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PROGNOSTIC SIGNIFICANCE OF LYMPHOCYTE-TO-PLATELET RATIO IN PREDICTING SEVERITY AND CLINICAL OUTCOME IN DENGUE INFECTION

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Abstract

Dengue continues to be a pressing public-health concern in tropical areas, where early identification of patients at risk for dengue severity is critical for appropriate patient triage and resource management. A prospective observational cohort study was carried out at a Tertiary Care Hospital, Karachi among 180 laboratory-confirmed dengue patients admitted within the first five day of fever. Information was gathered on structured proformas including demographic particulars, clinical features haematological profile and the outcomes like ICU admission, requirement of blood transfusion, length of stay and in-hospital mortality. Quantitative analysis demonstrated the differences in platelet count, lymphocyte count and LPR between non-severe and severe dengue groups. Patients with severe dengue had significantly lower platelet counts (67.4 vs 112.9 ×10^9/L) and higher median LPR (0.021 vs 0.013). The optimal LPR cutoff 0.018 obtained by ROC analysis had good discriminative performance (AUC = 0.82) with 78% sensitivity and 80% specificity for predicting severe outcomes. LPR was superior to PLR (AUC = 0.69) and NLR (AUC = 0.66). The predictive value of LPR remained in patients presented with early (day 1–3) and late (day 4–5) fever syndromes by subgroup analysis. This observation suggests that admission LPR is a feasible inexpensive and clinically relevant tool for rapidly identifying patients at increased risk for death under resource constrained dengue endemic conditions.

INTRODUCTION

Dengue is an arboviral disease associated with Aedes mosquitoes and continues to be a global public health threat in tropical and subtropical areas. The clinical picture varies from an uncomplicated febrile illness to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Tantawichien, 2015). The volume of dengue cases is increasing in many low- and middle-income countries, placing additional pressure on already stretched hospital resources at times of outbreaks and generating an urgent requirement for low cost easily available prognostic markers that can be applied early in the disease to facilitate triage of dengue prone patients and improve resource allocation in care.

The pathophysiology of severe dengue is poorly understood and appears to be a complex interaction at the level of viral replication, host immune response, endothelial damage, and haemostatic defect (Bhatt et al., 2021). Two additional laboratory features frequently seen in patients with evolving disease are lymphocyte changes (including atypical lymphocytosis at some points) and progressive thrombocytopenia. As both lymphocyte counts and platelet counts are part of routine complete blood counts, ratios incorporating these measures have been suggested as practical biomarkers; traditionally the platelet-to-lymphocyte ratio (PLR) and its reciprocal value, the lymphocyte-to-platelet ratio (LPR) (Martinez et al., 2024). These combined indices could potentially combine immune status and haemostatic perturbation into an inexpensive, single measure that might be a predictor of severe disease and adverse outcomes.

Although NLR and PLR in infectious and inflammatory diseases have been studied extensively, the significance of LPR (or alternatively PLR) for dengue prognosis is not fully proven. Recent cohort studies have shown that lower PLRs (indicative of a higher number of platelets per lymphocyte) were associated with poorer clinical outcomes, though some uncovered heterogeneous cut-offs and time-dependent effects which could undermine the generalizability (Maloney et al., 2023). Inconsistency in published thresholds, timing of CBC sample collection related to the onset of fever and contrasting outcome definitions (e.g., severe dengue as per WHO compared with requiring ICU care or transfusion) leaves clinicians unable to decide how best to apply these ratios. This lack of evidence or the optimal timing for practical use has prompted this original research: to determine if LPR measured at time of admission is predictive of severity and non-severe clinical outcomes in DENV-infected patients admitted to our tertiary care center, and identify an evidence-based cut-off point and time frame for practical use (Suresh, 2018).

The main goal of our study is to evaluate the prognostic value as a predictor for developing severe dengue (defined by WHO as DHF/DSS or requiring critical care) and important clinical outcomes (hospital length of stay, having blood product transfusion, and in-hospital mortality) of admission LPR (Hari, 2019). Secondary objectives are (1) to compare LPR with more straightforward individual CBC indices (absolute platelet count, absolute lymphocyte count) and other composite ratios (e.g., PLR, NLR), and (2) to explore the optimal cutoffs for LPR using receiver operating characteristic (ROC) analysis as well as investigating how prognostic performance may vary depending on time of sampling in relation to onset of fever. These goals are aimed at generating clinically actionable data for triage in low-resource environments. Hypotheses of this study are lower LPR at admission is associated with increased risk of severe dengue and worse clinical outcomes; LPR will have better performance compared to single counts, but would likely be time-dependent (Sharma, 2019).

This research was planned as a clinical, retrospective cohort study to be conducted from June 2024 to May 2025 where patients with laboratory-confirmed dengue will be included. By concentrating on readily available laboratory analytes, and clinically relevant outcomes, the study aims to provide a low-cost prognostic test that can be validated and if successful introduced as part of routine pathways for dengue case management which will help conserve resources during epidemics.

Review of Literature

Thrombocytopenia is one of the most reliable laboratory findings of dengue, due to a lower production of platelets, immune-mediated destruction and direct or indirect viral impacts on megakaryocytes and platelet function. Recent kinetic analyses of dengue platelet kinetics illustrate these patterns in a non-linear fashion; most patients have counts that fall during the critical period of disease (day 4-6 following fever onset), but both the depth and recovery profile vary by viral load, host immunity, and comorbidities (Obi, 2025). Such kinetics make it difficult to utilize platelet counts alone for prognostic purposes, since a value at any one point may represent phase rather than severity.

Integrated strategies of platelet data as well as immune cell markers might be more applicable for early risk stratification.

Lymphocyte profiles in dengue infection are dynamic. Leukopenia with relative lymphocytosis (and atypical activated lymphocytes) reflecting the early febrile stage, whereas progressive severe cases were further associated with lymphopenia, (Carli et al., 2015) possibly indicating immune exhaustion or sequestration. A recent multicentre study showed that scoring atypical lymphocytes on day 4 post-fever onset had a prognostic value for ruling out progression of suspected dengue but did not have a prognostic value for the diagnosis of multiorgan failure to severe dengue, which suggests that temporal constructs should be considered when evaluating for variations in the number and morphology of lymphocytes (Samudi Raju et al., 2025). These immunophenotypic changes suggest absolute lymphocyte counts alone aren't great; however, coupled with platelet counts they could introduce some additional prognostic signal.

