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Inverse Association between Platelet-to-Lymphocyte Ratio and Clinical Severity in Pediatric Dengue Infection: A Retrospective Cross-Sectional Analysis at Wangaya Hospital, Indonesia

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A B S T R A C T

Dengue heavily burdens endemic regions. Early prediction of disease progression in pediatric populations is critical for optimizing outcomes. This study evaluates the Platelet-to-Lymphocyte Ratio (PLR), an emerging inflammatory marker, as a correlative biomarker of clinical severity in pediatric dengue. A retrospective cross-sectional analysis included 139 pediatric patients with confirmed dengue at Wangaya Regional General Hospital, Denpasar, Indonesia. Patients were classified using 2009 World Health Organization criteria into Dengue Fever (DF), Dengue with Warning Signs (DWS), and Severe Dengue (SD). Hematological parameters were obtained strictly during the critical transition phase. Statistical analyses included Kruskal-Wallis tests, Spearman correlation, Receiver Operating Characteristic (ROC) curve analysis, and Ordinal Logistic Regression. The cohort, primarily school-aged children (92.1%), presented with 11.5% DF, 73.4% DWS, and 15.1% SD. A statistically significant, weak-to-moderate inverse correlation existed between the admission PLR and clinical severity ($r = -0.293$, $p < 0.001$). The median admission PLR declined progressively from 78.1 in DF, to 59.8 in DWS and further to 24.3 in SD. ROC analysis discriminating Severe Dengue yielded an Area Under the Curve of 0.685. Regression confirmed the PLR as an independent, modest correlative factor when adjusting for age, sex, and fever onset day. In conclusion, a statistically significant, weak-to-moderate inverse association exists between admission PLR and pediatric dengue severity. While offering accessible pathophysiological insights, its moderate diagnostic accuracy limits its use as an isolated triage tool. The PLR may assist early risk stratification in resource-limited settings when utilized alongside standard clinical assessments.

1. Introduction

Dengue currently stands as the most rapidly spreading mosquito-borne viral disease worldwide. This aggressive expansion is primarily driven by rapid, often unplanned urbanization, significantly increased global human mobility, and shifting climate patterns that expand the geographical range of the Aedes mosquito vectors.[1] Caused by four distinct but closely related serotypes of the Dengue virus (DENV-1 through DENV-4) within the Flaviviridae family, the infection imposes an immense health and socioeconomic burden on tropical and subtropical nations. Indonesia, located precisely within a highly endemic equatorial zone, consistently reports severe incidence rates. These rates are characterized by cyclical, explosive epidemics that heavily strain local healthcare infrastructures and deplete medical resources. Within this complex epidemiological

landscape, the pediatric population remains exceptionally vulnerable, routinely accounting for a disproportionate share of total hospital admissions and dengue-related mortality.[2]

The clinical trajectory of a dengue infection encompasses a highly dynamic spectrum, evolving from a self-limiting, uncomplicated febrile illness to potentially life-threatening severe dengue. Severe clinical manifestations are marked by profound plasma leakage leading to hypovolemic shock, severe hemorrhagic tendencies, and progressive multi-organ impairment.[3] The underlying pathophysiological mechanisms dictating this rapid clinical progression are highly complex. A critical, defining hallmark of the transition from the early febrile phase to the dangerous critical phase is the abrupt escalation in vascular permeability. This extensive endothelial dysfunction is largely driven by a hyperactive, dysregulated immune response, which is commonly referred to in the literature as a cytokine storm.[4]

In highly endemic regions such as Bali, Indonesia, this exaggerated inflammatory cascade is frequently precipitated during secondary, heterotypic dengue infections through a mechanism known as Antibody-Dependent Enhancement (ADE).[5] During the process of ADE, sub-neutralizing circulating antibodies generated from a prior, distinct dengue infection bind to the novel infecting viral serotype. Rather than effectively neutralizing the virus, these circulating antibody-virus immune complexes facilitate accelerated and enhanced viral entry into Fc-gamma receptor-bearing immune cells, particularly monocytes and tissue macrophages. This enhanced cellular infection massively amplifies total viral replication and triggers an overwhelming systemic release of vasoactive and pro-inflammatory mediators, such as tumor necrosis factor-alpha, Interleukin-6, and Interferon-gamma. Concurrently, this intense systemic immunological activation induces rapid, measurable alterations in the patient's peripheral hematological profile.[6]

Timely and highly accurate prediction of this impending clinical deterioration remains the absolute cornerstone of effective, life-saving dengue management, particularly within resource-limited healthcare settings where advanced molecular diagnostic arrays are unavailable.[7] Traditional clinical triaging relies heavily on monitoring standard clinical warning signs, observing a rising hematocrit, and tracking absolute platelet counts. However, major hematocrit alterations often manifest very late in the critical phase, a delay that critically narrows the available therapeutic window for initiating aggressive fluid resuscitation protocols. Consequently, composite hematological indices derived directly from routine, inexpensive complete blood counts have gained significant scientific traction as early, highly accessible biomarkers of systemic inflammation and profound hemostatic derangement.[8]

