



Original Research Article

Evaluation of inflammatory biomarkers as predictors of disease severity in patients with dengue fever

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Abstract

Background: Dengue fever is a major mosquito-borne viral infection with a wide clinical spectrum ranging from uncomplicated febrile illness to severe dengue with plasma leakage, shock, organ dysfunction, and mortality. Early prediction of disease severity remains challenging due to overlapping clinical features during the initial phase. Inflammatory biomarkers may provide valuable insights into immune activation and help identify patients at risk of severe disease.

Objective: To evaluate the association of inflammatory biomarkers with disease severity and assess their predictive role in patients with dengue fever.

Methods: A prospective observational study was conducted among 110 patients with laboratory-confirmed dengue infection. Clinical findings, hematological parameters, biochemical investigations, and inflammatory biomarkers including C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-10 (IL-10) were evaluated. Patients were classified according to disease severity, and biomarker levels were compared between severe and non-severe dengue groups. Receiver operating characteristic (ROC) analysis was performed to determine predictive accuracy.

Results: Among 110 patients, 38 (34.5%) developed severe dengue, while 72 (65.5%) had non-severe disease. Severe dengue patients demonstrated significantly higher levels of inflammatory biomarkers compared with non-severe cases. Ferritin levels were significantly elevated in severe dengue patients (986.4 ± 420.6 ng/mL vs 462.8 ± 238.5 ng/mL; $p < 0.001$), followed by IL-6 (112.5 ± 48.7 pg/mL vs 38.4 ± 18.6 pg/mL; $p < 0.001$) and CRP (28.6 ± 12.4 mg/L vs 14.2 ± 8.6 mg/L; $p < 0.001$). ROC analysis showed ferritin had the highest predictive performance (AUC 0.842), followed by IL-6 (AUC 0.816).

Conclusion: Inflammatory biomarkers, particularly ferritin and IL-6, were significantly associated with severe dengue and demonstrated potential predictive value. Incorporation of these biomarkers with routine clinical parameters may improve early risk stratification and management of patients with dengue fever.

Keywords: Dengue fever; inflammatory biomarkers; ferritin; C-reactive protein; interleukin-6; disease severity; predictive markers.

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Introduction

Dengue infection is one of the most important mosquito-borne viral diseases worldwide and represents a major public health challenge,

particularly in tropical and subtropical regions. It is caused by dengue virus (DENV), an RNA virus belonging to the genus *Flavivirus*, and transmitted

mainly by infected female *Aedes aegypti* and *Aedes albopictus* mosquitoes.[1] Despite a low case fatality rate with appropriate management, the high number of infections occurring annually results in significant morbidity, healthcare burden, and economic impact. Increasing urbanization, climate change, and expansion of mosquito habitats have contributed to the rising global incidence of dengue.[2] The clinical spectrum of dengue infection varies widely, ranging from asymptomatic infection and uncomplicated dengue fever to severe forms such as dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), plasma leakage, bleeding manifestations, organ dysfunction, and death.[3] Although most patients recover with supportive care, a subset develops severe disease, particularly during the critical phase, usually between the fifth and seventh day of illness.[4] This phase is characterized by increased vascular permeability, plasma leakage, thrombocytopenia, coagulation abnormalities, and systemic inflammatory responses. Early identification of patients at risk of progression to severe disease remains a major challenge in dengue management.[5] Currently, dengue severity assessment is primarily based on clinical findings such as persistent vomiting, abdominal pain, bleeding manifestations, platelet count, hematocrit changes, fluid accumulation, and organ involvement.[6] However, these parameters may become evident only after disease progression has occurred. Since early clinical features of mild and severe dengue frequently overlap, reliable biomarkers that can predict disease severity before clinical deterioration are urgently needed. The pathogenesis of severe dengue involves a complex interaction between viral factors and an exaggerated host immune response.[7] Viral infection activates innate and adaptive immune pathways, resulting in increased production of inflammatory cytokines, chemokines, and acute-phase proteins. Excessive immune activation causes endothelial dysfunction, increased vascular permeability, complement activation, platelet destruction, and coagulation disturbances, contributing to severe manifestations such as plasma leakage and shock.[8] Inflammatory biomarkers have emerged as promising predictors of dengue severity due to their ability to reflect immune activation and systemic inflammation. Several biomarkers, including C-reactive protein (CRP), ferritin, interleukins (IL-6, IL-8, IL-10), tumor necrosis factor- α (TNF- α), and procalcitonin, have been studied for their association with disease progression.[9] Elevated levels of these markers have been linked with severe dengue, prolonged hospitalization, organ involvement, and adverse outcomes. CRP, an acute-phase protein produced in response to inflammatory cytokines, serves as an indicator of systemic inflammation. Although CRP elevation in dengue is generally less marked than in bacterial infections, increased levels have been

