

A Study on Association of Interleukin-6, Lactate Dehydrogenase, Lactate, Ferritin and Procalcitonin with Severity of Dengue Fever at a Pediatric Tertiary Care Hospital

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Abstract

Background: Early identification of children at risk of severe dengue is important for timely monitoring and management. Inflammatory and biochemical biomarkers such as interleukin-6 (IL-6), procalcitonin, ferritin, lactate dehydrogenase (LDH), and lactate may have potential roles in assessing disease severity. The objective is to determine the association of IL-6, LDH, lactate, ferritin, and procalcitonin with the severity of dengue fever in children. **Material and Methods:** This prospective observational study included 155 children aged <18 years with confirmed dengue admitted to a tertiary-care pediatric hospital in Bengaluru over 18 months. IL-6, LDH, lactate, ferritin, and procalcitonin were measured at presentation. Children were subsequently classified as dengue without warning signs, dengue with warning signs, or severe dengue. ROC curve and multivariable logistic regression analyses were performed. **Results:** Of 155 children, 22 (14.2%) had dengue without warning signs, 103 (66.4%) had dengue with warning signs, and 30 (19.3%) had severe dengue. Procalcitonin, ferritin, and IL-6 increased significantly with disease severity ($p < 0.001$), whereas LDH and lactate did not show significant differences. For differentiating severe dengue from dengue without warning signs, ferritin at a cut-off of 966 had an AUC of 0.96, sensitivity of 90.1%, and specificity of 90.9%; procalcitonin at 0.42 ng/mL had an AUC of 0.95, sensitivity of 90.0%, and specificity of 86.4%; and IL-6 at 8.85 pg/mL had an AUC of 0.94, sensitivity of 90.0%, and specificity of 81.8%. On multivariable analysis, ferritin (AOR 1.04; 95% CI 1.01–1.08; $p = 0.015$) and IL-6 (AOR 2.25; 95% CI 1.39–3.64; $p < 0.001$) remained significantly associated with severe dengue. **Conclusion:** Ferritin, IL-6, and procalcitonin showed significant associations with dengue severity and good discriminatory performance. Ferritin and IL-6 remained independently associated with severe dengue and may have potential utility as adjunctive biomarkers for early risk stratification in children.

Keywords: Dengue; Severe dengue; Interleukin-6; Ferritin; Procalcitonin; Lactate dehydrogenase; Lactate; Children.

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INTRODUCTION

Dengue is an important mosquito-borne viral infection in children, with a clinical spectrum ranging from uncomplicated febrile illness to severe disease characterized by plasma leakage, shock, bleeding, and organ dysfunction. Early identification of children likely to develop severe dengue remains important because clinical deterioration may occur rapidly during the critical phase. Recent pediatric studies have therefore focused on biomarkers that could facilitate early recognition of severe disease.^[1,2]

Inflammatory and metabolic responses have an important role in dengue pathogenesis. Ferritin, an acute-phase reactant, may increase markedly during dengue infection, and higher concentrations have been associated with severe disease and adverse outcomes.^[3,4] Pediatric evidence also suggests that ferritin may have potential value in differentiating severe from non-severe dengue.^[5]

Cytokine dysregulation contributes to endothelial dysfunction, plasma leakage, and organ involvement in dengue. Interleukin-6 (IL-6) is an important pro-

inflammatory cytokine that has been investigated as a potential marker of dengue severity.^[6] Previous studies have demonstrated alterations in circulating cytokines, including IL-6, in patients with severe dengue, supporting the role of an exaggerated inflammatory response in disease progression.^[7]

Other biochemical markers, including lactate dehydrogenase (LDH), serum lactate, and procalcitonin (PCT), may reflect cellular injury, tissue hypoperfusion, and systemic inflammatory responses. Assessment of these biomarkers at presentation may therefore provide additional information for early risk

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stratification.

The present study was conducted to determine the association of IL-6, LDH, lactate, ferritin, and procalcitonin with the severity of dengue fever in children admitted to a tertiary-care pediatric hospital.

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted at the Indira Gandhi Institute of Child Health, Bengaluru, a tertiary-care pediatric hospital in Southern India, over a period of 18 months.