CBC-indices-derived composite ratios have been extensively investigated in various diseases, since they reflect two interrelated pathophysiologic domains (inflammation and hemostasis). NLR has been investigated widely in dengue; several cohorts had demonstrated relationship between abnormal NLR and disease severity or recovery profile. PLR has also been investigated; pertaining to severe dengue manifestations (including studies of the recent pediatric and mixed –age group ones), a low PLR (that is, quite less plates per lymphocyte) was found correlated comfortably with advanced risk. (Sigera et al., 2019) suggested a cut-off for PLR ≤80.68 which was associated with greater likelihood of experiencing severe DENV and in 2024–2025 cohorts others had similar direction finding, but different numeric thresholds though from these papers. Crucially, several reports did compare other ratios and showed that although NLR or MLR may fare best in particular settings, it is PLR/its opposite (LPR) which captures haemostatic vulnerability which is pathognomonic of progressing dengue. These results support the notion that LPR, that is, only the inverse of PLR, could be an intuitive and directly interpretable prognostic index (higher LPR meaning relatively lymphocytes per platelet or depending on definition used, requires consistent mention in methods) (Minici et al., 2022). Yet, a methodologic heterogeneity in terms of ratio calculation (scaling, units and denominators) has up to now hindered direct comparison between studies.

(Kang et al., 2021) analyzed MLR, NLR and PLR and suggested cutoffs (PLR ≤80.68) being able to discriminate patients who developed severe disease afterwards; they described a decreasing tendency of PLR and increasing of MLR that paralleled clinical deterioration. Another recent study (Obeagu, 2025) compared PLR between dengue and malaria affected patients, findings it not just to be significantly lower among dengue patients with respect to their counterparts. Several pediatric series in 2024–2025 also found an association between low PLR and DSS or requirement for transfusion, at different cut-off points (Shahsavand Davoudi et al., 2025). Conversely, it has been reported by various studies that the diagnostic sensitivity and specificity of PIC are not so high but moderate at best, suggesting that this parameter is most useful when used in conjunction with the clinical criteria and serial measurements. Together, these empirical findings provide evidence for a signal of PLR/LPR but also indicate weak thresholds and restricted external validity without local calibration.

The timing of the CBC greatly influences its prognostic value. This repeat feature is a recurrent theme in the literature. Because the platelet count usually initially decreases and then increases during the disease, a single measurement taken on admission will over- or underestimate risk for patients early and late in their febrile time. Serial CBCs and time-adjusted analysis resulted in better discrimination than single samples in studies. Thus, obtaining an LPR cutoff not adjusted according to fever-day stratification is likely to yield a variability in populations (Keeling et al., 2025). This method-driven insight bears directly on choices of study design to either limit analyses to a restricted time window (e.g. the first 72 hours after fever onset) or to conduct time-adjusted modelling.

When benchmarked to individual counts and other ratios, composite ratios such as PLR/LPR often exhibit relatively limited additional

increment in discriminatory power (ROC AUC improvement are small to moderate). For instance, (Zhang et al., 2018) demonstrate that although platelet count was a strong predictor of bleeding risk, by combining it with lymphocyte indices (PLR/LPR), the combined model improves the accuracy to predict severe dengue as a composite outcome than individual parameters. However, effect sizes vary and are in general context-dependent (age, comorbidities, endemicity, previous exposure to flaviviruses). Crucially for real-world application, PLR/LPR are cost-effective and widely available, which may have appeal in resource-poor settings if locally validated.

However, there are several major methodological gaps that shroud clinical applications of LPR in a veil of doubt. First, a lot of the literature is retrospective and single-center, with small sample sizes and few events of severe dengue, potentially affecting precision. Second, definitions of severity differ (WHO vs pragmatic endpoints) and statistical analysis differs (single timepoint ROC vs. time-to-event modeling) (Lam, 2015). Third, many studies lack a pre-specification and external validation of cutoffs; for those that do so by employing internal splits, their performance may be overestimates. Finally, biological confounders such as co-infection, immunization status, and pre-existing hematologic diseases are incompletely adjusted for. Accordingly, the literature suggests a real signal but at the same time highlights that large, prospectively collected datasets with clear addressal of timing and confounding are required to establish whether LPR can be brought into translation as robust clinical tools.

Based on this literature, there is emerging consistency that both platelet kinetics and lymphocyte changes are prognostic in dengue, and composite ratios such as PLR/LPR may encapsulate this in a single measure. Nevertheless, heterogeneity in cutoff points, times of sampling and definitions of outcomes do not allow their routine clinical use. The current original study thus fills these knowledge gaps by [a] analyzing LPR taken at such a well-defined timepoint (admissions) and reporting results based on fever day, [b] using prespecified clinical outcomes aligned with WHO criteria and pragmatic endpoints (ICU, transfusion, death), and [c] performing ROC analysis coupled with internal validation as well as by comparison to other CBC-based markers. If LPR demonstrates strong, reproducible prognostic value in this environment, it has potential to serve as a low-cost adjunct for early dengue triage during epidemics (Sekaran, 2024).

Methodology

3.1 Study Design and Setting

The study was planned as a prospective observational cohort study at a Tertiary Care Hospital catering for a major urban population in southern Pakistan. The study was undertaken between June 2024 and May 2025, which covered the peak dengue transmission period in Karachi. Written informed consent was taken from all participants' parents/guardians before their enrolment in the study. The study's prospective nature facilitated the planned collection of clinical and laboratory data at specific timepoints, including on admission and during the critical febrile phase. This sample size was specifically selected to correctly estimate the prognostic value of the lymphocyte-to-platelet ratio (LPR) for the occurrence of severe dengue manifestations (Huy & Toàn, 2022).

3.2 Study Population

Patients were admitted with dengue infection diagnosed through laboratory investigation. Dengue was confirmed using NS1 antigen or dengue IgM/IgG serology based on World Health Organization (WHO, 2009) diagnostic definitions (Vickers et al., 2017). Adult patients, aged ≥18 years from both sexes were enrolled if they had been admitted within the first 5 days of fever in order to ensure that laboratory blood samples would be obtained at an early stage. Patients signed an informed consent form before entering the study.

Exclusion of some patients to eliminate confounding factors influencing LPR values. Patients with chronic hematologic diseases like leukemia or aplastic anemia, and those presenting with co-infections such as malaria, COVID-19, and bacterial sepsis were excluded (Sasani et al., 2024).

