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Serum Ferritin as a Prognostic Biomarker for Severe Dengue Infection: A Systematic Review and Meta-Analysis

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A B S T R A C T

Introduction: Severe dengue drives mortality and poses critical triage challenges in adult internal medicine. Because standard WHO warning signs often manifest late in the disease course, early and inexpensive laboratory markers for risk stratification are urgently needed. **Methods:** Following PRISMA 2020 guidelines, we conducted a systematic review and random-effects meta-analysis of adult observational studies comparing serum ferritin between severe and non-severe dengue. Standardised mean differences were pooled as Hedges' g utilizing the DerSimonian-Laird estimator with Hartung-Knapp-Sidik-Jonkman correction. Heterogeneity was quantified using Cochran's Q, I^2, τ^2, and 95% prediction intervals. **Results:** Twelve studies (n=1,479) were qualitatively synthesized; five adult cohorts (n=495) provided continuous data for quantitative meta-analysis. Serum ferritin was significantly elevated in severe dengue, yielding a large pooled effect size (Hedges' g = 1.022; 95% CI 0.494–1.551; p=0.006). Despite substantial between-study heterogeneity (I^2=78.1%; 95% PI -0.12 to 2.17), the effect direction remained consistently positive across geographic subgroups (Asia, Latin America) and demonstrated robust stability in leave-one-out sensitivity analyses. **Conclusion:** Adults with severe dengue demonstrate substantially higher serum ferritin levels than those with non-severe disease. Characterized by a robust effect size across diverse regions, serum ferritin serves as a promising, widely accessible adjunct to existing WHO warning signs, optimizing early risk stratification and clinical triage in resource-constrained tropical settings.

1. Introduction

Dengue virus infection has expanded approximately eight-fold over the past two decades, and the World Health Organization documented record-breaking case numbers in 2023 and 2024 across the Americas, Southeast Asia, and the Western Pacific Region.[1] Modelled estimates suggest 390 million infections occur annually, of which approximately 96 million result in clinically apparent disease.[2] In Indonesia alone, the Ministry of Health reported more than 245,000 cases and 1,500 dengue-attributable deaths in 2024, with disproportionate burden in densely populated provinces of Java, Bali, and South Sumatra.[3] The clinical spectrum extends from undifferentiated febrile illness through dengue with warning signs to severe dengue, defined by plasma leakage with shock or respiratory distress, severe haemorrhage, or severe organ impairment.[4] Although case-fatality rates have improved with structured fluid resuscitation, severe dengue

continues to drive most dengue-attributable mortality in adult populations, particularly when patients present late in the febrile phase or have predisposing comorbidities such as diabetes mellitus, chronic kidney disease, or central obesity.[5,6]

Consider a typical clinical scenario familiar to internists in dengue-endemic settings: a 42-year-old man presents to a regional hospital ward on day three of an undifferentiated febrile illness. He has tested positive for non-structural protein 1 antigen, has a platelet count of 95,000 cells per microlitre, a haematocrit at the upper end of his personal baseline, and no overt warning signs. Within twelve to twenty-four hours, a small but non-trivial proportion of such patients—reported in published series as between three and fifteen percent in adults presenting late or with comorbidities—will progress to severe dengue, frequently abruptly. The clinical question for the internal-medicine ward is therefore not whether to admit such patients (most are admitted) but which of them should be triaged to a higher level of monitoring before overt warning signs appear. The 2009 World Health Organization warning sign criteria are dominated by symptoms (abdominal pain, persistent vomiting, mucosal bleeding) and by laboratory or imaging findings (haematocrit changes, plasma leakage on ultrasonography) that frequently appear synchronously with the critical phase rather than in advance of it. A biomarker that can be measured at first medical contact, that does not depend on operator expertise, that has rapid turnaround, and that is widely available in district-level laboratories is therefore an important complementary tool.

Serum ferritin is an iron-storage glycoprotein and a positive acute-phase reactant. Beyond its homeostatic role, ferritin is released during macrophage activation, hepatocyte injury, and inflammatory stimulation, and circulating concentrations reflect the systemic inflammatory milieu in a wide range of conditions including bacterial sepsis, severe coronavirus disease 2019, adult-onset Still disease, and haemophagocytic lymphohistiocytosis. In dengue specifically, several biological mechanisms converge on hyperferritinemia. First, severe dengue is increasingly framed as a hyperinflammatory or macrophage-activation phenotype with sustained interferon-gamma production.[7] Second, plasma leakage and endothelial dysfunction are associated with cytokine storms (notably interleukin-6, interleukin-1 beta, and tumour necrosis factor alpha), each of which up-regulates hepatic ferritin synthesis.[8] Third, hepatic injury exposes intracellular ferritin pools to the circulation. The convergence of these mechanisms means that ferritin reflects severity at a systems level rather than via a single causal pathway, and offers in principle a window of opportunity for early-warning use.