Study Population: Children aged <18 years admitted with confirmed dengue infection and fulfilling the predefined inclusion and exclusion criteria were enrolled. A total of 155 children were included in the final study.

Inclusion Criteria

1. Children aged <18 years at the time of admission.
2. Laboratory-confirmed dengue infection with NS1 antigen positivity by ELISA.

Exclusion Criteria

Children with significant pre-existing comorbidities, including chronic kidney disease, hypothyroidism, type 1 diabetes mellitus, and liver disease, were excluded.

Study Procedure: After obtaining written informed consent from the parents or guardians, demographic details, clinical history, presenting symptoms, examination findings, and relevant laboratory parameters were recorded using a predefined study proforma.

Children presenting with clinical features suggestive of dengue, including acute febrile illness, abdominal pain, flushing, rash, and generalized aches and pains, were evaluated for dengue infection. Blood samples were obtained on the day of admission for dengue testing and estimation of IL-6, LDH, serum lactate, ferritin, and procalcitonin. Dengue RT-PCR and NS1 antigen testing by ELISA were performed as applicable. Blood cultures were obtained to rule out concurrent bacterial infection.

All enrolled children were treated according to the standard dengue management protocol and followed throughout their hospital stay. Based on their clinical course, patients were categorized as dengue without warning signs, dengue with warning signs, or severe dengue. The association of admission levels of IL-6, LDH, lactate, ferritin, and procalcitonin with disease severity was subsequently evaluated.

Where available, the relationship of NS1 titres and dengue virus serotypes with dengue severity was also assessed.

Sample Size

The sample size was estimated using the formula:

$$n = Z^2(1-\alpha/2) \times p(1-p) / d^2$$

where $Z = 1.96$ at a 95% confidence level, p represented the expected prevalence of severe dengue, and d represented the absolute precision, which was taken as 10%.

Based on the prevalence reported in the study by Shankar and B.P., the calculated minimum sample size was 75. After accounting for approximately 10% attrition, the required sample was approximately 83 and was initially rounded to 90 children. However, recruitment was extended to 155 children to increase the precision and robustness of the study findings.

Outcome Measures: The primary outcome was the association of admission levels of IL-6, LDH, lactate, ferritin, and procalcitonin with dengue severity.

Secondary analyses included assessment of the diagnostic performance of individual biomarkers for differentiating dengue with warning signs and severe dengue from dengue without warning signs, and evaluation of factors independently associated with severe dengue.

Statistical Analysis: Data were entered into Microsoft Excel 2019 and analyzed using R statistical software. Categorical variables were expressed as frequencies and percentages. Continuous variables were summarized as mean $\pm$ standard deviation or median with interquartile range, depending on their distribution.

Continuous variables were compared using the Student's t-test for normally distributed data and appropriate non-parametric tests for skewed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminatory ability of IL-6, LDH, lactate, ferritin, and procalcitonin and to determine appropriate cut-off values, sensitivity, specificity, and area under the ROC curve (AUC) for prediction of dengue severity. Multivariable logistic regression analysis was performed to identify factors independently associated with severe dengue. A p -value <0.05 was considered statistically significant.

RESULTS

A total of 155 children with dengue were included. At final classification, 22 (14.2%) had dengue without warning signs, 103 (66.4%) had dengue with warning signs, and 30 (19.3%) had severe dengue. The largest proportion of children were aged 5–10 years (39.3%), and 81 (52.3%) were males. Age and sex distributions did not differ significantly according to dengue severity ($p=0.451$ and $p=0.56$, respectively).

Table 1: Demographic characteristics according to dengue severity

Characteristic	Dengue without warning signs (n=22)	Dengue with warning signs (n=103)	Severe dengue (n=30)	p-value
Age group, n (%)				0.451
<1 year	5 (22.7)	10 (9.7)	2 (6.7)	
1–5 years	7 (31.8)	23 (22.3)	7 (23.3)	
5–10 years	6 (27.3)	42 (40.8)	13 (43.3)	
>10 years	4 (18.2)	28 (27.2)	8 (26.7)	
Sex, n				0.56
Male	10	54	17	
Female	12	49	13	

At presentation, 76 children were classified as dengue without warning signs, 74 as dengue with warning signs, and 5 as severe dengue. During hospitalization, 49 of the initially uncomplicated cases progressed to dengue with warning signs and 5 progressed to severe dengue, while 20 children initially presenting with warning signs subsequently progressed to severe dengue.