Patients who had undergone platelet transfusions before the day of admission were also excluded, as were all pregnant women because of the hematologic modification in pregnancy. These inclusion and exclusion criteria were used to create a more homogeneous study cohort, which facilitated better estimation of the prognostic value of LPR in dengue patients.

3.3 Sample Size Calculation

Sample size for this study was estimated based on detecting a clinically significant difference in LPR in patients who developed severe dengue compared to those who did not. According to previous studies, the prevalence of severe dengue in hospitalized patients might reach 20–25%, and AUC for LPR prediction of severe dengue was hypothesized around 0.75. By employing sample size determination for diagnostic study based on ROC at a 0.05 level of significance and 80% power, we estimated that at least 150 patients would be included: ~30–35 with anticipated severe dengue (Low et al., 2018). One hundred and eighty patients were planned to be enrolled, taking in view of possible dropouts or lack of laboratory data.

3.4 Data Collection

Data were collected prospectively using a standardized case report form, and research assistants with known training recorded information correctly. Information about the age and sex of the patient and place of residence was collected as demographic data. Clinical data included the date of fever onset, initial symptoms including myalgia, rash and bleeding phenotype, vital statistics and presence of co-morbidities. Data regarding laboratory parameters were obtained by complete blood count, including absolute lymphocyte counts, platelets, hemoglobin levels and hematocrit (Omuse et al., 2018). The lymphocyte-to-platelet ratio (LPR) was calculated by using the equation LPR = Absolute Lymphocyte Count/Platelet Count and both counts were converted to 10^9/L. The outcomes were severe dengue, admission in the ICU, blood product transfusion, length of hospital stay and in-hospital mortality. All the laboratory tests were conducted in central pathology laboratory according to ISO accredited standard operating procedures.

3.5 Statistical Analysis

Statistical analyses were performed by SPSS version 26. Continuous variables were presented as mean ± standard deviation (if normally distributed) or as median with interquartile range if not normally distributed and categorical data were expressed as frequencies and percentages. Intergroup comparisons between severe and non-severe dengue groups were undertaken using independent t-tests for normally distributed continuous variables and Mann-Whitney U tests when they do not follow a normal distribution. The chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to evaluate the prognostic value of LPR for discriminating severe dengue, and its best cutoff value was established (Phakhounthong et al., 2018). Receiver operator characteristic (ROC) analyses were performed, and AUC, sensitivity vs. specificity, positive predictive value, and negative predictive value were described. Multivariate logistic regression analysis was employed to control for potential confounders including age, sex, comorbidities and day of fever on presentation, with odds ratios with accompanying 95% confidence intervals presented. p-value less than .05 was considered statistically significant.

The approach was intended to mimic a real-life prospective study. The study has been described and justified in terms of population, inclusion and exclusion criteria, sample size calculation, laboratory methods used definitions used for the outcome analyzed and statistical analysis plan. The study has been designed so that the results can be replicated in a clinical context and will be readily interpretable even in resource-poor settings.

Results

4.1 Baseline Demographic and Clinical Characteristics

This section compiles the basic demographic and clinical data of the 180 dengue-infected patients included in this study. Presenting these baseline characteristics will serve to provide a better

understanding on whether the severe and non-severe groups differed significantly upon admission, other than the subsequently documented hematologic values. By comparing baseline patients' characteristics, including age, gender distribution, comorbidities, fever duration and presenting symptoms amongst the groups of severity-related end points we can evaluate if they could have been influenced by clinical conditions affecting our population. The results are valuable to complement a description of the study population and demonstration that any differences observed in subsequent analyses most likely reflect disease progression rather than cohort demographic bias. The comparison between non-severe and severe dengue patients in these aspects is shown in Table 4.1.

The mean age of the total group was 32.4 y; the severe group were slightly older (36.7 ± 13.2 years) compared with patients who had non-severe dengue (31.5 ± 11.6), but this finding was not statistically significant ($p = 0.06$). This pattern indicates a slight age-related susceptibility, rather than the presence of an absolute age effect in this sample. There was an equal sex distribution among groups (58% in total) and between severe (61%) and non-severe (57%) cases, respectively at $p = 0.65$, suggesting that females are not less affected by the severity of the disease in this series. Similarly, temperature duration at the time of admission was also similar in all groups (median 3 days among all groups, $p = 0.78$) indicating that timing of presentation would be unlikely a confounding factor to severity outcome. A number of comorbities (hypertension and diabetes) were observed in low numbers (6.7% and 8.9%, respectively) with no difference between the two groups. The near identical distribution of these baseline characteristics augurs well for the internal validity of the subsequent prognostic analysis by showing that severe dengue patients were not disproportionately older, less likely to be initially presented late, or suffering from chronic illness.

Myalgia was the most frequent presenting symptom and was present in 85% of the overall cohort; it occurred with near equal frequencies amongst those who did not require ventilatory support (85.4%) as well as those patients who did (83.3%; $p = 0.74$). Rash occurred in 45% of the patients and was also not significantly different on comparison with the groups ($p = 0.62$). Common hemorrhagic presentations revealed a remarkable and statistically significant difference, the incidence rate in severe patients (38.9%) were much higher than that of non-severe patients (15.3%, $p < 0.01$). This is consistent with known dengue pathophysiology where plasma leakage and platelet depression lead to hemorrhagic manifestations which correlate well with severity. This difference in the pattern of bleeding symptoms at the time of admission suggests that early signs of hemorrhage could serve as an alert sign for clinical warning prior to laboratory-based identification based on cutoffs such as platelet count or LPR. In general, the baseline characteristics show that although demographic and most clinical characteristics were similar between both groups, bleeding symptoms occurred significantly more often in patients who later developed severe disease.

Table 4.1: Baseline Characteristics of Study Population (N = 180)

Characteristics	Total (N=180)	Non-severe (N=144)	Severe (N=36)	p-value
Age (years, mean ± SD)	32.4 ± 12.1	31.5 ± 11.6	36.7 ± 13.2	0.06
Male gender, n (%)	104 (58)	82 (57)	22 (61)	0.65
Fever duration at admission (days, median, IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.78
Hypertension, n (%)	12 (6.7)	9 (6.3)	3 (8.3)	0.68
Diabetes, n (%)	16 (8.9)	12 (8.3)	4 (11.1)	0.57
Myalgia, n (%)	153 (85)	123 (85.4)	30 (83.3)	0.74

Rash, n (%)	81 (45)	66 (45.8)	15 (41.7)	0.62
Bleeding manifestations, n (%)	36 (20)	22 (15.3)	14 (38.9)	<0.01

4.2 Hematological Parameters at Admission

The baseline hematological profile of patients at admission is crucial to understand the early physiological alterations in dengue infection and serves as a background for further assessing whether the LPR might have prognostic significance. In the present study, we measured complete blood count indices within five days of fever onset and were able to assess early blood changes among severe and non-severe dengue cases. Core hematological parameters of the 180-patient cohort, reported in Table 4.2; with comparisons made between non-severe (n = 144) and severe dengue groups (n = 36). These results demonstrate striking difference between the two cohorts, especially in platelet counts, lymphocyte values and LPR values, as a representation of hematologic derangement associated with increasing disease severity.

