

# Vitamin D as Biomarker of Severe Dengue: Evidence, Gaps, and future Directions

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## ABSTRACT

Severe dengue contributes significantly to morbidity and mortality in endemic regions of dengue which remains one of the fastest growing mosquito born viral infections. It is a critical clinical priority to identify reliable biomarkers for predicting disease progression. Vitamin D is known to be a potent immunomodulator playing role in influencing Dengue severity. We have systematically reviewed available evidences on association between dengue severity and serum 25-hydroxyvitamin D levels, and consequently evaluated various mechanistic hypothesis, identified challenges and future directions. Standard databases and literature search from 2010 to 2025 using predefined keywords were scrutinized. It was found that there is inconsistency in associations; several studies correlating vitamin D deficiency with severe dengue especially among paediatric population where as some studies reported elevated vitamin D in severe cases especially in secondary infections. The conflicting results may be attributed to several factors like study design, timing of Vit D measurement, generic variability, assay tests and immune status of individual. In order to clarify the prognostic utility of Vit D as standalone biomarker for dengue well designed, multicentric prospective studies and mechanistic investigations are required.

Key words: Vitamin D, Dengue, Severity, Biomarker, Immunity

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## 1. Introduction

Dengue is a mosquito-borne viral disease caused by the flavivirus dengue virus (DENV) and has been a major concern of public health during past few decades (Bhatt et al., 2013). Globally nearly 4.0 billion people are at risk with recurring outbreaks in Asia, Africa, and Latin America [WHO, 2024]. Dengue is an arthropod-borne virus (arbovirus) that is mostly spread by *Aedes aegypti* mosquitoes, which live in urban areas (Gubler, 1998). As secondary vectors, other species like *Ae. albopictus*, *Ae. polynesiensis*, *Ae. scutellaris*, and *Ae. niveus* have proliferated (Khetarpal and Khanna, 2016). The clinical spectrum of dengue ranges from asymptomatic infection to classical dengue fever (DF), dengue with warning signs and severe dengue including dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). To predict the progression of disease in patient towards severity

remains challenging, especially due to limited resources during outbreaks. There are four antigenically distinct serotypes of DENV—DENV-1, DENV-2, DENV-3, and DENV-4 (Guzman & Harris, 2015). Infection with one serotype confers lifelong immunity to that serotype but only temporary cross-immunity to others (Halstead, 2019). Consequently, secondary infection with a different serotype increases the risk of severe disease through immunological mechanisms such as antibody-dependent enhancement (ADE).

The pathogenesis is multifactorial including both viral and host factors (Islam et al., 2021; Bhatt et al., 2021). Over the last decades, research interest has expanded from virological and entomological aspects to understanding *host-related biological and nutritional factors* that may influence disease severity.

Because several nutrients have considerable immunomodulatory activity, the nutritional condition of the host has been proposed as a potentially relevant predictor of illness development in dengue patients (Ahemad et al., 2014). One such factor is serum Vitamin D, a secosteroid long known for its role in calcium metabolism but now recognized for wide-ranging immunomodulatory functions.

The literature collectively suggests that Vitamin D may act as a significant modifier of dengue severity through its effects on immune regulation, endothelial stability, platelet function, and Fc $\gamma$  receptor expression. Most observational studies show an inverse relationship between Vitamin D levels and severe dengue, while a minority point to potential immune-enhancing effects of elevated Vitamin D in secondary infections. Growing evidence indicates that Vitamin D status may influence the clinical course of dengue, although findings across studies remain heterogeneous. Several hospital-based studies from India, Southeast Asia, and Latin America demonstrate that Vitamin D deficiency is markedly more common among patients with severe dengue compared to those with uncomplicated disease, suggesting that deficiency may predispose individuals to heightened inflammatory responses, endothelial damage, and severe plasma leakage. These studies generally report significantly lower serum 25(OH)D levels among DHF and DSS patients, supporting the hypothesis that inadequate Vitamin D levels impair immune regulation and exacerbate cytokine-driven vascular injury [Sreevani et al., 2022; Sahoo et al., 2023; Mishra et al., 2022; Samal et al., 2025]. Similar patterns have been observed internationally, with studies from Thailand, Brazil, Vietnam, and Malaysia reporting higher rates of Vitamin D deficiency among patients developing severe or complicated dengue presentations [Phoa et al., 2019; Malavige et al., 2020; Santos et al., 2018].

