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Complete blood count-derived inflammatory indices for discriminating febrile seizures from epilepsy in children: a retrospective comparative study

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Research Article

Keywords: Febrile seizures, Epilepsy, Child, Inflammation, Complete blood count, Neutrophil-to-lymphocyte ratio, Systemic immune-inflammation index, Systemic inflammation response index, Aggregate index of systemic inflammation

Posted Date: November 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11635916/v1

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Additional Declarations: The authors declare no competing interests.

Abstract

Background

Inflammation is implicated in febrile seizures and epilepsy, but the clinical value of inflammatory indices derived from the complete blood count (CBC) remains uncertain. We compared the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) between children with febrile seizures and those with epilepsy and evaluated their discriminative and incremental value.

Methods

This single-center retrospective study included 100 children with febrile seizures, 98 with epilepsy, and 102 healthy controls evaluated between January 2021 and April 2026. In the patient groups, the first CBC from the first eligible presentation was analyzed. Groups were compared using Kruskal–Wallis and Holm-adjusted Mann–Whitney U tests. Discrimination was assessed by receiver operating characteristic analysis. Log2-transformed indices were entered into separate logistic regression models adjusted for age and sex, and incremental discrimination over an age–sex base model was summarized as the change in the area under the curve (ΔAUC).

Results

Median age differed among the febrile seizure, epilepsy, and control groups (1.75, 4.00, and 3.50 years, respectively; $p < 0.001$), whereas sex distribution did not. NLR, SII, SIRI, and AISI differed among the groups, but PLR did not. SIRI and AISI were highest in febrile seizures, intermediate in epilepsy, and lowest in controls. Discrimination between febrile seizures and epilepsy was poor: the AUC was 0.606 (95% confidence interval [CI] 0.527–0.683) for AISI and 0.591 (95% CI 0.510–0.669) for SIRI. After adjustment for age and sex, each doubling of NLR, SII, SIRI, and AISI was associated with higher odds of febrile seizures (adjusted odds ratios 1.35–1.54), but adding these indices to the base model (AUC 0.792) increased the AUC by only 0.012–0.016.

Conclusions

CBC-derived inflammatory indices, particularly SIRI and AISI, differed across groups but did not distinguish febrile seizures from epilepsy with clinically useful accuracy and added little beyond age and sex. Without a febrile non-seizure control group, seizure-related effects could not be separated from those of fever and infection. These indices are best regarded as exploratory markers of systemic inflammation rather than stand-alone diagnostic tests.

Introduction

Febrile seizures, which affect approximately 2–5% of children and typically occur between 6 and 60 months of age, are the most common seizures of early childhood and, by definition, occur in the absence of central nervous system infection, acute metabolic disturbance, or previous afebrile seizures [1–3]. Epilepsy, by contrast, comprises a heterogeneous group of disorders characterized by an enduring predisposition to generate epileptic seizures [4–6]. Although the two conditions are clinically and pathophysiologically distinct, inflammatory mechanisms have been implicated in both seizure generation and post-ictal physiology.

In febrile seizures, fever-related immune activation may lower the seizure threshold. Alterations in pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, as well as in anti-inflammatory mediators, have been reported in affected children [7–13]. In epilepsy, neuroinflammation has been linked to glial activation, impaired blood–brain barrier integrity, and peripheral immune responses [14–16]. The relationship is probably bidirectional: inflammatory signaling can increase neuronal excitability, and seizure activity can in turn modify central and peripheral inflammatory responses [15, 16].

These observations have prompted interest in inexpensive peripheral markers derived from the routine complete blood count (CBC). The neutrophil-to-lymphocyte ratio (NLR) reflects the balance between neutrophil- and lymphocyte-mediated immune responses [17], whereas the platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) combine neutrophil, lymphocyte, monocyte, and platelet counts in different formulations [18–22]. Because they are calculated from routine CBC results, these indices require no additional blood sampling or laboratory cost, which makes them attractive candidate markers of systemic inflammation in pediatric acute care.

