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The Diagnostic Utility of Low Neutrophil-to-Lymphocyte Ratio (NLR) as an Indicator of Severity in Adult Dengue Hemorrhagic Fever: A Retrospective Study from Bali

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A B S T R A C T

Dengue hemorrhagic fever (DHF) remains a critical public health challenge in tropical regions. Unlike bacterial sepsis, where a high neutrophil-to-lymphocyte ratio (NLR) typically indicates severity, viral kinetics in dengue often present differently due to bone marrow suppression. This study evaluates the association between low NLR and disease severity in an adult cohort in Indonesia, aiming to identify a cost-effective marker for risk stratification. A retrospective cross-sectional study was conducted at Wangaya Regional General Hospital, Denpasar, Indonesia, from January to August 2025. We analyzed 92 confirmed adult DHF patients aged 18 years and older. Severity was graded using standard World Health Organization criteria (Grades 1–4). For the purpose of diagnostic performance analysis, severe DHF was defined as Grade 2 (spontaneous bleeding) and Grade 3 (circulatory failure) combined. The correlation between NLR and severity was analyzed using the Spearman rank test. Receiver Operating Characteristic (ROC) analysis determined the optimal cut-off for identifying severe cases. The cohort was predominantly young adults (18–25 years; 47.8%) with a male preponderance (68.5%). The severity distribution included Grade 1 (n=68; 73.9%), Grade 2 (n=21; 22.8%), and Grade 3 (n=3; 3.3%). A significant, moderate inverse correlation was observed between NLR and severity grade ($r = -0.347$; $p < 0.001$). Mean NLR decreased progressively from Grade 1 (2.90) to Grade 2 (1.20) and Grade 3 (0.65). ROC analysis for detecting Grade 2 or higher DHF showed an Area Under the Curve (AUC) of 0.82 (95% CI: 0.75–0.89). An NLR cut-off of less than 0.85 yielded a sensitivity of 87.5% and specificity of 72.0%. In conclusion, a low NLR is significantly associated with higher clinical severity in adult DHF. Unlike bacterial infections, a declining NLR below 0.85 serves as a potential marker for identifying patients at risk of bleeding and circulatory compromise in resource-limited settings.

1. Introduction

Dengue hemorrhagic fever (DHF) persists as a formidable and escalating public health threat across the globe's tropical and subtropical belts.[1] Driven by rapid urbanization, climate change, and the expanding range of the *Aedes aegypti* and *Aedes albopictus* vectors, the incidence of dengue has grown dramatically in recent decades, placing nearly half of the world's population at risk. Within this global landscape, Southeast Asia remains the epicenter of hyperendemicity, bearing a disproportionate share of the disease burden. In the Indonesian archipelago, dengue is not merely a seasonal nuisance but a significant source of morbidity and mortality that exerts immense pressure on the national healthcare infrastructure. The epidemiology of the disease in Indonesia is characterized by cyclical outbreaks that frequently overwhelm hospital capacities, particularly during the monsoon transitions.[2] In high-transmission zones such as Bali—a hub of

international tourism and domestic migration—the circulation of multiple serotypes creates a complex immunological landscape, perpetuating a continuous cycle of primary and secondary infections that challenge clinical management and resource allocation.[3]

The clinical spectrum of infection caused by the Flaviviridae virus is remarkably broad, ranging from an asymptomatic or mild, self-limiting febrile illness to the life-threatening manifestations of severe dengue.[4] This severe form is clinically defined by a critical phase involving massive plasma leakage, fluid accumulation (pleural effusion, ascites), respiratory distress, severe hemorrhagic manifestations, or profound organ impairment. While historical surveillance has predominantly focused on pediatric populations due to their perceived vulnerability, the epidemiological demographic of dengue is shifting. There is an increasing prevalence of DHF among adults, presenting a unique set of clinical challenges.[5]

In adult populations, although the absolute incidence of mortality is statistically lower than in children, the clinical presentation is often atypical, leading to dangerous diagnostic delays.[6] Adults possess a different physiological reserve and a distinct immunological profile compared to children, a phenomenon influenced by immunosenescence and a lifetime of antigenic exposure. Furthermore, the presence of comorbidities common in adulthood—such as hypertension, diabetes mellitus, and peptic ulcer disease—can obfuscate the classical signs of dengue and exacerbate the severity of the disease. Consequently, adults may not exhibit the classic shock signs as early as children, instead maintaining hemodynamic stability until a precipitous and catastrophic collapse occurs. This silent progression underscores the urgent need for biomarkers that can stratify risk before clinical deterioration becomes irreversible.