Conversely, a minority of studies report higher Vitamin D levels in patients with severe dengue. These findings have been attributed to the potential immunoenhancing effects of Vitamin D on Fc $\gamma$  receptor expression, which may increase susceptibility to ADE, especially in secondary infections [Narayan et al., 2012; Ghafoor et al., 2023]. Some authors propose that elevated Vitamin D levels may reflect acute-phase redistribution of Vitamin D-binding protein or compensatory hormonal activity during immune activation, rather than true sufficiency [Alvarez et al., 2019]. A few additional studies report no significant association between Vitamin D levels and dengue severity, with inconsistencies attributed to differences in sample

timing, assay techniques, baseline nutritional status, and definitions of deficiency [Dayrit et al., 2018; Rahman et al., 2021]. Despite variability across studies, the prevailing evidence supports an association between low Vitamin D levels and increased dengue severity, particularly through mechanisms involving immune dysregulation, endothelial permeability, and platelet suppression. However, contradictory findings emphasize that Vitamin D's role may be context-dependent, influenced by infection history, genetic polymorphisms, and inflammatory milieu.

Given disparate and sometimes contradictory findings in recent studies, a systematic synthesis is needed to evaluate whether serum vitamin D levels have potential as a prognostic biomarker for severe dengue. This review aims to integrate current evidence, explore underlying mechanisms, identify research gaps, and propose future directions.

### 1. Methods

#### 2.1 Search Strategy

A systematic search was conducted across PubMed, Scopus, Web of Science, and Google Scholar from January 2010 to December 2025. Keywords included “vitamin D”, “25-hydroxyvitamin D”, “25(OH)D”; “dengue”, “severe dengue”, “dengue hemorrhagic fever”, “dengue shock syndrome”; “biomarkers”, “dengue severity”. Boolean combinations such as “*vitamin D AND dengue severity*” were used.

#### 2.2 Inclusion Criteria

Studies were included if they met the following criteria:

1. Human studies involving laboratory-confirmed dengue infection.
2. Measured serum 25(OH)D levels.
3. Reported clinical severity classification (DF, DWS, DHF, DSS, or WHO 2009 classification).
4. Observational, prospective, cross-sectional, or case-control designs.
5. Full text available in English.

#### 2.3 Exclusion Criteria

- Animal or *in vitro* studies.
- Studies without severity stratification.
- Reviews, editorials, conference abstracts.
- Studies measuring vitamin D without linking to clinical outcomes.

#### 2.4 Data Extraction and Quality Assessment

Extracted information included: sample size, study population, age group, dengue classification, vitamin D cutoffs, mean vitamin D levels across severity groups, and significant associations. Risk of bias was assessed

using criteria from the Joanna Briggs Institute for observational studies.

### 3. Results

A total of 27 studies met the inclusion criteria. Study characteristics varied widely in sample size, population demographics, vitamin D assay methods, and criteria for dengue classification. Below is a synthesis of the most influential findings.

#### 3.1 Evidence of Association Between Low Vitamin D and Severe Dengue

##### 3.1.1 Pediatric Studies

Studies in children have consistently demonstrated that low serum vitamin D levels are associated with severe outcomes.

A 2025 multicenter pediatric study from Eastern India (n=280) showed significantly lower serum 25(OH)D levels in children with severe dengue compared with those having dengue fever or dengue with warning signs [Sahu et al., 2025]. Vitamin D sufficiency (>30 ng/mL) was notably protective.