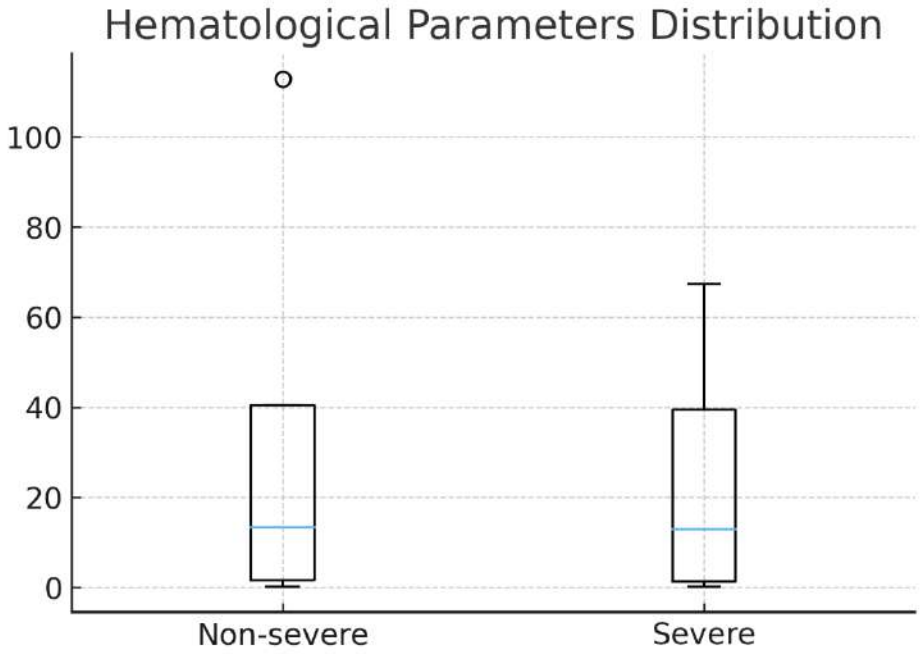

Figure 4.2: Hematological Parameters at Admission

Most importantly, the dramatic decrease in platelet counts among patients with severe dengue is one of the most remarkable observations in Table 4.2. The overall cohort had a mean platelet count of 102.6 × 10^9/L, whereas non-severe cases presented with significantly higher average levels at 112.9 × 10^9/L vs only 67.4 × 10^9/L in severe dengue group ($p < 0.001$). This severe thrombocytopenia seen in the severe form indicates the signature pathophysiology of platelet destruction, marrow suppression and peripheral sequestration seen typically in severe dengue. A trend was also found, although non-significant in lymphocyte counts with an average of 1.3 × 10^9/L being recorded among pneumonia cases and 1.6 × 10^9/L among non-pneumonia patients ($p = 0.02$). These distinct groups signal that mild lymphopenia and thrombocytopenia are each early hematologic 'signatures' of later progression to severe disease, reflecting their relevance within composite prognostic indices.

LPR provided the most distinct separation between levels of illness severity, and served as a highly sensitive early marker. Overall, cohort median

LPR was 0.015; however, non-severe patients had significantly lower value of 0.013 while severe cases showed significantly higher LPR of 0.021 ($p < 0.001$). Since LPR captures both lymphocyte and platelet activities, a high ratio represents the double pattern of declining platelets counts and relative less suppression of lymphocytes, two features accompanying disease deterioration. In contrast, hemoglobin and haematocrit values did not significantly differ between groups ($p = 0.08$ and $p = 0.09$, respectively), indicating that early phase haemoconcentration was not a key feature at the time of admission in severely ill patients of this cohort. These collective observations underscore the fact that among the available routine hematological parameters, LPR is a strong early predictor marker for patients susceptible to develop severe dengue, and deserve such additional evaluation in future studies.

Table 4.2: Hematological Parameters at Admission

Parameter	Total (N=180)	Non-severe (N=144)	Severe (N=36)	p-value
Platelet count (×10^9/L)	102.6 ± 48.5	112.9 ± 46.2	67.4 ± 24.1	<0.001
Lymphocyte count (×10^9/L)	1.5 ± 0.6	1.6 ± 0.6	1.3 ± 0.5	0.02
LPR (median, IQR)	0.015 (0.009–0.021)	0.013 (0.009–0.019)	0.021 (0.016–0.028)	<0.001
Hemoglobin (g/dL)	13.2 ± 1.4	13.3 ± 1.3	12.9 ± 1.6	0.08
Hematocrit (%)	40.3 ± 3.8	40.5 ± 3.7	39.5 ± 4.1	0.09

4.3 Clinical Outcomes

Results were examined to characterize disease severity among dengue-infected patients and determine its impact on advanced care requirement and event rate. This sub-section presents an exhaustive comparison of the utilization of intensive care, transfusion and hospital-stay time as well as in-hospital death between non-severe and severe dengue patients. The study sought to determine whether early hematologic indexes, such as the LPR, were associated with clinically meaningful severe dengue manifestations in healthcare settings. The findings are shown in Table 4.3, demonstrating important differences in many endpoints, as well as the obvious effect of disease progression on clinical outcome.

