender, age, hemogram parameters (white blood cells, hemoglobin, erythrocyte, neutrophil, lymphocyte, monocyte,

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eosinophil, platelet), arterial bold gas values, drugs used, presence of drug-resistant epilepsy, and the duration of the disease were examined. The patients included in the study were divided into two groups of similar ages and genders as DRE (whose seizures continue despite treatment with two or more antiepileptic drugs) and drug-nonresistant epilepsy patients according to ILAE classification by considering the patients' anamnesis, clinical history, seizure frequency, and antiepileptic drugs currently used. The patients were included in the study according to the following criteria:

A. Inclusion criteria

Being 18 years old and above, presenting to the emergency service with an epileptic seizure within the last 60 minutes, being a patient diagnosed with epilepsy by a neurologist and treatment being started, having whole blood count and blood gas examination at presentation to the emergency service are our inclusion criteria.

B. Exclusion criteria

Being younger than 18 years old, presenting to the emergency service with an epileptic seizure prior to the last 60 minutes, presenting with seizure-like clinical conditions and symptomatic seizure (trauma, deep anemia (Hb value being 7 g/dl and below), hypoglycemia, syncope, etc.), presenting with the first seizure, having no laboratory examinations performed at presentation to the emergency service, having coagulation result in hemogram and blood gas, being suspected with experiencing a nonepileptic psychogenic seizure, having undergone vagal nerve stimulation (VNS) or epilepsy surgery are our exclusion criteria.

2.2. Statistical Analysis

Statistical analyses were performed through SPSS (Statistical Packagefor the social sciences; SPSS Inc., Chicago, IL) 22 package software. Descriptive data were expressed as numbers and percentages for categorical variables and mean±standard deviation (Mean±SD) for continuous variables. Chi-square analysis (Pearson Chi-square) was used in the intergroup comparison of categorical variables. Compliance of continuous variables with normal distribution was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U test was employed in the pairwise comparison of the groups. The spearman correlation test was used to examine the relationship between continuous variables. The statistical significance level in the analyses was set at $p<0.05$.

3. Results

Two hundred six epilepsy patients in total, 77 drug-resistant and 129 drug-nonresistant epilepsy patients, were included in the study. Of the patients in the DRE group, 64.9% were male, and 35.1% were female. 65.9% of the patients in the DNRE group were male, while 34.1% were female. No significant difference was found between the groups in terms of gender ($p=0.889$). The mean age of the patients in the DRE group was determined to be 40.00±12.96 years, while it was 38.67±14.72 years in the DNRE group. There was no statistically significant difference between the groups in terms of age ($p=0.248$). The mean disease duration of the patients in the DRE group was found to be higher than that of the patients in the DRNE group ($p<0.001$) (Table 1).

Table 1. Comparison of the groups in terms of demographic characteristics and disease duration

		DRE (n=77)		DNRE (n=129)		p
		Number	%	Number	%	
Gender	Male	50	64.9	85	65.9	0.889*
	Female	27	35.1	44	34.1	
Age Mean±SD		40.00±12.96		38.67±14.72		0.248**
Disease Duration Mean±SD		12.47±4.08		10.04±434		**<0.001****

*Chi-square analysis, **Mann-Whitney U testwas applied.
DRE: Drug-resistant epilepsy, DNRE: Drug-nonresistant epilepsy

No significant difference was observed between the groups in terms of leukocyte ($p=0.729$), platelet ($p=0.132$), neutrophil ($p=0.676$), lymphocyte ($p=0.398$), monocyte ($p=0.658$), NLR ($p=0.355$), PLR ($p=0.846$), MLR ($p=0.064$), pH ($p=0198$), pO2 ($p=0.288$), pCO2 ($p=0.349$) and lactate ($p=0.358$) (Table 2).

A negative and significant correlation was found between age and platelet count in the correlation analysis. A positive and significant correlation was found between leukocyte and platelet, neutrophil, lymphocyte, monocyte, NLR, pO2, and lactate; a negative and significant correlation was determined between leukocyte and PLR and pH. Platelet was found to have a positive and significant correlation with neutrophil, lymphocyte, monocyte, PLR, and lactate and a negative and significant correlation with pH. Also, a positive and significant correlation existed between neutrophil and monocyte, NLR, MLR, and lactate. A positive and significant correlation between lymphocyte and monocyte, pO2, and lactate, and a negative and significant correlation between lymphocyte and NLR, PLR, MLR, and pH were determined. There was a positive and significant correlation between monocyte and MLR, pO2, and lactate, while a negative and significant correlation was found between monocyte and PLR. NLR correlated positively and significantly with PLR, MLR, and pH and negatively and significantly with lactate. It was found that PLR has a positive and significant correlation with MLR and pH and a negative and significant correlation with lactate. MLR was found to correlate positively with pH and negatively

with lactate significantly. In addition, a negative and significant correlation was determined between pH, pO2, and lactate. Finally, pO2 correlated positively with lactate and negatively with pCO2 (Table 3).