Several studies have examined NLR and other CBC parameters in children with febrile seizures [23–29], and more recent work has extended this approach to composite indices such as SII and SIRI [30]. Studies in epilepsy have focused mainly on NLR, with heterogeneous findings related to seizure timing, epilepsy phenotype, and treatment status [31–33]. Febrile seizure studies have generally used febrile or healthy children as comparators, and few have directly compared febrile seizures with another seizure population, particularly using monocyte-containing indices such as SIRI and AISI. Such a comparison is informative because a marker proposed for febrile seizures should, if it reflects a seizure-type-specific process rather than a nonspecific inflammatory response, also distinguish febrile seizures from other seizure disorders. Moreover, statistically significant group differences do not necessarily translate into clinically useful discrimination.

The primary aim of this study was to compare NLR, PLR, SII, SIRI, and AISI between children with febrile seizures and those with epilepsy and to evaluate the ability of these indices to discriminate between the two conditions. Secondary aims were to compare the indices with values in healthy children, to assess

their association with febrile seizures versus epilepsy after adjustment for age and sex, and to estimate their incremental discriminative value over an age–sex base model.

Materials and methods

Study design and setting

This single-center retrospective comparative study was conducted at the Department of Pediatrics, Yalova Training and Research Hospital, Yalova, Türkiye. Electronic hospital and laboratory records of children evaluated between 1 January 2021 and 1 April 2026 were reviewed. The study was approved by the Yalova University Non-Interventional Clinical Research Ethics Committee (protocol no. 2026/195), which waived the requirement for informed consent (see Declarations). The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [34].

Study groups and eligibility criteria

Febrile seizure was defined as a seizure accompanied by fever in a child aged 6–60 months, in the absence of central nervous system infection, significant acute metabolic disturbance, or a history of afebrile seizures [1–3]. Eligibility was ascertained from the clinical assessment and diagnosis documented in the medical record. The epilepsy group comprised children with a diagnosis of epilepsy consistent with the practical clinical definition and classification framework of the International League Against Epilepsy (ILAE) [4–6]. Healthy controls were children without known acute or chronic disease who had undergone CBC testing during routine clinical evaluation.

Children were excluded if they had chronic systemic disease, permanent neurological sequelae, a history of hypoxic–ischemic encephalopathy, central nervous system infection, acute metabolic disturbance, trauma, hematological disease, or immunodeficiency, or if they had received immunosuppressive or systemic corticosteroid therapy. Children without CBC data were also excluded. For children with more than one eligible presentation, only the first was included.

Data collection and laboratory measurements

Demographic and laboratory data were extracted from electronic medical records. In both patient groups, the first CBC obtained at the first eligible presentation during the study period was analyzed; in healthy controls, the CBC obtained during the routine evaluation was used. Biochemical parameters comprised glucose, urea, creatinine, total protein, albumin, sodium, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP). CBC parameters comprised white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, mean corpuscular volume (MCV), red cell distribution width (RDW), and absolute neutrophil, lymphocyte, and monocyte

counts. Because CRP is not routinely measured in healthy children, it was compared only between the febrile seizure and epilepsy groups.

CBC-derived inflammatory indices

The indices were calculated from absolute cell counts ($\times 10^3/\mu L$) as follows [18–22]: NLR = neutrophils/lymphocytes; PLR = platelets/lymphocytes; SII = (neutrophils × platelets)/lymphocytes; SIRI = (neutrophils × monocytes)/lymphocytes; and AISI = (neutrophils × monocytes × platelets)/lymphocytes. Because these indices share hematological components and are mathematically interrelated, each was evaluated in a separate model rather than simultaneously.

Outcome measures

The primary outcome was the ability of each index to discriminate febrile seizures from epilepsy. Secondary outcomes were the distribution of the indices across the three groups, their discrimination of each patient group from healthy controls, their age- and sex-adjusted associations with febrile seizures, and their incremental discriminative value over an age–sex base model.