associated with severe disease manifestations.[10] Ferritin, a marker of macrophage activation and immune dysregulation, has also been implicated in severe dengue due to its association with excessive inflammation and cytokine-mediated immune activation. Cytokines such as IL-6 and TNF- α promote endothelial activation and vascular permeability, whereas IL-10 reflects immune regulation during severe infection. An imbalance between pro-inflammatory and anti-inflammatory responses is considered an important mechanism in dengue disease progression.[11] Previous studies evaluating inflammatory biomarkers as predictors of dengue severity have reported variable findings due to differences in patient populations, timing of biomarker assessment, and disease classification criteria. Therefore, further prospective evaluation using standardized clinical parameters is required to determine their predictive accuracy and clinical applicability.[12] The present study titled "Evaluation of Inflammatory Biomarkers as Predictors of Disease Severity in Patients with Dengue Fever" aims to assess the association between selected inflammatory biomarkers and dengue severity.

Methodology:

A prospective observational study was conducted to evaluate the role of inflammatory biomarkers as predictors of disease severity in patients with dengue fever. The study was carried out in the Department of Medicine at a tertiary care hospital. The study period included patient recruitment, clinical assessment, laboratory investigations, biomarker evaluation, and follow-up until the final clinical outcome was documented.

Study Population

The study included patients who presented with clinical features suggestive of dengue fever and were confirmed to have dengue infection based on laboratory investigations. A total of 110 patients diagnosed with dengue fever were enrolled in the study.

Study Objectives

The primary objective of the study was to evaluate the association between inflammatory biomarkers and disease severity in patients with dengue fever.

The secondary objectives were:

- To assess the levels of selected inflammatory biomarkers in patients with dengue fever.
- To compare inflammatory biomarker levels between patients with mild and severe dengue.
- To determine the predictive value of inflammatory biomarkers for identifying patients at risk of severe dengue.

Inclusion Criteria

Patients fulfilling the following criteria were included:

- Patients aged ≥ 18 years.
- Patients with clinical features suggestive of dengue fever.
- Laboratory-confirmed dengue infection by dengue NS1 antigen and/or IgM/IgG antibody testing.
- Patients willing to provide informed consent for participation.
- Patients admitted during the febrile or early critical phase of illness.

Exclusion Criteria

Patients were excluded if they had:

- Evidence of bacterial or other viral infections.
- Pre-existing chronic inflammatory or autoimmune disorders.
- Known hematological disorders affecting inflammatory markers.
- Chronic liver disease, renal failure, or malignancy.
- Patients receiving immunosuppressive therapy.
- Incomplete clinical or laboratory data.

Clinical Assessment and Data Collection

After enrollment, detailed clinical history was obtained, including age, sex, duration of fever, presenting symptoms, warning signs, and history of comorbid illnesses. A complete physical examination was performed for all participants. Clinical parameters including temperature, blood pressure, pulse rate, respiratory rate, hydration status, bleeding manifestations, hepatomegaly, and signs of plasma leakage were recorded. Patients were monitored throughout hospitalization for development of warning signs, complications, and progression to severe dengue. Disease severity was classified according to the World Health Organization (WHO) dengue classification criteria into:

- Dengue fever without warning signs.
- Dengue fever with warning signs.
- Severe dengue.

Laboratory Investigations

Baseline investigations were performed for all enrolled patients. These included:

- Complete blood count with platelet count and hematocrit.
- Liver function tests.
- Renal function tests.

- Coagulation profile where clinically indicated.
- Dengue confirmation testing using NS1 antigen and/or IgM/IgG antibody assays.

Assessment of Inflammatory Biomarkers

Blood samples were collected during the early phase of illness after confirmation of dengue infection. Serum inflammatory biomarkers were assessed using standard laboratory methods.