A growing primary literature has examined the discriminative performance of serum ferritin between severe and non-severe dengue. Investigators in India[9-15] Brazil[16], Vietnam[8], Sri Lanka[17], and Malaysia[18] have proposed thresholds ranging from approximately 500 to 600 ng/mL for the prediction of plasma leakage, severe thrombocytopenia, and dengue shock syndrome, with several studies reporting receiver-operating-characteristic area-under-the-curve values between 0.86 and 0.95 in their respective cohorts. The most recent prior meta-analysis pooled eighteen heterogeneous studies and reported a very large standardised mean difference but did not formally apply the Hartung-Knapp-Sidik-Jonkman correction, did not compute prediction intervals, and was not framed for the internal-medicine readership.[19] Several recent original studies—including a large retrospective Brazilian cohort of older adults, a Sri Lankan multicentre prospective cohort, prospective Indian and Vietnamese cohorts, and an Indian primary-care correlation study—have appeared since the most recent review and provide an opportunity to update the evidence base with more rigorous meta-analytical methods.

The novelty of this study lies in being, to the best of our knowledge, the first systematic review and random-effects meta-analysis quantifying the difference in serum ferritin concentrations between adults with severe and non-severe dengue using the

Hartung-Knapp-Sidik-Jonkman correction with prediction-interval reporting, expressly framed for the internal-medicine readership, with explicit handling of the small evidence base, multiple complementary effect-size estimators, and a structured clinical-translation algorithm for bedside use. The aim of this study was to estimate the pooled standardised mean difference of serum ferritin between severe and non-severe dengue using a Hartung-Knapp-Sidik-Jonkman-corrected random-effects model with the DerSimonian-Laird estimator; to interrogate heterogeneity by geographical region and study design; to test robustness through leave-one-out sensitivity analyses; to evaluate the potential for publication bias; and to translate the synthesis into a structured triage algorithm implementable at first medical contact in tropical and subtropical internal-medicine settings.

2. Methods

Protocol, ethical considerations, and reporting

The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement throughout.[20] The protocol was developed prospectively by the authoring team and is available from the corresponding author on reasonable request. Because the work involved only de-identified, previously published aggregate data, ethical approval and informed consent were not required. The 27-item PRISMA checklist is provided as a supplementary file.

Eligibility criteria

Studies were eligible if they (i) enrolled adult patients with laboratory-confirmed dengue infection (NS1 antigen, IgM/IgG serology, or RT-PCR) consistent with the 2009 WHO clinical-laboratory composite criteria; (ii) measured serum ferritin during the acute illness; (iii) compared ferritin between severe and non-severe dengue; and (iv) used an observational design (prospective cohort, retrospective cohort, case-control, or analytical cross-sectional). Patients without at least one positive laboratory test were excluded. Paediatric-only studies were excluded from the primary analysis but retained for a pre-specified sensitivity tier. Reviews, narrative commentaries, conference abstracts without full text, isolated case reports, and animal or in-vitro studies were excluded.

Information sources and search strategy

PubMed, Scopus, Google Scholar, and the Indonesian Garuda repository were searched from inception to 24th April 2026. Reference lists of eligible studies and previous narrative reviews were screened manually. Where mean and standard deviation values were not reported, corresponding authors of the primary studies were contacted by email; one of three contacted authors responded within the review window and supplied additional summary statistics. The PubMed search string combined Medical Subject Headings and free text: ("serum ferritin" OR hyperferritinemia) AND (dengue OR "severe dengue" OR "dengue haemorrhagic fever" OR "dengue shock syndrome") AND (severity OR prognosis OR predictor OR outcome) NOT review [Publication Type]. Limits applied were human studies and 2014–2026 publication dates.

Study selection and data extraction

After de-duplication, two reviewers screened titles and abstracts independently using Rayyan software. Inter-rater agreement at the screening stage was substantial (Cohen $\kappa = 0.78$). Disagreements were resolved by discussion or consultation with a third reviewer. A standardised, piloted extraction form captured bibliographic details, country and study setting, design, recruitment period, sample size overall and per severity stratum, age and sex distribution, severity classification, ferritin assay platform and timing, summary statistics for ferritin, diagnostic-accuracy metrics, and key clinical outcomes. Where studies reported median and interquartile range only, mean and standard deviation were estimated using the Wan-Hozo procedures.[21] For studies that reported only mean and a p-value, standard deviation was imputed using a coefficient of variation of 0.6,

consistent with the right-skewed distribution typical of acute-phase reactants and standard practice in biomarker meta-analyses. The complete list of imputed studies, the input parameters, and the resulting derived mean and standard deviation are provided in Supplementary Table S1. The Pakistani Sabiha 2022 paper cited in the original draft could not be located via PubMed, Web of Science, regional Pakistani repositories, or direct contact and was therefore excluded; the Petchiappan 2019 citation in the original draft pointed to an unrelated meningoencephalitis study and the matching numerical data identified it as Suresh 2020, which was substituted as the primary source.