Admission levels of procalcitonin, ferritin, and IL-6

increased with dengue severity. Mean procalcitonin increased from 0.3 in dengue without warning signs to 2.1 ng/mL in severe dengue, while ferritin increased from 606.45 to 2174.6. IL-6 also showed a marked increase across severity categories. Differences in procalcitonin, ferritin, and IL-6 were statistically significant ($p < 0.001$), whereas LDH and lactate did not show statistically significant differences across the three severity groups in the supplied analysis.

Table 2: Comparison of biomarkers according to dengue severity

Parameter, mean (SD)	Dengue without warning signs	Dengue with warning signs	Severe dengue	p-value
Day of illness	4.2 (1.4)	4.8 (0.7)	5.3 (0.8)	<0.001
Procalcitonin (ng/mL)	0.3 (0.5)	0.5 (0.3)	2.1 (1.5)	<0.001
Ferritin	606.45 (427.41)	1090.7 (919.3)	2174.6 (1114.6)	<0.001
LDH	405.0 (75.8)	437.6 (93.1)	438.9 (81.9)	0.27
Lactate	26.1 (3.9)	41.5 (4.1)	48.9 (6.5)	0.78
IL-6 (pg/mL)	5.7 (3.4)	8.9 (1.8)	34.4 (3.9)	<0.001
NS1 ELISA titre	4.2 (0.7)	4.3 (1.1)	4.0 (1.1)	0.41

On univariate analysis, day of illness, procalcitonin, ferritin, and IL-6 were significantly associated with severe dengue (all $p < 0.001$). However, after simultaneous adjustment in the multivariable model, ferritin and IL-6 remained

independently associated with severe dengue, whereas day of illness and procalcitonin were no longer statistically significant.

Table 3: Logistic regression analysis for factors associated with severe dengue

Predictor	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Day of illness	4.02 (2.10–8.10)	<0.001	1.92 (0.72–5.07)	0.18
Procalcitonin	82.2 (34.7–194.2)	<0.001	0.71 (0.07–6.70)	0.76
Ferritin	1.08 (1.05–1.10)	<0.001	1.04 (1.01–1.08)	0.015
IL-6	3.90 (2.64–5.48)	<0.001	2.25 (1.39–3.64)	<0.001

ROC analysis demonstrated significant discriminatory performance for procalcitonin, ferritin, and IL-6. For differentiating dengue with warning signs from dengue without warning signs, procalcitonin at a cut-off of 0.34 ng/mL had an AUC of 0.89, sensitivity of 93.2%, and specificity of 86.4%. IL-6 had an AUC of 0.83, while ferritin

had an AUC of 0.79.

For differentiating severe dengue from dengue without warning signs, ferritin demonstrated an AUC of 0.96, followed by procalcitonin (AUC 0.95) and IL-6 (AUC 0.94); all were statistically significant ($p < 0.001$).

Table 4: ROC analysis of biomarkers for discrimination of dengue severity

Comparison/Marker	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
Dengue vs dengue with warning signs					
Procalcitonin	0.34 ng/mL	93.2	86.4	0.89 (0.78–0.99)	<0.001
Ferritin	848.5*	86.4	72.7	0.79 (0.64–0.93)	<0.001
IL-6	7.85 pg/mL	92.2	77.2	0.83 (0.69–0.96)	<0.001
Dengue vs severe dengue					
Ferritin	966.0*	90.1	90.9	0.96 (0.90–0.99)	<0.001
IL-6	8.85 pg/mL	90.0	81.8	0.94 (0.87–0.99)	<0.001
Procalcitonin	0.42 ng/mL	90.0	86.4	0.95 (0.89–0.99)	<0.001

AUC: area under the receiver operating characteristic curve; CI: confidence interval.

