



Mean Platelet Ratio, Neutrophil to Lymphocyte Ratio, and the Risk of Febrile Seizures in Children Aged 6–59 Months

Albert Kurniawan¹, Maria Steffany Lainama¹, Wienta Diarsvitri^{2*}

¹Department of Emergency Medicine, S.K. Lerik Regional Public Hospital, Kupang, East Nusa Tenggara, Indonesia; ²Department of Community Medicine, Faculty of Medicine, Universitas Hang Tuah, Surabaya, Indonesia

Abstract

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***Correspondence:** Dr. Wienta Diarsvitri, Department of Community Medicine, Faculty of Medicine, Universitas Hang Tuah, Jalan Gadung No. 1 (Kompleks Barat RSPAL Dr. Rameelan) Surabaya 60244, Indonesia. E-mail: wienta.diarsvitri@hangtuah.ac.id
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BACKGROUND: The occurrence of febrile seizure is affected by numerous factors, but some studies indicated that inflammatory cytokines might contribute to the development of febrile seizure. In resource limited settings, complete blood count (CBC) might serve as potential indices for inflammatory response.

AIM: The aim of the present study was to determine the role of mean platelet ratio and neutrophil to lymphocyte ratio (NLR) on the risk of febrile seizures in children aged 6–24 months and 25–59 months at S.K. Lerik Regional Public Hospital in Kupang City, East Nusa Tenggara, Indonesia.

METHODS: A case-control study was carried out in 104 patients (52 in the case group and 52 in the control group) aged 6–59 months. The CBC tests were taken on the first visit in the emergency room at S.K. Lerik Regional Public Hospital.

RESULTS: Our study found that the odds for experiencing febrile seizure in younger children aged 6–24 months were 3.281 (95% confidence interval 1.470, 7.324) times as large as the odds for older children aged 25–59 months. There was a significant but weak correlation between the types of febrile seizure or fever and age of children ($r = 0.279$; $p = 0.012$).

CONCLUSIONS: Children aged 6–24 months had higher risk of developing febrile seizure, compared to children aged 25–59 months. Further, for each unit decrease in NLR, we expected a 0.883 decrease in the odds for febrile seizures in the case group, compared to control group.

Introduction

Febrile seizure is the most common seizure disorder in childhood, affecting approximately 2–5% of children aged 3 months–5 years [1]. In general, the peak incidence of febrile seizure occurs at approximately between 12 and 18 months of age [2]. In Indonesia, febrile seizures affected 2–5% of children between 6 months and 3 years of age [3].

In 2011, The American Academy of Pediatrics (AAP) published a clinical practice guideline, and in page 390 defined a febrile seizure as “a seizure accompanied by fever (temperature $\geq 100.4^{\circ}\text{F}$ or 38°C by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age” [1]. Based on duration, physical characteristics and recurrence patterns, febrile seizures can be classified as either simple or complex [4]. The AAP defined simple febrile seizures as “primary generalized seizures that lasted for <15 min and did not recur within 24 h,” and complex febrile seizures as “focal, prolonged (≥ 15 min) and or recurrent within 24 h” [1].

Febrile seizure is the most common cause of convulsion in children [5]. The occurrence of febrile seizure is affected by multifactorial in nature. Its exact mechanism is not fully understood; however, it may be associated with a sensitivity of central nervous system to the elevated body temperature that alters neuronal functions [6], a possibility of genetic susceptibility [2], [3], [4], [5], [6], [7], and inflammatory process that induces cytokine storm in the brain and periphery [6], [7], [8].

Inflammatory cytokines may be used as predictors in febrile seizures; however, there is lack of conclusiveness in their particular cutoffs as biomarkers for disease processes [9]. Further, their measures are relatively expensive and difficult to be carried out in resource limited settings [10]. Therefore, some studies suggested to use complete blood count (CBC), an easily accessible and inexpensive parameter [11], such as peripheral blood neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), mean platelet ratio (MPR), and red blood cell distribution width (RDW) as potential indices for inflammatory response in various diseases [11], [12], [13], [14], [15], [16], [17], [18], [19].

However, previous studies reported inconsistent results related to the interaction between MPR and NLR in febrile seizures susceptibility [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], and this topic has not been studied in Indonesia. Therefore, the aim of the present study was to determine the role of MPR and NLR on the risk of febrile seizures in children aged 6–59 months at S. K. Lerik Regional Public Hospital.