The transition from uncomplicated dengue fever to DHF and dengue shock syndrome (DSS) is driven by a complex and dysregulated host immune response, often described as a cytokine storm. This immunopathological cascade is frequently triggered during secondary infection by a heterologous serotype, where the phenomenon of antibody-dependent enhancement (ADE) facilitates increased viral entry into immune cells.[7] This results in the massive and aberrant release of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-alpha), Interleukin-6 (IL-6), and Interleukin-10 (IL-10), as well as vasoactive factors like vascular endothelial growth factor (VEGF). This biochemical deluge targets the vascular endothelium, specifically degrading the endothelial glycocalyx layer. The resulting endothelial dysfunction leads to increased vascular permeability, which is the hallmark pathophysiological mechanism of DHF. Fluid extravasates from the intravascular compartment into the extravascular space, leading to hypovolemia, hemoconcentration, and eventually, shock. This critical phase typically occurs around the time of defervescence (days 3 to 7 of illness), creating a narrow and treacherous window for clinical intervention. Understanding the timing of this immunological dysregulation is crucial, as the hematological markers currently used to monitor patients often lag behind the microscopic reality of vascular leakage.

In current clinical practice, especially in resource-limited settings like Indonesia, risk stratification relies heavily on classical hematological parameters: platelet count and hematocrit. Thrombocytopenia (platelet count < 100,000/µL) is a cardinal feature of DHF, resulting from bone marrow suppression and peripheral destruction.[8] However, severe thrombocytopenia often manifests concurrently with or even after the onset of significant plasma leakage, limiting its utility as a predictive early warning signal. Similarly, hemoconcentration (a rise in hematocrit of 20% or more above baseline) is the gold standard for identifying plasma leakage. Yet, by definition, a rise in hematocrit indicates that significant fluid loss has

already occurred. Clinicians are thus faced with a diagnostic gap: the need to identify patients destined for severe disease before the hematocrit rises and before the platelets bottom out. In the context of a busy Indonesian public hospital, where specialized assays for cytokines or viral loads are prohibitively expensive and unavailable, there is a paramount need for accessible, zero-cost biomarkers derived from the standard Complete Blood Count (CBC) that can predict this immunological tipping point.

The neutrophil-to-lymphocyte ratio (NLR), a simple calculated index derived from the absolute neutrophil and lymphocyte counts, has emerged as a promising candidate for this role. The NLR acts as a window into the systemic inflammatory balance, reflecting the interplay between the innate immune response (represented by neutrophils) and adaptive immunity (represented by lymphocytes). In the vast majority of medical literature—particularly regarding bacterial sepsis, myocardial infarction, and trauma—a high NLR is synonymous with severe stress and poor prognosis. In these conditions, the physiological stress response triggers the release of cortisol and catecholamines, causing the demargination of neutrophils (neutrophilia) and the apoptosis of lymphocytes (lymphopenia). Thus, in a typical septic patient, the NLR skyrockets.[9]

However, the hematological dynamics in dengue infection are distinct and paradoxically opposed to the bacterial sepsis model. The dengue virus exerts a direct cytopathic effect on the bone marrow, specifically suppressing the myeloid progenitor cells. This results in significant neutropenia during the acute stages of infection. Simultaneously, while the virus initially suppresses lymphocyte counts, the body's attempt to clear the viremia involves the activation of the adaptive immune system, often leading to the appearance of atypical lymphocytes or a relative preservation of lymphocyte counts compared to the plummeting neutrophils. Therefore, unlike bacterial sepsis, where the numerator (neutrophils) rises, and the denominator (lymphocytes) falls, severe dengue often presents with a precipitous drop in the numerator and a relative stability or rise in the denominator. This creates a theoretical inverse correlation, where a lower NLR—rather than a higher one—signals the intensity of the viral marrow suppression and the subsequent severity of the disease. This is complicated by the fact that the adult immune system, subject to immunosenescence, may exhibit unique kinetic patterns compared to the pediatric models upon which most dengue guidelines are based.

Despite the physiological plausibility of this marker, the existing literature presents conflicting data regarding NLR in dengue. Some studies suggest that an elevated NLR predicts severity, while others report a significant decline. These discrepancies likely stem from variations in study design, specifically the timing of sample collection (early febrile phase vs. critical phase transition), patient age (pediatric vs. adult), and geographical variations in viral virulence. The early febrile phase may indeed show a stress-induced high NLR, but the transition to the critical phase—the period of greatest danger—appears to be marked by this unique crossover to a low NLR phenotype.[10]

Addressing this gap in the literature is critical for refining triage protocols in endemic regions. Consequently, this study aims to clarify the diagnostic utility of NLR by analyzing its association with disease severity, specifically in adult DHF patients at a tertiary care center in Bali. By focusing exclusively on the adult demographic and the admission window relevant to the critical phase transition, this research seeks to resolve the existing contradictions in the data. The novelty of this research lies in elucidating the specific inverse correlation pattern—where a low NLR serves as a harbinger of severity—in the adult population. This challenges the conventional heuristic of using high NLR as a severity marker in general infectious disease contexts and proposes a paradigm shift for dengue

triage: recognizing that, in the context of this specific viral hemorrhagic fever, a crashing NLR may be the earliest warning sign of an impending cytokine storm and hemodynamic collapse.