Statistical analysis

Analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed with the Shapiro–Wilk test; because the data were not normally distributed, they are presented as median (25th–75th percentile). Categorical variables are presented as number (percentage) and were compared using Pearson's chi-square test. Continuous variables were compared across the three groups using the Kruskal–Wallis test; when the overall test was significant, pairwise Mann–Whitney U tests were performed with Holm adjustment for the three pairwise comparisons of each variable. CRP, available only in the patient groups, was compared using the Mann–Whitney U test.

Discriminative performance was assessed by receiver operating characteristic (ROC) analysis, and areas under the curve (AUCs) with 95% confidence intervals (CIs) were tested against the null value of 0.5. Febrile seizure was defined as the positive state in the febrile seizure versus epilepsy comparison. Exploratory cut-off values were identified using the Youden index, and the corresponding sensitivity and specificity were reported.

For the febrile seizure versus epilepsy comparison, each index was log2-transformed and entered into a separate binary logistic regression model adjusted for age (continuous, in years) and sex, with febrile seizure coded as 1 and epilepsy as 0. Odds ratios (ORs) therefore represent the change in odds per doubling of the index. A model containing only age and sex served as the base model, and the change in AUC after the addition of each index (ΔAUC) was calculated. Because ΔAUC was considered exploratory, no formal comparison of correlated AUCs was performed.

Missing data were not imputed, and analyses were based on available data; creatinine was missing for one healthy control. No a priori sample size calculation was performed; the sample size was determined by the number of eligible children during the study period. All tests were two-sided, and $p < 0.05$ was considered statistically significant. ROC and regression analyses of the multiple, interrelated indices were considered exploratory and were not adjusted for multiplicity.

Use of large language models

ChatGPT (OpenAI) and Claude (Anthropic) were used to assist with English-language editing, organization, and clarity during manuscript preparation. These tools were not used to generate, analyze, or interpret study data. All scientific content, statistical results, interpretations, and references were reviewed and verified by the authors, who take full responsibility for the manuscript.

Results

Study population and demographic characteristics

The final analytic cohort comprised 300 children: 100 with febrile seizures, 98 with epilepsy, and 102 healthy controls. Median age was 1.75 (1.00–3.00) years in the febrile seizure group, 4.00 (2.00–6.00) years in the epilepsy group, and 3.50 (3.00–5.00) years in the control group ($p < 0.001$). Sex distribution did not differ significantly among the groups ($p = 0.123$) (Table 1).

Table 1
Demographic characteristics of the study groups

Characteristic	Febrile seizure (n = 100)	Epilepsy (n = 98)	Healthy control (n = 102)	p
Age, years, median (25th–75th percentile)	1.75 (1.00–3.00)	4.00 (2.00–6.00)	3.50 (3.00–5.00)	< 0.001
Sex, n (%)				0.123
Female	43 (43.0)	56 (57.1)	48 (47.1)	
Male	57 (57.0)	42 (42.9)	54 (52.9)	

Age was compared using the Kruskal–Wallis test and sex using Pearson's chi-square test.

Laboratory findings and inflammatory indices

WBC counts were higher in both patient groups than in healthy controls but did not differ between the febrile seizure and epilepsy groups. Neutrophil and monocyte counts differed significantly in all pairwise comparisons, whereas lymphocyte and platelet counts did not differ among the groups. Compared with the other two groups, the febrile seizure group had lower hemoglobin and hematocrit, higher RDW, higher glucose and AST, and lower sodium; MCV was lower than in the epilepsy group. CRP, measured only in

the patient groups, was higher in the febrile seizure group than in the epilepsy group ($p = 0.001$) (Table 2).

Two patterns emerged among the inflammatory indices. NLR and SII were higher in both patient groups than in healthy controls but did not differ between the febrile seizure and epilepsy groups. By contrast, SIRI and AISI were highest in the febrile seizure group, intermediate in the epilepsy group, and lowest in controls, with significant differences in all pairwise comparisons. PLR did not differ among the groups ($p = 0.984$) (Table 2).

