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ORIGINAL ARTICLE

High neutrophil-to-lymphocyte ratio is not a risk factor of severe dengue infection in children

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ABSTRACT

BACKGROUND

Dengue infection in children globally shows a significant increasing trend in incidence and remains a heavy public health burden. Dengue infection can progress rapidly to death, especially in children. The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory biomarker that represents an immune response to the disease. This study investigated NLR as a risk factor of dengue infection severity in children.

METHODS

A cross-sectional study was conducted involving 237 children, (110 girls and 127 boys) aged 1-18 years with dengue infection. Patients were categorized into dengue fever (DF) and dengue hemorrhagic fever (DHF) according to WHO 2011 criteria. Demographic characteristics, clinical manifestations, and hematological parameters, including hemoglobin (Hb), leukocyte count, thrombocyte count, hematocrit (HCT), and NLR, were extracted. Bivariate and multivariate logistic regression analysis were used to analyze the data.

RESULTS

The study demonstrated that 59.9% of cases were classified as DF and 40.1% as DHF, with a mean age of 9.99 ± 4.84 years. The mean NLR was 0.99 ± 0.98 in DHF and 1.51 ± 1.38 in DF. Univariate regression analysis stated that NLR≥2 was associated with dengue severity. However, multivariate regression analysis stated that NLR was not a risk factor of dengue severity, adjusted from demographic characteristics and hematologic parameters. Hemoglobin and platelets are the independent factors of dengue severity.

CONCLUSION

Neutrophil-to-lymphocyte ratio is a simple biomarker but not a risk factor of dengue fever severity in children. There is evidence suggesting that the relationship between NLR and dengue fever severity is complex, with varying trends in different phases of the disease.

Keywords : Dengue infection, clinical manifestation, hematological profile, neutrophil-to-lymphocyte ratio.

INTRODUCTION

Dengue infection is a disease transmitted by the *Aedes aegypti* and *Aedes albopictus* due to the dengue virus (DENV). Primary DENV infection may be asymptomatic or manifest as mild dengue fever (DF). However, severe forms of dengue result in coagulation disorders, blood vessel wall fragility, and vascular permeability. This condition is known as dengue hemorrhagic fever (DHF), which in a later stage may lead to hypovolemic shock, namely dengue shock syndrome (DSS). Dengue infection has become endemic in more than 100 countries worldwide, including the WHO regions of America, Africa, Southeast Asia, the Eastern Mediterranean, and the Western Pacific.[1]

The incidence of dengue infection in children globally showed a significant trend from 1990 to 2021 and remains a heavy public health burden.[2] A multicenter study in Bangladesh reported that 28% of dengue infections in children aged <15 years were categorized as severe dengue.[3] Moreover, atypical presentation, including neurological manifestations in children with dengue, also occurs. The immune response in children is still developing, resulting in an imbalance in immune cells, particularly neutrophils and lymphocytes, which affects the progression of dengue infection. The clinical symptoms of dengue infection vary widely, from asymptomatic to fatal dengue shock syndrome. Limited verbal expression in children can affect the presentation of dengue fever and make diagnosing it more difficult.[4] Severe dengue infection, if not treated properly, can cause rapid death, especially in children. Previous studies in Yogyakarta and Surabaya reported that children with severe dengue infection had a mortality rate of 14%.[5,6]

The neutrophil-to-lymphocyte ratio (NLR) is a prognostic biomarker widely used in inflammation, infection, and cardiovascular disease. Neutrophils are innate immune cells that fight pathogens through phagocytosis, degranulation, and reactive oxygen species (ROS) production. Neutrophils have been reported to be able to prevent the spread of viral infections and clear viruses through interactions with host cells.[7] Previous studies reported that NLR was linked to dengue severity, and some studies reported NLR as a predictor of shock and plasma leakage in DHF.[8,9] A study conducted by Fuadah et al. in Bandung,[10] reported that the mean NLR in DHF was lower compared to DF, which means that NLR was significantly inversely correlated with dengue severity. Furthermore, a prospective study conducted on 250 randomly selected dengue patients, showed that NLR ≥2 on the third day of fever was associated with a statistically significant higher frequency of DHF, DSS, expanded dengue syndrome (EDS), and severe dengue.[11]

Previous studies have demonstrated an association between NLR and the severity of dengue infection in children, however the findings have been inconsistent. Recent studies found a lower NLR associated with poor outcomes in dengue infection.[12,13] One study indirectly concluded that NLR <2 was a bad prognostic indicator. A NLR < 2 was associated with a higher frequency of DHF, DSS, EDS, and severe dengue in the participants of this study.[14]

This study used NLR samples as soon as feasible after the patient was admitted to the hospital, reflecting real-world practices. Thus, the aim of this study was to determine the NLR as a risk factor of dengue infection severity in children.