Table 2: Comparison of blood parameters of the groups

	DRE (n=77)	DNRE (n=129)	p*
	Mean±SD	Mean±SD	
WBC	9.55±3.72	9.57±3.55	0.729
PLT	232.16±82.57	252.88±78.89	0.132
N	5.83±2.99	5.62±2.83	0.676
L	2.86±1.49	3.07±1.55	0.398
M	0.74±0.38	0.69±0.29	0.658
NLR	2.66±2.35	2.38±2.13	0.355
PLR	101.80±62.46	102.41±57.19	0.846
MLR	0.30±0.19	0.26±0.13	0.064
pH	7.32±0.10	7.33±0.11	0.198
pO2	44.90±17.18	107.04±683.03	0.288
pCO2	42.40±7.22	71.45±334.29	0.349
Lactate	4.67±4.20	5.16±4.56	0.358

*Mann-Whitney U test was applied.
WBC: White blood cell, PLT: Platelet, N: Neutrophil, L: Lymphocyte, M: Monocyte
NLR: Neutrophil/Lymphocyte ratio, PLR: Platelet/Lymphocyte ratio, MLR: Monocyte/Lymphocyte ratio
DRE: Drug-resistant epilepsy, DNRE: Drug-nonresistant epilepsy

Table 3. Correlation between age, disease duration, and blood parameters

		Age	Disease duration	WBC	PLT	N	L	M	NLR	PLR	MLR	pH	pO2	pCO2
Disease duration	r	-.002												
	p	.982												
WBC	r	.035	-.126											
	p	.616	.071											
PLT	r	**-.143**	-.065	**.337**										
	p	**.041**	.352	**.000**										
N	r	.042	-.114	**.835**	**.302**									
	p	.552	.102	**.000**	**.000**									
L	r	-.066	-.005	**.551**	**.230**	.093								
	p	.344	.942	**.000**	**.001**	.185								
M	r	-.066	-.043	**.704**	**.309**	**.474**	**.551**							
	p	.347	.541	**.000**	**.000**	**.000**	**.000**							
NLR	r	.086	-.074	**.139**	.034	**.614**	**-.685**	-.105						
	p	.219	.289	**.047**	.627	**.000**	**.000**	.132						
PLR	r	-.017	-.041	**-.328**	**.302**	.087	**-.820**	**-.355**	**.678**					
	p	.804	.559	**.000**	**.000**	.214	**.000**	**.000**	**.000**					
MLR	r	.028	-.039	-.021	.034	**.326**	**-.637**	**.228**	**.711**	**.622**				
	p	.693	.582	.763	.626	**.000**	**.000**	**.001**	**.000**	**.000**				
pH	r	-.006	-.029	**-.242**	**-.138**	-.105	**-.297**	-.137	**.152**	**.199**	**.155**			
	p	.931	.681	**.000**	**.047**	.133	**.000**	.050	**.029**	**.004**	**.026**			
pO2	r	-.045	-.056	**.206**	.073	.128	**.172**	**.267**	-.049	-.133	.068	**-.163**		
	p	.520	.422	**.003**	.296	.067	**.013**	**.000**	.488	.056	.334	**.019**		
pCO2	r	.000	.071	-.090	-.015	-.094	.015	-.081	-.024	-.008	-.067	**-.218**	**-.347**	
	p	.999	.309	.198	.835	.177	.832	.248	.729	.905	.337	**.002**	**.000**	
Lactate	r	.099	-.056	**.374**	**.225**	**.198**	**.407**	**.343**	**-.163**	**-.272**	**-.089**	**-.667**	**.298**	-.062
	p	.155	.423	**.000**	**.001**	**.004**	**.000**	**.000**	**.019**	**.000**	**.205**	**.000**	**.000**	.376

WBC: White blood cell, PLT: Platelet, N:Neutrophil, L:Lymphocyte, M:Monocyte
NLR: Neutrophil/Lymphocyte ratio, PLR: Platelet/Lymphocyte ratio, MLR: Monocyte/Lymphocyte ratio

4. Discussion

According to WHO's Global Burden of Disease study, epilepsy is a neurological disease with the second most frequent economic burden and a cause of disability (19). Many mechanisms, such as genetic predisposition, developmental dysfunctions, neuronal death, dysfunctional synaptic changes, and hyperexcitable neuronal transmission, are held responsible for the pathogenesis of epilepsy (20). In many situations that especially lead to brain damage, an acute neuroinflammatory response occurs in which proinflammatory molecules increase and the blood-brain barrier (BBB) is disrupted (21, 22). In preclinic epilepsy model studies recently conducted, it has been emphasized that the increased inflammation in the brain regions where the seizure starts and spreads leads to neuronal hyperexcitability, which has a role in seizure generation (23, 24). The contribution of local and systemic inflammatory response in epileptogenesis has been clarified by demonstrating the increase in chemokine and cytokine values (20).