Table 2
Laboratory parameters and inflammatory indices in the study groups

Parameter	Febrile seizure (n = 100)	Epilepsy (n = 98)	Healthy control (n = 102)	p
Biochemical parameters				
Glucose (mg/dL)	128.50 (108.25–152.00)[a]	102.00 (90.18–122.00)[b]	84.95 (79.68–88.25)[c]	< 0.001
Urea (mg/dL)	22.25 (17.60–27.78)	23.30 (17.48–28.58)	24.25 (20.65–28.18)	0.130
Creatinine (mg/dL)	0.38 (0.32–0.45)[a]	0.40 (0.33–0.46)[a]	0.35 (0.31–0.40)[b]	0.006
Total protein (g/dL)	6.90 (6.60–7.10)	6.80 (6.42–7.10)	6.90 (6.70–7.10)	0.114
Albumin (g/dL)	4.68 (4.40–4.90)	4.59 (4.30–4.82)	4.60 (4.40–4.73)	0.258
Sodium (mmol/L)	136.00 (134.00–138.00)[a]	138.00 (135.75–139.00)[b]	139.00 (138.00–140.25)[c]	< 0.001
Potassium (mmol/L)	4.31 (4.02–4.70)[a]	4.44 (4.17–4.70)[a]	4.59 (4.35–4.88)[b]	< 0.001
Chloride (mmol/L)	102.00 (100.00–104.00)[a]	103.00 (101.00–105.00)[ab]	103.00 (102.00–105.25)[b]	0.001
AST (U/L)	38.00 (32.00–45.75)[a]	30.00 (24.75–38.00)[b]	31.00 (28.00–35.48)[b]	< 0.001
ALT (U/L)	16.00 (13.00–21.00)[a]	15.40 (11.75–20.70)[a]	13.00 (11.00–16.25)[b]	< 0.001
CRP (mg/L)	5.25 (1.43–15.79)[a]	1.85 (0.39–8.67)[b]	–	0.001
Complete blood count				
WBC ($\times 10^3/\mu L$)	11.91 (8.34–17.57)[a]	10.40 (7.48–13.63)[a]	8.04 (7.18–8.93)[b]	< 0.001
Hemoglobin (g/dL)	11.20 (10.50–11.98)[a]	12.00 (11.10–12.83)[b]	12.00 (11.40–12.63)[b]	< 0.001
Hematocrit (%)	33.55 (31.73–35.43)[a]	36.00 (33.58–38.10)[b]	35.25 (33.50–36.73)[b]	< 0.001

Data are median (25th–75th percentile). Overall comparisons used the Kruskal–Wallis test, followed by Holm-adjusted pairwise Mann–Whitney U tests; within a row, values sharing a superscript letter do not differ significantly. CRP was not measured in healthy controls and was compared between the patient groups using the Mann–Whitney U test. Creatinine was available for 101 controls. AISI, aggregate index of systemic inflammation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; MCV, mean corpuscular volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell

