Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Paediatrics

Role of Neutrophil-Lymphocyte Ratio in the Differentiation Between Simple and Complex Febrile Seizure in Children

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DOI: https://doi.org/10.36347/sjams.2026.v14i06.002 | **Received:** 04.04.2026 | **Accepted:** 15.05.2026 | **Published:** 02.06.2026

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Abstract **Original Research Article**

Background: Febrile seizures (FS) are categorized into simple febrile seizures (SFS) and complex febrile seizures (CFS). Differentiating between these types is clinically important due to the higher risk of complications associated with CFS. The neutrophil-lymphocyte ratio (NLR), an inflammatory marker, may aid in this distinction. ***Aim:*** To evaluate the role of neutrophil-lymphocyte ratio in differentiating between simple and complex febrile seizures in children. ***Methods:*** This cross-sectional analytical study was conducted from March 2023 to February 2024 at the Department of Paediatrics, Sir Salimullah Medical College Mitford Hospital. A total of 114 children were enrolled, including 57 with SFS and 57 with CFS, selected by purposive sampling. Clinical and laboratory data were recorded, and blood samples were collected within 20 minutes of hospital arrival. Statistical analysis was performed using SPSS version 26. ***Results:*** The mean NLR was significantly higher in children with CFS compared to those with SFS (p=0.00011), indicating a strong association between elevated NLR and complex febrile seizures. ***Conclusion:*** Neutrophil-lymphocyte ratio is a useful and readily available biomarker for differentiating between simple and complex febrile seizures in children.

Keywords: Febrile seizures, Simple febrile seizure, Complex febrile seizure, Neutrophil-lymphocyte ratio, Pediatric neurology.

INTRODUCTION

Febrile seizures (FS) are the most common cause of convulsions in young children, usually occurring between 6 months and 5 years of age in association with fever exceeding 100.4°F, without evidence of central nervous system infection.[1] According to the American Academy of Pediatrics, the diagnosis of FS requires the absence of intracranial infection, metabolic disorders, or a history of afebrile seizures. FS are broadly classified into simple febrile seizures (SFS) and complex febrile seizures (CFS). Simple febrile seizures are generalized, last less than 15 minutes, and do not recur within 24 hours, whereas complex febrile seizures are characterized by prolonged duration (>15 minutes), recurrence within 24 hours, and/or focal neurological features. [2,3] The reported prevalence is approximately 69.3% for SFS and 28.3% for CFS. [4]

The differentiation between SFS and CFS is clinically important because CFS is associated with a higher risk of neurological complications and adverse outcomes. The pathogenesis of febrile seizures is multifactorial, involving genetic predisposition, increased neuronal sensitivity to fever, and inflammatory responses. Cytokine-mediated inflammation, particularly involving interleukin-1β (IL-1β) and tumor necrosis factor (TNF), plays a significant role in seizure generation. [6] Neutrophils contribute to the secretion of these cytokines, while cortisol-induced stress responses may result in neutrophilia and relative lymphopenia, thereby influencing the neutrophil-to-lymphocyte ratio. [6]

The neutrophil-to-lymphocyte ratio (NLR) is a simple, cost-effective, and readily available inflammatory marker calculated from peripheral blood counts. [7] It has been widely used to assess systemic inflammation and has shown prognostic value in various

inflammatory and neurological conditions [6]. Recent studies have demonstrated that NLR is significantly higher in children with complex febrile seizures compared to those with simple febrile seizures. [8,9] Therefore, assessing NLR may provide a useful tool for differentiating between SFS and CFS in clinical practice.

Objective

General Objective:

To assess and compare the neutrophil-lymphocyte ratio in children with simple and complex febrile seizures.

Specific Objectives:

- To measure the neutrophil count in children with simple and complex febrile seizures.
- To measure the lymphocyte count in children with simple and complex febrile seizures.
- To determine the neutrophil-lymphocyte ratio (NLR) in both groups.
- To compare the neutrophil-lymphocyte ratio (NLR) between simple and complex febrile seizure groups.

MATERIALS AND METHODS

Study Design: Cross sectional analytical study

Place of Study: Department of Paediatrics in Sir Salimullah Medical College Mitford Hospital, Dhaka.

Period of study: The study was conducted over a period of 1 year from March 2023 to February 2024.

Study population: Children with febrile seizure admitted in Paediatric department who fulfilled the inclusion and exclusion criteria were included in the study

Sampling technique: Purposive sampling

Sample size: The sample size of this study is determined by following equation- (Julious *et al.*,2010)

$$n = \frac{(Z_\alpha + Z_\beta)^2 \times (\sigma_1{}^2 + \sigma_2{}^2)}{(\mu_1 - \mu_2)^2}$$

Here,

n = sample size

$Z\alpha = 1.96$ (at 95% level of confidence); $Z_\beta = 0.85$ (at 80% power)

The following values are taken from the study of

σ_1 = Standard deviation (SD) of mean of NLR in Simple Febrile Seizure patients= 2.6

σ_2 = Standard deviation (SD) of mean of NLR in Complex Febrile Seizure patients=4.1

μ_1 = Mean of NLR in Simple Febrile Seizure patients=2.6

μ_2 = Mean of NLR in Complex Febrile Seizure patients=4.5

Total study subjects (n) = $(1.96 + 0.85)^2 \times (2.6^2 + 4.1^2)/(2.6- 4.5)^2\} = 53$

Finally, 57 patients were included in each group.