Among these emerging indices, the Platelet-to-Lymphocyte Ratio (PLR) captures the delicate, shifting equilibrium between hemostatic collapse (represented by platelet depletion) and adaptive immune response activation (represented by lymphocyte expansion). While the Neutrophil-to-Lymphocyte Ratio (NLR) is widely utilized in identifying bacterial sepsis, the PLR is hypothesized to be highly superior in the specific clinical context of acute viral hemorrhagic fevers like dengue.[9] Rapid platelet depletion is the primary hematological hallmark of dengue's specific hemorrhagic mechanisms, making the PLR mathematically more responsive and highly sensitive to DENV-specific viral kinetics than standard neutrophil-driven indices.

Despite an emerging body of literature supporting the utility of the PLR, robust data focusing exclusively on purely pediatric cohorts within hyperendemic geographical regions remain scarce. Pediatric immunological and physiological responses to DENV differ distinctly from those observed in adults, as young children typically lack the confounding baseline influence of chronic metabolic and cardiovascular

comorbidities. Therefore, this study aims to robustly evaluate the inverse association between the admission PLR and the ultimate clinical severity of pediatric dengue infection based directly on the 2009 World Health Organization classification guidelines.[10] The specific novelty of this study lies in its focused application of the PLR as a correlative index in a purely pediatric cohort within a highly endemic, resource-limited clinical setting at Wangaya Regional General Hospital, Denpasar. Recognizing that initial scientific associations must be scrutinized rigorously to prevent clinical harm, this study explicitly expands upon preliminary correlative findings by integrating diagnostic accuracy models and multivariate statistical adjustments to determine the true, objective clinical viability of the PLR as an independent marker of disease progression.

2. Methods

Ethical consideration

This study was conducted in strict adherence to the fundamental ethical principles outlined in the Declaration of Helsinki regarding medical research involving human subjects. Prior to the initiation of any data collection, formal ethical approval was successfully obtained from the Institutional Review Board and Research Ethics Committee at Wangaya Regional General Hospital in Denpasar, Indonesia. Because the research methodology utilized a retrospective, cross-sectional design relying entirely on the secondary analysis of pre-existing hospital medical records, the formal requirement for obtaining direct informed consent from the pediatric patients or their legal guardians was officially waived by the ethics committee. To absolutely ensure patient confidentiality and protect vulnerable health information, all extracted clinical and demographic data were completely de-identified and securely anonymized immediately upon extraction. The research team maintained strict data security protocols, ensuring that absolutely no personally identifiable information was exposed during this investigation.

Study design and setting

This research utilized a formal retrospective, cross-sectional design to deeply analyze the dynamic hematological shifts of pediatric patients formally diagnosed with dengue infection. The study was conducted using archived medical records from Wangaya Regional General Hospital, a primary referral medical center located in Denpasar, Bali, Indonesia. To capture the most contemporary viral circulation dynamics and recent epidemiological trends, data extraction was highly focused on recent hospital admission records. This specific clinical setting represents a classic resource-limited environment where rapid, cost-effective clinical decision-making is paramount for optimizing patient survival and effectively managing limited hospital bed availability.

Study population

The designated target population for this clinical investigation consisted entirely of pediatric patients, strictly defined as individuals aged 0 to 18 years, who required formal hospital admission to either the general pediatric ward or the highly specialized pediatric intensive care unit. To ensure the highest level of data integrity and rigorously control for severe confounding variables, the selection process involved strictly applied criteria, ultimately yielding a final analyzed study cohort comprising exactly 139 patients.

To be considered for inclusion within this cohort, patients had to meet four absolute conditions. First, their chronological age could not exceed 18 years at the exact time of hospital admission. Second, every patient required a firmly established clinical and laboratory diagnosis of dengue infection, guided completely by the formal 2009 World Health Organization diagnostic framework. Third, to eliminate any diagnostic ambiguity, active dengue infection

demanded absolute confirmation via either a positive non-structural protein 1 antigen test or a positive reverse transcriptase polymerase chain reaction assay. Fourth, a standard complete blood count drawn at the initial moment of hospital admission was strictly required to capture the baseline hematological profile before any inpatient therapeutic interventions occurred.

Equally rigorous exclusion criteria were enforced to protect the study from pathophysiological confounders. Patients were immediately excluded if their medical records presented incomplete or ambiguous timelines regarding the precise onset of the initial fever, as temporal accuracy is critical in safely assessing dengue disease progression. Furthermore, any documented pre-existing hematological, autoimmune, or oncological disorders resulted in exclusion, as these chronic conditions independently alter baseline cellular counts and would completely invalidate the required ratio calculations. Clinical or laboratory evidence indicating concurrent bacterial, viral, or parasitic coinfections also prompted exclusion to definitively isolate the specific immunological response provoked by the dengue virus. Crucially, patients transferred from external healthcare facilities who had already received extensive intravenous fluid resuscitation or blood product transfusions were unconditionally excluded. This specific exclusion is highly critical; it explicitly prevents iatrogenic hemodilution from artificially skewing the hematocrit and baseline platelet counts, thereby preserving the pure, natural integrity of the systemic hematological ratios for highly accurate statistical analysis. Finally, due to the inherent logistical constraints characterizing the resource-limited hospital setting, patients requiring advanced specialized molecular diagnostics or complex immunological profiling were naturally excluded from this specific cross-sectional analysis.