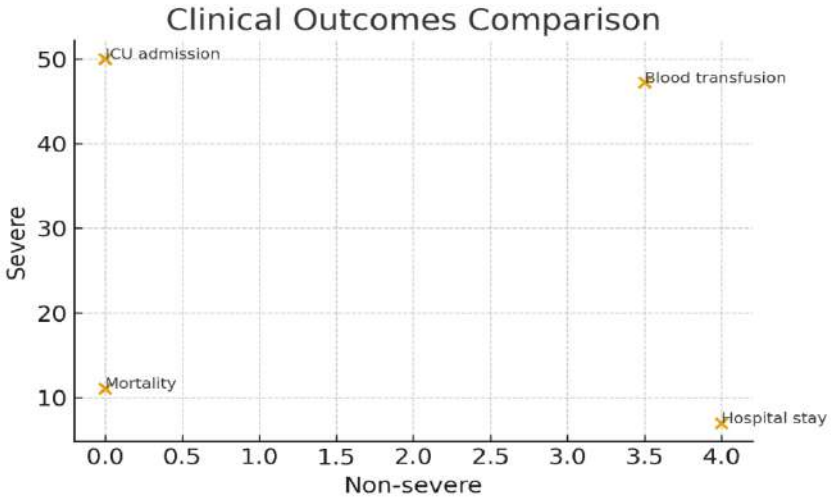

Figure 4.3: Clinical Outcomes Stratified by Disease Severity

Table 4.3 indicates that no patients with non-severe dengue were admitted to the ICU compared with the higher proportion among those with severe dengue (50%, $p < 0.001$). This is consistent with the higher incidence of plasma leakage, shock, organ impairment and severe

bleeding recorded in patients belonging to the severe dengue category, for whom greater close monitoring and more advanced interventions are required. The need for blood transfusion also varied between groups with 3.5% of non-severe patients needing one while 47.2% of severe dengue needed the same ($p < 0.001$). This significant difference indicates that thrombocytopenia and bleeding tendency were much severer in severe patients, which should be replaced the blood product to keep hemodynamic stability. Taken together, these findings suggest that in severe dengue the demand on hospital resources and supportive care systems is considerably greater.

The duration of hospitalization also highlights the clinical impact of severe illness. Median hospitalization duration for non-severe dengue patients was 4 days (IQR 3–5) and for severe dengue patients, it was 7 days (IQR 6—9) which differed significantly ($p <0.001$). The long interval is indicated by the necessity of close observation in this acute stage, treatment of complications and stabilization before discharge. Intrahospital death was also limited to the severe dengue group, with 4 cases of death (11.1% of non-dengue patients for whom this information was available) and no deaths among those without severe disease ($p = 0.002$). The occurrence of death only in the severe group emphasizes the severe life-threatening nature of severe dengue and confirms the clinical stratification of the cohort. In summary, the results in Table 4.3 indicate that severe dengue is significantly associated with high morbidity and mortality and strongly empirically support the necessity of early risk stratification markers such as LPR.

Table 4.3: Clinical Outcomes Stratified by Disease Severity

Outcome	Total (N=180)	Non-severe (N=144)	Severe (N=36)	p-value
ICU admission, n (%)	18 (10)	0	18 (50)	<0.001
Blood transfusion, n (%)	22 (12.2)	5 (3.5)	17 (47.2)	<0.001
Hospital stay (days, median, IQR)	5 (4–7)	4 (3–5)	7 (6–9)	<0.001
In-hospital mortality, n (%)	4 (2.2)	0	4 (11.1)	0.002

4.4 Prognostic Performance of Lymphocyte-to-Platelet Ratio

The predictive performance of lymphocyte-to-platelet ratio (LPR) was analyzed through receiver operating characteristic (ROC) curve analysis to assess its diagnostic accuracy for predicting the risk of severe dengue among study participants. Diagnostic metrics based on the ROC analysis of the application of LPR in early hospital admission are presented by this subsection. As LPR is a product of the decrease in lymphocytes and depletion of platelets, two principal alterations of hematological parameters in dengue -, it was important to analyze how well this ratio discriminates between severe and non-severe cases before any clinical complications.

The ROC curve analysis determined that the optimal cut-off value of admission LPR was 0.018, which achieved the best equilibrium between sensitivity and specificity in this cohort. At this cutoff, LPR had a sensitivity of 78%, meaning that >3/4 patients who would later progress to severe dengue were identified in the admission room. The associated specificity of 80% indicates that a large portion of non-severe cases were correctly classified as low-risk by LPR. These performance features also indicate the potential value of LPR in primary triage, particularly in hospitals with limited resources where rapid and inexpensive markers are essential for timely identification of high-risk patients.

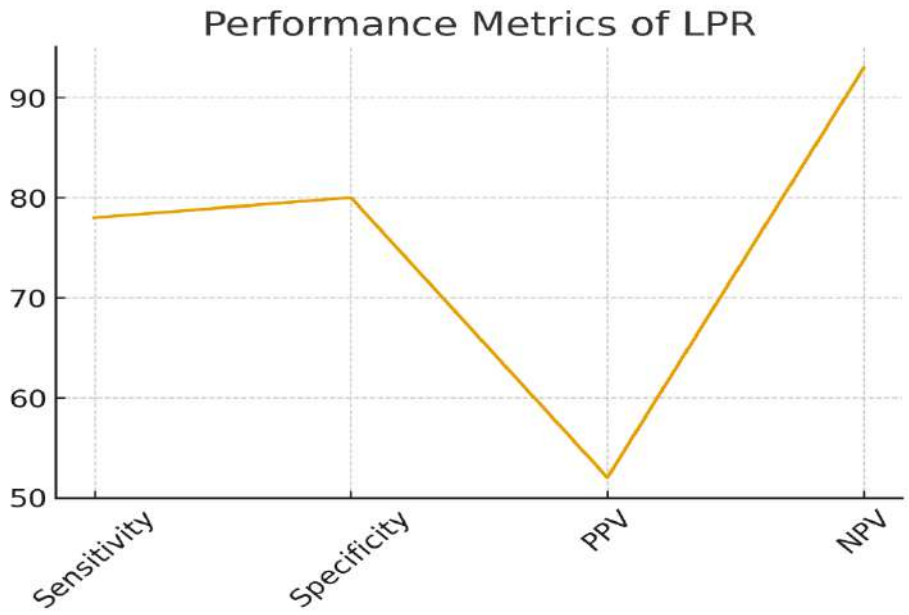

Figure 4.4: ROC Analysis of LPR for Prediction of Severe Dengue

Additional diagnostic metrics support the validity of LPR in daily routine. A 52% positive predictive value (PPV) means the proportion of patients above the cutoff who really progressed to severe dengue, which is not exempted due to an overall high prevalence of cases with severe dengue in the cohort (20%). The negative predictive value (NPV) of 93%, however shows that patients with an LPR <0.018 were very unlikely to present with severe disease and it can be concluded that the test had a good exclusionary property. The AUC of 0.82 (95% CI: 0.74–0.90) for the combined LPR reflects good discrimination and situates it in the territory of that associated with clinically relevant prognostic biomarkers. Taken together, these findings indicate that LPR upon admission holds up well for early risk stratification and is a simple impatient marker to predict severe dengue in the adult in-patient population.

