

ORIGINAL PAPER

The significance of the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio in the aetiology of febrile seizures in children

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ABSTRACT

Introduction: Febrile seizures are seizure episodes associated with fever, occurring in the absence of central nervous system infection or other specific seizure-inducing causes. The aim of this study is to evaluate the relationship between neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) indicators with febrile seizures, which may help explain the role of inflammation in the aetiology of this condition.

Material and methods: This was a retrospective study. The study group consisted of 54 cases of children diagnosed with simple febrile seizures, and the control group (CG) included 54 patients of comparable age hospitalized due to infections accompanied by fever but without seizures. The analysis included data obtained from available medical history and laboratory tests performed upon admission to the hospital (gender, age, month of hospitalisation, absolute counts of neutrophils, lymphocytes, platelets, C-reactive protein (CRP), white blood cells, mean corpuscular volume, concentrations of sodium, potassium, total calcium, iron, and glucose). Additionally, NLR and PLR indicators were calculated for each patient.

Results: It was observed that febrile seizures occurred more frequently in boys than in girls, with the highest number of hospitalisations for febrile seizures recorded in February and September. Higher values of neutrophils, NLR, PLR, and glucose, as well as lower levels of CRP, sodium, and lymphocyte counts, were found in children with febrile seizures compared to children in the CG.

Conclusions: Higher values of NLR and PLR indicators in children with febrile seizures, compared to children with fever without seizures, may confirm the role of inflammation in the pathogenesis of febrile seizures. The availability, low cost, and demonstrated sensitivity and specificity of these indicators may translate into their clinical application value.

KEY WORDS:

C-reactive protein, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, febrile seizures, inflammation indicators.

INTRODUCTION

Febrile seizures are seizure episodes that occur with fever, in the absence of central nervous system infection or other specific seizure-inducing causes. They

occur in children aged between 6 months and 5 years, with a peak incidence at 12–18 months of age [1, 2]. In Western Europe and the United States, 2–5% of children under the age of 5 experience at least one febrile seizure in their lifetime, 6–9% in Japan, and 5–10% in India [3].

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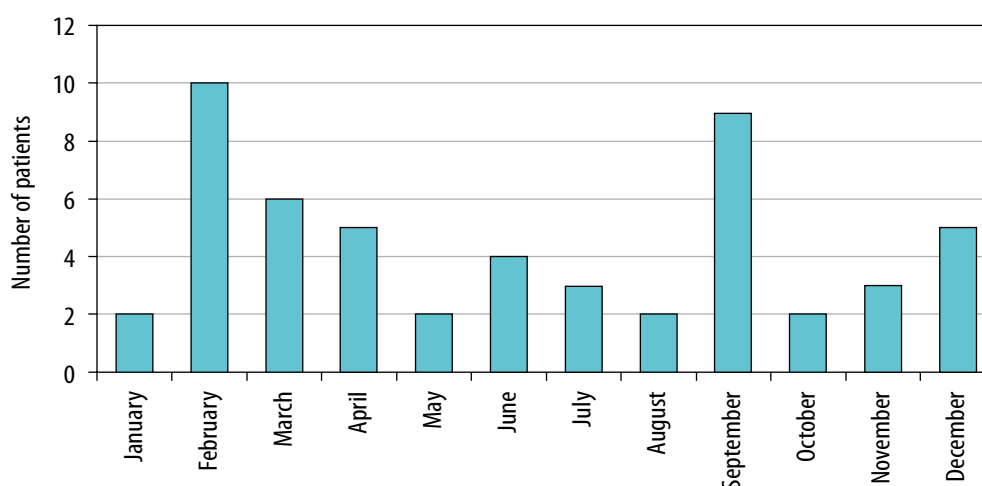