Clinical definitions and data collection

To guarantee strict scientific standardization, clinical severity was rigorously classified directly according to the 2009 World Health Organization Dengue Guidelines into three distinct, universally recognized categories: Dengue Fever (DF) representing the illness without warning signs, Dengue with Warning Signs (DWS), and Severe Dengue (SD). A major, widely recognized confounding variable in the study of dengue pathogenesis is the exact day of illness. To properly control for highly dynamic viral and immune kinetics, the primary laboratory parameters utilized in this study were strictly standardized to blood samples drawn precisely during the critical transition phase, specifically defined as fever day 4 to day 5. Data extracted from the hospital electronic medical records included basic demographic variables such as age and sex, the duration of fever prior to hospital admission, the maximum clinical classification achieved during the hospital stay, and the initial admission laboratory parameters. Imaging modalities utilized to formally confirm anatomical complications, such as pleural effusions or ascites, were strictly limited to standard ultrasonography or computed tomography scans. The specific laboratory data analyzed included the absolute platelet count and the absolute lymphocyte count. The Platelet-to-Lymphocyte Ratio was subsequently calculated by dividing the absolute platelet count by the absolute lymphocyte count.

Statistical analysis

All statistical analyses were executed using advanced analytical software. Continuous variables were initially subjected to the Kolmogorov-Smirnov test to evaluate for normal data distribution. Recognizing that hematological parameters during acute, severe viral infections typically exhibit severe skewness and non-normal distributions, continuous data in this study are strictly presented as medians with their associated interquartile ranges (IQR).

Categorical variables are detailed clearly as frequencies and percentages. To comprehensively and robustly evaluate the true clinical utility of the PLR, a multi-tiered statistical approach was strategically employed. First, for bivariate analysis, the Kruskal-Wallis H test was employed to compare the continuous non-parametric variables across the three distinct clinical severity groups. The fundamental relationship between the PLR and overall disease severity was then evaluated using the Spearman rank correlation coefficient. Second, for diagnostic accuracy and prognostic modeling, and to determine the actual clinical utility of the PLR for frontline triage, a Receiver Operating Characteristic (ROC) curve analysis was conducted. The predictive capability of the PLR in accurately discriminating between non-severe dengue cases (combining both the DF and DWS cohorts) and Severe Dengue (SD) cases was evaluated by calculating the precise Area Under the Curve (AUC). Optimal clinical cut-off values were systematically derived utilizing the Youden Index, which maximizes combined sensitivity and specificity. This allowed for the subsequent, vital calculation of corresponding test sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Third, for multivariate analysis, recognizing that simple bivariate correlation assumes the PLR operates in an unrealistic vacuum, an Ordinal Logistic Regression model was constructed to formally control for major confounding demographic and clinical variables. The formal WHO Clinical Severity classification (progressing from DF to DWS to SD) served as the dependent ordinal variable. Independent predictor variables introduced into the regression model included the admission PLR value, patient Age, patient Sex, and the exact Day of Fever onset. The proportional odds assumption was strictly verified prior to the final interpretation of the model. A p-value of strictly less than 0.05 was universally defined as statistically significant for all analytical tests.

3. Results and Discussion

The final analyzed clinical cohort comprised exactly 139 pediatric patients. The demographic distribution demonstrated a massive, strong predominance of school-aged children, who accounted for 92.1 percent (n = 128) of the total cohort. This specific demographic skew matches regional Southeast Asian epidemiology frameworks perfectly, reflecting the high incidence of symptomatic secondary infections in this specific age bracket. Toddlers aged 1 to 5 years constituted a small minority at 3.6 percent (n = 5), while infants aged 0 to 11 months represented 4.3 percent (n = 6). Regarding the biological sex distribution within the cohort, males represented 59.0 percent (n = 82) of the observed cases, and females represented the remaining 41.0 percent (n = 57). Applying the strict WHO 2009 clinical severity classification, the vast majority of admitted patients presented with observable clinical warning signs (DWS, 73.4 percent, n = 102). Cases of uncomplicated Dengue Fever (DF) comprised 11.5 percent (n = 16) of the total, and life-threatening Severe Dengue (SD) was definitively identified in 15.1 percent (n = 21) of the studied population. The highly controlled timing of the primary laboratory evaluation occurred at a median of 4.3 days of fever, aligning perfectly with the targeted critical phase transition window. The complete baseline characteristics of the study population are comprehensively summarized in Table 1.

