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Original Article

Using complete blood count markers to predict febrile seizures

Ufik Maulena[1], Muchammad Fahrul Udin[2]

Abstract

Background The complete blood count test includes some markers of inflammation. Febrile seizures have been associated with inflammatory processes.

Objective To investigate for possible relationships between the occurrence of febrile seizures (FS) and complete blood count (CBC) parameters.

Methods Two hundred children aged 6-60 months presenting with fever at the emergency department between January 2022 - August 2023 were included. These subjects were divided into a FS group (n=100) and a control fever without seizures group (n=100). Demographic and complete blood count data were compared using logistic regression test.

Results The frequency of FS was significantly higher in younger children [mean age 23.89 (SD 15.88) months]. The FS group had lower lymphocyte counts but significantly higher white blood cell (WBC), neutrophils, platelets, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) values than the control group. Multivariate analysis revealed that NLR (OR=0.84; P=0.001), PLR (OR=0.939; P=0.001), WBC (OR =0.773; P=0.001), neutrophil- platelet ratio (NPR) (OR=0.000; P=0.001), platelets (PLT) (OR=0.996; P=0.017), lymphocytes (OR=1.239; P=0.0001), and neutrophils (OR=1.047; P=0.022) had significant associations with FS while other parameters did not.

Conclusion Patients with FS had significantly higher levels of inflammatory markers, such as NLR, PLR, WBCs, PLTs, neutrophils, and NPR, and lower levels of lymphocytes than children with fever but no seizures, as determined by complete blood count findings. **[Paediatr Indones. 2025;65:XXX; DOI: https://doi.org/10.14238/pi65.6.2025.XXX]**.

Keywords: *febrile seizures; complete blood count test; children; fever*

In children aged 6 to 60 months, febrile seizures(FS) affect 2-4% of American children and 8-10% of Asian children.[1] In Indonesia in 2019, 14,254 children had FS, according to the Ministry of Health.[2] Febrile seizure is a seizure that occurs in a toddler or infant at body temperatures above 38°C, without evidence of central nervous system disorders.[3]

Febrile seizures can be simple or complex, depending on the duration, presence of focal characteristics, and recurrence.[4] Simple febrile seizures (SFS) occur less than 15 minutes with no focal neurological disturbance and do not recur within 24 hours. Whereas complex febrile seizures (CFS) last more than 15 minutes and focal abnormalities recur within 24 hours. The chance of developing epilepsy as an adult-increase in children who experience complex CFS.[5]

Inflammation has been known to be associated with FS for more than 20 years.[6] Three pro-inflammatory cytokines, tumor necrosis factor-α

From Madinah Hospital[1] and Pediatric Department, Dr. Syaiful Anwar General Hospital[2], Malang, East Java, Indonesia.

Corresponding author: Ufik Maulena. Madinah Hospital. Jalan Raya Sukosari No. 32, Malang, East Java, Indonesia. Phone: +62354328144, Email: maulenaufik@gmail.com.

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(TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), are generated by macrophages as local inflammation occurs. Pro-inflammatory cytokines like these are generated concurrently with anti-inflammatory cytokines such as interleukin 1 receptor antagonist (IL-1Ra). But if the localized inflammation response is not under control, pro-inflammatory mediators leak into the bloodstream and cause systemic inflammation. As a result, the blood-brain barrier (BBB) cells are stimulated to produce and release more cytokines, increasing the levels of peripheral cytokines that interact with them and allow them to enter the central nervous system (CNS).[7]

The IL-1 stimulates the formation of bonds between glutamate and α-amino-3-hydroxy-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in increased sodium influx and potassium ion efflux as the membrane is depolarized. The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) decreases the excitability of glutamate in neurons as a form of negative feedback by interacting with one of its two receptors, GABA-A or GABA-B. However, the interaction between GABA and GABA-A receptors weakens when IL-1 levels rise. Seizures are triggered by glutamatergic and GABAergic circuit dysregulation.[8]

These inflammatory cytokines can be used to assess the degree of inflammation in those experiencing FS. Since it is still difficult and expensive to obtain these tests, recent study has suggested that components in a patient's complete blood count findings may be a more accessible and less expensive way to identify inflammation in those who have a FS.[9] The NLR, PLR, erythrocyte distribution width (RDW), and mean platelet volume (MPV) are a few inflammatory indicators that have been previously examined.[10] The purpose of this study was to investigate for possible relationships between the occurrence of FS and CBC parameters.