FIGURE 1. Seasonality of febrile seizures in the study group

We may distinguish between simple febrile seizures, which are generalised, last less than 15 minutes, and do not recur within 24 hours, and complex febrile seizures, characterised by at least one of the following: they are focal, last more than 15 minutes, or more than one seizure occurs within 24 hours [1–3]. It is estimated that 65–80% of febrile seizures are simple seizures [4]. Their exact causes have not yet been fully explained. They are most commonly associated with viral infections, which can accompany up to 82% of febrile seizure cases [5, 6]. In recent years, there has been growing interest in the role of inflammation in the aetiology of febrile seizures. Scientific research suggests that pro-inflammatory and anti-inflammatory cytokines may play a particular role in the pathophysiology of febrile seizures [2, 6]; however, measuring their levels is costly and has limited availability. Inflammatory markers, in addition to parameters such as C-reactive protein (CRP) or leukocytosis, include the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR). The neutrophil-lymphocyte ratio is the ratio of the absolute number of neutrophils to the absolute number of lymphocytes, and PLR is the ratio of the absolute number of platelets to the absolute number of lymphocytes. The relevance of these indicators has been demonstrated in the assessment of the clinical course of diseases in patients with conditions such as sepsis, pneumonia, COVID-19, cardiovascular diseases, autoimmune diseases, burns, and cancers [7–12].

The aim of the study is to evaluate the association of NLR and PLR indicators with febrile seizures, which may help clarify the role of inflammation in the aetiology of this condition.

MATERIAL AND METHODS

The conducted study was retrospective. Data were obtained from the medical records of patients treated at the Department of Paediatrics in Zabrze 2014–2024.

A total of 108 patients aged between 9 months and 4.5 years were included in the study. The study group (SG) consisted of 54 cases of children diagnosed with simple febrile seizures, while the control age-matched group (CG) included 54 patients hospitalised due to infections accompanied by fever without seizures. The exclusion criteria for both the study group and CG were a positive personal or family history of seizures of aetiologies other than febrile seizures; for the CG, a history of febrile seizures was also an exclusion criterion. Three patients were hospitalised twice due to febrile seizures; for the purposes of analysis, each hospitalisation was treated as a separate case.

In the study group, a higher occurrence of febrile seizures was observed in boys ($n = 34$, 62.75%) compared to girls ($n = 20$, 37.25%).

A positive family history of febrile seizures was noted in 15.67% of patients ($n = 8$).

The highest number of hospitalisations due to febrile seizures was recorded in February and September (Figure 1). Febrile seizures were most commonly accompanied by symptoms of upper respiratory infections in 74.51% ($n = 38$) of patients. In the remaining patients, diagnoses included then following: gastroenteritis, sixth disease, hand, foot, and mouth disease, teething syndrome, unspecified viral infection, and fever of unknown origin.

In 27.45% ($n = 14$) of patients the seizure episode was not the first occurrence.

Information obtained from medical histories was anonymised.

The analysis included data derived from available medical history and laboratory tests performed on patient admission to the ward. The time elapsed from the onset of the seizure to the collection of samples in the SG could not be precisely assessed especially due to the lack of sufficient data on the time involved in transport to hospital. The time from registration in the emergency department to sample collection in most cases does not exceed 3 hours (8–199 minutes; mean 86.81 minutes,

TABLE 1. Comparison of selected parameters between the study group and the control group

Studied parameter	Study group	Control group	p-value
Age (months) (median [IQR])	24.00 [16.25, 32.00] n = 54	22.50 [14.25, 31.50] n = 54	0.494
Glycemia [mg/dl] (median [IQR])	108.25 [98.47, 133.52] n = 52	95.15 [80.88, 112.05] n = 48	< 0.001
Neutrophil count [g/l] (median [IQR])	10.02 [5.41, 12.87] n = 54	5.46 [3.57, 8.33] n = 54	0.002
Lymphocyte count [g/l] (median [IQR])	1.83 [1.28, 2.84] n = 54	3.34 [2.05, 4.59] n = 54	< 0.001
NLR (median [IQR])	4.82 [3.28, 7.26] n = 54	1.65 [1.09, 2.83] n = 54	< 0.001
Platelet count [g/l] (median [IQR])	284.50 [231.00, 338.00] n = 54	264.00 [231.50, 335.25] n = 54	0.423
PLR (median [IQR])	150.01 [115.45, 230.25] n = 54	77.19 [57.98, 124.26] n = 54	< 0.001
CRP [mg/l] (median [IQR])	7.58 [2.59, 19.31] n = 54	27.31 [5.67, 72.28] n = 54	0.001
WBC [g/l] (median [IQR])	12.99 [8.59, 17.60] n = 54	10.23 [8.20, 14.68] n = 54	0.155
MCV [fl] (median [IQR])	76.70 [74.00, 79.15] n = 54	76.20 [74.32, 78.70] n = 54	0.951
Sodium [mmol/l] (median [IQR])	137.00 [134.00, 138.00] n = 54	137.25 [135.00, 138.82] n = 54	0.038
Potassium [mmol/l] (mean [SD])	4.36 (0.39) n = 54	4.40 (0.46) n = 54	0.642
TIBC [μmol/l] (mean [SD])	57.33 (7.78) n = 31	52.93 (8.30) n = 22	0.054
Total calcium [mmol/l] (mean [SD])	2.42 (0.13) n = 49	2.43 (0.1) n = 28	0.75
Iron [μmol/l] (median [IQR])	2.95 [2.38, 3.62] n = 33	3.10 [2.40, 4.20] n = 27	0.743

