



Research Article/Özgün Araştırma

The relationship between febrile seizure and hematological parameters in children

Çocuklarda febril nöbet ile hematolojik parametreler arasındaki ilişki

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**Abstract**

**Aim:** The aim of this study was to investigate whether hematological parameters play a significant role in the relationship between hematological parameters and seizure occurrence in children with febrile seizures (FS) by comparing them to a healthy control group with no fever or seizures.

**Materials and Methods:** One-hundred forty-one patients diagnosed with FS and with available a complete blood count results and a control group of 143 children were finally enrolled.

**Results:** The study group consisted of 141 patients, 57 girls (40.4%) and 84 boys (59.6%) (M/F=1.4). Mean age at the time of first FS was 22.89 ± 13.95 months. Ninety-two (65.2%) of the study group were diagnosed with simple FS, 32 (22.7%) with complex FS, and 17 (12.1%) with febrile status epilepticus (FSE).

**Conclusion:** Since our neutrophil, lymphocyte, eosinophil, and mean platelet volume (MPV) results were statistically significant in patients with FS, it is thought that these markers may represent potential predictive parameters in that condition.

**Keywords:** Eosinophil; Febrile seizure; Lymphocyte; MPV; Neutrophil.

**Öz**

**Amaç:** Bu çalışmanın amacı, ateşli nöbet (FN) geçiren çocuklarda hematolojik parametreler ile nöbet oluşumu arasındaki ilişkide hematolojik parametrelerin önemli bir rol oynayıp oynamadığını, ateşi ve nöbeti olmayan sağlıklı bir kontrol grubu ile karşılaştırarak araştırmaktır.

**Gereç ve Yöntem:** FN tanısı almış ve hemogram sonuçları bulunan 141 hasta ve 143 sağlıklı çocuk kontrol grubu olarak çalışmaya dahil edildi.

**Bulgular:** Çalışma grubu 57 Kız (%40,4), 84 Erkek (59,6) olmak üzere 141 hastadan (E/K=1,4) oluşmaktadır. Hastaların ilk FN geçirme yaş aralığı 22,89 ± 13,95 aydır. Hasta grubunun 92'si (%65,2) basit FK, 32'si (%22,7) komplike FN ve 17'si (%12,1) febril status epileptikus (FSE) tanısı almıştı.

**Sonuç:** Çalışmamızda FN'li hastalarda nötrofil, lenfosit, eozinofil ve ortalama trombosit hacmi (MPV) sonuçlarının istatistiksel olarak anlamlı tespit edilmesi nedeniyle bu belirteçlerin FN'de öngörücü parametreler olabileceği düşünülmektedir.

**Anahtar Kelimeler:** Eozinofil; Febril nöbet; Lenfosit; MPV; Nötrofil.

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## Introduction

Febrile seizure (FS) is an age-dependent event that emerges with fever, exhibits a generally benign course, and represents the most frequent seizure type in childhood. The International League Against Epilepsy (ILAE) defines FS as a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures.<sup>1</sup> FS is more frequently seen in early childhood when the seizure threshold is low, the fever response is more pronounced, and susceptibility to infections is more common. FS is seen between the ages of three months and six years and generally emerges with fever during the course of viral or bacterial infections. The highest incidence is seen between 12 and 18 months.<sup>2</sup> Although the gender difference is not pronounced, it is reported to be more common in boys.<sup>3</sup> There are two subtypes, simple and complex. Simple FS involves generalized seizures less than 15 min in duration and not recurring within 24 h, while complex FS refers to seizures that are generally focal in nature and last longer than 15 min, and that may be observed more than once in 24 h. In FSE, seizures persist without restoration of consciousness or last for 30 min or longer. However, in 2015 FSE was defined as seizures lasting 5 min or longer.<sup>4</sup>

Although the etiology of FS is not yet fully understood, age, high body temperature, viral infections, immunization, and family history have been implicated as risk factors. Complete blood laboratory tests, which are available in all hospitals and widely employed, are requested to assist with status determination in children presenting with acute fever. Complete blood count tests are simple and easily available and help to determine cell numbers and ratios in blood. They are used in the control and follow-up of numerous diseases. Similar to other diseases, they are an important and useful test in FS, particularly in differential diagnosis. This study was intended to determine whether or not hematological markers can represent a predictive parameter in FS.