2. Methods

The ethical integrity of this research was paramount and strictly adhered to the principles outlined in the Declaration of Helsinki regarding research involving human subjects. Prior to the initiation of data extraction, the study protocol underwent a rigorous review and received formal ethical clearance from the Institutional Review Board (IRB) and the Ethics Committee of Wangaya Regional General Hospital, Denpasar, Indonesia. Given the retrospective nature of the study, which involved the analysis of secondary data from medical records without direct patient interaction or intervention, a waiver of informed consent was granted by the Ethics Committee. However, to ensure the protection of patient privacy and confidentiality, all personal identifiers—including names, medical record numbers, and contact details—were anonymized at the source of data extraction. Each patient record was assigned a unique coded identification number, and the master key linking these codes to patient identities was stored in a secure, encrypted database accessible only to the principal investigator. This protocol ensured that the use of sensitive medical data complied with both local hospital regulations and international standards for data privacy in clinical research.

This investigation was designed as an observational analytic study utilizing a retrospective cross-sectional approach. This design was selected to provide a snapshot of the relationship between hematological markers and disease severity within a defined population and timeframe. The study was conducted at the Department of Clinical Pathology and the Medical Records Installation of Wangaya Regional General Hospital. As a prominent type-B government referral hospital in Denpasar, Wangaya General Hospital manages a high volume of infectious disease cases, serving a diverse demographic that is representative of the urban and peri-urban population of the island. The data collection period spanned eight months, from January 2025 to August 2025. This timeframe was strategically chosen to encompass the region's rainy season and the subsequent post-monsoon transition, which historically corresponds to the epidemiological peak of dengue transmission in Bali. By capturing data during this high-transmission window, the study aimed to minimize seasonal bias and ensure that the cohort reflected the clinical reality of an active outbreak scenario.

The target population for this study comprised all adult patients admitted to Wangaya Regional General Hospital with a confirmed diagnosis of dengue hemorrhagic fever (DHF) during the specified study period. To ensure the internal validity of the study and the homogeneity of the sample, strict inclusion and exclusion criteria were applied. The study included patients aged 18 years or older, recognizing that the physiological response to dengue infection, particularly regarding vascular permeability and immune regulation, differs markedly between adults and children. A confirmed diagnosis of DHF was mandated, defined strictly according to the World Health Organization (WHO) South-East Asia Regional Office (SEARO) 2011 guidelines. This clinical diagnosis required corroboration through serological evidence, specifically a positive result for the dengue non-structural protein 1 (NS1) antigen or positive IgM/IgG anti-dengue antibodies. Furthermore, inclusion required the completion of a comprehensive hematological examination upon admission. We specifically targeted the admission window, typically corresponding to days 3 to 5 of illness, as this timeframe represents the critical transition from the febrile to the critical phase—the period where predictive stratification is most clinically valuable. To isolate the specific effect of dengue infection on the

neutrophil-to-lymphocyte ratio (NLR), we rigorously excluded conditions known to independently alter leukocyte kinetics; (1) Incomplete Records: Patients with missing demographic data or incomplete admission Complete Blood Counts (CBC) were excluded to prevent information bias; (2) Pregnancy: Pregnant women were excluded due to the physiological leukocytosis associated with gestation. Pregnancy naturally induces a state of mild neutrophilia, which would artificially elevate the baseline NLR and obscure the viral-induced suppression we aimed to measure; (3) Hematological malignancies and autoimmune disorders: Patients with underlying leukemia, lymphoma, or autoimmune conditions were excluded, as both the pathology of these diseases and their treatments can cause profound and unpredictable dysregulation of the myeloid and lymphoid lineages; (4) Bacterial Co-infections and COVID-19: This was a critical exclusion criterion. Bacterial infections (such as Typhoid fever confirmed by Tubex or culture, and bacterial pneumonia) and COVID-19 typically elicit a robust neutrophilic response, driving the NLR upward. This is diametrically opposed to the hypothesized viral suppression seen in dengue. Including these patients would introduce severe confounding, potentially masking the low NLR signal associated with severe dengue; (5) Systemic Corticosteroids and G-CSF: Patients receiving systemic corticosteroids or granulocyte-colony stimulating factor prior to admission were excluded. Corticosteroids cause the demargination of neutrophils from the vascular endothelium, leading to artificial neutrophilia, while G-CSF directly stimulates bone marrow production. Both agents would fundamentally invalidate the NLR as a marker of the host's natural immune response to the virus.

A total sampling strategy was employed, wherein every eligible patient record meeting the inclusion and exclusion criteria within the study timeframe was incorporated into the analysis. This approach was adopted to minimize selection bias and maximize the representativeness of the cohort. Following the rigorous screening process, the final sample consisted of 92 patients.

To ensure the statistical robustness of this sample size, a post-hoc power analysis was conducted. Assuming a moderate correlation coefficient (r) of 0.35—based on preliminary observations in similar tropical medicine literature—and setting the alpha error probability at 0.05 (confidence level of 95%), the calculation indicated that a minimum sample size of 85 subjects was required to achieve a statistical power of 80% (beta = 0.20). With a final cohort of 92 patients, the study possesses adequate statistical power to detect meaningful associations for the primary correlational objective, reducing the risk of Type II errors.