CRP – C-reactive protein, IQR – interquartile range, n – number of patients, NLR – neutrophil-lymphocyte ratio, PLR – platelet-lymphocyte ratio, SD – standard deviation, TIBC – total iron-binding capacity, WBC – white blood cells

SD 47.71 minutes). Factors considered included gender, age, month of hospitalisation, absolute counts of neutrophils, lymphocytes, platelets, CRP, white blood cells (WBC), mean corpuscular volume (MCV), and concentrations of sodium, potassium, total calcium, iron, and glucose. Additionally, the NLR (the ratio of the absolute number of neutrophils to the absolute number of lymphocytes) and PLR (the ratio of the absolute number of platelets to the absolute number of lymphocytes) were calculated for each patient. Besides comparing the results between the SG and the CG, an analysis of these ratios was also conducted within the respective age subgroups.

Data were presented as mean and standard deviation for variables with a normal distribution or as median with the first and third quartiles for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. To compare variables between groups with a normal distribution, Student's *t*-test was applied, while for non-normally distributed variables, the Mann-Whitney Wilcoxon test was used. Spearman's rank correlation coefficient was used

to assess correlations. The suitability of the investigated parameters as potential markers of febrile seizures was evaluated using a single-factor generalised linear model with a logit link function. The results were presented as odds ratio with a 95% confidence interval, as well as sensitivity and specificity, along with a proposed cut-off point for the variable determined using the Youden method. Analyses were conducted using the R language in the RStudio environment. Values of $p < 0.05$ were considered significant.

RESULTS

Significant differences were observed in blood glucose levels, neutrophil counts, lymphocyte counts, NLR, PLR, CRP, and sodium concentrations between the study group and CG. No differences were found regarding the other laboratory parameters (Table 1).

No child in the SG was found to have hypoglycaemia or significant hyponatraemia, hypernatraemia, hypokalaemia, or hyperkalaemia.

TABLE 2. Receiver operating characteristic analysis of selected parameters

Studied parameter	AUC	Cut-off point	Specificity	Sensitivity
Glycaemia [mg/dl]	0.718	96.250	0.563	0.808
Neutrophil count [g/l]	0.671	9.650	0.815	0.537
Lymphocyte count [g/l]	0.765	3.900	0.444	0.963
NLR	0.812	3.095	0.778	0.759
Platelet count [g/l]	0.545	279.500	0.611	0.537
PLR	0.802	94.967	0.667	0.870

NLR – neutrophil-lymphocyte ratio, PLR – platelet-lymphocyte ratio

Table 2 presents the results of the receiver operating characteristic analysis, used as a tool to assess predictive accuracy. Among the analysed parameters, the highest sensitivity and specificity related to febrile seizures in children were found for NLR (specificity 78.8%, sensitivity 75.9%) and PLR (specificity 66.7%, sensitivity 87%).

The study showed a positive correlation between the NLR and PLR indices in both the study group and CG, as well as between the PLR and CRP indices in the study group (Figure 2). No statistically significant correlation was found between the NLR and CRP indices in either group.