## Materials and Methods

### Type of the study

This is an original research study including the patients diagnosed with FS at the Adıyaman University Training and Research Hospital pediatric emergency and pediatric neurology clinics, Turkey, between July 2014 and May 2022, and with available complete blood count results.

### Population and sample of the study

Inclusion criteria were diagnosis of FS, being within the FS age range, body temperature elevation, absence of central nervous system infection, exclusion of other causes of seizure, and absence of any other disease capable of causing neuromotor retardation. It has been determined that the minimum participant size should be 87, with a confidence level of 95%.

### Data collection tools

All patients' files were reviewed retrospectively, and age at first FS, diagnosis of simple or complex FS or FSE, and neutrophil, lymphocyte, eosinophil, platelet, and MPV findings were retrieved and recorded. Patients were classified into three groups, simple FS, complex FS, and FSE. The groups were established for the purpose of identifying and prognostic differences.

### Analysis of data

The study data were analyzed on Statistical Package for the Social Sciences (SPSS) version 22 software. The Independent sample t-test was applied in the comparison of two independent groups when normal distribution assumptions were met, while the Mann-Whitney U test was employed when these were not met. The chi-square test was applied to investigate differences between categorical variables, with exact test results being considered in case of expected frequency percentages being lower than 25%. Sensitivity and specificity for neutrophil, lymphocyte, eosinophil, and MPV values were determined using ROC analysis. Continuous variables were expressed as both mean  $\pm$  standard deviation and median [minimum-maximum] values. Categorical variables were

summarized as numbers and percentages.  $p$  levels  $<0.05$  were regarded as statistically significant.

### Ethics committee approval

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval for the study was obtained from the institutional review board (no.2022/7-53).

### Results

The records of 191 patients presenting to the Adiyaman University Training and Research Hospital pediatric neurology clinic between July 2014 and May 2022 and diagnosed with FS were examined retrospectively. Fifty patients with risk factors affecting neurological development, with afebrile seizures, or with inadequate file data were excluded. One-hundred forty-one patients diagnosed with FS and with available

a complete blood count results and 143 healthy children were finally enrolled. No significant differences were observed between the patient and control groups in terms of age or sex ( $p>0.05$ ).

The study group consisted of 141 patients, 57 girls (40.4%) and 84 boys (59.6%), with a F/M ratio of 1.4. The mean age at first FS was  $22.89 \pm 13.95$  months. Ninety-two (65.2%) of the patient group were diagnosed with simple FS, 32 (22.7%) with complex FS, and 17 (12.1%) with FSE. No significant associations were determined between the disease groups and patients' hematological parameters.

Statistically significant differences were determined between the study groups in terms of neutrophil ( $p<0.001$ ), MPV ( $p<0.001$ ), eosinophil ( $p=0.001$ ), and lymphocyte ( $p=0.001$ ) values, but no significant difference was observed in platelet ( $p=0.115$ ) values (Table 1). Lymphocyte values were lower in the patient group, while neutrophil, eosinophil, and MPV values were higher than in the control group.

**Table 1.** Differences in hematological parameter results between the patient and study groups

	Group		$p$ -value
	Patient (n=141) Mean±SD	Control (n=143) Mean±SD	
Neutrophil	5.94±4.45	3.02±2.17	$<0.001^*$
Lymphocyte	4.12±2.40	4.88±1.90	$=0.001^*$
Eosinophil	0.25±0.50	0.23±0.21	$=0.001^*$
Platelet	310.15±108.87	329.52±97.55	$=0.115^+$
MPV	6.82±1.36	6.09±1.16	$<0.001^+$