Selection criteria:

Inclusion criteria

- Age: 6 months to 5 years
- Sex: Both
- Patient with first febrile seizure

Exclusion criteria

- Children with chronic illness

Ethical consideration:

Before the commencement of the study, the research protocol was approved by Ethical Committee of Sir Salimullah Medical College Mitford Hospital, Dhaka. The aims and objectives of the study, along with its procedures, risks, and benefits, were explained to the patients in easily understandable local language, and then informed consent was taken from each patient. It was assured that all records would be kept confidential, and the procedure would be helpful for both the physician and patients in making a rational approach regarding the management of the case.

Study procedure:

All admitted children in paediatric ward between 6 months to 5 years with febrile seizures were approached for this study in my study period. Then according to inclusion and exclusion criteria, I have selected SFS and CFS patients. Admission of simple febrile seizure patients were more than complex febrile seizure. To fulfill my sample size, I had to wait for 57 cases of CFS patients even after getting 57 cases of SFS patients. After proper counselling about the objectives and procedure of the study, a written informed consent was taken from each patient's legal guardian. The participants were allowed to withdraw themselves from the study even after participation whenever they desired. Data were collected by researcher by interviewing of parents or guardians, clinical examinations, and then recorded in a separate case record form.

RESULT

Table I: Comparison of age between children with Simple and Complex Febrile Seizure (N=114)

Age group (months)	Simple febrile seizure (n=57)	Complex febrile seizure (n=57)	*p*-value
6-12	13(22.8%)	18(31.6%)	
13-24	26(45.6%)	20(35.1%)	
25-36	5(8.8%)	13(22.8%)	

37-48	4(7.0%)	4(7.0%)	
49-60	9(15.8%)	2(3.5%)	
Mean±SD	26.0±16.9	22.82±13.7	0.271
Range (min-max)	(6-60)	(6-60)	

Data were expressed as mean ± SD
An unpaired t-test was performed to compare the two groups,
p<0.05=significant.

The comparison of age between children with simple febrile seizure (mean age: 26.0±16.9 months) and complex febrile seizure (mean age: 22.82±13.7 months) did not reveal a statistically significant difference (p=0.271).

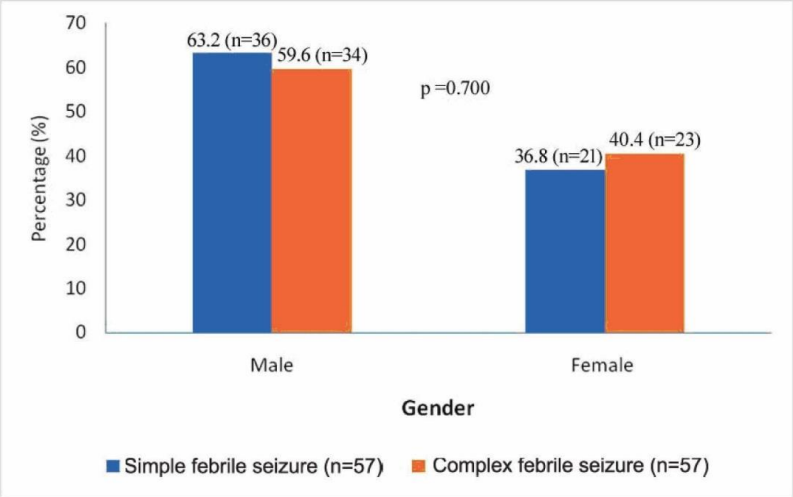

Figure-1: Bar diagram showing comparison of sex between simple and complex febrile seizure

In Simple febrile seizure group, 63.2% were male, while in Complex febrile seizure group, 59.6% were male. The observed difference in gender distribution between the two groups is not statistically significant (p=0.700)

Table II: Comparison of NLR among characteristics of Complex febrile seizure (N=57)

	Complex febrile seizure (n=57)			***p*-value**
	Duration of seizure >15 min (n=30)	Focal (n=15)	Recurrence (n=12)	
NLR	4.66±1.90	3.74±1.3	4.21±1.20	0.229

Data were expressed as mean ± SD
An ANOVA test was performed to compare more than two groups,
p<0.05=significant

Table II shows NLR slightly higher in the focal seizure group (3.74±1.3) compared to the other two groups, duration of seizure >15 minutes (4.66±1.90) and recurrence of seizure within 24 hours (4.21±1.20), respectively. (p value=0.229)