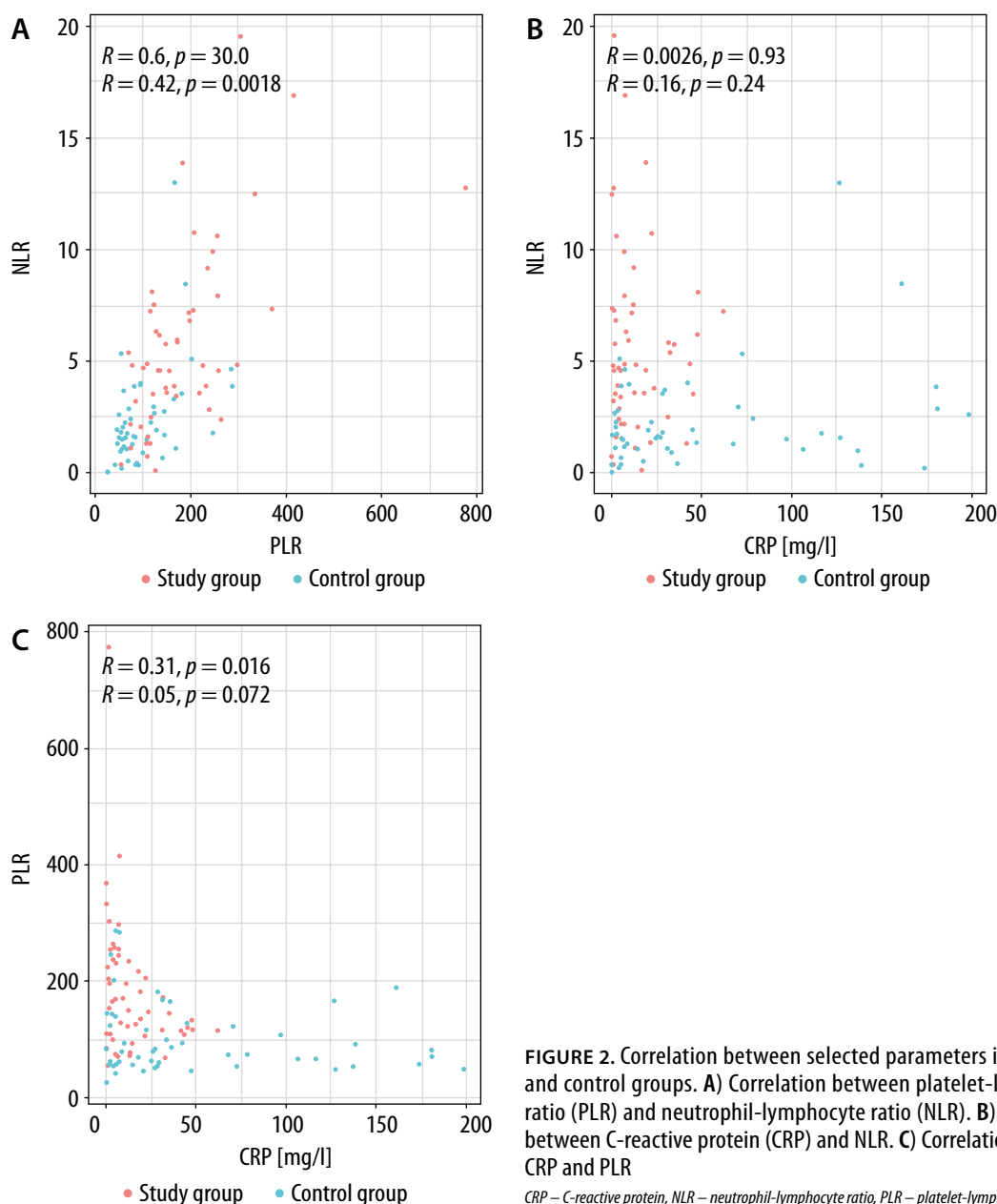


FIGURE 2. Correlation between selected parameters in the study and control groups. A) Correlation between platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR). B) Correlation between C-reactive protein (CRP) and NLR. C) Correlation between CRP and PLR