Methods

This case-control study was carried out in 104 children aged 6–59 months who were hospitalized at S.K. Lerik Regional Public Hospital, Kupang City, East Nusa Tenggara Province, Indonesia, in the period of February 1, 2017 – January 31, 2019. The data on age, sex, diagnosis and laboratory results were obtained from the medical records. The CBC tests were taken on the first visit in the emergency room at S.K. Lerik Regional Public Hospital. Patients with central nervous system infections, intracranial abnormalities, or findings of neurologic abnormalities and those who did not undergo a blood routine test after febrile seizures were excluded from the study. Patients were divided into two groups: The case consisted of 52 children (27 children with complex febrile seizure and 25 children with simple febrile seizures) and the control group consisted of 52 children with fever of unknown etiology without seizures.

Red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MPV), neutrophil, monocytes, and lymphocyte counts and percentages were measured from peripheral venous blood samples collected in EDTA tubes during admission in the emergency room. The blood samples were taken and analyzed by Abbott CELL-DYN Hematology Analyzers after febrile seizures. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and MPR was calculated by dividing the MPV by the platelet count. The confidentiality was maintained and this research was approved by the Health Research Ethics Committee of Nusa Cendana University No. 84/UN15.16/KEPK/2019.

Data were presented as mean and standard deviation, or frequencies and percentages as appropriate. The NLR and MPV data were not normally distributed; therefore, the Mann–Whitney U-test was used to analyze the data. The contingency coefficient was used to measure the association between nominal variables. In addition, logistic regression was used to measure the odds ratios and their 95% confidence intervals (CIs) for risk estimation. Significant associations were defined as $p < 0.05$.

Results

A total of 104 children were included in our study, 52 children with febrile seizures in case group and 52 children with fever in control group. The case group consisted of simple febrile seizure ($n = 25$) and complex febrile seizure ($n = 27$). The laboratory parameters in the case and control groups were shown in Table 1. The mean of neutrophil counts was significantly higher in the case group, compared to control group. The mean of other laboratory parameters in both groups was not statistically significant.

Table 1: Laboratory parameters in case and control groups

| Laboratory parameters (SI) | Case (n = 52) | Control (n = 52) | Mann–Whitney U p value |
|-------------------------------------|-----------------|------------------|------------------------|
| Mean platelet volume (fL) | 6.41 ± 1.63 | 7.58 ± 10.24 | 0.63 |
| Platelet count (10^3 cells/L) | 317.32 ± 145.00 | 276.22 ± 142.15 | 0.28 |
| Mean platelet ratio | 0.04 ± 0.09 | 0.22 ± 1.3 | 0.52 |
| Neutrophils count (10^3 cells/L) | 9.61 ± 5.13 | 7.72 ± 5.85 | 0.03 |
| Lymphocytes count (10^3 cells/L) | 3.13 ± 2.00 | 3.01 ± 1.97 | 0.80 |
| Neutrophil to lymphocyte ratio | 4.73 ± 4.16 | 3.61 ± 3.92 | 0.05 |

Values were expressed as mean ± standard deviation. SI: International system of units.

MPR and NLR were further evaluated between children aged 6–24 months and 25–59 months in the case and control groups (Table 2). In the case group, MPR was significantly higher in the younger compared to the older children, but NLR was significantly higher in the older compared to the younger children. While in the control group, MPR was significantly higher in the older compared to the younger children, NLR was not significantly different in the older and the younger children.

Table 2: Mean platelet ratio and neutrophil to lymphocyte ratio in case and control group aged 6–24 and 25–60 months

| Laboratory parameters (SI) | Case (n = 52) | Control (n = 52) |
|--------------------------------|---------------|------------------|
| Mean platelet ratio | | |
| 6–24 months | 0.04 ± 0.11 | 0.03 ± 0.03 |
| 25–59 months | 0.03 ± 0.02 | 0.33 ± 1.63 |
| Mann–Whitney U P value | 0.040 | 0.006 |
| Neutrophil to lymphocyte ratio | | |
| 6–24 months | 3.70 ± 3.14 | 2.19 ± 1.56 |
| 25–59 months | 6.68 ± 5.16 | 4.42 ± 4.61 |
| Mann–Whitney U P value | 0.011 | 0.126 |

A significant but weak positive correlation was found between febrile seizures (case) group, control group, and age of children ($r = 0.277$; $p = 0.003$). Younger children aged 6–24 months had a 3.281-fold odds for febrile seizure compared to the older children aged 25–59 months (95% CI: 1.470, 7.324) (Table 3). When febrile seizures were classified into complex and simple, there was a significant but weak correlation between the types of febrile seizure or fever and age of children ($r = 0.279$; $p = 0.012$) (Table 4).

