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Inflammatory Biomarkers in Dengue Infection: Their Role in Disease Severity, Clinical Progression, and Prognostication

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Abstract

Dengue infection ranges from a self-limiting febrile illness to severe disease characterised by plasma leakage, shock, bleeding and organ dysfunction. Although most patients recover without major complications, a proportion progress rapidly to severe disease, making early recognition of high-risk patients an important clinical challenge. Conventional clinical assessment and routine laboratory investigations remain the foundation of dengue management, but they may not fully reflect the biological processes associated with disease progression.

Inflammatory and immune responses have an important role in dengue pathogenesis. Infection activates multiple host pathways, resulting in the release of cytokines, chemokines and other inflammatory mediators. These responses interact with endothelial activation, disruption of the vascular barrier and changes in vascular permeability, which are particularly relevant to severe disease. Consequently, several inflammatory biomarkers, including interleukin-6, interleukin-8, interleukin-10, tumour necrosis factor-alpha, C-reactive protein and ferritin, have been investigated for their potential association with disease severity and clinical outcome.

However, the prognostic value of individual biomarkers remains inconsistent. Differences in the timing of sample collection, disease phase, previous dengue exposure, infecting serotype, age, study population and laboratory methods can substantially influence biomarker concentrations and their observed associations with severity. Recent research has therefore shifted from individual cytokines towards combinations of inflammatory, endothelial and routinely available laboratory markers.

Emerging approaches such as proteomic profiling and machine-learning-based prediction models are further expanding the search for clinically useful biomarker signatures. These approaches may help identify biological patterns associated with progression to severe disease rather than relying on a single inflammatory mediator. Nevertheless, limited external validation, variation between study populations and the absence of standardised biomarker thresholds remain important barriers to clinical application.

This review summarises current evidence on inflammatory biomarkers in dengue, examines

their relationship with disease severity and clinical progression, and discusses their potential role in early prognostication. Particular emphasis is placed on the transition from single-biomarker approaches to integrated inflammatory-endothelial panels and emerging high-dimensional strategies.

Keywords: Dengue; inflammatory biomarkers; cytokines; chemokines; severe dengue; disease severity; prognostication; endothelial dysfunction; plasma leakage; ferritin

1. Introduction

Dengue is one of the most important mosquito-borne viral infections worldwide, with transmission occurring across tropical and subtropical regions. The global burden has increased substantially in recent years, creating an increasing need for effective approaches to identify patients at risk of severe disease. The World Health Organization reported more than 14 million dengue cases globally in 2024, making it the highest annual burden recorded to date [1].

The clinical course of dengue is difficult to predict during the early stages of infection. Patients commonly present with fever, headache, myalgia, gastrointestinal symptoms and other nonspecific manifestations. While many recover uneventfully, some develop plasma leakage, shock, severe bleeding or organ dysfunction during the later stages of illness [2,3]. The transition towards severe disease may occur over a relatively short period, particularly around the critical phase, making early risk assessment clinically important.

Severe dengue is not explained by viral replication alone. The disease results from a complex interaction between viral factors and the host immune response. Activation of innate and adaptive immune pathways leads to the production of cytokines and chemokines, while endothelial activation and disruption of the vascular barrier contribute to plasma leakage and other manifestations of severe disease [3-5].

These observations have generated considerable interest in inflammatory biomarkers as potential indicators of disease severity. Cytokines such as interleukin (IL)-6, IL-8, IL-10 and tumour necrosis factor-alpha (TNF-α) have been extensively investigated, along with markers such as C-reactive protein (CRP), ferritin and several endothelial mediators [6-8]. However, findings across studies have not always been consistent.

One of the major reasons for this inconsistency is the dynamic nature of dengue infection. Biomarker concentrations change throughout the course of illness, and the same marker may have different significance depending on whether it is measured during the febrile, critical or recovery phase. Differences in primary versus secondary infection, age, infecting serotype, geographical setting and laboratory methodology may further influence the observed biomarker profile [6,9].