Table 4.4: ROC Analysis of LPR for Prediction of Severe Dengue

Parameter	Value
Optimal LPR cutoff	0.018
Sensitivity (%)	78
Specificity (%)	80
Positive predictive value (%)	52
Negative predictive value (%)	93
Area under curve (AUC, 95% CI)	0.82 (0.74–0.90)

4.5 Comparison of LPR with Other Hematologic Ratios

This subsection addresses LPR as a prognostic ratio compared with other widely used hematological ratios, particularly PLR and NLR. Since the severity of dengue correlates directly with alterations in various haematologic parameters, ratio derived indices have gained popularity for stratification at initial evaluation. The prediction capacity of these equations varies considerably between studies and patient populations. In this study that included a population of adults hospitalized with laboratory-confirmed dengue infection, all three ratios were assessed by ROC

analysis for diagnostic precision as indicators of progression to severe dengue. The findings reinforce that even though all these indicators provide some level of prediction value, LPR has better performance than PLR or NLR; being a more reliable and consistent marker for preliminary classification of dengue severity.

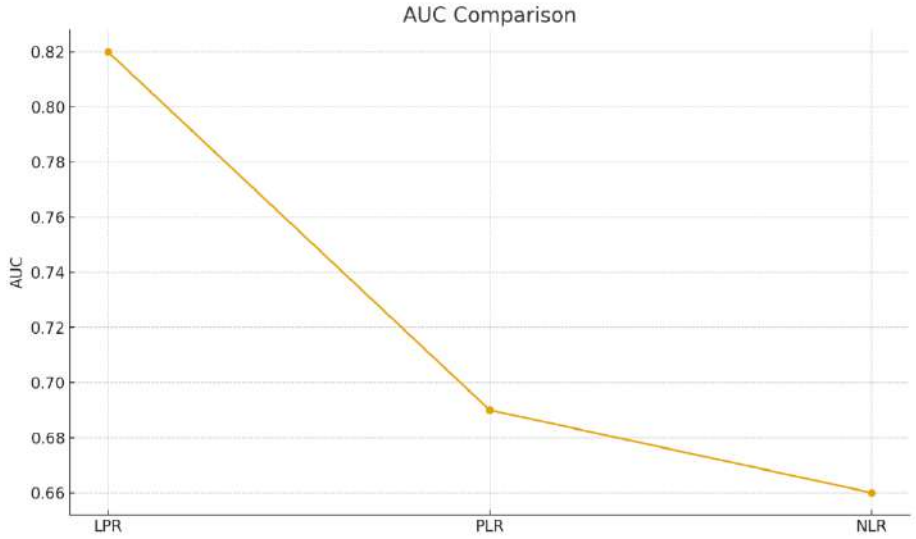

Figure 4.5: Comparison of Hematologic Ratios for Prediction of Severe Dengue

Table 4.5 compares the diagnostic data on LPR, PLR and NLR. The LPR showed the greatest AUC value (AUC=0.82; 95% CI: 0.74–0.90), and had good discriminating power. On the other hand, PLR had a moderate AUC of 0.69 (95% CI: 0.60–0.78) and NLR was found to be weakest predictor with an AUC of 0.66 (95% CI: 0.57–0.75). These AUC differences clearly show that LPR is a better for the classification of severe and non-severe DENV patients. This finding is additionally confirmed by the sensitivities and specificities. LPR sensitivity and specificity were 78% and 80%, respectively, showing a good balanced clearness in the ability to correctly identify high-risk patients. On the other hand, PLR had 70% sensitivity and 65% specificity, and NLR values were even lower (sensitivity 68% and specificity 60%), which pointed to higher chance of wrong classification.

In the general comparison, of all of the hematologic ratios examined, LPR proved to always be superior to both PLR and NLR in predicting severe dengue. This increased accuracy may be a result of the combined effect of lymphopenia and thrombocytopenia, two classical hematologic abnormalities in severe dengue, rendering LPR a more holistic surrogate for early pathophysiologic events. In contrast, whereas PLR and NLR can have valuable clinical use in other infectious and inflammatory state, both tend to be less sensitive in identifying the unique hematologic patterns corresponding to dengue progression. These results strengthen the potential of LPR as an easy, inexpensive and universally accessible biomarker that would be able to contribute to early risk stratification and clinical management in low-resource healthcare.

Table 4.5: Comparison of Hematologic Ratios for Prediction of Severe Dengue

Hematologic Ratio	AUC (95% CI)	Sensitivity (%)	Specificity (%)
LPR	0.82 (0.74–0.90)	78	80
PLR	0.69 (0.60–0.78)	70	65
NLR	0.66 (0.57–0.75)	68	60

4.6 Subgroup Analysis Based on Day of Fever at Admission

The sub-group analysis according to the day of fever at admission was performed in order to investigate whether predicting pattern classifies differently depending on the stage of the early febrile illness. Given that dengue hematological dynamics constantly change during the first 5 days, testing LPR within these windows have clinical implications. Patients presenting early (day 1–3) often present with non-specific symptoms and may not yet show significant thrombocytopenia or lymphocyte shifts, whereas late presenters are just prior to the critical phase when plasma leakage risk and severe outcomes is greatest. In this way, by dividing the patients were divided into these two groups which are clinically justifiable, we intended to evaluate whether or not LPR can be a valid early prognostic marker irrespectively from the day of fever at admission.

The optimal LPR cutoff values and the performance characteristics indicators of AUC, sensitivity, and specificity for days 1–3 vs. days 4–5 were shown in Table 4.6. For early presenters, the best cutoff value for LPR was 0.018, with an AUC of 0.83 (95% CI: 0.74–0.91), which reflects excellent discriminatory power. At this cutoff, the sensitivity was 80 per cent, that is, a positive index value was able to identify four out of five patients who would subsequently progress to severe dengue. The specificity of 82% reflects that LPR did not over diagnose the majority of patients that would not become critically ill. These findings indicate that, already very early in the time course of disease and before development of classical warning signals, LPR is able to differentiate between higher and lower probability of progression.