Parameter	Febrile seizure (n = 100)	Epilepsy (n = 98)	Healthy control (n = 102)	p
Platelets (×10^3/μL)	323.00 (262.50–395.50)	298.50 (247.25–386.25)	323.50 (279.00–358.00)	0.421
MCV (fL)	76.70 (72.85–79.40)[a]	79.85 (76.65–82.55)[b]	77.65 (74.50–79.60)[a]	< 0.001
RDW (%)	14.50 (13.70–15.58)[a]	13.80 (13.10–14.63)[b]	13.90 (13.40–14.63)[b]	0.001
Neutrophils (×10^3/μL)	7.58 (3.82–11.35)[a]	5.46 (3.95–8.97)[b]	3.86 (3.16–4.73)[c]	< 0.001
Lymphocytes (×10^3/μL)	3.22 (1.78–5.22)	3.14 (1.78–4.57)	3.07 (2.54–3.81)	0.841
Monocytes (×10^3/μL)	0.99 (0.60–1.39)[a]	0.75 (0.51–1.05)[b]	0.43 (0.36–0.50)[c]	< 0.001
Inflammatory indices				
NLR	2.27 (1.24–3.71)[a]	1.76 (1.06–3.85)[a]	1.27 (0.97–1.62)[b]	< 0.001
PLR	107.58 (65.52–165.90)	103.12 (70.02–150.50)	104.75 (85.48–123.05)	0.984
SII	769.11 (405.77–1243.92)[a]	563.60 (313.09–1138.55)[a]	414.15 (281.41–523.02)[b]	< 0.001
SIRI	2.12 (0.97–4.07)[a]	1.35 (0.70–2.93)[b]	0.54 (0.37–0.77)[c]	< 0.001
AISI	751.86 (323.71–1355.15)[a]	441.28 (205.95–1009.38)[b]	172.97 (112.11–248.45)[c]	< 0.001

Data are median (25th–75th percentile). Overall comparisons used the Kruskal–Wallis test, followed by Holm-adjusted pairwise Mann–Whitney U tests; within a row, values sharing a superscript letter do not differ significantly. CRP was not measured in healthy controls and was compared between the patient groups using the Mann–Whitney U test. Creatinine was available for 101 controls. AISI, aggregate index of systemic inflammation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; MCV, mean corpuscular volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell

Discrimination between febrile seizures and epilepsy

Discrimination between febrile seizures and epilepsy was poor (Table 3; Fig. 1). The highest AUCs were observed for AISI (0.606; 95% CI 0.527–0.683) and SIRI (0.591; 95% CI 0.510–0.669), whereas the AUCs for NLR, PLR, and SII did not differ significantly from 0.5. At the exploratory cut-off of 319.5, AISI had a sensitivity of 77.0% and a specificity of 42.9%.

Table 3
Performance of inflammatory indices in discriminating febrile seizures from epilepsy

Index	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p
NLR	0.543 (0.462–0.624)	1.54	69.0	43.9	0.295
PLR	0.502 (0.421–0.583)	115.3	46.0	64.3	0.954
SII	0.565 (0.487–0.644)	611.0	64.0	52.0	0.116
SIRI	0.591 (0.510–0.669)	1.59	64.0	54.1	0.027
AISI	0.606 (0.527–0.683)	319.5	77.0	42.9	0.010

Febrile seizure was the positive state. Cut-offs were derived using the Youden index and are exploratory. p values test each AUC against 0.5. AISI, aggregate index of systemic inflammation; AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index

Comparisons with healthy controls

AUCs were higher when each patient group was compared with healthy controls. SIRI yielded the highest AUC for both febrile seizures versus controls (0.878) and epilepsy versus controls (0.800), followed by AISI (0.848 and 0.769, respectively), whereas PLR showed no discrimination (Table 4). These comparisons were not adjusted for age or sex.

Table 4
AUCs of inflammatory indices for pairwise discrimination between study groups

Index	Febrile seizure vs epilepsy	Febrile seizure vs control	Epilepsy vs control
NLR	0.543	0.729	0.664
PLR	0.502	0.503	0.490
SII	0.565	0.730	0.656
SIRI	0.591	0.878	0.800
AISI	0.606	0.848	0.769

Values are AUCs; the first-named group was the positive state. Analyses involving healthy controls were not adjusted for age or sex. AISI, aggregate index of systemic inflammation; AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index

Adjusted analyses and incremental discriminative value

In separate age- and sex-adjusted logistic regression models, each doubling of NLR, SII, SIRI, and AISI was significantly associated with higher odds of febrile seizures relative to epilepsy, whereas PLR was not (Table 5). The age–sex base model had an AUC of 0.792; adding an inflammatory index increased the AUC to at most 0.808 (ΔAUC + 0.016 for NLR and SIRI, + 0.014 for SII, + 0.012 for AISI, and + 0.004 for PLR).