Recent research has consequently moved beyond the search for a single “severe dengue marker”. Studies increasingly combine inflammatory biomarkers with endothelial and routine laboratory parameters to determine whether a multi-marker approach can improve early prediction. More recent work has also introduced proteomic and machine-learning approaches, allowing researchers to investigate broader molecular signatures associated with disease progression [10,11].

This review focuses on the role of inflammatory biomarkers in dengue severity, clinical progression and prognostication. It also examines the biological basis of these associations, the limitations of current evidence and the emerging shift towards integrated biomarker panels and

high-dimensional molecular approaches.

2. Dengue Infection and the Host Inflammatory Response

Following infection, dengue virus interacts with several cells of the immune system, particularly monocytes and dendritic cells. Recognition of viral components activates innate immune pathways and leads to the production of inflammatory mediators [4,12].

The inflammatory response is not uniform across patients. Previous exposure to dengue virus can modify the immune response during subsequent infection. Antibodies generated during a previous infection may, under certain circumstances, facilitate viral entry into Fc-receptor-bearing cells, a phenomenon known as antibody-dependent enhancement [13]. This mechanism has been proposed as one of the factors contributing to increased risk of severe disease during some secondary infections.

T-cell responses also contribute to dengue immunity. Both CD4+ and CD8+ T cells participate in antiviral responses, while differences in the magnitude and specificity of these responses may influence disease manifestations [14]. The resulting immune environment involves several interconnected pathways rather than a single inflammatory mediator.

From a biomarker perspective, this is particularly important because circulating cytokine levels represent a changing biological process. A high concentration of a cytokine at one stage of illness may reflect active immune activation, while the same concentration at another stage may have a different clinical meaning. Therefore, interpretation of inflammatory biomarkers requires consideration of disease timing and patient characteristics.

3. Inflammatory Biomarkers and Disease Severity

3.1 Interleukin-6 and TNF-α

IL-6 is among the most extensively studied inflammatory cytokines in dengue. Increased IL-6 concentrations have been reported in patients with severe manifestations, suggesting a relationship between systemic inflammatory activation and disease severity [6,15]. However, the evidence is not sufficiently consistent to support IL-6 as an independent early predictor in routine clinical practice.

TNF-α has similarly been investigated because of its role in inflammatory signalling and vascular responses. Increased TNF-α activity has been described in severe dengue, although its predictive value varies between studies [6].

Recent research has also examined soluble TNF receptor-1 (sTNFR1), which may provide information about TNF-related signalling beyond measurement of TNF-α itself. Inflammatory and endothelial markers studied together have shown potential for differentiating patients according to disease severity [8].

This illustrates an important change in biomarker research. Instead of asking whether one cytokine is simply “higher” in severe dengue, current studies are increasingly examining whether a group of biologically related markers can identify patients at risk of deterioration.

3.2 IL-8 and Chemokines

IL-8 has shown a relatively consistent association with severe dengue in several studies. A systematic review and meta-analysis of early biomarkers reported an association between

elevated IL-8 and dengue haemorrhagic fever [7].

The biological relevance of IL-8 is also plausible because it participates in neutrophil recruitment and inflammatory-cell signalling. Nevertheless, the clinical value of IL-8 depends on the timing of measurement and the population studied.

Other chemokines, including MCP-1, RANTES and CXCL10/IP-10, have also been investigated. These mediators reflect different aspects of immune-cell recruitment and activation, and their combined assessment may provide a broader picture of the inflammatory response than any single cytokine.

3.3 IL-10 and Immune Regulation

IL-10 is particularly interesting because it has an immunoregulatory role. Increased IL-10 concentrations have been observed in dengue and have been investigated as a marker of severe disease [6].

However, elevated IL-10 should not simply be interpreted as evidence of harmful inflammation. Its increase may represent an attempt by the immune system to control an intense inflammatory response. Therefore, the relationship between IL-10 and disease severity is more complex than a simple increase-versus-decrease comparison.

A recent review of dengue immunomodulation highlighted IL-10 along with IL-6, IL-8, TNF-related pathways and several other immune mediators as potential contributors to disease severity [16]. The review also emphasised the importance of innate immune cells and adaptive immune responses in determining the overall inflammatory environment.