Approximately 30% of epilepsy patients have been classified as DRE, and despite effective therapy, seizure control could not be achieved (5). The ILAE (International League Against Epilepsy) defined DRE as a disease in which freedom from seizure could not be achieved despite combining two or more tolerable and appropriately chosen drugs (7). In these patients, difficulty in seizure control, psychological dysfunction, decreased quality of life, and increased mortality risk are more frequently seen (22). In addition, patients who present to emergency services with frequent epileptic seizures continue to create a significant economic and work burden (25). In our study, we aimed to examine systemic inflammatory indices and blood gas parameters in order to evaluate clinical progression in patients who presented to our emergency service with epileptic seizures and were grouped according to their anamnesis, clinical history, and medication history.

Systemic inflammatory indices such as neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios are applied in many diseases as cheap and available biomarkers (26-30). Systemic inflammatory indices are one of the important parameters that can be used in acute neurological diseases, as in many diseases (10-12, 26). Stredny et al. emphasized the importance of determining a peripheral biomarker instead of invasive methods for reliable predictability of epilepsy seizures (15). In many studies, the usability of these biomarkers in the differentiation of epileptic seizures from nonepileptic conditions has been investigated (13, 16-18, 31).

In a case-control study comparing epilepsy patients with healthy control group patients, the mean NLR ratio was significantly higher in epilepsy patients (p=0.026) (13). Our study found NLR and MLR levels in DRE patients to be statistically insignificant but relatively high. In another study, a significant relationship was found between retrospective NLR levels of 116 patients followed up in intensive care with status epilepticus and their intensive care unit (ICU) requirement and hospital stay durations (p=0,046, p=0,020, respectively) (14). In our study, in DRE patients whose NLR levels were higher, disease duration was significantly longer than in DNRE patients ($p<0.01$).

In a study conducted by Gunes et al. comparing patients presenting with generalized tonic-clonic seizure and healthy control group patients, NLR and PLR levels were found to be statistically significant in the first 60 minutes and subacute (in hour 72 of epileptic seizure) periods ($p<0.01$, $p<0.05$, respectively). In that study, it was shown that a one-unit increase in NLR caused an increase in seizure risk by 1.95 times and was associated with epileptic seizure and neutrophil-mediated inflammation (16). In our study, the NLR ratio rather than the PLR value was higher in DRE patients, which suggests that neutrophil-mediated inflammations could be more prominent.

Moreover, studies were conducted on the diagnostic property of changes in serum lactate levels during seizures (17, 18). In a study by Magnusson et al., increased serum lactate levels were demonstrated to be a valuable biomarker for predicting epileptic seizures in individuals who experience transient loss of consciousness (17). In another study, serum lactate levels (suggested cut-off value 2.43 nmol/l) in the first two hours were found to be significantly higher in generalized tonic-clonic seizures compared to psychogenic nonepileptic seizures (PNES) and syncope patients ($p<0.001$, $p<0.001$, respectively) (18). In our study, serum lactate levels were increased in both groups, but no significant difference was observed between the groups.

Although there are studies which examined systemic inflammatory indices and blood gas comparing epilepsy patients and non-epilepsy patients, studies on the differences within epilepsy patients are few. Our study examined these parameters between DRE and DNRE patients, but we could not determine a statistically significant difference.

In order to understand treatment options for epilepsy, it is necessary to examine the underlying mechanisms in depth. Determining certain biomarkers is important in terms of estimating the course of the disease in order to especially predict the progression of the disease in DRE patients, who constitute nearly 30% of all epilepsy patients. As a result of the study, it was seen that there was no significant difference between DRE patients and DNRE patients in terms of the parameters used as systemic inflammatory biomarkers in epilepsy patients.

Limitations of Study

Our study has a few limitations. The first of these is the small number of patients. Our second limitation is that the study is retrospective. Another limitation of our study is that it is single-centered.

Conflict of interest
The author has no conflicts of interest to declare.

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Ethical statement
Ethical approval for the study was obtained from Malatya Turgut Ozal University Non-Interventional Clinical Research Ethics Committee with the decision numbered 2022/92 and dated 10.05.2022.

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None to declare.

Authors' contributions
Concept: T.E., Design: T.E., Data Collection or Processing: T.E., Analysis or Interpretation: T.E., Literature Search: T.E., Writing: T.E.

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