CRP – C-reactive protein, NLR – neutrophil-lymphocyte ratio, PLR – platelet-lymphocyte ratio

TABLE 3. Comparison of selected parameters in the study group between the first episode and subsequent episodes

Studied parameter	First episode	Subsequent episode	First episode vs. subsequent episode, <i>p</i> -value	First episode vs. control group, <i>p</i> -value	Subsequent episode vs. control group, <i>p</i> -value
Age (months, median [IQR])	22.00 [14.00, 31.25] <i>n</i> = 40	31.00 [24.50, 34.00] <i>n</i> = 14	< 0.05	0.82	< 0.05
Glycaemia [mg/dl] (median [IQR])	106.80 [97.03, 126.33] <i>n</i> = 38	117.35 [98.60, 147.45] <i>n</i> = 14	0.37	< 0.05	< 0.05
Neutrophil count [g/l] (median [IQR])	10.20 [5.82, 13.96] <i>n</i> = 40	6.97 [3.55, 11.02] <i>n</i> = 14	0.19	< 0.05	0.38
Lymphocyte count [g/l] (median [IQR])	1.83 [1.32, 2.99] <i>n</i> = 40	1.79 [1.20, 1.98] <i>n</i> = 14	0.31	< 0.05	< 0.05
NLR (median [IQR])	4.83 [3.55, 7.26] <i>n</i> = 40	4.23 [2.23, 7.15] <i>n</i> = 14	0.50	< 0.05	< 0.05
Platelet count [g/l] (median [IQR])	290.50 [230.75, 365.00] <i>n</i> = 40	262.50 [233.75, 311.00] <i>n</i> = 14	0.28	0.26	0.80
PLR (median [IQR])	150.01 [113.85, 226.91] <i>n</i> = 40	156.14 [119.51, 243.69] <i>n</i> = 14	0.62	< 0.05	< 0.05
CRP [mg/l] (median [IQR])	10.53 [3.65, 21.81] <i>n</i> = 40	5.66 [2.33, 14.45] <i>n</i> = 14	0.30	< 0.05	< 0.05
WBC [g/l] (median [IQR])	13.95 [9.57, 18.33] <i>n</i> = 40	10.17 [6.66, 14.56] <i>n</i> = 14	0.17	0.06	0.82
MCV [fl] (median [IQR])	75.40 [73.53, 79.00] <i>n</i> = 40	77.50 [76.73, 79.50] <i>n</i> = 14	0.14	0.54	0.29
Sodium [mmol/l] (median [IQR])	137.00 [133.8, 138.00] <i>n</i> = 40	136.50 [134.55, 137.75] <i>n</i> = 14	0.69	< 0.05	0.31
Potassium [mmol/l] (mean [SD])	4.38 (0.40) <i>n</i> = 40	4.30 (0.35) <i>n</i> = 14	0.33	0.87	0.35
TIBC [μmol/l] (mean [SD])	56.79 (7.91) <i>n</i> = 25	58.88 (7.68) <i>n</i> = 8	0.64	0.12	0.09
Total calcium [mmol/l] (mean [SD])	2.43 (0.14) <i>n</i> = 39	2.40 (0.12) <i>n</i> = 11	0.29	0.96	0.35
Iron [μmol/l] (median [IQR])	3.00 [2.3, 3.7] <i>n</i> = 26	2.90 [2.45, 3.55] <i>n</i> = 8	0.96	0.80	0.78

CRP – C-reactive protein, IQR – interquartile range, *n* – number of patients, NLR – neutrophil-lymphocyte ratio, PLR – platelet-lymphocyte ratio, SD – standard deviation, TIBC – total iron-binding capacity, WBC – white blood cells

No significant differences were observed (*p*-value > 0.05) in the values of laboratory parameters, including NLR and PLR indicators, between the first episode and subsequent episodes (second and third) in the study group (Table 3).