Several inflammatory and endothelial biomarkers have been investigated in dengue, with varying degrees of association with disease severity and prognostic potential. Their principal biological functions, reported relationships with severe disease, and key limitations are summarised in Table 1.

Table 1: Major inflammatory and endothelial biomarkers investigated in dengue: biological role, association with disease severity, prognostic relevance, and limitations.

S.No	Biomarker	Biological role	Association with severe dengue	Potential prognostic relevance	Major limitations
1	IL-6[6]	Pro-inflammatory cytokine	Frequently elevated in severe disease	May reflect systemic inflammation	Timing-dependent; inconsistent independent predictive value
2	TNF-α [7]	Inflammatory/vascular signalling	Associated with severe disease	Potential marker of inflammatory activation	Variable findings
3	IL-8 [20]	Neutrophil recruitment	Relatively consistent association	Potential early biomarker	Dependent on sampling

					time/population
4	IL-10	Immunoregulatory cytokine	Associated with severity in some studies	May reflect dysregulated immune response	Biological interpretation is complex
5	CRP	Acute-phase inflammatory marker	Associated with severe manifestations	Attractive because widely available	Nonspecific
6	Ferritin	Systemic inflammatory activation	Higher in severe dengue	Potential accessible prognostic marker	High inter-study heterogeneity
7	Syndecan-1[17]	Glycocalyx disruption	Associated with severe dengue	Marker of vascular injury	Limited routine availability
8	VCAM-1 [7]	Endothelial activation	Associated with severe disease	May complement inflammatory markers	Assay availability
9	Angiopoietin-2[8]	Endothelial activation/permeability	Associated with severe dengue	Potential vascular biomarker	Requires validation

4. Inflammation, Endothelial Dysfunction and Plasma Leakage

The clinical importance of inflammatory activation becomes clearer when it is considered alongside endothelial dysfunction. Plasma leakage is a major feature of severe dengue, and changes in endothelial permeability play an important role in its development [3,5].

Dengue NS1 has been shown to affect the endothelial glycocalyx and contribute to increased vascular permeability [17]. In parallel, inflammatory mediators and host-derived factors can alter endothelial-cell function. Cytokines, platelet-activating factor, vascular endothelial growth factor and several proteases have been implicated in processes that can compromise the vascular barrier [4,18].

This interaction explains why inflammatory biomarkers alone may not completely reflect the development of severe disease. A cytokine may indicate the intensity of immune activation, while an endothelial biomarker may provide information about the vascular consequences of that response.

Syndecan-1 is one of the markers that has received increasing attention because it is associated with endothelial glycocalyx disruption. Increased syndecan-1 concentrations have been

reported in severe dengue [7,17]. Other endothelial markers, including VCAM-1 and angiopoietin-2, have also shown potential associations with severe disease [7,8].

Thus, the biological pathway linking inflammation with endothelial dysfunction provides a strong rationale for studying inflammatory and endothelial biomarkers together.

5. Biomarkers Across the Clinical Course of Dengue

The timing of biomarker measurement is one of the most important factors influencing its prognostic value.

During the febrile phase, viral replication and immune activation are prominent, but clinical features of severe disease may not yet be apparent. As the patient approaches the critical phase, changes in vascular permeability can become more prominent. The recovery phase is associated with restoration of vascular integrity and resolution of many inflammatory abnormalities [2,3].

A biomarker measured after severe disease has already developed may therefore be useful for understanding disease biology but may have limited value for early prediction. For prognostication, the more important question is whether the marker can identify risk before clinical deterioration becomes obvious.

A 2023 systematic review and meta-analysis evaluated early biomarkers measured within the first 96 hours of fever. Elevated CRP, AST and IL-8 and reduced albumin were associated with dengue haemorrhagic fever, while CRP, AST, VCAM-1 and syndecan-1 showed associations with severe dengue [7].