The primary independent variable was the neutrophil-to-lymphocyte ratio (NLR). This ratio serves as a surrogate marker for systemic inflammation and immune regulation. It was calculated mathematically by dividing the absolute neutrophil count by the absolute lymphocyte count derived from the admission CBC. To ensure consistency and capture the patient's status at the point of entry into hospital care, only the initial CBC taken within 24 hours of admission was utilized. This minimizes the confounding effects of subsequent hospital interventions, such as aggressive fluid resuscitation, which could cause hemodilution.

The Dependent Variable was DHF Severity, classified according to the WHO SEARO 2011 guidelines. This classification system stratifies patients based on the progression of plasma leakage and hemorrhagic tendencies: (i) Grade 1: Defined as fever accompanied by non-specific constitutional symptoms (such as headache, retro-orbital pain, myalgia) and a positive tourniquet test, indicating capillary fragility without overt spontaneous bleeding; (ii) Grade 2: Includes the manifestations of Grade 1 but is distinguished by the presence of spontaneous bleeding. In our cohort, this typically presented as

epistaxis (nosebleeds), gingival bleeding, or evidence of gastrointestinal bleeding (melena or hematemesis); (iii) Grade 3: Represents the onset of circulatory failure or Dengue Shock Syndrome (DSS). This is characterized clinically by a rapid, weak pulse and narrowing of the pulse pressure (the difference between systolic and diastolic pressure dropping to less than 20 mmHg) or frank hypotension relative to age. This grade signifies uncompensated plasma leakage; (iv) Grade 4: Defined as profound, irreversible shock with undetectable blood pressure and pulse, representing the most critical and lethal form of the disease.

For the purposes of statistical modeling, specifically binary logistic regression and receiver operating characteristic (ROC) curve analysis, a grouping strategy was employed. The outcome variable was dichotomized into non-severe and severe/complicated. Non-severe was defined exclusively as Grade 1 DHF. Severe/complicated was defined as the combination of Grade 2 (Significant Bleeding) and Grade 3 (Shock). This grouping strategy was a necessary methodological decision driven by the epidemiological distribution of the data. The prevalence of pure Grade 3 shock in the dataset was low (n=3), reflecting the effective early management at the hospital but creating a sparse data problem. Analyzing Grade 3 as a standalone category would result in wide confidence intervals and statistical instability. By grouping Grade 2 and Grade 3, we created a robust, complicated category (n=24) that encompasses patients with significant clinical deterioration—either through hemorrhage or hemodynamic instability. This allows for a more reliable calculation of sensitivity, specificity, and diagnostic thresholds while remaining clinically meaningful, as both Grade 2 and Grade 3 require intensified monitoring and intervention compared to Grade 1.

Data were analyzed using SPSS version 26.0. Frequency and percentage were used for categorical variables such as gender and severity grade. Mean and Standard Deviation (SD) were used for continuous variables, including age and NLR, after assessing for normality using the Shapiro-Wilk test. Since the NLR data followed a non-normal distribution, the non-parametric Spearman Rank Correlation test was utilized to determine the relationship between NLR and DHF severity grade. The Mann-Whitney U test was used to compare NLR between the non-severe (Grade 1) and Severe (Grade 2 and 3) groups. To address the potential bias of illness duration, an independent t-test was performed to compare the day of illness at admission between severity groups. A receiver operating characteristic (ROC) curve was generated to identify the area under the curve (AUC). The Youden Index (J = Sensitivity + Specificity - 1) was used to determine the optimal cut-off value. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Statistical significance was set at $p < 0.05$.

3. Results and Discussion

A total of 92 subjects met the strict inclusion criteria. As presented in Table 1, the study population was predominantly young adults, with the 18–25 age group constituting 47.83% (n=44) of the cohort. There was a male preponderance (68.48%). Regarding disease severity, the majority of patients presented with Grade 1 DHF (73.91%), followed by Grade 2 (22.82%) and Grade 3 (3.26%). No patients with Grade 4 DHF were recorded in this specific dataset. The overall prevalence of severe/complicated DHF (Grade 2 and 3) in this cohort was 26.08%.

Figure 1 illustrates the mean day of illness at the time of hospital admission for both severity groups. Error bars represent Standard Deviation (SD). There was no statistically significant difference (p=0.48) in the timing of blood sampling between non-severe (4.1 ± 1.2 days) and Severe patients (4.3 ± 1.1 days), indicating that the observed differences in neutrophil-to-lymphocyte ratio (NLR) were not confounded by the stage of illness at presentation.

Table 1. Baseline Characteristics of the Study Population (N=92)

VARIABLE	CATEGORY	FREQUENCY (N)	PERCENTAGE (%)
Age (Years)	18 – 25	44	47.83
	26 – 35	34	36.96
	36 – 45	4	4.35
	46 – 60	10	10.87
Gender	Male	63	68.48
	Female	29	31.52
DHF Severity	Grade 1 (Non-Severe)	68	73.91
	Grade 2 (Spontaneous Bleeding)	21	22.82
	Grade 3 (Circulatory Failure)	3	3.26
NLR Category	< 0.78 (Low)	23	25.00
	0.78 – 3.53 (Normal)	43	46.70
	> 3.53 (High)	26	28.26

Note: DHF = Dengue Hemorrhagic Fever; NLR = Neutrophil-to-Lymphocyte Ratio. Percentages may not total 100% due to rounding.