METHODS

Research design

This was a retrospective cross-sectional study conducted in Husada Utama Hospital, Surabaya, from February – March 2025.

Study subjects

A total of 237 participants were enrolled in this study. The inclusion criteria were: 1) children aged 1-18 years 2) with a clinical diagnosis of dengue according to WHO 2011 criteria, and 3) hospitalized at Husada Utama from January to December 2024. Children with secondary infection, chronic illness, and incomplete medical records were excluded. Patients were categorized into DF and DHF according to WHO 2011 criteria. DF according to WHO 2011 criteria were classified as fever plus ≥2 of the following: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, with no evidence of plasma leakage. Laboratory parameters included leukopenia ≤5000 cells/mm^3, thrombocytopenia <150.000 cells/mm^3, rising hematocrit (5-10%), and no plasma loss. DHF according to WHO 2011 criteria are characterized by fever, hemorrhagic manifestations, thrombocytopenia <100.000 cells/mm^3, and evidence of plasma leakage (HCT rise ≥20%, pleural effusion, ascites).[15]

Table 1. Distribution of clinical characteristics of the subjects (n=237)

Characteristics	DF (n=142)	DHF (n=95)	p-value
Age (years)	9.23 ± 4.77	11.12 ± 4.75	0.004
Sex (Male)	64 (45.1)	46 (48)	0.612
Fever	142 (100)	95 (100)	1.000
Headache	127 (89.4)	88 (92.6)	0.406
Myalgia	136 (95.7)	95 (100)	0.042
Arthritis	100 (70.4)	79 (83.15)	0.025
Nausea	83 (58.4)	73 (76.8)	0.003
Vomiting	62 (43.6)	40 (42.1)	0.812
Abdominal pain	35 (24.6)	30 (31.5)	0.241
Skin rash	9 (6)	8 (8)	0.543
Bleeding	14 (9.8)	2 (2)	0.922

Note : Data presented as n (%); DF : dengue fever; DHF : dengue hemorrhagic fever

Data collection

All data were obtained from electronic medical records. The demographic data recorded included age, sex, hospital stay, and clinical manifestations (e.g., fever, headache, myalgia, arthritis, nausea, vomiting, abdominal pain, skin rash, and incidence of bleeding). Hematological parameters, including hemoglobin (Hb), hematocrit (HCT), leukocyte count, thrombocyte count, and neutrophil-to-lymphocyte ratio (NLR), were obtained on the earliest available day of hospitalization. Dengue severity was categorized into DF and DHF according to the WHO 2011 criteria. Children with secondary infection, chronic illness, and incomplete medical records were excluded.

Statistical analysis

Statistical analysis was performed using SPSS 25. Baseline characteristics were compare using the Mann-Whitney U test. Normality tests was performed using Kolmogorov-Smirnov. Non-normally distributed data were shown as mean and compared with the Mann-Whitney U test. Continuous variables were presented as mean ± standard deviation (SD). All variables were converted into binary data. First all variables were run in simple logistic regression, then variables with $p<0.25$ were subjected to multivariate logistic regression, with $p<0.05$ being considered statistically significant.

Ethical clearance

The study ethics was approved by the Husada Utama Hospital Ethics Committee on February 4th, 2025 under number 08/KEP-RSHU/II/2025.

RESULTS

The results of the study revealed that 59.9% of cases were classified as DF, while 40.1% were classified as DHF, with a mean age of 9.99 ± 4.84 years. The number of female patients (53.6%) was higher than that of male patients. The length of hospital stay was 4.2 ± 1.35 days. Fever was the most common symptom, followed by myalgia, headache, arthritis, nausea, vomiting, and abdominal pain. Clinical characteristics are presented in Table 1, while hematological parameters are shown in Table 2. All hematological parameters appeared to be significantly different between the DF and DHF groups ($p<0.05$). The DHF group tended to have increased Hb and HCT, with lower thrombocyte count, leukocyte count, and NLR ratio.