Table 5
Adjusted associations of inflammatory indices with febrile seizures and incremental discriminative value

Index	Adjusted OR (95% CI)	p	Model AUC	ΔAUC
NLR	1.542 (1.141–2.083)	0.005	0.808	+ 0.016
PLR	1.347 (0.912–1.990)	0.134	0.796	+ 0.004
SII	1.490 (1.116–1.991)	0.007	0.806	+ 0.014
SIRI	1.414 (1.110–1.802)	0.005	0.808	+ 0.016
AISI	1.354 (1.081–1.696)	0.008	0.804	+ 0.012

Each index was log2-transformed and evaluated in a separate logistic regression model adjusted for age and sex (febrile seizure = 1, epilepsy = 0). ORs represent the change in odds per doubling of the index. The age–sex base model had an AUC of 0.792; ΔAUC is the change from the base-model AUC. AISI, aggregate index of systemic inflammation; AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index

Discussion

In this study of five CBC-derived inflammatory indices, SIRI and AISI showed a graded distribution across the three groups, whereas NLR and SII separated both patient groups from healthy controls but not from each other. Most importantly, these differences did not translate into clinically useful discrimination, and the indices added little to an age–sex base model.

Previous febrile seizure studies have focused mainly on NLR. Liu et al. reported higher NLR in children with febrile seizures than in febrile controls [23], and a meta-analysis of 17 studies by Hosseini et al. reached a similar conclusion [24]. Other pediatric studies have reported broadly similar, although not entirely consistent, findings for NLR and other CBC-based markers [25–29]. Söğütlü and Altaş extended this work to composite indices in 100 children with febrile seizures, 100 febrile children without seizures, and 100 healthy children, and found NLR, SII, and SIRI to be among the indices that were higher in the febrile seizure group [30]. Our study adds a direct comparison with another seizure population—children with epilepsy—and includes AISI. In this comparison, the indices showed limited specificity for febrile seizures, suggesting that the elevations reported in earlier studies may partly reflect a nonspecific systemic inflammatory response rather than a seizure-type-specific signature.

The clearer gradient for SIRI and AISI may partly reflect their cellular composition. In our cohort, neutrophil and monocyte counts differed among the groups, whereas lymphocyte and platelet counts did

not; indices incorporating monocytes may therefore capture more of this separation. In patients with temporal lobe epilepsy, Bolayır reported higher monocyte-to-lymphocyte and neutrophil-to-lymphocyte ratios than in healthy controls but no significant difference in PLR [32]. PLR likewise did not differ among the groups in our study, suggesting that its performance in seizure-related inflammation is inconsistent across populations rather than necessarily uninformative.

The biological interpretation of monocyte-containing indices requires caution. Experimental work suggests that activated peripheral mononuclear cells can enhance neuronal excitability and sustain seizure activity when blood–brain barrier integrity is compromised [16]. However, SIRI and AISI are composite mathematical measures, and an observational study cannot establish a direct pathogenic role for monocytes. Reverse causality is also plausible, because seizures themselves can alter systemic and central inflammatory responses [15, 16].

Findings in the epilepsy group should likewise be interpreted in relation to timing. A systematic review of seven studies reported higher NLR in patients with epilepsy than in healthy controls, particularly in the acute and subacute phases [31], and an adult case–control study also found elevated NLR [33]. Peripheral inflammatory changes may therefore partly reflect the effect of recent seizures rather than a stable feature of chronic epilepsy. In our cohort, the higher WBC and neutrophil counts and measurable CRP in the epilepsy group suggest that many samples were obtained during acute presentations, possibly reflecting post-ictal changes or intercurrent infection; however, because the seizure-to-sampling interval and antiseizure medication use could not be determined reliably, this could not be examined directly.