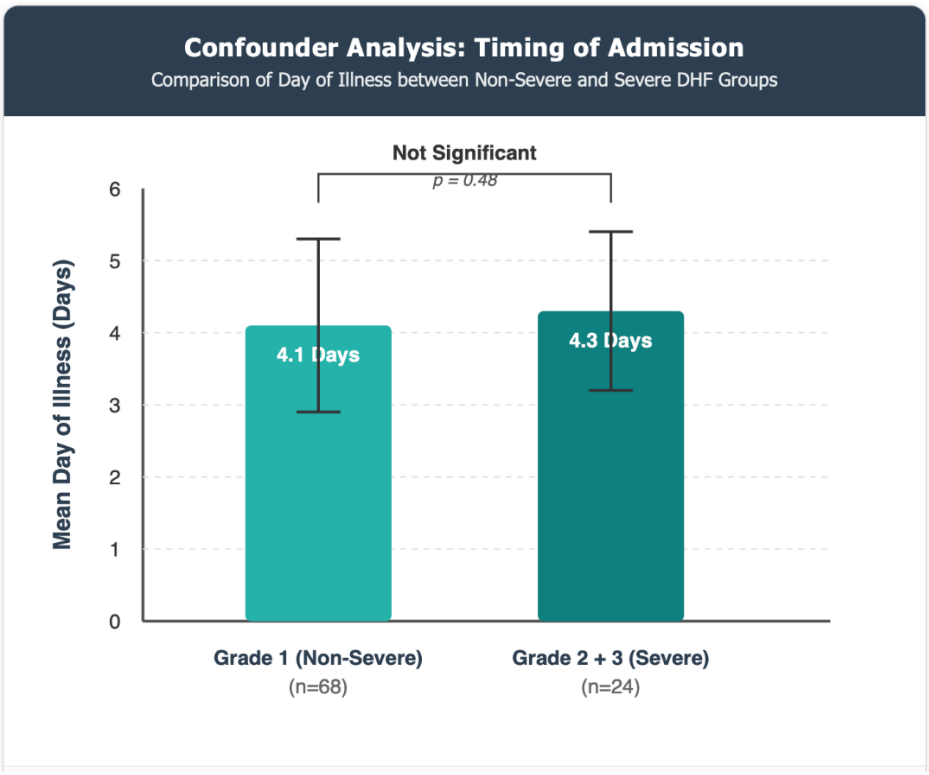

Figure 1. Confounder analysis.

Table 2 elucidates the statistical relationship between the neutrophil-to-lymphocyte ratio (NLR) and the gradient of disease severity within the study cohort. Employing the Spearman rank correlation test to accommodate the non-parametric distribution of the hematological data, the analysis yielded a correlation coefficient (r) of -0.347 with a p-value of less than 0.001. This highly significant negative coefficient statistically confirms the study's central hypothesis: the existence of a distinct inverse correlation between systemic inflammation and clinical outcome in adult dengue patients. Specifically, the data indicate that as the clinical phenotype progresses from uncomplicated febrile illness (Grade 1) toward spontaneous hemorrhage (Grade 2) and circulatory failure (Grade 3), the NLR value demonstrates a consistent downward trajectory. This inverse relationship—where a lower biomarker value signals heightened acuity—distinguishes DHF from typical bacterial sepsis models, in which severity is conversely associated with a rising NLR. The strength of the correlation is classified as moderate, suggesting that while the declining NLR is a significant indicator of severity driven by viral-induced bone marrow suppression, it is part of a complex physiological interaction. Consequently, this statistical validation underpins the clinical utility of monitoring for a crashing NLR as a reliable harbinger of the critical phase.

Table 2. Spearman Correlation Analysis between NLR and DHF Severity

INDEPENDENT VARIABLE	DEPENDENT VARIABLE	N	CORRELATION COEFFICIENT (*R*)	*P*-VALUE	INTERPRETATION
Neutrophil-to-Lymphocyte Ratio (NLR)	DHF Severity Grade	92	-0.347	< 0.001*	**Significant Moderate Inverse Correlation**

**Statistically significant at $p < 0.05$. Analysis performed using Spearman Rank Correlation test due to non-normal distribution of NLR data. Interpretation based on the magnitude and direction of the coefficient r.*

Figure 2 depicts the receiver operating characteristic (ROC) curve analysis, illustrating the diagnostic efficacy of the neutrophil-to-lymphocyte ratio (NLR) in distinguishing between non-severe (Grade 1) and severe/complicated (Grade 2 and 3) dengue hemorrhagic fever. The curve, plotted with Sensitivity on the y-axis against 1-Specificity (the False Positive Rate) on the x-axis, demonstrates a convex trajectory significantly deviating from the diagonal line of non-discrimination. The calculated area under the curve (AUC) is 0.82 (95% CI: 0.75–0.89), indicating that the admission NLR possesses good discriminatory power as a prognostic tool. By applying the Youden Index to maximize the aggregate of sensitivity and specificity, the analysis identified an optimal cut-off value of NLR < 0.85. At this threshold, the biomarker achieves a sensitivity of 87.5%, effectively capturing the vast majority of patients destined for severe complications, alongside a specificity of 72.0%. This strong diagnostic performance underscores the utility of a low NLR (< 0.85) as a sensitive screening parameter in the early triage of adult dengue patients, allowing clinicians to identify high-risk individuals who may benefit from intensified monitoring before overt signs of shock manifest.