Table 2. Comparison of hematologic characteristics between DF and DHF

	DF (n=142)	DHF (n=95)	p-value
Hb	13 ± 1.3	14.7 ± 1.94	0.000
HCT	39.1 ± 3.76	44.1 ± 5.6	0.000
Thrombocyte count	125.73 ± 38.6	61.3 ± 33.05	0.000
Leukocyte count	4223.7 ± 3033.68	5067 ± 3032.74	0.013
NLR	1.51 ± 1.38	0.99 ± 0.98	0.001

Note : Data presented as mean ± SD (standard deviation). DF : dengue fever; DHF : dengue hemorrhagic fever; Hb : hemoglobin; HCT : hematocrit; NLR : neutrophil-to-lymphocyte ratio

Table 3. Bivariate logistic regression analysis of risk factors of dengue severity in children

Variables	OR	95% C.I.	p value
Age ≥ 10 years	1.44	0.85 – 2.43	0.172
Arthritis	0.47	0.24 – 0.9	0.023
Nausea	0.45	0.25 – 0.8	0.007
NLR ≥ 2	3.69	1.69 – 8.05	0.001
Hb ≥ 14 g/dL	9.324	5.11 – 17	<0.001
PLT < 100.000 mm^3	28.59	13.55 – 60.34	<0.001
HCT ≥ 40%	7.326	4.01 – 13.56	<0.001
WBC < 5000/mm^3	0.575	0.32 – 1.01	0.055

Note : Data presented as odds ratio (OR) with 95% confidence interval (CI); NLR : neutrophil lymphocyte ratio; Hb : hemoglobin; HCT : hematocrit; PLT : platelet count; WBC : white blood cell count

Bivariate logistic analysis showed that NLR≥2 was associated with dengue severity (OR: 3.69 ;95% C.I.: 1.69–8.05) (Table 3). Multivariate logistic analysis stated that NLR ≥ 2 was not a risk factor of DHF (adjusted OR 2.42; 95% CI 0.76-7.75; p=0.135). (Table 4).

DISCUSSION

The study demonstrated that among 237 children admitted to the hospital, 59.9% were classified as DF and 40.1% as DHF, with a mean age of 9.99 ± 4.84 years. The DHF group was found to be older than the DF group. This study is in line with the study by Fuadah et al. in Bandung, stating that DHF patients were predominantly school-aged children.[10] Fever was the most common symptom, followed by myalgia, headache, arthritis, nausea, vomiting, and abdominal pain. A meta-analysis demonstrated that fever and musculoskeletal pain were the first presenting symptoms in the early stage of dengue, while vomiting, nausea, abdominal pain, and bleeding were strong predictors of the severity of dengue.[16] The present study revealed that NLR ≥2 was a risk factor of dengue hemorrhagic fever (DHF), based on bivariate logistic regression. Children with NLR ≥2 exhibited a greater risk of developing DHF compared to those with lower NLR. In multivariate binary logistic regression, following adjustment for age, clinical symptoms, hemoglobin, hematocrit, platelet count, and leukocyte count, the value of NLR ≥2 was no longer a risk factor of DHF. NLR cut offs of <2 and ≥ 2 were used in this study based on a previous research study demonstrating that lower NLR values are associated with dengue severity. [17] The study by Wazib et al.[11] has shown that higher NLR values (≥2) on the third day of fever were associated with an increased risk of developing dengue shock syndrome (DSS) and other severe forms of dengue. A study conducted by Sharma et al.[18] stated that DHF patients had an NLR of 1-2, while those with DF had an NLR value of > 3 on the third day of fever. The neutrophil lymphocyte ratio can undergo dynamic changes in the course of the dengue infection. The NLR tends to increase due to increased neutrophil count in the early phase of dengue infection but decreases as neutropenia and lymphocytosis develop, especially in severe cases.