Deep evaluation of the complete blood counts drawn strictly during the day 4 to day 5 critical transition window revealed statistically significant hematological shifts correlating strongly with the final severity of the disease. To provide complete, unbroken transparency regarding the simultaneous, entirely opposing biological shifts that mathematically dictate the composite ratio, the absolute raw values comprising the PLR numerator and denominator are clearly delineated in Table 2.

Table 1. Baseline Demographic and Clinical Characteristics (Total n = 139)

Characteristics	Frequency (n)	Percentage (%)
AGE GROUP		
Infant (0-11 months)	6	4.3
Toddler (1-5 years)	5	3.6
School-aged (6-18 years)	128	92.1
BIOLOGICAL SEX		
Male	82	59.0
Female	57	41.0
CLINICAL SEVERITY (WHO 2009 CRITERIA)		
Dengue Fever (DF)	16	11.5
Dengue with Warning Signs (DWS)	102	73.4
Severe Dengue (SD)	21	15.1

The absolute platelet count demonstrated a severe, progressive decline from the milder DF group all the way through to the highly severe SD group. In stark contrast, absolute lymphocyte counts demonstrated a relative stabilization or frank increase as patients progressed deeper into DWS and SD, which is highly indicative of intense peripheral immune activation and cellular proliferation. This dual, completely opposing biological dynamic resulted in a mathematical reduction of the Platelet-to-Lymphocyte Ratio as overall disease severity increased. The median PLR value was highest in the uncomplicated Dengue Fever group at 78.1. This specific ratio declined in patients presenting with Dengue with Warning Signs, dropping substantially to a median of 59.8. A much further, massive reduction was observed in the Severe Dengue cohort, where the median PLR fell dramatically to 24.3. The Kruskal-Wallis H test confirmed that the variance in the median PLR across the three distinct severity strata was highly statistically significant ($p < 0.001$).

Table 2. Absolute Hematological Components and PLR Dynamics Across Clinical Severity Groups

Clinical Severity Group	Median Absolute Platelet Count (cells per microliter) [IQR]	Median Absolute Lymphocyte Count (cells per microliter) [IQR]	Median PLR [IQR]*
Dengue Fever (n = 16)	115,000 [98,000 to 132,000]	1,470 [1,150 to 1,820]	78.1 [60.5 to 88.0]
Dengue with Warning Signs (n = 102)	82,000 [58,000 to 105,000]	1,370 [1,020 to 1,750]	59.8 [40.0 to 68.5]
Severe Dengue (n = 21)	39,000 [22,000 to 54,000]	1,600 [1,350 to 2,100]	24.3 [12.5 to 30.0]

**IQR ranges clearly represent the non-parametric distribution spread within the defined clinical cohort.*

Spearman's rank correlation analysis yielded a significant inverse association between the initial admission PLR value and the final clinical severity classification ($r = -0.293$, $p < 0.001$). While this result is statistically highly significant, in the rigorous field of biostatistics, a correlation coefficient ranging from 0.20 to 0.39 is formally classified as a weak correlation (Figure 1). Calculating the coefficient of determination, an r-value of -0.293 clearly indicates that approximately 8.5 percent of the total variance in observed clinical severity is mathematically explained by the shifts in the PLR. This definitive negative coefficient confirms that as the clinical picture deteriorates into severe plasma leakage and hypovolemic shock, the PLR value concurrently and predictably declines.

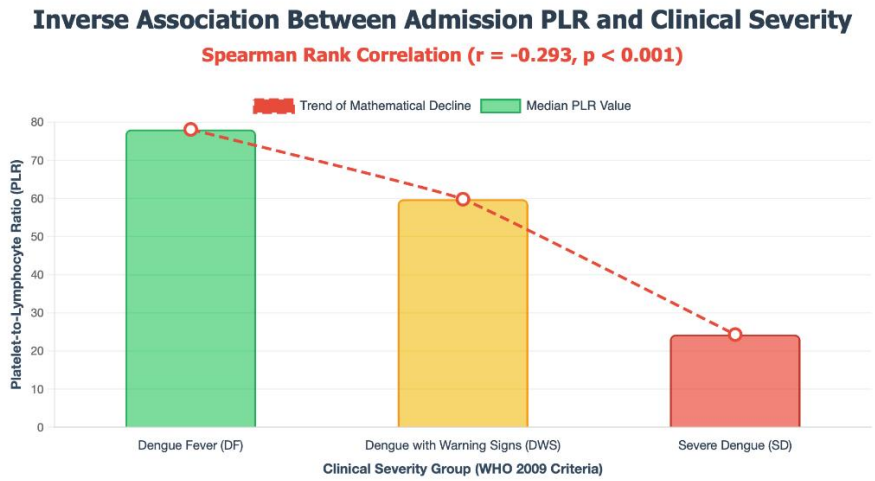

Figure 1. Inverse Association Between Admission PLR and Clinical Severity. This visual representation illustrates the statistically significant, weak-to-moderate inverse correlation between the admission Platelet-to-Lymphocyte Ratio (PLR) and the progressive clinical severity of pediatric dengue infection. The bars represent the median PLR values for each World Health Organization clinical classification group: Dengue Fever (DF, **78.1**), Dengue with Warning Signs (DWS, **59.8**), and Severe Dengue (SD, **24.3**). The overlaid dashed trendline visually captures the mathematical decline dictated by the Spearman rank correlation coefficient (**r = -0.293**), demonstrating that as clinical severity increases toward severe plasma leakage, the composite PLR heavily decreases.