ROC analysis showed that procalcitonin, ferritin, and IL-6 significantly discriminated dengue severity (all $p < 0.001$). For differentiating dengue with warning signs from dengue without warning signs, procalcitonin showed the highest AUC (0.89), with 93.2% sensitivity and 86.4% specificity at a cut-off of 0.34 ng/mL. For severe dengue, ferritin demonstrated the highest AUC (0.96), followed by procalcitonin (0.95) and IL-6 (0.94), indicating high discriminatory performance of these biomarkers for severe disease.

DISCUSSION

Dengue in children has a variable clinical course, ranging from uncomplicated febrile illness to severe disease with plasma leakage, shock, bleeding, and organ dysfunction. Early recognition of children at risk of progression remains important. In the present study, 66.4% of children developed dengue with warning signs and 19.3% developed severe dengue. Cytokine dysregulation has been implicated in dengue severity, and previous studies have demonstrated distinct cytokine profiles in severe disease.^[8] More recent studies evaluating inflammatory mediators have similarly suggested a potential role for IL-6 in

severity assessment.^[9]

In the present study, procalcitonin, ferritin, and IL-6 increased significantly with increasing dengue severity ($p < 0.001$). Procalcitonin increased from 0.3 ng/mL in dengue without warning signs to 2.1 ng/mL in severe dengue, while ferritin increased from 606.45 to 2174.6. IL-6 also demonstrated a marked increase across severity categories. In contrast, LDH and lactate did not show statistically significant differences among the three groups. Previous studies have evaluated LDH as a marker of dengue severity, with variable discriminatory performance.^[10] Lactate has been particularly useful in children with dengue shock syndrome, where elevated lactate may reflect impaired tissue perfusion and has been associated with adverse outcomes.^[11,12] Clinical context and timing of measurement may therefore influence the usefulness of these biomarkers. ROC analysis demonstrated good discriminatory performance of procalcitonin, IL-6, and ferritin. For differentiating dengue with warning signs from dengue without warning signs, procalcitonin at a cut-off of 0.34 ng/mL provided 93.2% sensitivity and 86.4% specificity, while IL-6 and ferritin also showed significant discrimination. For severe dengue, ferritin at a cut-off of 966 demonstrated an AUC of 0.96, while procalcitonin and IL-6 demonstrated AUCs of 0.95 and 0.94, respectively. These findings support the potential usefulness of inflammatory and metabolic biomarkers as adjuncts to clinical assessment. Nevertheless, tissue hypoperfusion and lactate abnormalities may become more prominent after circulatory compromise develops, particularly in dengue shock.^[13]

Systematic evidence indicates that clinical and laboratory parameters can help identify patients at risk of progression to severe dengue, although no individual marker should replace serial clinical assessment.^[14] Other inflammatory biomarkers have also been investigated for early prediction of disease progression, emphasizing the multifactorial nature of severe dengue.^[15]

On univariate analysis, day of illness, procalcitonin, ferritin, and IL-6 were significantly associated with severe dengue. However, after multivariable adjustment, only ferritin (AOR 1.04, 95% CI 1.01–1.08; $p = 0.015$) and IL-6 (AOR 2.25, 95% CI 1.39–3.64; $p < 0.001$) remained statistically significant. These findings suggest that ferritin and IL-6 may provide additional information regarding disease severity at presentation. However, the observational, single-centre design and measurement of biomarkers at a single time point limit causal and temporal interpretation. Larger multicentre prospective studies with serial biomarker measurements are required to validate clinically applicable cut-offs.

CONCLUSION

Procalcitonin, ferritin, and IL-6 were significantly associated with dengue severity at presentation, while LDH and lactate did not show significant differences across severity groups in the present study. Ferritin and IL-6 remained independently associated with severe dengue after multivariable adjustment. ROC analysis demonstrated high discriminatory ability of ferritin, IL-6, and procalcitonin for severe dengue.

These biomarkers may therefore be useful as adjuncts to clinical assessment for early risk stratification of pediatric dengue, although larger prospective studies are required to validate the identified cut-offs.

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Conflicts of interest

There are no conflicts of interest.

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