The central clinical finding is the gap between statistical association and discrimination. Although SIRI and AISI differed between febrile seizures and epilepsy, their AUCs were only 0.591 and 0.606, respectively, close to the level of chance. For AISI, a sensitivity of 77.0% with a specificity of 42.9% does not support its use as a stand-alone classifier, and the Youden-derived cut-offs should be regarded as sample-specific exploratory values rather than clinical thresholds. Similarly, NLR, SII, SIRI, and AISI remained associated with febrile seizures after adjustment for age and sex, yet improved the base-model AUC by only 0.012–0.016. The relatively high AUC of the base model (0.792) is probably driven largely by the marked age difference between groups, which partly reflects the age-restricted definition of febrile seizures. Thus, an independent association did not imply meaningful incremental classification.

The higher AUCs obtained against healthy controls should not be interpreted as seizure-specific diagnostic performance. Fever and acute infection are inherent to febrile seizures but absent in healthy controls, so part of the observed separation may reflect systemic inflammatory status. Notably, our SIRI AUC for febrile seizures versus healthy controls (0.878) was close to the value of 0.868 reported by Söğütlü and Altaş [30]. In that study, SIRI also discriminated febrile seizures from febrile non-seizure controls (AUC 0.737), suggesting that fever alone may not explain all differences; however, cross-study comparisons cannot isolate a seizure-specific effect.

Several differences in other laboratory parameters were also observed in children with febrile seizures, including lower hemoglobin and hematocrit, higher RDW, lower MCV than in the epilepsy group, and lower sodium. These findings are broadly consistent with reported associations of febrile seizures with poor iron indices [35] and of recurrent seizures during the same febrile episode with lower sodium [36]. However, they were secondary, unadjusted observations, and because iron studies and seizure recurrence data were not systematically available, they should be considered hypothesis-generating.

Strengths and limitations

The strengths of this study include the evaluation of three clinical groups at a single center during the same period; the inclusion of newer composite indices (SII, SIRI, and AISI) alongside NLR and PLR; and the assessment of ROC performance and incremental model value rather than group differences alone. Evaluating each index in a separate regression model also avoided collinearity arising from their mathematical interdependence.

Several limitations should be considered. First, no febrile non-seizure control group was included; therefore, seizure-related effects cannot be separated from those of fever and infection, particularly in comparisons with healthy controls. Second, age differed markedly among the groups. Although age was included in the regression models, residual confounding is possible because leukocyte subsets change with age in early childhood, and comparisons with healthy controls were unadjusted. Selection of controls from children who underwent CBC testing during routine clinical evaluation may also have introduced selection bias.

Third, the interval between the most recent seizure and blood sampling, details of antiseizure treatment, and epilepsy type, etiology, and duration could not be standardized or analyzed. Fourth, because of the single-center retrospective design, febrile seizure subtype, fever magnitude, seizure duration, and viral or bacterial etiology could not be reliably obtained for all participants; CRP was unavailable in healthy controls, and iron indices were not systematically measured.

Finally, NLR, SII, SIRI, and AISI share hematological components and should not be interpreted as markers of independent biological processes. The ROC and regression analyses involved several related indices without multiplicity adjustment. Model AUCs and ΔAUC values were estimated in the same sample and may be optimistic, as no formal comparison of AUCs, internal validation, or external validation was performed.

Conclusions

CBC-derived inflammatory indices differed among children with febrile seizures, children with epilepsy, and healthy controls, with SIRI and AISI showing the clearest graded pattern. However, none of the indices discriminated febrile seizures from epilepsy with clinically useful accuracy, and their incremental value beyond age and sex was small. These indices should therefore be regarded as exploratory markers of systemic inflammation rather than stand-alone diagnostic tests. Prospective studies including febrile

non-seizure controls, age-balanced groups, and standardized seizure-to-sampling intervals are needed to determine whether they have any seizure-specific clinical value.