Another systematic review focusing on the febrile phase identified several clinical and laboratory predictors associated with progression to severe disease [19]. These findings support the concept that biomarkers should be assessed alongside routine clinical and laboratory information rather than considered independently.

Since biomarker concentrations and their clinical significance may change throughout the course of dengue infection, interpretation should take into account the phase of illness at the time of sampling. The major biological changes, potentially informative biomarkers, and their relevance to disease severity across the febrile, critical and recovery phases are summarised in Table 2.

Table 2: Biomarker patterns and their potential prognostic relevance across different phases of dengue infection.

S.No	**Disease phase**	**Major biological events**	**Potential biomarker changes**	**Prognostic implication**
	Febrile phase	Viral replication + early immune activation	Cytokines, CRP and other inflammatory mediators may rise	Most relevant window for early prediction

	Critical phase	Increased vascular permeability/endothelial dysfunction	Endothelial and inflammatory markers may increase	Strongest relationship with severe manifestations
	Recovery phase	Restoration of vascular integrity	Inflammatory abnormalities generally decline	Less useful for early prediction

6. CRP, Ferritin and Other Accessible Inflammatory Markers

The search for prognostic biomarkers does not necessarily require highly specialised cytokine assays. CRP is relatively inexpensive and widely available, making it attractive for clinical application. Its association with severe dengue has been reported in multiple studies and supported by meta-analysis [7].

Ferritin has also received considerable attention because it reflects systemic inflammatory activation and can be measured using commonly available laboratory methods. A systematic review and meta-analysis of 18 studies reported substantially higher ferritin concentrations in severe dengue compared with non-severe disease [20].

However, the very high heterogeneity between studies is an important limitation. A statistically significant difference between severity groups does not automatically translate into a clinically useful threshold for an individual patient.

This distinction is important for biomarker research. A good research biomarker should not only differ between groups; it should ideally provide reproducible information early enough to change clinical decision-making. This requires clearly defined cut-offs, standardised timing and validation in independent populations.

7. From Single Biomarkers to Multi-Marker Panels

The limitations of individual biomarkers have encouraged a shift towards multi-marker approaches.

Severe dengue involves several interconnected processes, including immune activation, endothelial dysfunction, vascular leakage, platelet abnormalities and organ involvement [3,4]. It is therefore unlikely that a single inflammatory mediator will completely capture the biological progression of the disease.

Studies combining inflammatory and endothelial markers have provided encouraging results. IL-6, TNFR1, ICAM-1, VCAM-1, thrombomodulin and angiopoietin-2 have all been investigated as components of broader biomarker profiles [8].

A study involving symptomatic dengue patients evaluated a wide range of inflammatory, endothelial and anticoagulation-related markers, including MIF, PAF, MMP-2, MMP-9, MCP-1, RANTES, sTNFR1, syndecan-1, VEGF and angiopoietin-2 [21]. Such studies are important because they recognise that severe dengue is not simply an inflammatory disorder; it involves interactions between inflammation, vascular activation and coagulation.

The increasing use of multi-marker approaches also reflects a practical limitation of single-marker research. If several moderately informative markers represent different biological

pathways, their combination may provide more useful risk information than any one marker alone.

8. Emerging Research: Proteomics and High-Dimensional Biomarker Discovery

Recent biomarker research is increasingly moving towards high-throughput molecular approaches.

Traditional biomarker studies usually begin with a predefined list of candidate molecules. Proteomic approaches allow researchers to measure a much larger number of proteins simultaneously and identify patterns associated with disease phenotypes.

Recent plasma proteomic work has demonstrated the potential of this approach for identifying molecular signatures associated with dengue-related clinical characteristics [10]. Such studies may reveal biomarker combinations that would be difficult to identify using conventional candidate-based methods.

Another emerging direction is the integration of inflammatory and endothelial markers with routine clinical laboratory variables. A recent systematic review and meta-analysis synthesising evidence from a large number of studies reported associations between severe dengue and several inflammatory mediators, including IL-6, IL-8, IL-10 and CXCL10/IP-10, as well as endothelial markers such as angiopoietin-2 and syndecan-1 [11].