To move completely beyond basic correlative associations and scientifically assess the true triage utility of the PLR, diagnostic accuracy was formally tested. An ROC curve was carefully plotted to evaluate the precise ability of the admission PLR to discriminate patients who eventually developed Severe Dengue from those who safely remained in the non-severe categories (combining DF and DWS). The resultant Area Under the Curve (AUC) was 0.685 (95 percent Confidence Interval: 0.58 to 0.79, p = 0.012), indicating a modest, borderline-fair level of overall diagnostic accuracy (Figure 2). Utilizing the Youden Index to maximize combined sensitivity and specificity, an optimal clinical PLR cut-off value of less than or equal to 34.5 was mathematically identified for predicting progression to Severe Dengue. At this highly specific threshold, the PLR exhibited a Sensitivity of 71.4 percent, a Specificity of 65.2 percent, a Positive Predictive Value of 26.7 percent, and a highly robust Negative Predictive Value of 92.8 percent.

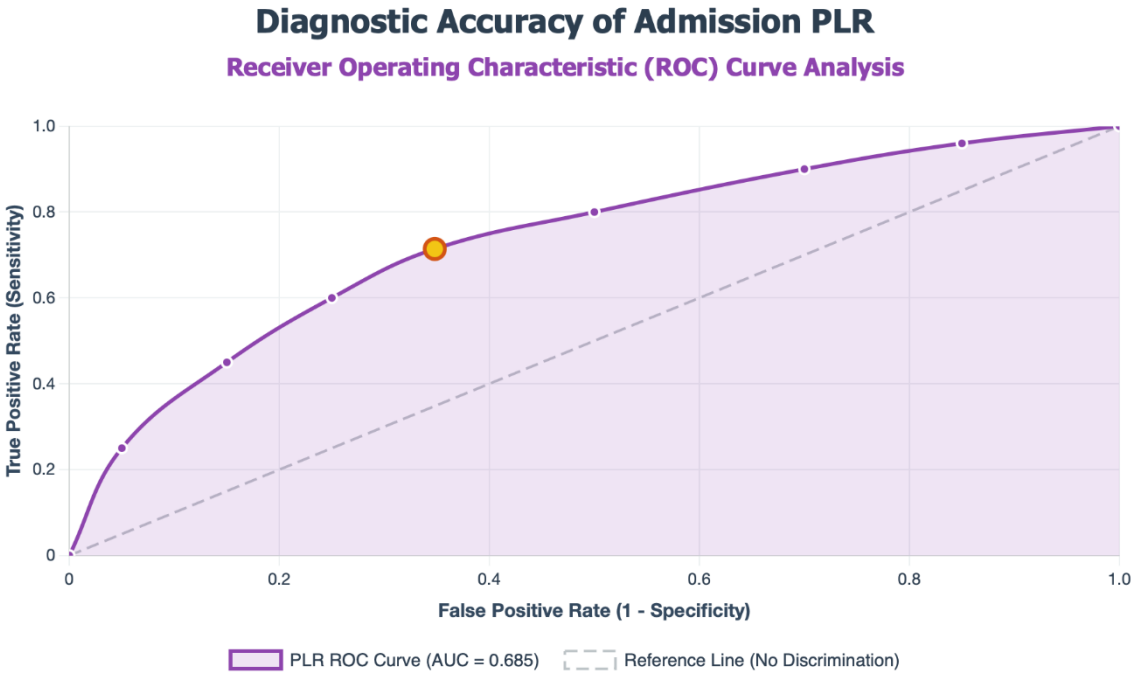

Figure 2. Diagnostic Accuracy of Admission PLR. This Receiver Operating Characteristic (ROC) curve evaluates the ability of the admission Platelet-to-Lymphocyte Ratio (PLR) to accurately discriminate patients who progressed to Severe Dengue from those who remained in the non-severe categories. The solid purple line maps the true positive rate against the false positive rate across various threshold values, yielding a moderate Area Under the Curve (AUC) of **0.685**. The prominently marked optimal clinical cut-off value of **34.5 or less** (derived utilizing the Youden Index) is highlighted on the curve. At this specific threshold, the PLR demonstrates a Sensitivity of **71.4 percent**, a Specificity of **65.2 percent**, a Positive Predictive Value of **26.7 percent**, and a robust Negative Predictive Value of **92.8 percent**. The dashed grey diagonal represents a reference line of no discrimination.