The evaluated biomarkers included:

- C-reactive protein (CRP).
- Serum ferritin.
- Interleukin-6 (IL-6).
- Tumor necrosis factor-alpha (TNF- α).
- Interleukin-10 (IL-10).

The biomarker levels were correlated with clinical severity, laboratory parameters, duration of hospitalization, and development of complications.

Outcome Assessment

Patients were followed until discharge or clinical outcome was established. The primary outcome was the development of severe dengue as defined by WHO criteria. The relationship between inflammatory biomarker levels and disease severity was evaluated to determine their predictive ability.

Statistical Analysis

Data were entered into a structured database and analyzed using SPSS .26. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range depending on data distribution. Categorical variables were presented as frequencies and percentages.

Comparison of continuous variables between groups was performed using the independent sample t-test or Mann-Whitney U test as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test.

Correlation between inflammatory biomarkers and clinical/laboratory parameters was assessed using Pearson's or Spearman's correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of inflammatory biomarkers for severe dengue. Sensitivity, specificity, area under the curve (AUC), and optimal cutoff values were calculated.

A p-value < 0.05 was considered statistically significant.

Results:

A total of 110 patients with laboratory-confirmed dengue fever were included in the present study and were evaluated for clinical characteristics, laboratory parameters, inflammatory biomarker

levels, and their association with disease severity. The mean age of the study population was 34.6 ± 12.8 years, with a predominance of male patients. The majority of patients belonged to the young and middle-aged adult groups. Baseline demographic characteristics of the study participants are presented in Table 1.

Among the 110 patients, 72 (65.5%) patients had dengue fever without severe manifestations, while 38 (34.5%) patients developed severe dengue according to WHO dengue classification criteria. Severe dengue patients had a higher frequency of warning signs such as abdominal pain, persistent vomiting, bleeding manifestations, and evidence of plasma leakage compared with patients without severe disease (Table 2, Figure 1).

Clinical and Laboratory Characteristics According to Disease Severity

Comparison of baseline laboratory parameters between mild and severe dengue groups demonstrated significant differences in platelet count, hematocrit, liver enzymes, and inflammatory markers. Patients with severe dengue had significantly lower platelet counts and higher hematocrit levels compared with patients without severe disease. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were also significantly elevated among severe dengue patients, suggesting greater systemic involvement (Table 3).

Comparison of Inflammatory Biomarker Levels Between Mild and Severe Dengue

The levels of inflammatory biomarkers showed significant variation according to disease severity. Patients with severe dengue demonstrated significantly higher levels of CRP, ferritin, IL-6, TNF- α , and IL-10 compared with patients without severe disease. The mean serum CRP level was significantly higher among severe dengue patients compared with non-severe dengue patients (28.6 ± 12.4 mg/L vs 14.2 ± 8.6 mg/L; $p < 0.001$). Similarly, ferritin levels were markedly elevated in severe dengue patients (986.4 ± 420.6 ng/mL vs 462.8 ± 238.5 ng/mL; $p < 0.001$). Significant elevation of cytokines including IL-6, TNF- α , and IL-10 was also observed among severe cases, indicating enhanced inflammatory activation (Table 4, Figure 2).

Correlation of Inflammatory Biomarkers with Disease Severity Parameters

Correlation analysis demonstrated a significant positive association between inflammatory biomarkers and markers of disease severity. Serum ferritin showed a strong positive correlation with

disease severity score and duration of hospitalization. IL-6 and TNF- α levels were significantly correlated with platelet reduction, hematocrit elevation, and evidence of plasma leakage. CRP levels also demonstrated a significant association with prolonged hospitalization and severe disease manifestations (Table 5).

Predictive Performance of Inflammatory Biomarkers for Severe Dengue

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of inflammatory biomarkers for identifying severe dengue cases. Among the evaluated biomarkers, ferritin demonstrated the highest predictive performance with an area under the curve (AUC) of 0.842, followed by IL-6 (AUC 0.816) and TNF- α (AUC 0.791). CRP also showed significant predictive ability with an AUC of 0.756. A ferritin cutoff value of >650 ng/mL predicted severe dengue with a sensitivity of 81.6% and specificity of 76.4%. IL-6 and CRP also demonstrated clinically useful predictive accuracy (Table 6, Figure 3).