Methods

This study was conducted retrospectively at the Madinah Hospital in Malang, East Java. Two hundred pediatric patients aged 6-60 months who came to the emergency room with fever from January 2022 - August 2023 were included. The patients were divided into two groups: 100 patients with FS and 100 patients with fever but without seizures. Data were taken from secondary data sources, namely patient medical records, including demographic data (age and sex) as well as CBC parameters, to be compared between groups.

Patients with CNS disorders (epilepsy, cerebral palsy, head trauma, meningitis, or encephalitis), metabolic disorders, a history of seizures without concurrent fever, or those who received blood transfusions in the previous 2 weeks or had received antibiotic therapy prior to laboratory testing, and those with incomplete data were excluded from this study. This sttudy protocol was approved by the local Ethics Committee.

At the emergency room, patients' venous blood specimens were placed in EDTA anticoagulant tubes in order to serve as parameters for the CBC tests. Leukocytes, neutrophils, lymphocites, NLR, neutrophils to platelet ratio (NPR), PLR, the mean corpuscular volume (MCV), platelet distribution width (PDW), mean platelet volume (MPV), and the platelet large cell ratio (P-LCR) were all evaluated. The time frame of specimen testing following a seizure ranged from 30 minutes to 24 hours. The NLR value was calculated by dividing the neutrophil count by the absolute lymphocyte value. The PLR value was obtained from the comparison of absolute platelets and lymphocytes. The NPR value is derived from the outcome of neutrophils to platelets ratio. Leukocytes, MCV, RDW, MPV, and P-LCR were among the other parameters displayed by the hematology analyzer at Madinah Hospital (*HETO H3800-Hematology-Analyzer, Shenzen Heto Medical Tech Corporation*, Shenzen, China).

Analysis of research data was done with *SPSS version 25.0 for Windows* software. Quantitative variables are expressed in terms of mean (standard deviation), while qualitative variables are expressed in terms of frequency or percentage (%). Chi-square test was used to assess for differences in the frequency of qualitative variables. Independent t-test was used to test the mean difference in quantitative variables, while the Mann-Whitney U test was used for nonparametric statistics. Logistic regression was used to measure odds ratios (ORs) and 95% confidence interval (CI) for risk estimation. Results with $P<0.05$ were considered to be statistically significant. The receiver operator characteristic (ROC) curve was used

to determine the cut-off point of the CBC parameters to predict FS as well as their sensitivity and specificity.

Results

The study involved 200 children at Madinah Hospital aged 6 months - 5 years. The mean age of the control group (n=100, 55% male) was 29.38 (SD 17.65) months. The mean age of the FS group (n=100) was 23.89 (SD 15.88) months and 62% were male. The FS group was further subdivided into two groups: SFS (n=74, 60.8% male) and CFS (n=26, 65.4% male). The SFS and CFS group's median age were 23.57 (SD 15.97) and 24.81 (SD 15.88) month. The frequency of FS was significantly higher in younger children (P<0.05) (**Table 1**). However, there were no significant differences (P>0.05) between the groups (FS *vs.* control and SFS *vs.* CFS) in terms of sex.

We compared inflammatory markers in the CBC in the FS and control groups. Statistical analysis results in **Table 2** revealed several mean parameters that were significantly higher in FS group than in the control group: NLR [4.49 (4.27) *vs.* 2.54 (2.18), respectively], PLR [20.89 (18.04) *vs.* 12.15 (7.88), respectively], NPR [0.013 (0.01) *vs.* 0.01 (0.01), respectively], leukocyte [13.99 (6.12) *vs.* 10.36 (4.33), respectively], thrombocyte counts [349.18 (94.29) *vs.* 321.43 (95.07), respectively], and neutrophil counts [66.74 (18.34) *vs.* 58.39 (18.84), respectively]. The lymphocyte counts [15.61 (8) *vs.* 34.58 (16.51), respectively] was significantly lower in the FS group than in the control group. We also compared CBC parameters in the simple and complex febrile seizure groups and found no significant differences between groups.