Table III: Comparison of NLR findings between simple and Complex febrile seizure (N=114)

Laboratory findings	**Simple febrile seizure (n=57) Mean±SD**	**Complex febrile seizure (n=57) Mean±SD**	***p*-value**
Neutrophil count	6597.9±2913.4	10998.3±4762.1	0.00031
Lymphocyte count	4419.4±2186.7	2774.2±1387.6	0.00024
NLR	1.786±1.079	4.355±1.642	0.00011

Data were expressed as mean ± SD
An **unpaired t-test** was performed to compare between two groups,
p<0.05=significant.
{Normal count of ANC = 1500-8500 cells/ per microlitre (World Health Organization, 2020)
Normal count of ALC = 3000-9500 cells/ per microlitre (World Health Organization. 2020)
Normal level for NLR ranges from 1.5 to 3.

Table-III provides a comparison of laboratory findings between simple and complex febrile seizure groups. The mean serum absolute neutrophil count was 6597.9 ± 2913.4 for simple febrile seizure and 10998.3 ±4762.1 for complex febrile seizure, significantly increased absolute neutrophil count in Complex febrile seizure ($p<0.00031$). The mean serum lymphocyte percentage was 4419.4±2186.7 for simple febrile seizure and 2774.2±1387.6 for complex febrile seizure, significantly decreased in the complex seizure group ($p<0.00024$). The mean NLR was 1.786 ± 1.079 for simple febrile seizure group and 4.355 ± 1.642 for the complex febrile seizure group, with highly significant differences between two groups ($p<0.0011$).

Discussion

Complex febrile seizures (CFS) present a significant neurological concern in pediatric populations due to their diverse clinical manifestations and potential complications. Differentiating between simple febrile seizures (SFS) and CFS is essential for appropriate management. This study aimed to evaluate the role of the neutrophil-lymphocyte ratio (NLR) as a marker for differentiating between these two entities. Previous evidence suggests that increased inflammatory activity occurs in the brains of children with CFS, supporting the use of inflammatory markers such as NLR in clinical assessment.[6]

In the present study, the mean age of children with SFS (26.0±16.9 months) was slightly higher than that of children with CFS (22.82±13.7 months), although the difference was not statistically significant ($p>0.05$). Similarly, male predominance was observed in both groups (63.2% in SFS and 59.6% in CFS), with no significant gender difference. These findings are consistent with previous studies by Goksugur *et al.,* (2014), Hassan *et al.,* (2021), and Liu *et al.,* (2018), all of which reported no significant differences in age and gender distribution between SFS and CFS groups. [10,11,6] Yigit *et al.,* (2017) also observed a lower mean age in CFS compared to SFS, although the difference was not statistically significant. These results suggest that demographic factors such as age and gender are not reliable indicators for differentiating seizure types. [3]

Regarding hematological parameters, this study demonstrated that children with CFS had significantly higher absolute neutrophil counts and lower absolute lymphocyte counts compared to children with SFS. Consequently, the NLR was markedly elevated in the CFS group (4.355±1.642) compared to the SFS group (1.786±1.079). These findings are in agreement with Yazar *et al.,* (2018), who reported higher neutrophil counts and lower lymphocyte counts in CFS, indicating a stronger inflammatory response. [12] Similarly, studies by Balikoglu *et al.,* (2023), Ornek *et al.,* (2020), and Yigit *et al.,* (2017) consistently reported significantly higher NLR values in children with CFS compared to SFS, reinforcing the association between elevated NLR and seizure complexity. [13,14,6]

The present study also assessed NLR across different characteristics of CFS, including prolonged seizure duration, focal features, and recurrence within 24 hours. Although NLR values varied among these subgroups, the differences were not statistically significant ($p=0.229$). Comparable findings were reported by Kubota *et al.,* (2020), who also observed no significant variation in NLR across different CFS characteristics. [8] This suggests that while NLR is effective in distinguishing between SFS and CFS, it may not reliably differentiate among subtypes or features of CFS.

Overall, the findings of this study indicate that NLR is significantly elevated in children with complex febrile seizures and can serve as a useful, cost-effective biomarker for differentiating between SFS and CFS. Its ease of calculation from routine blood tests makes it a practical tool for early clinical decision-making.

Limitations of the study

- Sample size is relatively small
- The study's single-center design may not capture broader demographic variations, affecting the external validity of the findings.

Conclusion

The neutrophil-lymphocyte ratio (NLR) is significantly higher in children with complex febrile seizures compared to those with simple febrile seizures. This finding highlights the potential role of NLR as a useful inflammatory marker for differentiating between the two types of febrile seizures. Given its simplicity, affordability, and availability from routine blood tests, NLR can be incorporated into clinical practice as an adjunct tool for early assessment. However, further large-scale, multicenter studies are recommended to validate its clinical utility and establish standardized cut-off values.

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