DISCUSSION

The aetiopathogenesis of febrile seizures in children is not fully understood, but increasing scientific evidence indicates a significant role of immunological and inflammatory mechanisms. Previous publications highlight the involvement of pro-inflammatory and anti-inflammatory cytokines. However, measuring these cytokines is associated with high costs, and factors such as the timing of sample collection, the severity of temperature,

the duration of fever, difficulties in cytokine measurement, the type of infection, and the size of the sample can potentially influence the discrepancies in results among different studies [13].

Neutrophil-to-lymphocyte ratio is a cost-effective and readily available marker of inflammation, demonstrating the dynamic relationship between innate (neutrophils) and adaptive cellular immune response (lymphocytes) during disease and various pathological conditions [9]. One of the possible explanations for the high NLR in patients with febrile seizures is its association with inflammatory activity [8, 14]. An increase in NLR is a result of elevated neutrophil count or decreased lymphocyte count [14]. Both neutrophils and lymphocytes participate in initiating the inflammatory response. Neutrophilia may also increase during intense muscle activity or as a result

of increased cortisol levels during seizures [15]. Activation of the sympathetic nervous system leads to lymphopenia, neutrophilia, and leukocytosis, which can trigger an increase in NLR [14]. Güneş *et al.* study demonstrated that non-febrile seizures are associated with inflammation mediated by neutrophils. Moreover, an increase in NLR by one unit increases the odds ratio of seizure occurrence 1.95-fold [16].

Another inflammatory marker, calculated as the ratio of platelet count to lymphocyte count, is PLR (platelet-lymphocyte ratio). It is also easily accessible and cost-effective because it is based on values obtained from blood morphology. To date, there have been few studies examining this parameter in relation to febrile seizures. Earlier studies indicated statistically insignificant differences in PLR between children with febrile seizures and those with fever without seizures [17, 18]. In contrast, our study demonstrated significantly higher PLR in children with febrile seizures compared to the CG. Similarly, Shi *et al.*, in their assessment of patients diagnosed with SARS-CoV-2 infection, found higher NLR and PLR in children with accompanying seizures (febrile seizures were diagnosed in 98% of this group) [19]. The association of PLR with febrile seizures warrants further investigation.

In our study, we found significantly higher NLR values in children diagnosed with simple febrile seizures compared to those with fever alone, which aligns with the majority of previous research [14, 15, 20]. Higher NLR and PLR values compared to the CG were also observed in children after the first episode and subsequent episodes of simple febrile seizures.

Similarly to Gontko-Romanowska *et al.*, no statistically significant differences in WBC values were found between the study group and the CG [20]. Additionally, in the current study, similarly to the aforementioned publication, the number of neutrophils was significantly lower and lymphocytes were significantly higher in the group of children with fever without seizures compared to those with febrile seizures. However, when comparing separately children with first-time and recurrent febrile seizures to the CG, it was found that the subgroup of patients with subsequent febrile seizures also had a higher, but statistically insignificant, percentage of neutrophils. This observation may be related to the small sample size of this subgroup and the age difference compared to children with fever but without seizures. Unlike in the study by Gontko-Romanowska *et al.*, no differences were found between the groups in terms of platelet counts.

In recent years, attention has been drawn to the need for predictive models that could help forecast episodes of febrile seizures based on blood morphology results and the calculated inflammatory response indices [14, 21]. In the present study, NLR and PLR indices exhibited the highest sensitivity and specificity among the analysed parameters (NLR – specificity 78.8%, sensitivity 75.9%; PLR – specificity 66.7%, sensitivity 87%). However, con-

sidering the short period between the onset of febrile infection symptoms and febrile seizure episodes, evaluating parameters measured after the seizure episode makes it challenging to use them as reliable markers for predicting the risk of febrile seizures. Instead, these parameters probably reflect the dynamic nature of the inflammatory process and may be helpful in distinguishing febrile seizures from other symptoms, including shivering, which caregivers often colloquially refer to as seizures.

Moreover, Shen *et al.* explored whether the NLR index could be used to predict recurrences of febrile seizures. In their study, children who experienced a subsequent seizure episode within a year had lower NLR values measured during the first episode compared to those who only had one febrile seizure during the year [22]. In our study, NLR, PLR, and other laboratory parameters were comparable between children with the first and subsequent episodes of febrile seizures. Similar observations were made by Erdede *et al.* [23]. A limitation of our analysis is the inability to predict whether the group with a first seizure incident includes children who may experience another episode in the future.