Multivariate analysis (**Table 3**) with 95% confidence intervals revealed several parameters that were significantly associated with the occurence of FS: NLR (OR=0.84; P=0.001), PLR (OR=0.939; P=0.001), WBC (OR=0.773; P=0.001), NPR (OR=0.000; P=0.001), neutrophils (OR=1.047;

Table 1. Analysis of the demographics of the control, FS, SFS, and CFS groups

Variables	FS group (n= 100)	Control group (n=100)	SFS group (n=74)	CFS group (n=26)	P value	
					FS *vs.* control	SFS *vs.* CFS
Mean age (SD), months	23.89 (15.88)	29.38 (17.65)	23.57 (15.97)	24.81 (15.88)	0.025	0.723
Sex, n (%)						
Male	62 (62)	55 (55)	45 (60.8)	17 (65.4)	0.315	0.679
Female	38 (38)	45 (45)	29 (39.2)	9 (34.6)		

Table 2. Analysis of laboratory findings in the various groups

Variables	FS group (n= 100)	Control group (n=100)	SFS group (n=74)	CFS group (n=26)	P value	
					FS *vs.* control	SFS *vs.* CFS
NLR	4.49 (4.27)	2.54 (2.18)	4.47 (4.21)	4.59 (4.53)	< 0.001	0.991
NPR	0.013 (0.01)	0.01 (0.01)	0.013 (0.01)	0.013 (0.01)	0.001	0.945
PLR	20.89 (18.04)	12.15 (7.88)	20.93 (17.81)	20.78 (19.06)	< 0.001	0.981
WBC, $10^3/mm^3$	13.99 (6.12)	10.36 (4.33)	13.88 (6.20)	14.33 (5.98)	< 0.001	0.615
Lymphocytes, %	15.61 (8)	34.58 (16.51)	15.74 (8.47)	15.22 (6.61)	<0.001	0.891
Neutrophils, %	66.74 (18.34)	58.39 (18.84)	66.49 (18.26)	67.48 (18.95)	0.001	0.73
MCV, fl	75.16 (7.38)	75.03 (7.33)	75.12 (7.49)	75.25 (7.22)	0.682	0.937
RDW, %	13.08 (1.13)	13.21 (1.17)	13.12 (1.19)	13.01 (0.97)	0.291	0.847
PLT, $10^3/mm^3$	349.18 (94.29)	321.43 (95.07)	354.57 (100.62)	333.85 (72.91)	0.044	0.24
MPV, fl	8.37 (0.88)	12.13 (37.87)	8.37 (0.91)	8.38 (0.85)	0.789	0.856
MPR	0.03 (0.01)	0.13 (1.01)	0.03 (0.01)	0.03 (0.01)	0.117	0.407
PDW, fl	9.55 (1.47)	9.37 (1.25)	9.52 (1.51)	9.65 (1.41)	0.418	0.645
P-LCR, %	16.33 (5.73)	16.03 (5.36)	16.38 (5.83)	16.22 (5.56)	0.778	0.972

P=0.022), PLT (OR=0.996; P=0.017), and lymphocytes (OR=1.239; P=0.0001). Of these parameters, lymphocytes had significantly lower in the FS group than in control, while others had significantly higher. However, MPR (OR=2.433; P=0.67) was not significantly associated with FS. These statistical analyzes indicate that lymphocyte and neutrophil counts, with ORs higher than 1, could be utilized to predict FS.

Based on the receiver operating characteristic (ROC) curve analysis (**Figure 1**), to distinguish occurrences of FS and fever without seizures, the optimum cut-off values were as follows: NLR 3,113 (60.7% sensitivity, 62.9% specificity, 0.645 AUC), PLR 14.245 (64% sensitivity, 65.2% specificity, 0.669 AUC), NPR 0.01 (36% sensitivity, 92.1% specificity, 0.631 AUC), WBC 12.190/mm3 (61.8% sensitivity, 61.8% specificity, 0.679 AUC), neutrophils 70.85% (50% sensitivity, 50% specificity, 0.634 AUC), PLT 338.500/mm3 (60.7% sensitivity, 56.2% specificity, 0.582 AUC), MPR 0.024 (52% sensitivity, 48% specificity, 0.436 AUC) (**Table 4**).