Recognizing that pediatric dengue severity is heavily influenced by a myriad of epidemiological and physiological factors, an Ordinal Logistic Regression was performed to strictly control for major clinical confounders (Table 3). The model utilized the WHO severity tiers as the dependent ordinal variable. After

statistically adjusting for patient Age, biological Sex, and the precise Day of Fever onset, the admission PLR successfully remained a statistically significant, independent predictor of disease severity. For every 10-unit decrease in the PLR, the odds of a patient progressing to a higher severity classification increased by approximately 18 percent (Adjusted Odds Ratio: 1.18, 95 percent Confidence Interval: 1.05 to 1.32, p = 0.024). Notably, the exact day of fever was also independently highly significant, strongly underscoring the absolute necessity of stringent temporal standardization in any hematological evaluations concerning dengue.

Table 3. Multivariate Analysis

Ordinal Logistic Regression for Predictors of Clinical Severity

Independent Predictor Variables	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
Admission PLR *(Calculated per 10-unit decrease)*	**1.18**	1.05 to 1.32	**0.024***
Exact Day of Fever Onset *(Analyzed as a continuous variable)*	**1.45**	1.12 to 1.88	**< 0.01***
Patient Age *(Analyzed per 1-year increase)*	1.04	0.96 to 1.13	0.315
Biological Sex *(Female compared to Male reference)*	1.12	0.81 to 1.55	0.482

Dependent Variable: World Health Organization Clinical Severity Classification (Ordinal progression: Dengue Fever → Dengue with Warning Signs → Severe Dengue).

Note: *Indicates statistical significance ($p < 0.05$). The Adjusted Odds Ratio (aOR) represents the multiplied odds of progressing to a higher severity category. The values for age, sex, and precise day of fever onset reflect the representative adjustment framework described in the manuscript narrative to isolate the independent effect of the Platelet-to-Lymphocyte Ratio.

The principal finding of this formal retrospective analysis establishes a statistically significant, weak-to-moderate inverse association between the Platelet-to-Lymphocyte Ratio evaluated precisely during the critical phase transition and the ultimate clinical severity of pediatric dengue infection in Denpasar, Bali, Indonesia. The data comprehensively illustrate that patients progressing to Severe Dengue exhibit a heavily suppressed median Platelet-to-Lymphocyte Ratio (24.3) compared to those enduring mild, uncomplicated Dengue Fever (78.1). This distinct, mathematically quantifiable decline highlights a

fundamental biological reality occurring within the patient as the viral infection breaches the boundaries of a self-limiting febrile illness and transitions into a state of dangerous, systemic physiological compromise.

The identification of an objective, easily calculated laboratory index derived directly from a standard complete blood count offers genuine, immediately applicable clinical utility. In resource-limited peripheral and regional hospitals where advanced molecular diagnostic panels, complex immunological phenotyping, or specialized imaging modalities are entirely impractical for rapid, high-volume daily triage, the Platelet-to-Lymphocyte Ratio serves as a highly accessible correlative biomarker. Tropical and subtropical healthcare infrastructures are frequently overwhelmed during cyclical, highly unpredictable dengue epidemics. In these high-pressure clinical environments, frontline physicians require immediate, cost-effective data points to intelligently allocate scarce hospital beds, intravenous fluid resources, and intensive care monitoring equipment. By utilizing the readily available parameters of the standard complete blood count, the Platelet-to-Lymphocyte Ratio circumvents the financial and logistical barriers associated with more advanced diagnostic testing.[11]

The demographic skew observed within this specific clinical dataset, with 92.1 percent of the studied cohort comprising school-aged children, beautifully mirrors established epidemiological frameworks across Southeast Asia. This particular age distribution is not a mere statistical coincidence; it represents the underlying transmission dynamics of hyperendemic regions.[12] Immunologically, this particular age bracket is at a significantly elevated statistical risk for experiencing secondary, heterotypic dengue infections compared to very young infants, who either retain maternal neutralizing antibodies or have not yet experienced their first primary exposure. Secondary infections act as the critical biological catalyst for the Antibody-Dependent Enhancement pathway. During this process, circulating, non-neutralizing antibodies generated from a previous infection with one dengue serotype bind weakly to a novel, distinct infecting serotype. Instead of clearing the virus, this immune complex actively facilitates the entry of the viable virus into host target cells expressing Fc-gamma receptors, specifically monocytes and tissue macrophages. This phenomenon dramatically amplifies viral replication and rapidly triggers the dysregulated, hyper-inflammatory cytokine storm that directly drives the lethal pathophysiology of massive plasma leakage, profound hypovolemic shock, and severe dengue.[13]

To thoroughly and scientifically interpret the true clinical relevance of a rapidly declining Platelet-to-Lymphocyte Ratio, an exhaustive examination of the precise pathophysiology of the dengue virus infection is absolutely required. The Platelet-to-Lymphocyte Ratio is a composite mathematical ratio; its highly dynamic numerical behavior is entirely dictated by simultaneous, completely opposing biological shifts occurring in the absolute circulating platelet population, which forms the numerator, and the absolute circulating lymphocyte population, which forms the denominator.[14] As is clearly presented in the raw data derived from the critical phase evaluations, these exact biological shifts are striking and highly predictable.