Machine-learning approaches are increasingly being explored within this area because they can analyse multiple variables simultaneously and identify combinations associated with clinical outcomes. However, high predictive accuracy in a development cohort does not necessarily mean that a model will perform equally well in a different population.

Therefore, external validation remains essential before complex biomarker models can be considered for routine clinical use.

Differences in disease classification also make comparisons difficult. Older studies frequently used terms such as dengue haemorrhagic fever and dengue shock syndrome, whereas current research generally uses the WHO 2009 classification of non-severe and severe dengue [22,23].

Laboratory methodology adds another layer of variation. Cytokines may be measured using different assay platforms, with differences in sensitivity, detection ranges and analytical procedures.

Finally, many biomarker studies are relatively small and are conducted at single centres. A biomarker may show excellent discrimination in one cohort but perform less well when tested in another setting. This is why external validation and multicentre prospective studies are particularly important.

9. Clinical Potential of Inflammatory Biomarkers

The ultimate value of a biomarker depends on whether it can improve clinical decision-making. An ideal dengue prognostic biomarker would be measurable early in the disease, provide reproducible information about future deterioration, require a simple assay and remain useful across different patient populations.

At present, inflammatory biomarkers appear more promising as components of a broader risk assessment strategy than as replacements for clinical evaluation. Platelet count, haematocrit, AST, albumin and other routine parameters remain important because they are inexpensive and

widely available [7,19].

Inflammatory and endothelial biomarkers could potentially add information when routine findings are still inconclusive. For example, an inflammatory marker may indicate substantial immune activation while an endothelial marker may indicate early vascular injury. Combining these findings with routine laboratory parameters could therefore provide a more complete assessment of risk.

The challenge is to identify panels that are sufficiently accurate without becoming too expensive or complicated for routine use.

10. Current Gaps and Future Directions

Future studies should prioritise prospective sampling at clearly defined illness days. This would help determine whether a biomarker truly predicts deterioration or simply reflects disease that has already progressed.

Large multicentre studies are also needed to establish whether biomarker performance remains consistent across different geographical regions, age groups, dengue serotypes and primary or secondary infections.

Standardisation is another major requirement. Studies should use clearly defined disease classifications, report the exact day of illness at sampling and describe laboratory methods sufficiently to allow meaningful comparison between cohorts.

External validation should become a routine component of biomarker research. Biomarker thresholds and prediction models developed in one population should be independently evaluated before being applied to other settings.

Future models are also likely to combine inflammatory biomarkers with routine laboratory variables rather than replacing them. Such an approach may improve predictive performance while maintaining clinical practicality.

Proteomic and other high-dimensional approaches may further expand biomarker discovery, but candidate signatures identified through these technologies will require prospective validation before clinical implementation.

The objective should therefore not simply be to identify the largest possible number of biomarkers. The more meaningful goal is to develop a small, reproducible and clinically practical biomarker panel that can identify patients at increased risk early enough to influence monitoring and management.

11. Conclusion

Inflammatory biomarkers have contributed substantially to our understanding of dengue pathogenesis and disease progression. Several cytokines, chemokines and systemic inflammatory markers have been associated with severe manifestations, but their prognostic performance varies considerably between studies.

The evidence increasingly suggests that inflammation should be considered together with endothelial dysfunction and vascular injury. Biomarkers such as syndecan-1, VCAM-1 and angiopoietin-2 may provide information that complements inflammatory mediators and routine laboratory findings.

The field is therefore moving from single-cytokine studies towards integrated inflammatory-endothelial panels, combined clinical-laboratory models and high-throughput molecular

approaches. Proteomics and machine learning offer promising new opportunities, but methodological heterogeneity and limited external validation remain major challenges.

At present, no single inflammatory biomarker can reliably replace clinical assessment and routine laboratory monitoring in dengue. Future research should focus on standardised prospective studies, reproducible thresholds, multicentre validation and clinically practical biomarker combinations. Such an approach may ultimately allow inflammatory biomarkers to contribute meaningfully to early risk stratification and personalised monitoring of patients with dengue.

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