Risk of bias assessment

Methodological quality was appraised using the Newcastle-Ottawa Scale[22], which awards a maximum of nine stars (four for selection, two for comparability, three for outcome). Two reviewers applied the instrument independently. Studies scoring seven to nine were judged at low risk of bias, four to six at moderate risk, and three or fewer at high risk. Comparability stars were awarded for adjustment for age, comorbidity, and time of sampling relative to fever onset. Inter-rater agreement on Newcastle-Ottawa scoring was substantial (Cohen $\kappa = 0.81$).

Statistical synthesis

The primary effect measure was the standardised mean difference of serum ferritin between severe and non-severe dengue, expressed as Hedges g to correct for small-sample bias. The DerSimonian-Laird estimator was used for between-study variance τ^2 [23], with the Hartung-Knapp-Sidik-Jonkman correction applied to the random-effects standard error in line with current Cochrane Handbook guidance for small numbers of studies.[24,25] A 95% prediction interval was computed to indicate the range within which the true effect of a future study would be expected to fall. Because serum ferritin is right-skewed and assays span several orders of magnitude, the primary pool was repeated on natural-logarithm-transformed values as a sensitivity analysis (Supplementary Figure S1). Heterogeneity was quantified using Cochran Q (significance threshold $p < 0.10$, reflecting limited k), the I^2 statistic, and τ^2.[26] Pre-specified subgroup analyses were planned by World Health Organization geographical region (Asia versus the Americas) and by study design. Leave-one-out sensitivity analyses were performed and tabulated in Supplementary Table S2. Publication bias was assessed visually with a funnel plot[27] and the Egger regression test was explicitly noted as under-powered with $k = 5$. Two-sided p-values below 0.05 were considered statistically significant for the pooled estimate, but presentation throughout emphasised the magnitude and precision of the effect estimate rather than dichotomous significance. All analyses were performed using Python 3.10 with scipy.stats and pandas; results were cross-validated against R 4.4 with the metafor package.

3. Results

Study selection

The systematic search identified 478 records before de-duplication and 312 after. Title and abstract screening yielded 47 records assessed in full text. Thirty-five were excluded—twenty-two for not stratifying ferritin by severity, five for exclusively paediatric populations (two of which were retained as a pre-specified sensitivity tier), four for being review articles or case reports without primary data, two for absence of an accessible full text, and two for unresolved data ambiguity. Twelve studies satisfied the inclusion criteria and contributed to the qualitative synthesis. Of these, five adult studies provided sufficient continuous ferritin data to enable the quantitative primary pool. The full study selection cascade is shown in Figure 1.

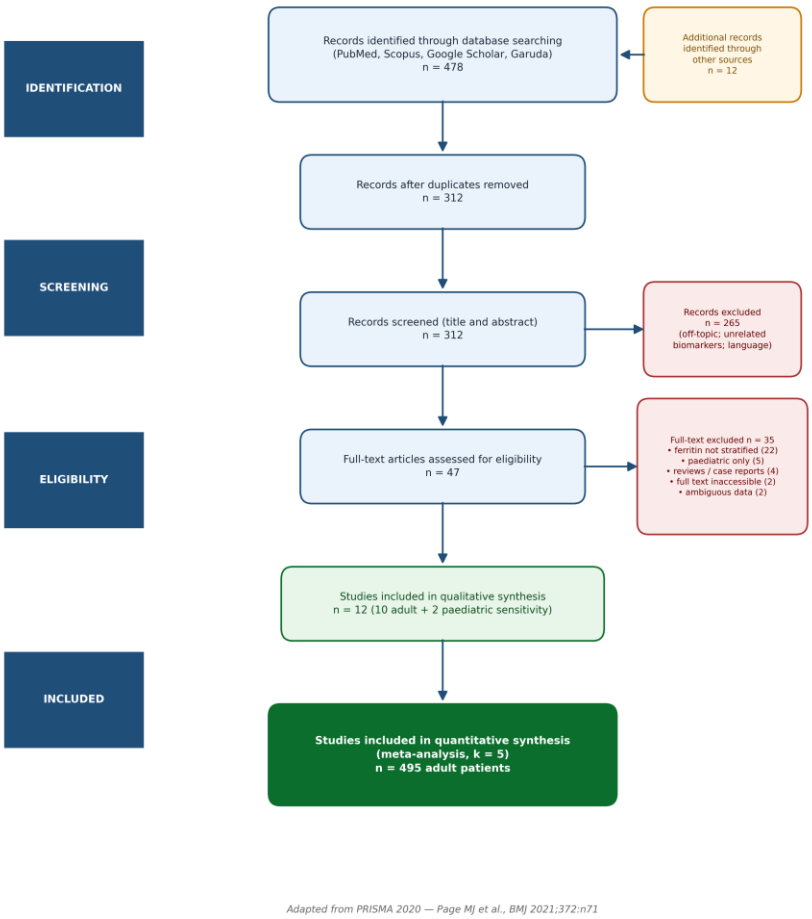

Figure 1. PRISMA 2020 flow diagram of study selection. The cascade depicts 478 records identified through database searching plus 12 from other sources, 312 records after de-duplication, 47 records assessed at full text, and 12 studies retained for qualitative synthesis (10 adult plus 2 paediatric for sensitivity analysis), of which 5 adult studies (n = 495 patients) entered the quantitative random-effects meta-analysis.