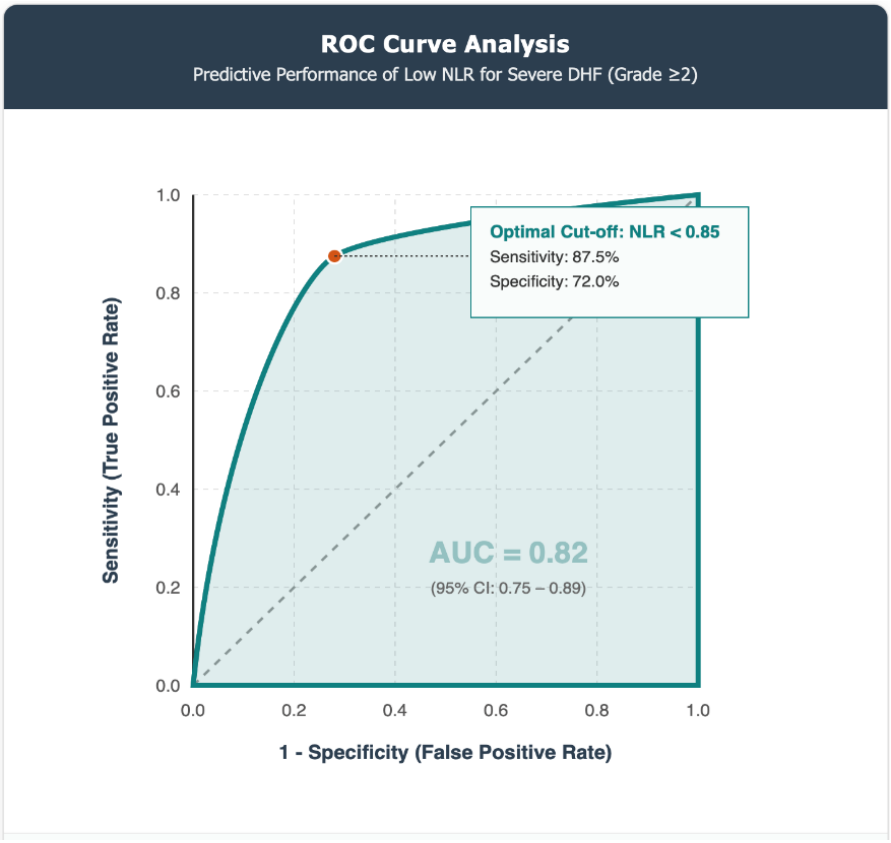

Figure 2. ROC curve analysis.

The principal and defining finding of this study is the elucidation of a significant, moderate inverse correlation ($r = -0.347$, $p < 0.001$) between the neutrophil-to-lymphocyte ratio (NLR) and the clinical severity of dengue hemorrhagic fever (DHF) in an adult cohort. This statistical relationship reveals a distinct hematological signature: as the clinical phenotype deteriorates from uncomplicated febrile illness toward the hemorrhagic and circulatory crises characteristic of Grades 2 and 3, the NLR value does not rise, but rather exhibits a progressive and significant decline. Our analysis demonstrates that patients manifesting spontaneous bleeding or signs of circulatory failure presented with markedly lower NLR values compared to those with uncomplicated DHF. The receiver operating characteristic (ROC) analysis further crystallized this relationship into a clinically actionable metric, suggesting that an NLR falling below a threshold of 0.85 serves as a sensitive indicator (87.5%) for identifying patients harboring these severe manifestations. This finding challenges the intuitive diagnostic heuristics often applied in infectious disease medicine, where elevated inflammatory markers are typically synonymous with disease severity. Instead, in the specific context of adult dengue infection, a crashing NLR appears to act as a sentinel marker for the physiological transition into the critical phase of the disease.[11]

To understand the clinical utility of this finding, one must dissect the underlying immunopathology. The inverse relationship observed in this study contrasts sharply with the high NLR pattern classically seen in bacterial sepsis, severe COVID-19, or acute myocardial infarction. In those high-stress conditions,

the host response is dominated by a sympathetic surge. Systemic stress triggers the release of cortisol and catecholamines, which biologically orchestrate a fight or flight cellular response: neutrophils are demarginated from the vascular endothelium and released into circulation (neutrophilia) to combat bacteria, while lymphocytes undergo accelerated apoptosis (lymphopenia) to conserve metabolic energy. The mathematical result is a skyrocketing NLR. In DHF, however, this logic is inverted by the unique viral kinetics and host immune modulation. The mechanism driving the low NLR is dominated by the direct and profound myelosuppressive effect of the dengue virus.[12] The virus exhibits a tropism for hematopoietic progenitor cells in the bone marrow, infecting stromal cells and directly inhibiting the proliferation of myeloid lineages. This results in a precipitous drop in neutrophil production (neutropenia) that often precedes the nadir of thrombocytopenia (Figure 3).