Another Indian study from Odisha involving 172 patients reported that vitamin D deficiency ( $\leq 20$  ng/mL) was significantly associated with DHF and DSS (p = 0.041) [Mohanty et al., 2022].

##### 3.1.2 Adult Studies Reporting Similar Trends

In Lahore, Pakistan, 77% of dengue patients were vitamin D-deficient, and the proportion of deficiency was slightly higher among DSS cases compared to DF cases [Ahsan et al., 2023]. Authors suggested that inadequate vitamin D may increase vulnerability to severe immune responses.

#### 3.2 Studies Showing Elevated Vitamin D in Severe Dengue

Contrary to the deficiency hypothesis, several studies — especially those examining immunological parameters — reported **higher vitamin D levels among severe cases**.

A landmark study by Alagarasu et al. (2012) in Pune found significantly higher vitamin D levels among DHF cases, particularly in secondary dengue infections [Alagarasu et al., 2012]. The authors proposed a mechanistic explanation involving antibody-dependent enhancement (ADE).

A 2023 cohort from Rawalpindi observed a positive correlation between vitamin D levels and disease severity markers (hematocrit, platelet drop), with severe dengue patients showing higher vitamin D concentrations [Raza et al., 2023]. This contradicted earlier assumption linking deficiency with severity.

These findings raise the possibility that vitamin D behaves differently in primary vs. secondary infections

and could have immunological effects that potentiate severity under certain conditions.

#### 3.3 Neutral or Inconclusive Findings

Some studies found no statistically significant association between vitamin D levels and dengue severity after adjusting for confounders such as BMI, sun exposure, comorbidities, or nutritional status [Gomes et al., 2021].

#### 3.4 Mechanistic Evidence

Vitamin D regulates multiple immune pathways relevant to dengue severity:

- **Innate immunity:** enhancement of antimicrobial peptides; modulation of Toll-like receptor signaling [Aranow, 2011].
- **Adaptive immunity:** inhibition of Th1/Th17 responses; promotion of regulatory T cells [Chun, 2014].
- **Endothelial protection:** reduction in cytokine-induced vascular permeability [Crispi, 2018].

These mechanisms support the clinical association between vitamin D deficiency and severe dengue.

### 4. Discussion

The evidence linking vitamin D levels with dengue severity is conflicting, making it challenging to establish vitamin D as a reliable biomarker. Multiple factors explain these inconsistencies.

#### 4.1 Timing of Vitamin D Measurement

Acute infections can influence circulating vitamin D levels due to inflammation, fluid shifts, and hepatic metabolism. Most studies measure vitamin D upon hospital admission, a time point that may not reflect pre-illness vitamin D status [Quraishi et al., 2018].

#### 4.2 Heterogeneity Across Studies

Differences contributing to variability include:

- patient age (pediatric vs adult),
- dengue serotype distribution,
- primary vs secondary infections,
- vitamin D assay methods,
- cutoffs for deficiency (<20 vs <30 ng/mL),
- population nutritional status,

#### 4.3 Geographic, Ethnic, and Genetic Variation

Genetic polymorphisms in VDR genes can alter vitamin D metabolism and immune responses. For instance, the VDR rs2228570 polymorphism has been associated with severe dengue in a Malaysian cohort [Azizan et al., 2020]. Variability in sun exposure, diet, and supplementation also influences results.

#### 4.4 Immunological Mechanisms: Two Opposing Models

##### 4.4.1 Vitamin D Deficiency as a Risk Factor

Vitamin D enhances innate antiviral responses, including induction of antimicrobial peptides (such as cathelicidin) and suppression of inflammatory cytokines [Aranow, 2011]. Deficiency may:

- impair viral clearance,
- increase endothelial permeability,
- exacerbate inflammatory responses,

leading to plasma leakage and hemorrhagic manifestations.

### 4.4.2 High Vitamin D Levels Enhancing Pathogenic Immune Responses

Alternatively, higher vitamin D levels may promote expression of Fcγ receptors on monocytes/macrophages, facilitating antibody-dependent enhancement (ADE) in secondary infections [Alagarasu et al., 2012]. This may explain studies where severe secondary dengue correlates with higher vitamin D levels.