Table 3. Multivariate analysis of laboratory findings

Variables	P value	OR	95%CI
NLR	0.001	0.814	0.728 to 0.911
PLR	0.001	0.939	0.909 to 0.970
WBC	0.001	0.773	0.701 to 0.852
NPR	0.001	0.000	0.000 to 0.000
Lymphocytes	0.001	1.239	1.163 to 1.319
Neutrophils	0.022	1.047	1.007 to 1.088
PLT	0.017	0.996	0.993 to 0.999
MPR	0.617	2.433	0.074 to79.486

Discussion

Our analysis revealed that FS were significantly more common in younger children, in contrast to a previous study.[11] However, our finding is consistent with few studies which found no difference regarding gender.[9,10]

Despite the fact that the etiopathogenesis of FS is unknown, certain immunological processes have been suggested to play a role. Previous study revealed that one of the main factors influencing FS is inflammation, which might be described as a decline in lymphocyte-dependent anti-inflammatory actions and a surge of neutrophil-mediated inflammatory responses. This results in a compromised BBB, which further promotes the return of neutrophils to the brain and the development of seizures and neuronal hyperexcitability.[12] Recently, NLR, PLR, RDW, and MPV have been described as systemic inflammation

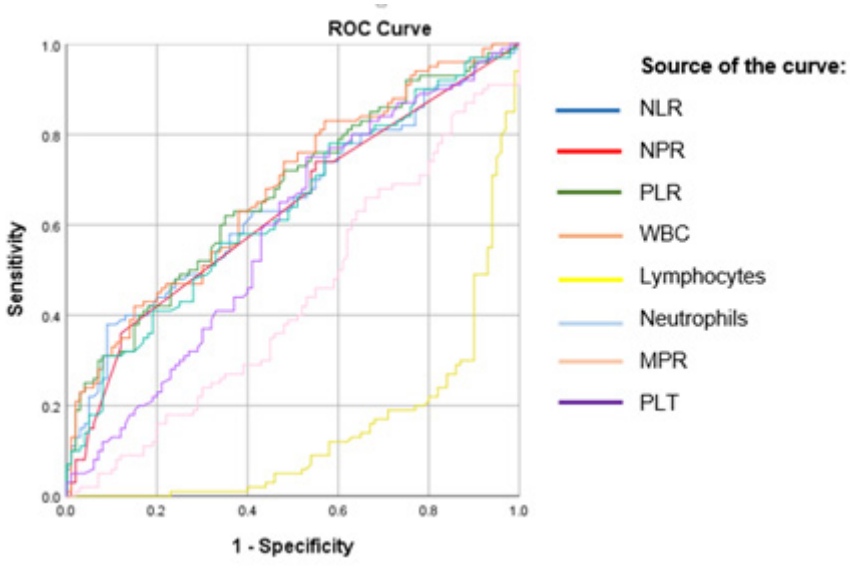

Figure 1. ROC curve of NLR, PLR, and WBC to predict febrile seizures

Table 4. Analysis of cut-off values of complete blood count parameters to predict febrile seizures in children

Variables	Cut-off values	Sensitivity, %	Specificity, %	AUC (95%CI)	P value
NLR	≥ 3,113	60.7	62.9	0.645 (0.568 to 0.721)	< 0.001
PLR	≥ 14.245	64	65.2	0.669 (0.595 to 0.743)	< 0.001
NPR	≥ 0.010	36	92.1	0.631 (0.553 to 0.708)	0.001
WBC, /mm^3	≥ 12.190	61.8	61.8	0.679 (0.606 to 0.752)	< 0.001
Lymphocytes, %	≥ 12.77	15.7	15.7	0.142 (0.090 to 0.194)	<0.001
Neutrophils, %	≥ 70.85	50	50	0.634 (0.557 to 0.710)	0.001
PLT, /mm^3	≥ 338.500	60.7	56.2	0.582 (0.503 to 0.662)	0.044
MPR	≥ 0.024	52	48	0.436 (0.356 to 0.515)	0.117

markers and used as indicators to predict the occurrence of some diseases, including FS.[11]

Many factors contribute to the inflammatory response mediated by neutrophils. By producing reactive oxygen species after phagocytosis, neutrophils play a significant defensive function, which has been linked to seizures. Furthermore, neutrophils promote the induction of several inflammatory mediators that are connected to the development of FS, including TNF-α and IL-1β. In addition, some neutrophils are capable of expressing the voltage-gated Na channel 1.3 (NaV1.3). When NaV1.3 is active, a high-frequency persistent Na flux can be produced. Lastly, a lower lymphocyte count suggests that the capability of the immune system to resist infection has consequently declined.[9]