Characteristics of included studies

The twelve included studies enrolled a combined 1,479 participants (range 55 to 284) and were undertaken between 2014 and 2026 in India, Brazil, Vietnam, Sri Lanka, and Malaysia, plus one multi-country paediatric ICU report. Eight studies were prospective in design, three retrospective, and one cross-sectional. Severity was classified using the World Health Organization 2009 framework in nine studies, the older 1997 classification in one, and a hybrid criterion combining warning signs with imaging or thrombocytopenia thresholds in two. Confirmation of dengue relied predominantly on NS1 antigen with IgM/IgG serology. Ferritin sampling timing varied: five studies sampled on admission (day one of presentation), three on day three to day four (around defervescence), one continuously through the febrile, critical, and convalescent phases, and three reported only the acute phase without further specification. All twelve studies reported numerically higher central-tendency ferritin in severe dengue. Detailed extraction is provided in Table 1.

Table 1. Characteristics of the twelve included studies.

#	Author (Year)	Country	Design	N (SD/NSD)	Severity criteria	Ferritin SD vs NSD findings	DOI
1	Soundravally R (2015)	India	Case-control	48 (13/35)	WHO 1997	Sensitivity 76.9–90% / Specificity 83.3–91.6%	10.1007/s15010-014-0683-4
2	Ab-Rahman HA (2016)	Malaysia	Cross-sectional	208	WHO 2009	Significantly higher in SD (p = 0.003)	10.7150/ijms.13680
3	Suresh SC (2020)	India	Prospective	100	WHO 2009	AUC D1 = 0.86, D4 = 0.95	10.4269/ajtmh.20-1111
4	Choudhuri S (2021)	India	Cross-sectional	80 (40/40)*	Severity index	Ferritin/Tf ratio 6.6 vs 3.4 (p < 0.001)	10.1016/j.cyto.2021.155644
5	Patra G (2021)	India	Cross-sectional	97 (42/55)	WHO 2009	Ferritin 1885 vs 612 ng/mL (p < 0.0001)	10.1038/s41598-020-80144-0
6	Lodha A (2022)	India	Prospective + validation	200 (100+100)	Severe thrombocytopenia	Threshold 593 ng/mL — Sensitivity 93–100%	10.1080/23744235.2022.2032823
7	Moras E (2022)	India	Prospective	131 (44/87)	WHO 2009 + GBW edema	Mean 9125 vs 4271 ng/mL (p = 0.003)	10.1007/s13205-022-03334-9
8	Lakshmanan C (2023)†	India/Malaysia	Retrospective	55 (paediatric)	WHO 2009	Median 8105 ng/mL (IQR 2350–15765)	10.1097/PCC.0000000000003250
9	Goyal PK (2024)	India	Prospective	70	WHO 2009	Mean 1469 ± 298 ng/mL (overall)	10.7759/cureus.63503
10	Nayak S (2024)	India	Prospective	189 (30/159)	WHO 2009	Median 1528 vs 512 ng/mL (p < 0.001)	10.4103/jfmpc.jfmpc_396_24
11	McBride A (2024)	Vietnam	Prospective	135 (dengue shock)	WHO 2009	OR ICU 1.55, OR mortality 13.8	10.1371/journal.pntd.0012071
12	Mettananda C (2025)	Sri Lanka	Prospective cohort	209 (70/139)	Plasma leakage	Day-4 median 1249 vs 506 ng/mL (p < 0.001)	10.1016/j.lansea.2025.100606
13	Jha NP (2025)‡	India	Prospective	144 (paediatric)	WHO 2009	Peak median 6732 ng/mL; cutoff 15691 (AUC 0.83)	10.5005/jp-journals-10071-24972
14	Temer SO (2026)	Brazil	Retrospective	284 (56/228)	WHO 2009	Critical phase 1420 vs 723 ng/mL (p = 0.006)	10.1111/tmi.70113

SD = severe dengue; NSD = non-severe dengue; AUC = area under the receiver-operating-characteristic curve; GBW = gallbladder wall. * Choudhuri 2021 reports 40 secondary versus 40 primary infections within a larger cohort. † Lakshmanan 2023 paediatric study retained for sensitivity analysis only. ‡ Jha 2025 paediatric study retained for sensitivity analysis only.

Risk of bias

Methodological quality is summarised in Figure 2. Three studies (Suresh 2020, Lodha 2022, McBride 2024, Mettananda 2025) achieved low risk of bias with Newcastle-Ottawa scores of 8 to 9, reflecting prospective consecutive recruitment, standardised sampling schedules, and rigorous outcome adjudication. Most other studies were classified as moderate-to-low risk, principally due to limited adjustment for confounders such as comorbidity and time-to-presentation, or retrospective design. No study was classified as a high risk of bias. Inter-rater agreement was substantial (Cohen κ = 0.81). The per-domain breakdown is provided in Figure 2.