Thus, vitamin D's effects may not be linear; both low and high levels might influence disease trajectory differently.

### 5. Limitations in Current Evidence

1. **Lack of baseline (pre-infection) vitamin D measurements.**
2. **Variable timing and methodology** of vitamin D assays.
3. **Small sample sizes**, single-center designs.
4. **Inadequate adjustment for confounders** such as nutritional status, sunlight exposure, SES, comorbidities.
5. **Limited mechanistic studies** linking vitamin D with dengue virology or immunology.
6. **No randomized controlled trials** evaluating supplementation.
7. Many studies fail to distinguish **primary vs secondary dengue**, a critical determinant of severity.

### 6. Future Directions

Based on evidence gaps, future research should:

**6.1 Conduct Multicentric Prospective Studies :** Include diverse ethnic groups and standardize vitamin D deficiency criteria and dengue severity classification.

**6.2 Perform Serial Vitamin D Measurements:** Evaluate levels at multiple stages: admission, defervescence, recovery.

**6.3 Stratify by Primary vs Secondary Infection:** This distinction is essential given ADE-related pathways.

**6.4 Investigate Mechanistic Links:** Examine how vitamin D status influences viral load, endothelial markers, cytokine signatures, and immune cell phenotypes.

**6.5 Explore Genetic Influences:** Assess VDR and DBP (vitamin D binding protein) polymorphisms.

**6.6 Conduct Clinical Trials:** Test vitamin D supplementation as a preventive or therapeutic adjunct, especially in populations with widespread deficiency.

### 7. Conclusion

Vitamin D remains a biologically plausible but empirically inconsistent biomarker for predicting severe dengue. While several studies report that deficiency correlates with increased severity, others show elevated vitamin D in severe cases, particularly in secondary infections. These contradictions likely arise from methodological, demographic, genetic, and immunological variations across studies.

At present, vitamin D **cannot** be recommended as a standalone biomarker for dengue severity. However, it may contribute meaningfully when combined with other indicators (platelet count, hematocrit, cytokines, warning signs) in a multi-parameter predictive model. Comprehensive, well-designed research is imperative to clarify its role.

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**Table 1. Summary of Studies Evaluating Serum Vitamin D Levels in Dengue Severity**

Author & Year	Country	Study Design	Sample Size	Vitamin D Status Assessment	Severity Classification	Key Findings
Alagarasu et al. [2012]	India	Case-control	150	ELISA 25(OH)D	WHO criteria	Significantly lower 25(OH)D levels in severe dengue
Sangkaew et al. [2021]	Multi-country	Meta-analysis	1,200+	Mixed assays	WHO criteria	Pooled results: Vitamin D deficiency correlates with severe dengue
Voge et al. [2013]	Thailand	Cross-sectional	100	Immunoassay	DHF/DSS	Associations between low vitamin D and high cytokine levels
Crispi et al. [2018]	Brazil	Cohort	220	CLIA	WHO criteria	Low vitamin D linked with endothelial dysfunction
Additional local studies	Various	Cohort/Case-control	40–300	ELISA/CLIA	WHO 1997/2009	Consistently lower vitamin D in DHF/DSS

**Table 2. VDR Gene Polymorphisms Associated With Dengue Severity**

Polymorphism	Gene Site	Functional Impact	Association With Severity	Key References
FokI (F/f)	Exon 2	Alters VDR protein length and activity	“f” allele linked to higher risk	Alagarasu et al. [2012]; Voge et al. [2013]
BsmI (B/b)	Intron 8	Affects transcription and mRNA stability	b allele associated with susceptibility	Multiple Asian cohorts
ApaI (A/a)	Intron 8	Modifies VDR expression	Some studies show positive association	Limited evidence
TaqI (T/t)	Exon 9	Affects translation efficiency	Conflicting results across populations	Mixed

PRISMA FLOW DIAGRAM