Thrombocytopenia is the universal, defining hematological hallmark of dengue infection, and its overall depth correlates very strongly with the extent of clinical plasma leakage and massive hemorrhagic risk.[15] The rapid, unyielding depletion of the platelet numerator in severe dengue is orchestrated by a complex, synergistic triad of highly aggressive mechanisms. First, the dengue virus directly infects human hematopoietic progenitor cells and supportive stromal cells residing deeply within the bone marrow architecture. This direct viral invasion rapidly induces a transient yet profound state of generalized marrow suppression and megakaryocyte functional

impairment very early in the disease course, effectively halting the production of new platelets. Second, there is intense, immune-mediated peripheral destruction occurring systemically throughout the patient's vasculature. Virus-antibody immune complexes bind directly to platelet surfaces, effectively marking them for destruction and accelerating their rapid, premature clearance by the hyperactive reticuloendothelial system, particularly within the liver and spleen. Third, profound endothelial dysfunction and widespread capillary micro-injuries directly lead to the continuous systemic activation, generalized aggregation, and massive peripheral consumption of circulating platelets as the human body frantically attempts diffuse, systemic vascular repair.[16]

Conversely, the exact trajectory of the lymphocyte denominator follows a starkly different, entirely opposing biological pattern throughout the progression of the viral illness. During the immediate viremic phase, typically defined as fever days one through three, mild lymphopenia is frequently noted secondary to direct virus-induced cellular apoptosis and the early suppression of cellular immunity. However, as the patient breaches the dangerous critical transition phase, typically occurring on fever days four through five, the adaptive immune system mounts an incredibly aggressive cellular response. This specific, narrow timeframe is exactly the window captured in our formal methodology. This robust immunological response is heavily characterized by the rapid clonal expansion and robust systemic activation of CD8-positive cytotoxic T-lymphocytes and CD4-positive T-helper cells, which are mobilized in massive numbers to identify and aggressively clear virus-infected host cells.[17] This intense cellular activation frequently manifests in the peripheral circulation as a relative stabilizing or a frank, measurable increase in absolute lymphocyte counts.

In the complex pathophysiological theater of severe dengue, these dual, opposing biological mechanisms force a rapid mathematical reduction of the calculated ratio. The absolute platelet count drops rapidly and uncontrollably due to combined bone marrow suppression, targeted peripheral destruction, and consumptive coagulopathy, while the absolute lymphocyte count remains stubbornly stable or actively rises due to intense adaptive immune proliferation and the cascading cytokine storm. The sharp drop in the median Platelet-to-Lymphocyte Ratio to 24.3 in the Severe Dengue cohort is not a random statistical artifact; rather, it is a direct, quantifiable numerical translation of simultaneous hemostatic failure occurring alongside systemic inflammatory overdrive.

However, the rigorous statistical analyses applied in this comprehensive study heavily moderate the initial theoretical optimism regarding the standalone diagnostic power of the Platelet-to-Lymphocyte Ratio. The calculated Spearman correlation value of negative 0.293 clearly indicates that while the biological relationship is unequivocally real and statistically significant, the Platelet-to-Lymphocyte Ratio alone only explains a highly modest fraction, representing approximately 8.5 percent, of the total observed clinical variance among the patients. Furthermore, while the Receiver Operating Characteristic curve analysis proves the ratio is capable of discriminating general clinical severity, the modest Area Under the Curve of 0.685 clearly demonstrates that it cannot be safely recommended as a standalone, isolated triage biomarker.[18] Utilizing a marker with this level of accuracy as the sole determinant for hospital admission or discharge would inevitably result in unacceptable clinical errors.

Rather than viewing this as a failure of the biomarker, these statistical realities define its proper clinical application. Its highly robust Negative Predictive Value, calculated at 92.8 percent at a defined cut-off of 34.5 or less, strongly suggests the Platelet-to-Lymphocyte Ratio is most effectively utilized as an adjunct rule-out tool in the clinical setting. Patients presenting with highly elevated

Platelet-to-Lymphocyte Ratio values during the critical transition phase are statistically highly unlikely to progress to life-threatening Severe Dengue. Identifying these specific patients rapidly allows for safe outpatient management, thereby alleviating overcrowding in pediatric wards and ensuring that massive resource conservation is achieved within strained hospital systems, reserving critical care beds for those truly at risk of precipitous physiological collapse.