\* Independent Sample t test, +Mann Whitney U test

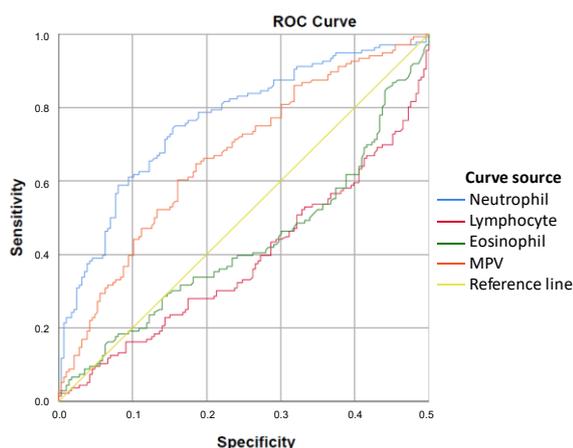
An optimal cut-off value of 3.03 for neutrophil count at ROC analysis (AUC: 0.763) exhibited 70.6% specificity and 72% sensitivity for FS ( $p<0.001$ ), an optimal cut-off value of 4.24 for lymphocyte count (AUC: 0.383) exhibited 41.3% specificity and 44% sensitivity for FS ( $p=0.001$ ), an optimal cut-off value of 0.135 for eosinophil count (AUC: 0.424) exhibited 41.3% specificity and 42.6% sensitivity for FS ( $p=0.028$ ), and an optimal cut-off value of 6.25 for MPV (AUC: 0.665) exhibited 62.9% specificity and 64.7% sensitivity for FS ( $p<0.001$ ) (Figure 1)

### Discussion

FS is the most common form of seizure in childhood, affecting 2-5% of children. It is reported to be more frequent in boys.<sup>3,5</sup> Our

study group being made up of 57 girls (40.4%) and 84 boys (59.6%) is consistent with the existing literature. Different age ranges for FS have been reported in previous studies, although the mean age at first seizure in the present research was 22.9 months. Sharawat et al. reported a figure of 24.9 months and Gontko-Romanowska et al. one of 22 months.<sup>6,7</sup> Simple FS is more common than complicated FS. FSE is less frequently seen. In their study of 428 children presenting with first seizure, Berg et al. reported that FS was the most common form, followed by complicated FS at 35% and FSE at 5%.<sup>8</sup> Simple FS was determined in 92 (65.2%) of the 141 patients in the present study, followed by complicated FS in 32 (22.7%), and FSE in 17 (12.1%). No statistically significant difference was

observed in terms of hematological parameters between the subgroups in the study group.



**Figure 1.** ROC curve analysis results for neutrophil, lymphocyte, eosinophil, and MPV values

Although the pathophysiology of FS is not yet entirely understood, studies have reported a relationship between FS and inflammation.<sup>9,10</sup> Pathogenic micro-organisms that enter the body trigger the release of inflammatory mediators by directing white blood cells and macrophages to the blood and infected tissues. These represent the first condition that precipitates fever and inflammation. The pyrogens that then form affect the hypothalamus by being released from white blood cells and macrophages. Uncontrolled temperature creates a major risk for FS.<sup>11</sup> Although there is a great variety of causes leading to seizure, the complete blood count is one of the tests that assist in the identification of the underlying condition. Among the hematological markers examined in the present study, lymphocyte counts were lower than in the control group, while neutrophil, eosinophil, and MPV values were higher. Gontko–Romanowska et al. reported a significant difference in neutrophil and lymphocyte counts in patients with FS compared to a control group.<sup>7</sup> In another study of patients with FS, Güneş et al. observed a significantly higher neutrophil count and a significantly lower lymphocyte count compared to a control group.<sup>12</sup> Additionally, Liu et al. observed a significant association between elevated neutrophil and low lymphocyte values.<sup>13</sup>

Specific viral infections such as human herpes virus-6, herpes simplex virus-1, respiratory syncytial virus, influenza, adenovirus, and cytomegalovirus have been linked to FS.<sup>14</sup> Exposure to viral infections in the early periods of life can represent a risk in terms of airway hypersensitivity and atopy. It is important for the cellular mechanisms underlying an atopic disposition to be understood. Inflammatory cells, such as antigen-presenting cells, mast cells, eosinophils, basophils, and lymphocytes, associated with asthma are known to precipitate or exacerbate airway hypersensitivity by releasing cytokines through viral infections.<sup>15</sup>

One of the first parameters frequently investigated in the diagnosis of allergic diseases is the blood eosinophil count. Although eosinophils are known to play an important role in allergic inflammation, there is still no evidence of an association with FS.<sup>15</sup> Very few studies have suggested that children undergoing FS may be at an increased risk of asthma in the future. Lin et al. emphasized the relationship between asthma and FS.<sup>16</sup> Eosinophils in the airways have an advanced inflammatory capacity in bronchial asthma.<sup>17</sup> The significant difference in eosinophil counts between the study and control groups in the present research suggests that eosinophils may be used as a marker for FS. In addition, an optimal cut-off value of 0.135 for eosinophil count at ROC analysis (AUC: 0.424) exhibited 41.3% specificity for FS and 42.6% sensitivity. To the best of our knowledge, this is the first report of a relationship between FS and the hematological parameter of the eosinophil count.