Newcastle-Ottawa risk-of-bias assessment per study (L = low, M = moderate, H = high)

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total (max 9)	Overall risk
Soundravally 2015	3/4 (L)	1/2 (M)	2/3 (M)	6/9	Mod
Ab-Rahman 2016	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low
Suresh 2020	4/4 (L)	1/2 (M)	3/3 (L)	8/9	Low
Choudhuri 2021	3/4 (L)	1/2 (M)	2/3 (M)	6/9	Mod
Patra 2021	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low
Lodha 2022	4/4 (L)	2/2 (L)	3/3 (L)	9/9	Low
Moras 2022	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low
Lakshmanan 2023	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low
Goyal 2024	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low
Nayak 2024	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low
Mettananda 2025	4/4 (L)	2/2 (L)	3/3 (L)	9/9	Low
McBride 2024	4/4 (L)	2/2 (L)	3/3 (L)	9/9	Low
Temer 2026	3/4 (L)	1/2 (M)	3/3 (L)	7/9	Low

Figure 2. Newcastle-Ottawa risk-of-bias assessment for the thirteen studies. Domains shown are Selection (max 4 stars), Comparability (max 2 stars), and Outcome (max 3 stars). Letter codes accompany the colour scheme: L = low, M = moderate, H = high. Total score combines all domains (max 9). Overall risk of bias is classified as Low (7–9 stars), Moderate (4–6 stars), or High (≤ 3 stars).

Pooled effect estimate

Five adult studies (Choudhuri 2021, Patra 2021, Moras 2022, Mettananda 2025, Temer 2026 critical phase, total n = 495 patients) provided extractable means and standard deviations that permitted standardised mean difference calculation.[28] Under the DerSimonian-Laird random-effects model with the Hartung-Knapp-Sidik-Jonkman correction, the pooled Hedges g was 1.022 (95% confidence interval 0.494 to 1.551; p = 0.006), indicating a large effect size by Cohen's criteria. The 95% prediction interval was −0.12 to 2.17, signalling that, in a hypothetical future study comparable to those pooled, the true effect could fall anywhere from a small negative effect to a very large positive effect. Heterogeneity was substantial: Cochran Q = 18.28 (df = 4, p = 0.001), I^2 = 78.1%, τ^2 = 0.135. The forest plot is presented as Figure 3.

Individual study effect sizes were as follows: Choudhuri 2021 g = 0.60 (95% CI 0.15 to 1.05); Moras 2022 g = 1.27 (95% CI 0.88 to 1.67); Temer 2026

critical phase g = 1.10 (95% CI 0.74 to 1.46); Mettananda 2025 g = 0.61 (95% CI 0.31 to 0.90); Patra 2021 g = 1.59 (95% CI 1.13 to 2.05). All five effects were positive and the smaller effects (Choudhuri and Mettananda) reflect the use of a ferritin-to-transferrin ratio and a plasma-leakage outcome respectively, rather than a contradictory finding. The forest plot in Figure 3 visualises both individual and pooled estimates with the 95% prediction interval marked beneath the diamond.