Abbreviations

AISI: Aggregate index of systemic inflammation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AUC: Area under the curve; CBC: Complete blood count; CI: Confidence interval; CRP: C-reactive protein; ΔAUC: Change in area under the curve; IL: Interleukin; ILAE: International League Against Epilepsy; MCV: Mean corpuscular volume; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PLR: Platelet-to-lymphocyte ratio; RDW: Red cell distribution width; ROC: Receiver operating characteristic; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; WBC: White blood cell

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Yalova University Non-Interventional Clinical Research Ethics Committee (Protocol no. 2026/195; 29 April 2026). Owing to the retrospective design, the ethics committee waived the requirement for informed consent from parents or legal guardians. Data were de-identified before analysis.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available owing to patient privacy but are available from the corresponding author on reasonable request, subject to the relevant ethical and institutional approvals.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no specific funding.

Authors’ contributions

EK contributed to conceptualization, data collection, and writing—review and editing. TA contributed to methodology, statistical analysis, and writing—original draft. GK contributed to data curation and writing

—review and editing. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Clinical trial number

Not applicable.

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Figures

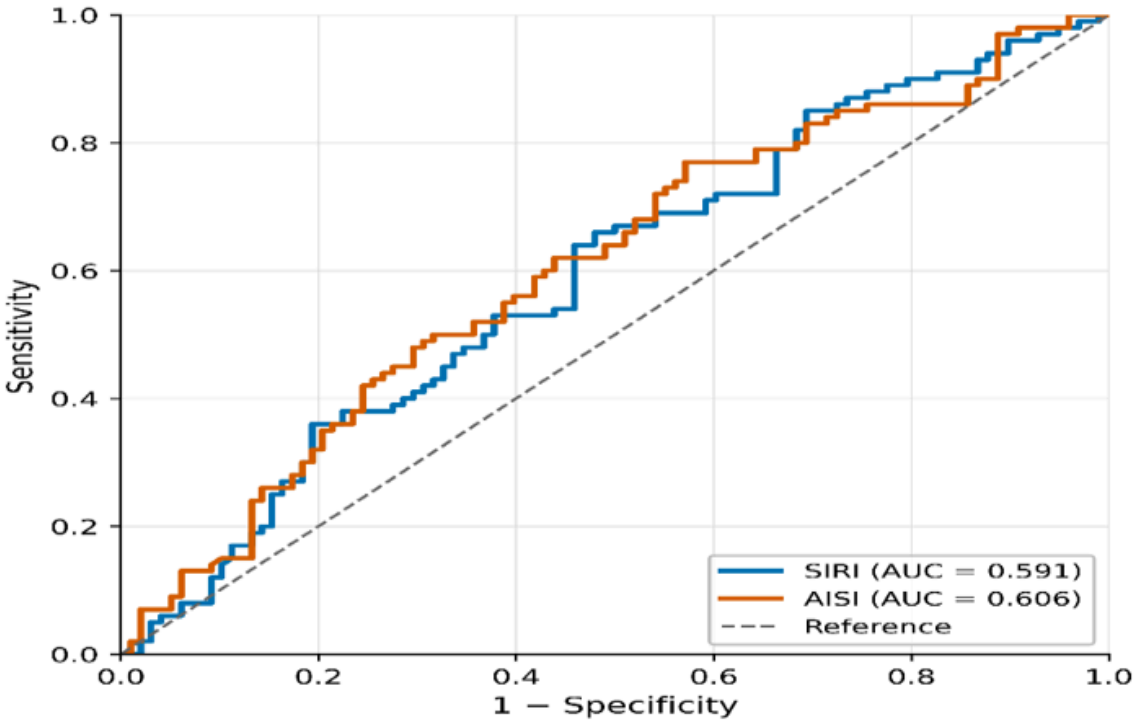


Figure 1

ROC curves of SIRI and AISI for discriminating febrile seizures from epilepsy. Febrile seizure was the positive state. The dashed diagonal line indicates no discrimination (AUC = 0.5). AISI, aggregate index of systemic inflammation; AUC, area under the curve; ROC, receiver operating characteristic; SIRI, systemic inflammation response index