Eosinophilia can arise from both infectious and non-infectious conditions, many of which have no distinguishing clinical features. Eosinophilia can stem from parasitic infections, as well as allergies, autoimmune diseases, malignancies or other underlying conditions.<sup>18</sup> Studies have shown that peripheral eosinophil count is suppressed in patients during acute bacterial and viral infections.<sup>19,20</sup> Therefore, the presence of eosinophilia in the context of an acute illness indicates a non-infectious (such as

autoimmune), parasitic, or fungal origin as the underlying cause of the disease. The detection of eosinophilia in our study was statistically significant and indicates that this marker could be a predictive parameter in FS.

High MPV may indicate large, more reactive platelets resulting from increased platelet turnover and can be employed as a marker of platelet activation and inflammation.<sup>21</sup> MPV values in the present study were significantly higher than in the control group. In addition to Liu et al.'s study<sup>13</sup>, Abuhandan et al. also reported a similar association to that in the present research.<sup>22</sup> Studies have also investigated the relationship between MPV and other systemic diseases.<sup>23</sup> The optimal cut-off value for MPV of 6.25 at ROC analysis in the present study (AUC: 0.665) exhibited 62.9% specificity and 64.7% sensitivity for FS. Additionally, the optimal cut-off value of 3.03 for the neutrophil count (AUC: 0.763), another of the hematological parameters investigated, exhibited 70.6% specificity for FS and 72% sensitivity, while the optimal cut-off value for the lymphocyte count of 4.24 (AUC: 0.383) exhibited 41.3% specificity for FS and 44% sensitivity. This shows an independent risk factor for FS.

Numerous studies in the literature have compared the laboratory results of individuals with febrile seizures to those of a control group with fever but no seizures.<sup>7,12</sup> In addition, it should be stated that there are studies incorporating research comparing the laboratory results of individuals experiencing febrile seizures and those in the healthy control group who are not experiencing seizures and fever. Although Tang and Chen found that the MPV value was significantly higher in patients with febrile seizures than in patients with fever but not febrile seizures and healthy control group without fever, no statistically significant difference was observed between the compared control groups.<sup>24</sup> Additionally, there are studies in the literature, but a limited number, comparing patients experiencing febrile seizures to healthy controls without a fever. In the study of Aydın et al., a significant difference was observed in the MPV value of patients with febrile seizures compared to the

healthy control group without fever and seizure.<sup>25</sup>

The principal limitations of this study are the low case numbers, its retrospective nature, and the fact that the research employed the hospital database. Further prospective studies with wider population-based case series are now needed to elicit more detailed results. The lack of a second control group of similar age and gender with fever and no seizure for comparison is also a notable deficiency, as it would have allowed for a clearer examination of whether the parameters discussed in this study were affected by seizure, infection, or both. The authors believe that including two control groups, one containing patients with fever but no seizures and the other with patients experiencing neither fever nor seizures, would have yielded more informative data.

## Conclusions

In conclusion, the neutrophil, lymphocyte, eosinophil, and MPV levels of the patients with FS differed significantly from those of the control group. The ROC curve analysis demonstrated that these values may be used as a possible assistant parameter to predict FS. The relationship between eosinophils and FS may be considered another important finding of this study. We suggest that inflammation resulting from eosinophil activation is important in bronchial asthma and that due to the relationship between eosinophils and FS in this study, children undergoing FS should be evaluated and followed up in terms of allergic diseases.

## Ethics Committee Approval

Ethical approval for the study was obtained from the institutional review board (no.2022/7-53). This study conformed to the Helsinki Declaration.

## Informed Consent

Data concerning the study were collected with the permission of the Adıyaman Provincial Health Directorate.

## Authors Contributions

All of the authors contributed at every stage of the study

## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

## Financial Disclosure

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## Statements

These research results have yet to be presented anywhere previously. Data related to the study is available on request.

## Peer-review

Externally peer-reviewed.

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