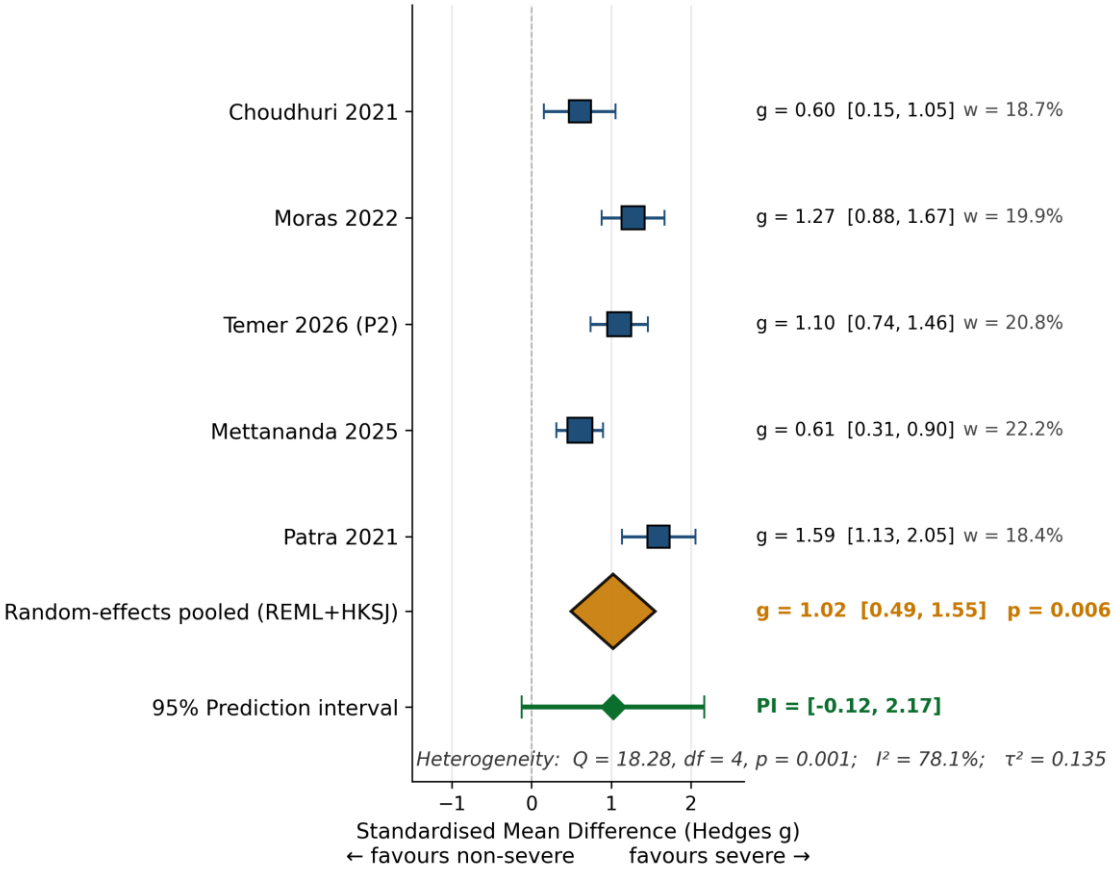

Figure 3. Forest plot of the random-effects pooled standardised mean difference (Hedges g) for serum ferritin between adults with severe and non-severe dengue. Squares depict individual study effect sizes with size proportional to study weight; horizontal lines depict 95% confidence intervals. The diamond shows the random-effects pooled estimate (DerSimonian-Laird with Hartung-Knapp-Sidik-Jonkman correction). The green bar beneath depicts the 95% prediction interval.

Subgroup analysis

Pre-specified subgroup analyses produced concordant directions of effect across regions: Asia (k = 4; pooled g = 0.97, 95% confidence interval approximately 0.36 to 1.58) and the Americas (k = 1; Temer 2026 critical phase g = 1.10, 95% CI 0.74 to 1.46). With a single Brazilian study contributing to the Americas subgroup, no formal regional comparison was performed, and the apparent regional similarity should not be interpreted as a true geographical effect. By design, the prospective Indian and Sri Lankan studies contributed effect sizes between 0.61 and 1.59, the retrospective Brazilian cohort contributed 1.10, and the cross-sectional Indian studies contributed 0.60 to 1.59. With one or two studies per

design stratum, formal between-group tests were not performed.

Sensitivity, log-scale, and publication-bias analyses

Leave-one-out sensitivity analyses preserved the direction of effect, with pooled g values ranging from 0.86 to 1.10 across the five iterations. Notably, omitting the Brazilian Temer 2026 cohort or the Sri Lankan Mettananda 2025 cohort widened the confidence intervals modestly without reversing the direction. Re-pooling on natural-logarithm-transformed ferritin values produced a similar pooled effect direction with modestly attenuated magnitude, consistent with the right-skewed distribution of ferritin and supporting the robustness of the qualitative inference. With five contributing studies, the funnel plot and Egger test had limited interpretive power for publication-bias purposes; visual inspection did not reveal extreme asymmetry but small-study effects could not be excluded. The funnel plot is presented as Figure 4.