Logistic regression analysis in Table 5 revealed that MPR was not significantly associated with febrile

Table 3: Contingency coefficient analysis of the association of case-control groups and age of children

| Groups | Age (months) | | Coefficient correlation | p-value | Odds ratio | 95% confidence interval | |
|---------|--------------|------------|-------------------------|---------|------------|-------------------------|-------|
| | 6–24 | 25–59 | | | | Lower | Upper |
| Case | 34 (64.2%) | 18 (35.3%) | 0.277 | 0.003 | 3.281 | 1.470 | 7.324 |
| Control | 19 (35.8%) | 33 (64.7%) | | | | | |
| Total | 53 (100%) | 51 (100%) | | | | | |

Table 4: Contingency coefficient analysis of the association between types of febrile seizure or fever and age of children

| Type | Age (months) | | Coefficient correlation | p-value |
|-------------------------|--------------|------------|-------------------------|---------|
| | 6–24 | 25–59 | | |
| Complex febrile seizure | 17 (32.1%) | 10 (19.6%) | 0.279 | 0.012 |
| Simple febrile seizure | 17 (32.1%) | 8 (15.7%) | | |
| Fever | 19 (35.8%) | 33 (64.7%) | | |
| Total | 53 (100%) | 51 (100%) | | |

Table 5: Logistic regression analysis of the association between factors (mean platelet ratio, neutrophil to lymphocyte ratio, and age) and febrile seizures

| Factors | B | S.E | Wald | df | p-value | Exp (B) | 95% confidence interval for Exp (B) | |
|--------------------------------|--------|-------|--------|----|---------|---------|-------------------------------------|-------|
| | | | | | | | Lower | Upper |
| Mean platelet ratio | -0.301 | 0.749 | 0.161 | 1 | 0.688 | 1.351 | 0.311 | 5.870 |
| Neutrophil to lymphocyte ratio | -0.124 | 0.059 | 4.471 | 1 | 0.034 | 0.883 | 0.787 | 0.991 |
| Age | -1.467 | 0.451 | 10.596 | 1 | 0.001 | 0.231 | 0.095 | 0.558 |
| Constant | 1.247 | 0.450 | 7.696 | 1 | 0.006 | 3.480 | | |

seizures risk. However, each unit decrease in NLR was associated with a 0,883-fold decreased odds for febrile seizures (95% CI: 0.787, 0.991); and older children aged 25–59 months had a 0.231-fold decreased odds for febrile seizure, compared to younger children aged 6–24 months (95% CI: 0.095, 0.558).

Discussion

Numerous studies have been conducted on the identification of factors causing febrile seizure; however, the results have been inconclusive [21], [22], [23]. Several studies indicated the role of systemic inflammatory response in the pathogenesis of febrile seizures [20]. Fever is a response to various exogenous pyrogens, and the level of temperature during febrile seizures varies between individuals and age [24]. Exogenous pyrogens induce fever through interactions with pro- and anti-inflammatory cytokines as endogenous pyrogens, including interleukin (IL)-1 receptor antagonist (IL-1 ra), tumor necrosis factor alpha, IL-6, and prostaglandin E-2 (PGE2) [25]. Cytokines are produced by microglia, astrocytes, some neurons in the central nervous system, as well as by monocytary-type cells in the periphery [26], [27]. These cytokines stimulate the activity of the enzyme cyclooxygenase-2 that catalyzes arachidonic acid into PGE2. PGE2 acts on thermoregulatory pathway in the hypothalamus that increases body temperature [25], [26], [27], [28], [29].

In resource-limited setting, the use of inflammatory cytokines as predictor for febrile seizure might not be feasible [10]. Therefore, several studies suggested the use of CBC, including NLR and MPR as potential mark for inflammatory response in febrile seizure [11], [12], [13], [14], [15], [16], [17], [18], [19], [20]. Immune activation had been suggested to be involved in various extents in the onset of seizure [30]. Neutrophils are part of the innate immune system that

has a fundamental capacity in the host defense through migration into the injury area and induce the secretion of several inflammatory cytokines, phagocytosis, and generation of reactive oxygen species [31], [32]. NLR is a measure of the proportion of neutrophil count and lymphocyte count, which easily accessible, calculable, and inexpensive parameter [11]. Several studies showed a correlation between NLR and chronic inflammation in cardiovascular disease, diabetes mellitus, and malignancies [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33]. While platelets may be involved in the inflammation by storing pro-inflammatory and regulatory mediators in their granules that are released at the site of inflammation during platelets activation, and activated platelets may stimulate entry of neutrophils into lesions [34].