The NLR is a distinctive marker of cellular immune activation.[13] It rises as a result of the proinflammatory state that is driven by neutrophils and other inflammatory cells during the early hyperdynamic phase of inflammation.[14] The NLR was significantly higher in our FS group than in our control group. Previous studies similarly reported that NLR was significantly higher in the FS group than control group.[10,15]

The RDW is an index frequently used to characterize the size differences of red blood cells. It has been noted to have a favorable correlation with inflammation markers as it can be used to diagnose and predict cancer, autoimmune and non-hematological disease. A previous study hypothesized that inflammation may be a link between RDW and FS, even if the precise processes underlying this correlation are still not understood.[16] However, this hypothesis was denied a previous study which found no differences in terms of RDW between the FS and control group,[14] similar to our findings.

The PLR has been demonstrated to be a predictor of disease activity and survival in individuals with cancer and a variety of inflammatory disorders.[17] A previous study reported that PLR was significantly higher in the FS group,[10] similar to our results.

We identified peripheral blood indicators associated with FS, such as the white blood cell profile, with particular emphasis on neutrophils and lymphocytes. Thus, compared to children with fever without seizures, children with FS demonstrated statistically significant increases in white blood cell and neutrophil levels but significantly decreased lymphocyte levels. A previous study reported that the FS group had significantly higher neutrophil and lower lymphocyte counts than the group without seizures.[18] However, our findings contradict a previous study, which showed no difference in white blood cell count between groups.[18]

The MPV and PLT count are important markers for assessing platelet activation and infection susceptibility. The average platelet size is measured by a machine-calculated value called MPV. It may be used as a gauge of platelet activation and the degree of inflammation since it represents the size and rate of platelet formation in bone marrow.[18] Unlike previous studies that showed significantly higher MPV and PLT counts in the control group,[18,19] we found no significant difference in terms of MPV values, but the control group had a significantly lower PLT count. Platelet distribution width (PDW) may also be tangentially related to platelet activity and function, but PDW was not significantly different between groups.[19]

The NPR was generated in order to reconcile the acute inflammatory response (which is expressed by neutrophils) with the pre-existing chronic inflammation (which is expressed by platelet).[20] The NPR has been reported as a beneficial and quick testing method for determining systemic inflammation.[21] In our study, NPR was significantly higher in the FS group compared to the control group, and it had the highest specificity (92%) in predicting FS. However, as far as we know, no one has yet studied the relationship between NPR and the incidence of FS. It is classified as an easy and inexpensive inflammatory index that has recently been studied.[20] Therefore, further research is certainly much needed.

A study analyzed the diagnostic value of NLR by ROC curve, and found that the AUC between the FS and the control groups was less than 0.7.[18] Specifically, our ROC curve analysis of NLR, PLR, WBC, neutrophil, and platelet to differentiate between the FS and control groups revealed that 3,113 was the ideal NLR cut-off value, with 60.7% sensitivity and 62.9% specificity. These outcomes align with the earlier study where the NLR had a cut-off value of 1.55 (the sensitivity and specificity were 72% and 58%).[9] Furthermore, the other optimal cut-off values were PLR 14.245, WBC 12,190, NPR 0.01, neutrophil 70.85, and platelet 338,500. The most sensitive parameter was PLR (64%), while the most specific was NPR (92.1%).

In comparing the SFS and CFS groups, a study found significant differences in NLR and MPV, but not in MPR, PLT, and RDW.[18] Moreover, other studies also found that NLR was significantly higher in CFS compared to SFS.[15,16] In contrast to earlier findings, we did not find a statistically significant difference in total blood count parameters between the SFS and CFS groups. Thus, further study is needed to elucidate the usefulness of these parameters to distinguish type of FS.

The main limitations of our research were its retrospective design and small sample size. Another long-term and prospective study involving a more extensive population is required to confirm the current findings and make a more robust case for potential diagnostic use. Patients with FS had higher levels of inflammatory markers, such as NLR, PLR, WBC, PLT, neutrophils, and NPR, as well as lower levels of lymphocytes, as determined by complete blood count test findings. These markers, however, are unable to help differentiate between CFS and SFS.

Conflict of interest

None declared.

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