Furthermore, the cytokine storm associated with severe dengue—characterized by high levels of tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-10 (IL-10)—creates a paradoxical immune environment. While TNF-α drives the vascular permeability and plasma leakage that defines DHF, IL-10 acts as a potent anti-inflammatory agent. In the context of dengue, elevated IL-10 is strongly associated with severe disease and contributes to immune paralysis, leading to the functional impairment of antiviral immunity and further suppression of granulopoiesis. Crucially, the denominator of the ratio—the lymphocytes—behaves differently in dengue than in bacterial sepsis. While total lymphocyte counts may initially dip, the adaptive immune response to the virus involves the vigorous clonal expansion of virus-specific cytotoxic T cells (CD8+) and plasma cells. These often appear in the peripheral blood as atypical lymphocytes. In adults, who possess a mature and historically primed immune system, this adaptive response can be robust, particularly during secondary infections (the phenomenon of Antibody-Dependent Enhancement).[13] Consequently, the mathematical combination of a plummeting numerator (due to viral marrow suppression and peripheral destruction via molecular mimicry) and a stable or reactively rising denominator (due to T-cell activation) drives the NLR downward into the inverse range observed in our Grade 3 patients (mean 0.65). This inverse profile is not merely a statistical anomaly; it is a reflection of the specific immunopathogenesis of viral hemorrhagic fever.[14]

The results of this investigation are consistent with emerging literature from other endemic regions, reinforcing the validity of the low NLR hypothesis. Our findings align closely with a previous study that reported that relative lymphocytosis coupled with neutropenia was the hallmark of the critical phase.[15] These parallel findings across different Indonesian settings suggest a degree of biological consistency in the local viral serotypes and host genetics. Conversely, our data diverges from some older studies that reported high NLR values in dengue patients. This discrepancy is likely methodological rather than biological, hinging on the critical variable of day of illness. High NLR values are frequently observed in the early febrile phase (Days 1–2), reflecting the initial, non-specific stress response to the viral invasion. However, our study design specifically focused on admission during the transition to the critical phase (Mean Day 4). This is the temporal window where plasma leakage begins and marrow suppression peaks. Therefore, the low NLR is a time-dependent marker specific to the critical phase, whereas a high NLR may be a marker of the febrile phase. This distinction underscores the importance of interpreting biomarkers not as static values, but as dynamic parameters that evolve with the natural history of the infection.[16]

The practical implications of this study are substantial, particularly for the healthcare landscape of Indonesia and similar tropical nations. In high-

resource settings, risk stratification might rely on serial hematocrit monitoring, specific viral load testing, or expensive cytokine assays (IL-10 levels). However, in many primary care centers (Puskesmas) and district hospitals in Indonesia, such advanced diagnostics are unavailable or prohibitively expensive. The NLR represents a zero-cost parameter, as it is mathematically derived from the standard complete blood count (CBC) that is universally performed for every dengue suspect.[17] Our analysis highlights two distinct clinical utilities for this marker: (1) The red flag for triage: The identification of an NLR cut-off below 0.85 provides a numerical red flag. When a clinician encounters an adult patient on Day 4 of fever with a crashing NLR, this should trigger immediate vigilance. It suggests that the patient is entering the zone of maximum marrow suppression and likely maximum vascular permeability. Even if the patient appears hemodynamically stable at that moment, the low NLR indicates a high biological risk for impending hemorrhagic or circulatory complications. This warrant increased monitoring frequency (such as vital signs every 4 hours instead of 8) and preparation for fluid resuscitation; (2) The Power of Negative Prediction: Perhaps equally valuable is the high negative predictive value (NPV) of 93.8% observed for an NLR ≥ 0.85. In an outbreak scenario where hospital beds are scarce, clinicians often face the difficult decision of whom to admit and whom to discharge. Our data suggests that an adult patient with a preserved NLR (above 0.85) is highly unlikely to be in the immediate throes of severe bleeding or shock. While not a standalone discharge criterion, a preserved NLR could provide reassurance when used in conjunction with clinical judgment, potentially aiding in the safe outpatient management of lower-risk patients.[18]