C-reactive protein is an acute-phase protein released from hepatocytes in response to inflammatory mediators such as IL-6 and IL-8. C-reactive protein levels typically rise approximately 6 hours after the initial immune response to inflammation [17]. Consistent with other authors, we observed significantly lower CRP concentrations in children with febrile seizures compared to those with fever without seizure episodes [14, 20, 21]. This may be related to the higher prevalence of viral infections accompanying febrile seizures, during which CRP levels are generally lower than in bacterial infections [24]. The seasonality of febrile seizures in our study occurred during the autumn-winter period, aligning with the peak incidence of viral infections in children [25]. This relationship has also been demonstrated in another Polish study involving 176 children, where approximately 26% of episodes occurred in autumn and 38% in winter [20]. In an analysis by Han *et al.*, which included 558,130 patients in South Korea, it was shown that the seasonal distribution of febrile seizures was high from late spring to summer. The authors linked these episodes to viral infections prevalent in the region during that time, particularly influenza and enterovirus infections [26].

In the article cited above, a higher prevalence of febrile seizures was also found in boys. Similarly, Leung *et al.* reported a higher incidence of febrile seizures in boys compared to girls (1.6 : 1), which aligns with our findings (1.68 : 1) and those of other authors [1, 9, 20].

Iron deficiency is considered a potential risk factor for febrile seizures [27]. It leads to dysfunction of the nervous system, can disrupt enzymatic reactions crucial for DNA, RNA, and monoamine metabolism, and affects the production and functioning of neurotransmitters in the brain and myelination disorders [28]. Additionally, iron plays

a vital role in regulating the immune system by stimulating the growth and differentiation of immune cells and inducing cytokine production [27]. Several studies have shown that the MCV and iron levels were significantly lower in children with febrile seizures compared to those with febrile illnesses without seizures [29, 30]. On the other hand, a meta-analysis by Kwak *et al.* suggests that iron deficiency anaemia characterised by low MCV and/or ferritin levels is associated with febrile seizures, whereas low iron levels alone may not be linked to them [27]. Furthermore, conflicting results were obtained in assessing total iron-binding capacity (TIBC) in the blood. Some studies showed statistically significant differences in TIBC values between the febrile seizure group and the CG of children with fever [31, 32]. Conversely, Tripathy *et al.* did not observe such a relationship [33]. Our results did not demonstrate differences in iron, MCV, and TIBC values between the study group and the CG.

In the presented study, glycaemia levels in children with febrile seizures were significantly higher compared to the CG, which may be associated with the phenomenon of stress hyperglycaemia [34–36]. This refers to glycaemia levels above 140 mg/dl in individuals with previously normal glucose tolerance under stress conditions [37]. Stress hyperglycaemia is caused by increased sympathetic nervous system activity, secretion of hormones such as adrenaline, glucagon, cortisol, growth hormone, and pro-inflammatory cytokines like TNF- α , IL-1, and IL-6 [18]. In our study, glycaemia above 140 mg/dl was observed in 21% of children in the study group and only in 4% of children in the CG.

Findings regarding the significance of sodium and potassium levels in febrile seizures are conflicting [38–41]. In our study, we demonstrated that sodium levels in the group of patients with febrile seizures and experiencing their first episode of simple febrile seizures are lower than in febrile patients without febrile seizures. It should be noted that none of the patients were found to have clinically significant hyponatraemia or hypernatraemia. Potassium values did not differ significantly between the groups.

CONCLUSIONS

The availability, low cost, and demonstrated sensitivity and specificity of these indicators may potentially enhance their clinical application value. Higher values of NLR and PLR indicators in children with febrile seizures, compared to febrile children without seizures, may support the role of inflammation in the aetiopathogenesis of febrile seizures. Based on the research conducted so far, it is not possible to definitively determine whether the severity of inflammation affects the occurrence of febrile seizures or whether these seizures have an additive effect on the increase in the inflammatory response. Clarification of these issues requires further research.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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