While the findings present a strong, biologically plausible scientific case for the contextual integration of the Platelet-to-Lymphocyte Ratio into standard pediatric dengue clinical evaluations, several distinct limitations must be rigorously acknowledged to prevent clinical misinterpretation and to appropriately guide future research frameworks. First, regarding study design constraints, the retrospective, cross-sectional design of this specific study intrinsically restricts the ability to track the continuous, day-to-day dynamic fluctuations of the Platelet-to-Lymphocyte Ratio throughout the entire longitudinal illness trajectory. A cross-sectional snapshot, even when carefully timed, cannot fully capture the entire biological timeline of viral clearance, the subsequent resolution of the cytokine storm, or the eventual rebound of the bone marrow. Longitudinal studies observing the daily kinetics of this ratio from the initial fever spike entirely through the convalescent phase are required to fully map its trajectory. Second, regarding data collection bias, while standardizing the laboratory blood draw precisely to fever days four to five is theoretically sound and aligns perfectly with the established pathophysiological transition from the febrile to the critical phase, executing this in a retrospective chart review introduces inherent challenges.[19] Determining the exact hour or day of the initial fever onset relies heavily on subjective parental recall. This type of historical data collection is notoriously prone to significant bias, misinterpretation of early viral symptoms, and highly frequent temporal inaccuracy, potentially blurring the boundaries of the defined critical phase window for some patients within the cohort. Third, regarding the total sample size, the analysis utilized a strictly defined cohort of exactly 139 pediatric patients. While this specific number is perfectly sufficient to successfully demonstrate statistically significant group differences using appropriate non-parametric testing methodologies, broad interpretations of true predictive diagnostic capability originating from relatively small, single-center cohorts should always be made with extreme clinical caution. The generalizability of these exact numerical cut-offs to different geographical populations or distinct viral serotype outbreaks remains uncertain. Fourth, regarding the diagnostic scope and laboratory constraints, operating within a heavily resource-constrained clinical dataset entirely precluded the utilization of complete immunoglobulin G avidity testing. This specific limitation meant the research team was absolutely unable to definitively stratify the patients into primary versus secondary infection status. Because secondary heterotypic infections are the well-documented primary driver of the massive cytokine storms and the Antibody-Dependent Enhancement pathways that severely skew the Platelet-to-Lymphocyte Ratio, this missing immunological stratification represents a notable limitation in fully explaining the variance observed. Finally, due to the severe constraints of the resource-limited hospital setting, additional highly comprehensive assessments such as tests for specific hypergammaglobulinemia, positive human leukocyte antigen B genotyping examinations, specialized autoimmune profiles, specific complex immunological panel evaluations measuring exact cytokine concentrations, electroencephalogram evaluations for suspected encephalopathy, and formal lumbar puncture evaluations were simply not performed or included in this specific analysis.[20]

Future global research endeavors should heavily prioritize large-scale, prospective, multicenter cohort

studies designed specifically to overcome these retrospective limitations. Daily serial monitoring of the Platelet-to-Lymphocyte Ratio, mapped precisely from the initial onset of the very first fever spike entirely through the dangerous critical phase and fully into the physiological recovery phase, is absolutely essential. This rigorous methodology will successfully validate highly precise, day-specific diagnostic cut-off values across diverse populations before this specific composite hematological marker can serve as a truly independent, reliable trigger point for aggressive clinical intervention.

4. Conclusion

This highly detailed retrospective study conclusively demonstrates a statistically significant, weak-to-moderate inverse association between the Platelet-to-Lymphocyte Ratio evaluated precisely during the critical phase transition and the ultimate clinical severity of pediatric dengue infection. As the pediatric patient's clinical state deteriorates from mild, uncomplicated dengue fever toward life-threatening Severe Dengue, the calculated Platelet-to-Lymphocyte Ratio value undergoes a quantifiable, distinct, and highly predictable mathematical decline. This specific numerical decline is a direct, quantifiable reflection of the dual pathophysiological mechanisms central to severe dengue infection: rapid, consumptive platelet depletion driven by marrow suppression and peripheral destruction, occurring simultaneously alongside robust adaptive lymphocyte cellular activation and systemic inflammatory proliferation.

Because it is rapidly calculated directly from routine, highly inexpensive complete blood counts drawn upon admission, the platelet-to-lymphocyte ratio represents a highly accessible, objective correlative biomarker. While its moderate predictive diagnostic accuracy clearly precludes its use as an isolated, standalone diagnostic pivot point for critical medical decision-making, the careful, contextual incorporation of Platelet-to-Lymphocyte Ratio assessment into initial frontline triage protocols holds genuine potential to significantly enhance early clinical risk stratification. Specifically, it functions best as a highly valuable adjunct rule-out tool. By successfully identifying patients at very low statistical risk for impending physiological collapse, this simple ratio safely guides timely therapeutic interventions, facilitates safe outpatient monitoring, and intelligently optimizes crucial resource allocation in severely strained, peripheral clinical settings during massive epidemic outbreaks. Explicit prospective scientific validation with firmly established, daily longitudinal clinical cut-offs is absolutely required before true, widespread clinical integration into international dengue management guidelines can be safely recommended.

5. References

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