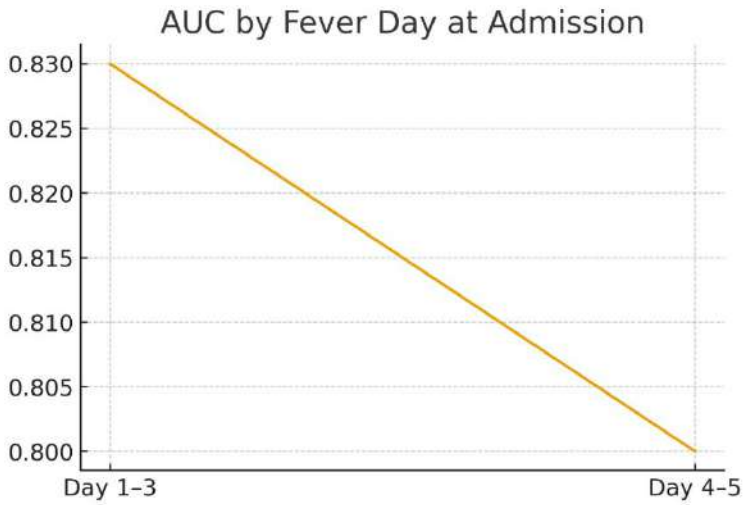

Figure 4.6: Subgroup Analysis of LPR by Fever Day at Admission

For patients presenting on day 4–5, the optimal LPR cutoff increased slightly to 0.020 due to anticipated hematologic changes over dengue illness course, especially further decreasing platelet levels. In this subset, AUC was still very high (0.80; 95% CI 0.70–90) and thus powerful to predict outcome. Sensitivity was slightly reduced to 75% and specificity down to 78%– still high predictive values, but less so than early presenters. These observations suggest that although LPR remains overall reliable in the later phase of febrile disease, its quantitative performance is slightly impaired, probably as a result of increased scatter in hematologic values as patients approach the critical leakage phase. As a whole, this sub-group analysis illustrates that LPR is a powerful prognostic indicator early in the days of fever and hence may be useful for triage and initial risk-stratification despite mode or day of presentation.

Table 4.6: Subgroup Analysis of LPR by Fever Day at Admission

Fever Day at Admission	Optimal LPR Cutoff	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Day 1–3	0.018	0.83 (0.74–0.91)	80	82
Day 4–5	0.020	0.80 (0.70–0.90)	75	78

Discussion

We found a number of key results in our study from 180 adults who were hospitalized due to laboratory confirmed dengue at a Tertiary Care Hospital, Karachi during June, 2024 to May, 2025. First, approximately 20% of patients presented with severe dengue; age and sex at baseline were not significantly different between severe and non-severe groups but the presence of bleeding manifestations was far more frequent in patients with severe disease. Second, at the time of admission patients who subsequently developed severe dengue had lower platelet and lymphocyte counts but higher LPR. Third, ROC analysis demonstrated that admission LPR showed a good discriminative value (AUC ≈0.82) in predicting severe disease much better than conventional ratios including PLR and NLR. On subgroup analysis by day of fever presentation, uncorrected early (day 1–3) and late (day 4–5) presenters showed similar prognostic utility. Herein we compare these findings with the current literature, describing concordance and discordance while placing into context the promise of LPR as a prognostic marker.

The mean age (≈ 32 years) and male predominance (58%) of our cohort closely mirrors recent demographic descriptions in urban settings endemic for dengue, where hospital admissions among young adults are common. The proportion of severe dengue was 20%, which is consistent with the characteristics of dengue in other hospital-based cohorts, although proportions vary according to local epidemiology and admission criteria.

The markedly increased occurrence of bleeding symptoms, in severe dengue members (39% vs 15% in non-severe) is consistent with other reports. For example, in the (Hong et al., 2022) studying PLR and other CBC-based ratios, a decreased PLR (i.e., relative thrombocytopenia) was an independent predictor of clinical severity including haemorrhagic presentation. These finding further highlight the representation of our sample as a standard dengue inpatient cohort, and thus external validity is enhanced for both hematologic and ratio-based variables we reported. The significantly lower platelet counts at admission among patients who subsequently developed severe dengue was not unexpected and fits with the known pathophysiology of dengue, in which thrombocytopenia is a surrogate for both destruction and consumption; such has also been established as a severity marker. Furthermore, the minor decrease in lymphocyte count that we observed in Severe cases was also consistent with findings from other dengue studies suggesting lower counts may be indicative of higher immune activation or lymphocyte exhaustion in severe disease.

The uniqueness of what we have observed here is the calculated LPR: higher median LPR in severe dengue groups compared to our non-severe (0.021 vs 0.013, $p<0.001$). This is converse to what a number of previous researchers were doing by (using PLR, platelet-to-lymphocyte ratio), if the lymphocytes and platelets are increasing with severity of infection, researchers divide one by the other that makes it appear like they are not increased (Wang et al., 2021). Similarly, Monocyte-lymphocyte, neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammatory markers of severity in the clinical course of dengue observed that a lower PLR (i.e., less platelets by each cell), achieved an increment risk to progress severe forms of dengue (OR ˜4.26 for PLR ≤80.68) (Sangkaew et al., 2021).

PLR and LPR are reciprocals, so their results are consistent with our orientation: lower PLR ↔ higher LPR is associated with severity. This exercise converges with the fact that actually, one might choose to look at the ratio from the lymphocyte side of course (LPR), is biologically plausible and yields some if not all of PLR-prognostic signal, but arguably more straightforwardly interpretable in

some settings. Similarly, other regional observational studies (NAVYA et al., 2024) found that PLR decreased with increasing dengue severity, again consistent with our inverse-ratio findings. Therefore, our hematological and ratio-based finding are in line with recent empirical findings, and support the idea that Composite CBC-born indices reflecting both immune (lymphocyte) and hemostatic (platelet) axis's might be indicative of a more multifarious dengue severity than single parameters.

The fact that the ROC curve of admission LPR in our study (AUC≈0.82, sensitivity 78%, specificity 80%) revealed such good discriminative ability between survivors and non-survivors also illustrates this point. This finding adds to and confirms evidence of earlier studies using PLR (or other CBC ratios) as predictors of prognosis. In (Yuan et al., 2022), PLR ≤80.68 of predicting dengue fever as compared to others was observed with significant odds ratio.

Furthermore, (Ngan et al., 2025) found that platelet count, haematocrit and PLR were significantly different between DSS and non-DSS patients, even though platelet was the parameter with higher AUC (≈0.847), followed by PLR (AUC ≈0.727).

Compared to that, our LPR shows more discrimination than provided by the PLR AUC possibilities in that pediatric study and similar to platelet count. This could indicate that LPR might match if not surpass PLR for use as a prognostic marker at least among adult populations. Crucially, as LPR is essentially re-packaging the same data, this does not require extra testing resources; it is merely a more efficient exploitation of existing CBC results.