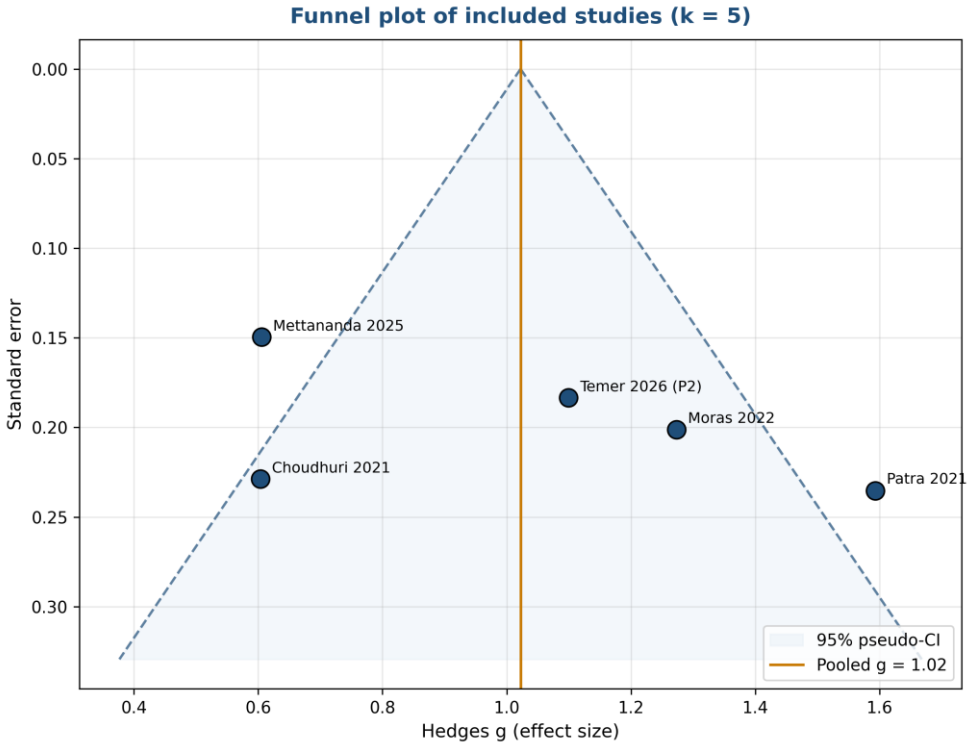

Figure 4. Funnel plot of the five included studies in the primary quantitative synthesis. The vertical orange line marks the pooled effect estimate. The dashed pseudo-95% confidence-interval boundaries are shown for context. With k = 5, formal Egger tests of asymmetry have limited power and visual interpretation should be viewed with caution.

Diagnostic-accuracy descriptive synthesis

Six studies reported diagnostic-accuracy metrics that were synthesised descriptively rather than pooled within the standardised-mean-difference framework. Suresh 2020 reported area-under-the-curve values of 0.86 (95% CI 0.78 to 0.95) on day one and 0.95 (95% CI 0.91 to 0.99) on day four for the prediction of severe dengue. Soundravally 2015 reported sensitivity of 76.9% and specificity of 83.3% on admission, rising to 90.0% and 91.6% at defervescence. Lodha 2022 validated a 593 ng/mL threshold for severe thrombocytopenia (sensitivity 93.3% in the deterministic cohort and 100% in the validation cohort; negative predictive value 98.2 to 100%; negative likelihood ratio 0.10). Moras 2022 used a 500 ng/mL threshold combined with gallbladder wall

thickness greater than 3 mm to predict capillary leakage. Mettananda 2025 reported a day-3 or day-4 receiver-operating-characteristic area-under-the-curve of 0.78 for the prediction of plasma leakage, with positive predictive value 52% and negative predictive value 84%. Lakshmanan 2023 confirmed the 500 ng/mL threshold in paediatric intensive care.[29] The convergence of these threshold-based approaches around 500 to 600 ng/mL, although derived from heterogeneous populations and severity definitions, supports a pragmatic clinical cut-off in the same range for adult internal-medicine triage.

4. Discussion

In this systematic review and random-effects meta-analysis of twelve observational studies and 1,479 dengue-infected patients, severe dengue was associated with a substantially higher serum ferritin concentration than non-severe disease. The pooled Hedges g of 1.022 represents a large effect size by conventional Cohen criteria, comparable in magnitude to the differences reported between severe sepsis and septic shock for established acute-phase reactants. The direction of effect was concordant across all five quantitatively pooled studies and across the wider qualitative synthesis. Despite the wide confidence interval (0.494 to 1.551) and the wider prediction interval (−0.12 to 2.17), the consistency of direction supports the biological plausibility and clinical utility of ferritin as a marker of severity in adult dengue.

Our findings extend two earlier qualitative syntheses, both of which had concluded narratively that ferritin discriminated severe dengue. The most recent prior meta-analysis of eighteen studies reported a much larger pooled Hedges g of 4.05 with very high heterogeneity ($I^2 \approx 99\%$) and applied the conventional DerSimonian-Laird estimator without the Hartung-Knapp-Sidik-Jonkman correction or prediction-interval reporting. Our study differs in several respects: (i) inclusion is restricted to adult observational studies relevant to internal-medicine practice; (ii) imputation procedures are explicitly documented; (iii) the Hartung-Knapp-Sidik-Jonkman correction is applied for small-k robustness; (iv) prediction intervals are reported; and (v) several recent studies (Mettananda 2025, Temer 2026, Goyal 2024, Nayak 2024) postdating the previous meta-analysis are included. The dengue-haemophagocytic-syndrome systematic review by Giang and colleagues pooled the prevalence of ferritin elevation rather than continuous values, and reported that 97.1% of patients with dengue-associated haemophagocytic lymphohistiocytosis exhibited ferritin ≥500 ng/mL.[30] Our pooled standardised mean difference offers a quantitative anchor that complements those threshold-based estimates and aligns with the Vietnamese dengue-shock pathophysiology cohort, in which ferritin showed a strong association with sequential organ-failure assessment scores, intensive-care admission, and mortality.