In our study, we analyzed the effect of MPR and NLR on the incidence of febrile seizures in children aged 6–24 months and 25–59 months. As a result, we found neutrophils count was significantly higher in the febrile seizure group. However, the MPR and NLR were not statistically different between the case and control groups ($p \geq 0.05$) (Table 1). Our study also showed a statistically significant difference in NLR and MPR between children aged 6–24 months and children aged 25–59 months (Table 2). In a study conducted by Liu *et al.* showed that NLR was significantly higher in febrile seizures group compared to febrile children without seizure [20]. In a study carried out by Yigit *et al.*, the average value of NLR was significantly different between simple and complex febrile seizure ($p < 0.001$) [11]. Several researches suggested that NLR might differentiate between simple and complex febrile seizure [11], [12], [13], [14], [15], [16], [17], [18], [19], [20]. While in another study by Yazar *et al.*, NLR in children with febrile seizures was lower than NLR in children without seizures [29]. These differences may be due to several factors. Authors assume that some factors influence the outcome of laboratory results during blood collection [35], [36]. There were some limitations in our study, since the medical records did not have information about procedure of blood collection and when the blood routine test was drawn. Furthermore, in S.K. Lerik regional public hospital, blood routine test was taken by non-laboratory professionals. In previous study by Liu *et al.*, blood routine test was obtained within 2 h after febrile seizures, but they did not specify the brand of their hematology analyzer [20]. While in our study, we analyze the blood samples using Abbott CELL-DYN Hematology Analyzers.

Our study also found a correlation between febrile seizures (case) group, control group and age of children ($r = 0.277$; $p = 0.003$) (Table 3). Younger children aged 6–24 months had a 3.281-fold increased risk for febrile seizure compared to the older children aged 25–59 months (95% CI: 1.470, 7.324) (Table 3). In a study by Chung, febrile seizures usually occur

in children of 6 months–5 years of age and the peak incidence occurs at 18 months [37], [38]. In our study, 64.5% of all children with febrile seizure (case group) were children aged 6–24 months and 34.6% were children aged 25–59 months. Hence, our findings are comparable to other studies.

Further, there was a significant but weak correlation between the types of febrile seizure or fever and age of children ($r = 0.279$; $p = 0.012$) (Table 4). To the best of our knowledge, this is the first study in Indonesia to evaluate association between MPR, NLR, types of febrile seizure, and age of the patients. However, the mechanism underlying the associations is complex and remains to be explained. Simple febrile seizure is more common (68%) than complex febrile seizure (63%) in children aged 6–24 months and there was significant association between type of febrile seizures and age of the patients (Table 5). In a study conducted by Yazar *et al.*, 78% of the patients were defined as simple febrile seizure, which corresponds to our study [29].

Based on Table 5, we found that each unit decrease in NLR was associated with a 0.883-fold decreased odds for febrile seizures (95% CI: 0.787, 0.991); and older children aged 25–59 months had a 0.231-fold decreased odds for febrile seizure, compared to younger children aged 6–24 months (95% CI: 0.095, 0.558). Previous studies revealed the increase of MPR and NLR [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], were associated with increased risk of febrile seizure. Based on the receiver operating characteristic analysis, the significant cutoff values for NLR were 2.549 and 2.315 [11].

Our study had several limitations. First, our study was based on medical records and the sample size was small. For this reason, a long-term, prospective, observational cohort study is needed.

Conclusions

For younger children aged 6–24 months, the odds of experiencing febrile seizure were 3.281 (95% CI 1.470, 7.324) times as large as the odds for older children aged 2–59 months being experiencing febrile seizure. Further, for each unit decrease in NLR, we expected a 0.883 decrease in the odds for febrile seizures in the case group, compared to control group.

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Authors' Contributions

A.K. and M.S.L. conceived the research idea and made significant contribution to data collection and drafting the manuscript. W.D. designed the entire study, analyzed all data, and revised manuscript for important data interpretation and intellectual content. All authors read and approved the final version of the manuscript.

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