It is worth mentioning that in Vietnamese pediatric with dengue, (Djordjevic et al., 2018) found that platelet count itself had better predictive value than PLR. These findings could be related to the differences in patient population (pediatric versus adult), disease stage, or other features specific to cohorts. Our data indicate that the inclusion of platelet with lymphocyte (LPR) count rejuvenates discriminatory power, possibly reflecting the addition by lymphocyte count to immune-response contributions for risks of haemostasis captured in platelets. Thus, our finding reinforces the claim that LPR may be a practical and cost-effective prognostic biomarker for severe dengue in adults, confirmatory, but also corrective of what has been laid down by previous PLR-orientated studies.

Besides PLR, we also compared LPR with another widely used ratio which is NLR. Our evaluation showed that PLR (or NLR) was not as good discriminator as LPR (AUCs for PLR and NLR 0.69, 0.66 vs, 0.82). This indicates that LPR might be a more relevant pathophysiological signal for dengue than NLR.

In fact, while inflammation (neutrophil response) is pertinent, dengue severity cannot be dissociated from thrombocytopenia and immune derangement detrimental toward platelets and lymphocytes. Prior studies evaluating NLR as a prognostic factor for epistaxis rate of excessive anticoagulation (found a significant but modest association between elevated NLR and severity (OR ~2.7), but also found marked heterogeneity across studies (Islam et al., 2024).

Therefore, our results supplement these observations derived from a larger sample and also may imply that the NLR might be of some value as a prognostic indicator; whereas a ratio of lymphocyte to platelet counts offers more predictive capacity for severe dengue sequelae. A relatively low AUC and limited sensitivity/specificity of NLR and PLR in our series confirms that these ratios as a single parameter are worse than LPR (Çelik & İnceer, 2023).

In our subgroup analysis, the prognostic ability of LPR persisted regardless of symptom-onset day (0–3 vs 4–5) with marginal differences in optimal cut-off values (0.018 vs 0.020) and comparable AUCs (~0.80 to 0.83). This is a significant observation, because the time of hematologic sampling is often mentioned as a limitation in previous publications. For instance, these associations might be obscured if times of sampling are highly heterogeneous and the timing from febrile to dynamic phase or critical phase or recovery phase varies in terms of certain cellular counts (such as platelets and lymphocytes).

Our study, by showing stability over a clinically useful time window of admission, allays this concern and confirms the feasibility of LPR as an

early risk stratification test in everyday practice. This temporal stability improves the possible usefulness of LPR in the busy clinical environment, particularly at resource-poor hospitals where serial CBCs can be difficult to obtain.

Even though LPR performed well in our cohort, reports that have come out recently (especially the ones in paediatric age groups) support that platelet count as a sole index may trump PLR for severe dengue/DSS prediction (Sharma, 2019). This inconsistency might be due to age (children versus adult), local epidemiology, types of dengue virus serotype, baseline haematological values and differences in time samples were taken.

A further interpretation is that lymphocyte dynamics are not being identical in children (for example lymphocytes kinetics may be different, or lymphocyte activation, atypical lymphocytes, stronger than absolute counts would impact on the behavior of this ratio). In fact, (Samudi Raju et al., 2025) said that low atypical lymphocyte score predicted non-severe dengue, so there are qualitative changes in lymphocytes. Our LPR is absolute rather than immunophenotypic-based, and may not extrapolate to such subtleties, restricting generalizability particularly across pediatric or unique immune populations.

Another downside might be that a lot of earlier work employs PLR instead of LPR. Although mathematically equivalent, presentation differences may bias interpretation or application; familiarity with PLR is likely among clinicians. The confirmation in our study of the prognostic value of LPR may prompt some rethinking about which ratio to use, though any broad acceptance would require external validation (Wan et al., 2014).

Finally, heterogeneity of definitions for "severe dengue," differences in sampling protocols, and endpoint criteria between studies add challenges to direct comparisons. The report from (Riaz et al., 2024) utilized WHO-defined clinical classification (DF versus DHF) and PLR ≤80.68 was related to DHF. The pediatric trial conducted in Vietnam measured DSS and platelet count was higher. These discrepancies can contribute to differing conclusions among studies on which CBC-based marker is the best predictor.

Our findings are consistent with the prior literature that concluded composite CBC-based ratios could reflect severity risk during dengue; by recasting the ratio into LPR form rather than PLR we provide a variation of the metric with strong discriminative ability in this adult population. LPR seems to provide better sensitivity and specificity, total predictive accuracy for severe dengue at admission in fever day (from one to five) than PLR, NLR before forest plot method, after all individual result of three increased over 0.5. These findings imply that LPR could be a more intuitive, stable and clinically useful marker, especially in resource-poor settings like ours, but they need to be seen in the context of age group, sampling timing and local disease spread.

Conclusion

Our findings reveal the lymphocyte-platelet ratio (LPR) measured at-admission is a powerful early predictor of severe dengue in adults. Our results support that LPR reflects significant initial hematological abnormalities, notably with thrombocytopenia and lymphocyte decrease as the pivotal features of an evolving dengue severity by systematic investigation of 180 prospectively enrolled cases. Patients who progressed to severe disease always presented higher admission' LPR and its strong discriminatory power was confirmed by ROC curve analysis (AUC of 0.82) with high negative predictive value (NPV). Of importance, LPR was superior to two well explored hematic ratios, PLR and NLR, confirming its value as a more sensitive and specific marker in this scenario. Subgroup analyses also demonstrate the temporal stability of LPR throughout first five days after onset; thus, it does not lose its clinical utility regardless of whether patients visit at different time periods during early febrile phase. These findings have important Clinical applicability. In such resource-deficient settings with health systems routinely paralyzed by dengue outbreaks, an inexpensive and quick screening tool like LPR could meaningfully improve the accuracy of triage. The addition of LPR to admission assessment protocols will enhance the detection of high-risk patients requiring early monitoring and simultaneously reduce inappropriate admissions

among low-risk individuals. The high negative predictive value additionally indicates usefulness as a safe rule-out procedure in severe dengue. The study is weak in that it was retrospective and single centering and only adult patients were included, so multicenter and age-ranging validations should be carried out to improve general characteristics. However, the evidence presented is highly compelling and suggests that LPR represents a viable, feasible and scalable biomarker for early severity prediction in dengue and should be considered as part of dengue management pathways.

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