Table 4. Multivariate logistic regression analysis of factors associated with dengue severity in children

Variables	Adjusted OR	95% CI	p-value
Age ≥ 10 years	0.58	0.19 – 1.71	0.321
Arthritis	0.98	0.29 – 3.25	0.967
Nausea	0.56	0.24 – 1.35	0.199
NLR ≥ 2	2.42	0.76 – 7.72	0.135
Hb ≥ 14 g/dL	4.86	1.65 – 4.35	**0.004**
PLT < 100.000 mm^3	20.02	8.71 – 6.02	**<0.001**
HCT ≥ 40%	2.48	0.82 – 7.45	0.107
WBC < 5000/mm^3	0.49	0.21 – 1.15	0.102

Note : Data presented as adjusted odds ratio (aOR) with 95% confidence interval (CI); NLR : neutrophil lymphocyte ratio; Hb : hemoglobin; HCT : hematocrit; PLT: platelet count; WBC : white blood cell count

Severe dengue infection triggers the composition of neutrophils and lymphocytes, which affects the NLR value. Dengue virus infects and damages various types of immune cells. During infection, mast cell activation induces pro-inflammatory cytokine and chemokine release, attracting neutrophils and other immune cells to the tissues. This process leads to a decrease in the number of neutrophils in the blood circulation due to migration of these cells to the tissues.[19,20] Activation of CD4+ and CD8+ T cells by the adaptive immune system eliminates viruses and triggers immunopathological responses. On the other hand, cross-reactive T-cell activation amplifies the inflammatory response and increases the severity of the disease and subsequently the number of lymphocytes in the blood.[19,20]

Another study revealed a significant difference between NLR and dengue severity.[21] An NLR value of <2 has been reported to be associated with thrombocytopenia, while NLR ≥2 has been associated with milder symptoms of dengue infection. [22] The NLR compares the number of neutrophils to lymphocytes, which reflects the balance between innate and adaptive immunity. The NLR values in this study were obtained on the earliest available day of hospitalization. Therefore, sampling time is a crucial factor in interpreting NLR values.

A study conducted by Prijatno et al.[9] reported a significant correlation between NLR and the incidence of shock in dengue with a cut-off point of 0.833. Similarly, another study established a significant correlation between lower NLR and the incidence of bleeding and shock in dengue patients.[23] The decrease in NLR in severe dengue infection cases is likely due to lymphocytosis and neutropenia, which are typical responses to severe viral infections.[19,24]

This study demonstrated that platelet count is the strongest predictor associated with DHF, followed by hemoglobin. The dengue virus activates neutrophils to produce neutrophil extracellular traps (NETs), which trap platelets coated with viral antigens.[25] This mechanism contributes to neutropenia and platelet consumption, thus linking the immune response to thrombocytopenia and vascular damage.[26] Neutrophil activation in dengue infection releases the granular protein myeloperoxidase, thereby increasing vascular leakage. Mast cell activation induces the release of the mediators chymase and tryptase. Platelets activated by the dengue virus interact with neutrophils, monocytes, and macrophages, resulting in increased inflammatory reactions that contribute to vascular leakage.[27]

This study has several limitations. First, it is of retrospective design. Some relevant data for comparison and diagnosis of dengue infection were not available in the medical records. In addition, a single-center study reduces generalization of the clinical and hematological results of dengue infection. The laboratory parameters especially NLR, were not obtained at the same onset of fever. This study was not designed to establish diagnostic or prognostic cut-off values for NLR but to analyze its association with disease severity. Further studies with larger sample sizes need to be conducted to monitor serial NLR and to evaluate the best time and cut-off points to stratify risk and the severity of dengue infection.

CONCLUSIONS

The neutrophil lymphocyte ratio is a simple biomarker, but not a risk factor of dengue infection severity in children. There is evidence suggesting that the relationship is complex, with varying trends in different phases of the disease.

Conflict of Interest

Competing interests: No relevant disclosures.

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Author Contributions

SRD contributed to conceptualization, data collection, statistical analyses, data interpretation, and manuscript writing. RVP contributed to conceptualization, methodology, statistical methods, and manuscript supervision. II contributed to conceptualization, supervised data collection, and manuscript supervision. All authors had read and approved to the final manuscript.

Data Availability Statement

The data supporting the findings of this study are accessible from the corresponding author upon reasonable request

Declaration of Use of AI in Scientific Writing

Nothing to declare.

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