Multivariate Analysis of Predictors of Severe Dengue

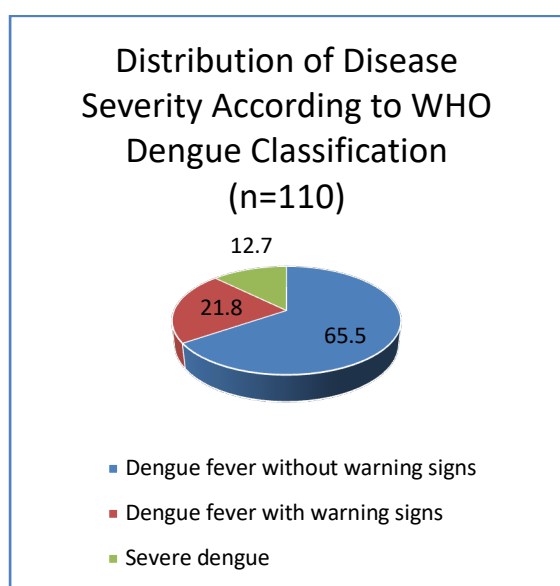
On multivariate logistic regression analysis, elevated ferritin, IL-6, and thrombocytopenia were found to be independent predictors of severe dengue. Patients with ferritin levels above the identified cutoff had significantly higher odds of developing severe dengue compared with patients with lower ferritin levels. Overall, the findings demonstrated that increased inflammatory biomarker levels were significantly associated with disease severity and may serve as useful predictors for early identification of patients at risk of severe dengue.

Table 1: Demographic Characteristics of Study Participants (n=110)

Variable	Number (%) / Mean $\pm$ SD
Age (years)	34.6 ± 12.8
Male	68 (61.8%)
Female	42 (38.2%)
Fever duration at admission (days)	4.8 ± 1.6
Diabetes mellitus	14 (12.7%)
Hypertension	11 (10.0%)

Table 2: Distribution of Disease Severity According to WHO Dengue Classification (n=110)

Disease category	Number (%)
Dengue fever without warning signs	72 (65.5%)
Dengue fever with warning signs	24 (21.8%)
Severe dengue	14 (12.7%)

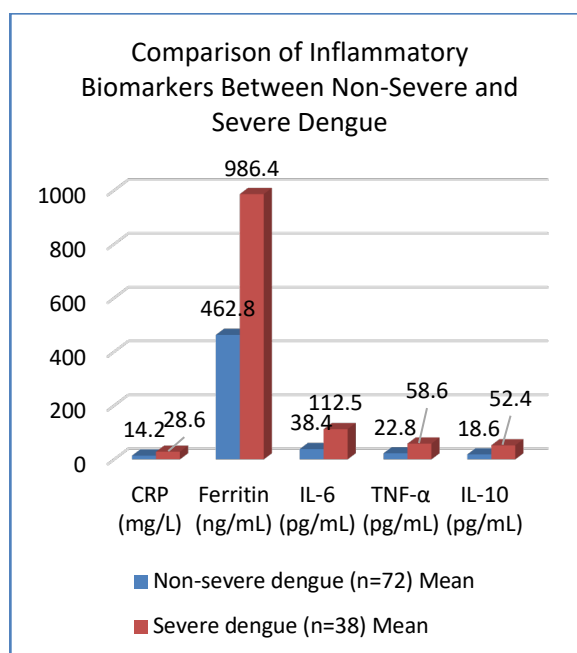
**Figure 1. Distribution of Disease Severity According to WHO Dengue Classification (n=110)****Table 3: Comparison of Clinical and Laboratory Parameters Between Non-Severe and Severe Dengue**

Parameter	Non-severe dengue (n=72)	Severe dengue (n=38)	p-value
Platelet count ($\times 10^9/L$)	78.4 $\pm$ 24.6	42.8 $\pm$ 18.5	<0.001
Hematocrit (%)	39.6 $\pm$ 4.2	44.8 $\pm$ 5.1	<0.001
AST (U/L)	86.5 $\pm$ 48.2	168.4 $\pm$ 92.6	<0.001
ALT (U/L)	72.6 $\pm$ 41.8	142.8 $\pm$ 76.4	<0.001