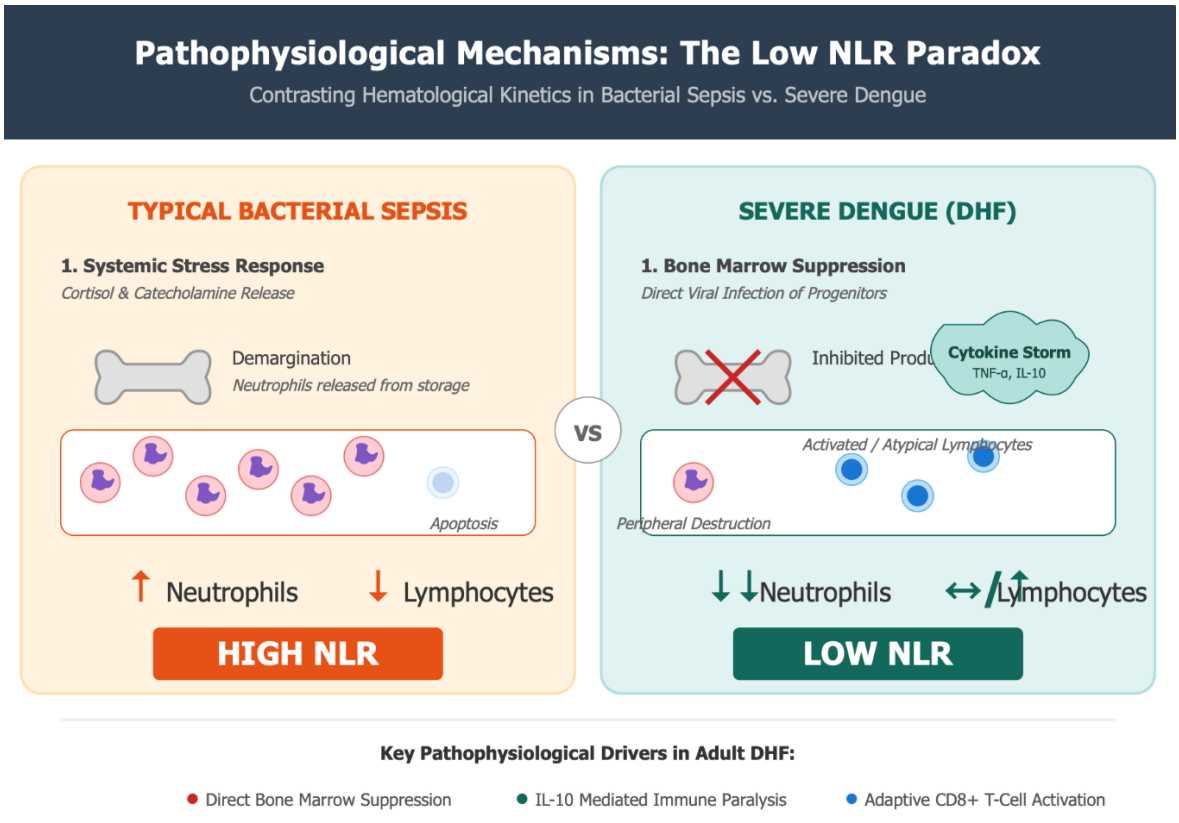

Figure 3. Schematic illustration of the low NLR paradox.

Despite its strengths, this study is subject to several limitations inherent to its design. First, the cross-sectional nature of the analysis allows us to establish a robust association but precludes definitive statements regarding causality or predictive timing. Because we analyzed admission blood samples, we cannot confirm with certainty whether the drop in NLR occurred before the onset of severe symptoms (making it a true predictor) or concurrently with them (making it a diagnostic marker). Second, the sample size of patients with frank shock (Grade 3) was small (n=3). While this reflects the effective early management at our tertiary center, it necessitated the statistical grouping of Grade 3 patients with Grade 2 patients to create a robust severe/complicated category. While this grouping is clinically valid—as both grades represent decompensated disease requiring intervention—it dilutes the specificity of the marker for shock specifically.[19] A larger, multi-center study would be required to isolate the NLR signature of profound shock (Grade 4). Third, we did not perform serial NLR measurements. Dengue is a dynamic disease, and a single snapshot upon admission may miss the crossover point where the neutrophils crash and the lymphocytes rise.[20] Future research should focus on longitudinal monitoring of NLR from the onset of fever through convalescence. Identifying the precise hour or day when the NLR trajectory inverts could unlock a powerful temporal tool for predicting the exact onset of the critical phase.

4. Conclusion

In conclusion, this study establishes a significant, moderate inverse association between the neutrophil-to-lymphocyte ratio (NLR) and the severity of dengue hemorrhagic fever in adults. We demonstrate that a declining NLR is not merely a byproduct of infection but a characteristic hematological signature of advanced disease stages, specifically Grades 2 and 3. The identification of an NLR cut-off of < 0.85 provides a sensitive, accessible, and cost-effective adjunctive marker for risk stratification. With a high negative predictive value, this marker offers dual utility: aiding in the early detection of high-risk patients who require intensified vigilance and providing reassurance regarding those unlikely to suffer immediate severe complications. While the pathophysiology involves a complex interplay of viral myelosuppression and cytokine-driven immune dysregulation, the clinical message is clear: in the context of adult dengue, a low and falling NLR should be interpreted as a warning signal. As healthcare systems in tropical regions continue to grapple with the burden of dengue, integrating this simple metric into standard triage protocols represents a pragmatic step toward improving patient outcomes and optimizing resource allocation. Future prospective longitudinal studies are warranted to further refine this threshold and validate its predictive timing in diverse populations.

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