Hospital stay (days)	4.2 $\pm$ 1.3	7.1 $\pm$ 2.4	<0.001
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Table 4: Comparison of Inflammatory Biomarkers Between Non-Severe and Severe Dengue

Biomarker	Non-severe dengue (n=72)	Severe dengue (n=38)	p-value
CRP (mg/L)	14.2 $\pm$ 8.6	28.6 $\pm$ 12.4	<0.001
Ferritin (ng/mL)	462.8 $\pm$ 238.5	986.4 $\pm$ 420.6	<0.001
IL-6 (pg/mL)	38.4 $\pm$ 18.6	112.5 $\pm$ 48.7	<0.001
TNF- α (pg/mL)	22.8 $\pm$ 10.4	58.6 $\pm$ 24.5	<0.001
IL-10 (pg/mL)	18.6 $\pm$ 9.2	52.4 $\pm$ 21.8	<0.001

**Figure 2. Comparison of Inflammatory Biomarkers Between Non-Severe and Severe Dengue****Table 5: Correlation of Inflammatory Biomarkers with Disease Severity Parameters**

Biomarker	Severity score	Platelet count	Hospital stay
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CRP	r=0.42, p<0.001	r=-0.36, p<0.001	r=0.39, p<0.001
Ferritin	r=0.62, p<0.001	r=-0.54, p<0.001	r=0.58, p<0.001
IL-6	r=0.56, p<0.001	r=-0.48, p<0.001	r=0.51, p<0.001
TNF- α	r=0.49, p<0.001	r=-0.41, p<0.001	r=0.46, p<0.001

Table 6: ROC Analysis of Inflammatory Biomarkers for Prediction of Severe Dengue

Biomarker	Cut-off value	AUC	Sensitivity (%)	Specificity (%)
Ferritin	>650 ng/mL	0.842	81.6	76.4
IL-6	>75 pg/mL	0.816	78.9	73.6
TNF- α	>40 pg/mL	0.791	73.7	72.2
CRP	>22 mg/L	0.756	71.1	68.1
IL-10	>35 pg/mL	0.774	76.3	70.8

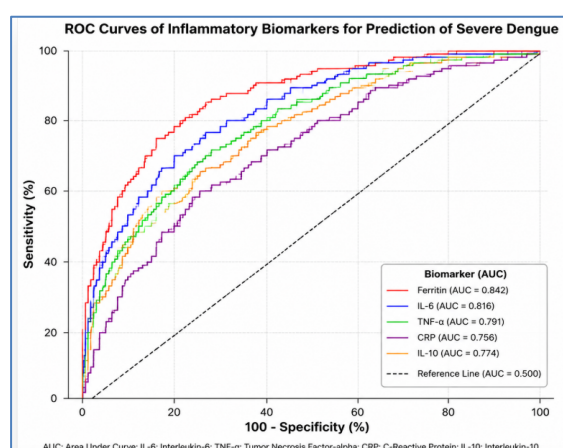


Figure 3. ROC Analysis of Inflammatory Biomarkers for Prediction of Severe Dengue

Discussion

Dengue fever remains a significant global health challenge due to its variable clinical spectrum, ranging from mild febrile illness to severe complications such as plasma leakage, shock, hemorrhage, and organ dysfunction. Early prediction of disease progression remains difficult because initial clinical manifestations often overlap between mild and severe cases. The present study evaluated 110 patients with confirmed dengue infection to assess the association of inflammatory biomarkers with disease severity. The study demonstrated that elevated levels of CRP, ferritin, IL-6, TNF- α , and IL-10 were significantly associated with severe dengue manifestations. In the present study, 38 (34.5%) patients developed severe dengue, whereas 72 (65.5%) patients had non-severe disease. Severe dengue patients showed greater systemic involvement, with significantly lower platelet counts, higher hematocrit levels, elevated liver enzymes, and longer hospital stay. These findings support the role of immune-mediated mechanisms, including endothelial dysfunction, inflammatory activation, and increased vascular permeability, in the progression of severe dengue. The pathogenesis of severe dengue is primarily driven by an exaggerated host immune response. Activation of immune pathways results in excessive production of cytokines, chemokines, and acute-phase proteins, leading to endothelial injury, plasma leakage, coagulation abnormalities, and organ dysfunction. Previous studies have also emphasized the importance of inflammatory mediators in determining dengue severity. Meta-analyses have reported that cytokines such as IL-6, IL-10, and other inflammatory markers are associated with severe disease outcomes and may serve as early predictors of progression. In the present study, CRP levels were significantly higher among severe dengue patients compared with non-severe cases (28.6 ± 12.4 mg/L vs 14.2 ± 8.6 mg/L; $p < 0.001$). This indicates increased systemic inflammatory activation in patients with severe disease. Similar observations have been reported by Nayak et al. [13] who demonstrated a significant association between elevated CRP levels and dengue severity. Sibia et al. [14] also reported increased CRP along with inflammatory cytokines such as IL-6 and TNF- α in patients with severe dengue, supporting the role of CRP as an adjunctive marker for disease progression. Ferritin showed one of the strongest associations with severe dengue in the present study. Severe cases had significantly higher ferritin levels compared with non-severe cases (986.4 ± 420.6 ng/mL vs 462.8 ± 238.5 ng/mL; $p < 0.001$). ROC analysis demonstrated that ferritin had the highest predictive performance among evaluated biomarkers (AUC 0.842) with a sensitivity of 81.6% and specificity of 76.4% at a cutoff value of >650 ng/mL. These findings are consistent with previous studies showing that hyperferritinemia reflects

macrophage activation, cytokine release, and immune dysregulation during severe dengue. Systematic reviews and cohort studies have identified ferritin as a promising prognostic biomarker associated with severe manifestations and adverse outcomes. The present study also demonstrated significantly elevated cytokine levels among severe dengue patients. IL-6 levels were markedly increased in severe cases (112.5 ± 48.7 pg/mL vs 38.4 ± 18.6 pg/mL; $p < 0.001$), along with increased TNF- α and IL-10 levels. IL-6 contributes to endothelial activation, acute-phase response, and inflammatory amplification, whereas TNF- α promotes vascular permeability and tissue inflammation. Increased IL-10 levels reflect activation of immune regulatory pathways and have been associated with severe dengue outcomes in previous studies. ROC analysis revealed that all evaluated inflammatory biomarkers showed significant predictive ability for severe dengue. Ferritin demonstrated the highest AUC (0.842), followed by IL-6 (0.816), TNF- α (0.791), IL-10 (0.774), and CRP (0.756). These findings suggest that inflammatory biomarkers may complement conventional clinical and laboratory parameters for early risk stratification. Previous studies have similarly suggested that combined assessment of inflammatory markers may improve prediction accuracy compared with individual biomarkers. Clinically, early identification of patients at risk of severe dengue may allow closer monitoring, timely fluid management, appropriate hospitalization, and prevention of complications. However, inflammatory biomarkers should be considered complementary tools and interpreted along with clinical warning signs, platelet trends, hematocrit changes, and organ function parameters. The present study was limited by its single-center design and moderate sample size. Serial measurement of biomarkers during different phases of dengue infection was not performed, which may provide further insight into biomarker kinetics. Future multicentric studies with larger cohorts and combined biomarker models are required. In conclusion, the present study demonstrated that elevated inflammatory biomarkers, particularly ferritin, IL-6, TNF- α , IL-10, and CRP, were significantly associated with dengue severity. These markers may serve as useful predictors for early identification of patients at risk of severe dengue and may contribute to improved clinical decision-making and patient outcomes.

Conclusion

The present study demonstrated that elevated inflammatory biomarkers, including CRP, ferritin, IL-6, TNF- α , and IL-10, were significantly associated with increased dengue disease severity. Among the evaluated markers, ferritin and IL-6

showed the highest predictive potential for identifying patients at risk of severe dengue. These biomarkers may serve as useful adjuncts to clinical and laboratory parameters for early risk stratification and timely management. Further multicentric studies with larger sample sizes are required to validate their routine clinical application.

Limitations

The study was limited by its single-center design and relatively small sample size, which may affect the generalizability of the findings. Serial assessment of inflammatory biomarkers during different phases of dengue infection was not performed, limiting evaluation of biomarker trends. Further multicentric studies with larger populations and longitudinal biomarker analysis are required to confirm these findings.

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