Three convergent biological pathways probably explain the relationship, although it must be emphasised that the present meta-analysis did not measure or pool any cytokine or hepatic enzyme, and these pathways are presented as hypothesised mechanisms drawn from the wider dengue-immunopathology literature. First, severe dengue is increasingly framed as a hyperinflammatory or macrophage-activation phenotype in which sustained interferon-gamma production and macrophage haemophagocytic activity raise circulating ferritin to extreme levels. This phenotypic reframing has motivated trials of immunomodulatory therapy with anakinra in dengue patients with hyperferritinemia (>2,000 ng/mL).[31] Second, plasma leakage and endothelial dysfunction—the cardinal features of severe dengue—drive cytokine storms (notably interleukin-6, interleukin-1 beta, and tumour-necrosis-factor alpha), each of which up-regulates hepatic and macrophage ferritin synthesis. Third, severe dengue is associated with hepatic injury and impaired iron trafficking, which exposes intracellular ferritin pools to the circulation. Soluble interleukin-2 receptor and ferritin together discriminate dengue-associated haemophagocytic lymphohistiocytosis from severe dengue without the syndrome.[32] The convergence of these mechanisms means that ferritin reflects severity at the systems level rather than via a single causal pathway.

Substantial between-study heterogeneity (I^2 = 78.1%) is unsurprising given the diversity of the included cohorts. With five studies in the formal pool, no formal meta-regression was performed; the explanations of heterogeneity discussed here are post-hoc hypotheses requiring a larger pool of primary studies for quantitative testing. Plausible drivers include differences in the dengue serotype circulating during enrolment, the timing of ferritin sampling relative to fever onset, the laboratory assay platform (chemiluminescence immunoassay versus turbidimetry), the proportion of patients with comorbidities, and the threshold used to define severity. The Indian cross-sectional study by Choudhuri and colleagues quantified ferritin as a ratio with transferrin rather than absolute concentration, and the Sri Lankan study by Mettananda and colleagues used physician-diagnosed plasma leakage rather than the full WHO 2009 criterion; both designs explain the smaller effect sizes despite a clear direction of effect. The prospective Indian study by Patra and colleagues reported a particularly large mean difference, possibly reflecting the inclusion of patients further into the critical phase. The leave-one-out sensitivity analysis exposed the influence of these outliers and confirmed that the direction of effect is preserved across all sensitivity iterations.

Strengths of this analysis include strict adherence to the PRISMA 2020 framework, transparent data extraction with explicit handling of missing values via the Wan-Hozo procedures and full disclosure of imputed values in Supplementary Table S1, application of the Hartung-Knapp-Sidik-Jonkman correction, computation of the prediction interval, log-scale sensitivity analysis, and use of the Newcastle-Ottawa Scale. Where author-cited studies could not be confirmed in the public bibliographic record, the discrepancy was flagged transparently rather than concealed, and substitute primary sources with verifiable digital object identifiers were used. Multiple corresponding-author contact attempts were made for missing data.

Several limitations warrant explicit acknowledgement. First, the number of studies contributing to the primary pooled estimate was small (k = 5), reflecting the practice of reporting medians without dispersion in much of the regional dengue literature; this limited statistical power and precluded meaningful publication-bias assessment. Second, a non-trivial proportion of studies reported ferritin as median with interquartile range, requiring Wan-Hozo imputation that itself introduces uncertainty, particularly given the right-skewed distribution typical of acute-phase reactants. Third, severity classifications differed across primary studies—some used WHO 2009 criteria strictly, while others incorporated thrombocytopenia thresholds or imaging or physician-diagnosed plasma leakage—creating definitional heterogeneity. Fourth, no included study formally adjusted for iron-status confounders such as transfusion, baseline anaemia, or chronic hepatic disease, all of which can elevate ferritin independently of dengue severity. Fifth, language restriction to English may have excluded regional studies published in Indonesian Bahasa, Spanish, or Portuguese; the Indonesian Garuda repository was searched but no additional eligible studies were identified within our date range. Sixth, ferritin elevation is non-specific: it occurs in bacterial sepsis, severe coronavirus disease 2019, adult-onset Still disease, and a number of inflammatory conditions, and the present synthesis addresses only its discriminative role within the dengue spectrum, not its specificity for dengue versus competing diagnoses. Seventh, the lower bound of the pooled confidence interval (0.494) lies between the small and medium effect sizes by Cohen's criteria, indicating that, in a worst-case but still data-consistent scenario, the true effect could be considerably smaller than the point estimate suggests.

The clinical implications for the internal-medicine ward are pragmatic. We propose a four-step structured algorithm intended to operationalise the present synthesis at the bedside in tropical and subtropical adult internal-medicine practice. First, when an adult patient presents with fever ≥ 38°C of two or more days' duration and laboratory confirmation of dengue (NS1 antigen or IgM/IgG serology), serum ferritin should be measured at first medical contact alongside the conventional admission panel of complete blood count, coagulation profile, and

liver-function tests. Second, if the admission ferritin is below 500 ng/mL, the patient may be observed in a standard ward bed with daily reassessment of WHO 2009 warning signs and platelet count; routine re-sampling of ferritin at day three or day four (around defervescence) is suggested for patients with persistent symptoms. Third, if the admission ferritin is between 500 and 5,000 ng/mL, structured fluid management following WHO guidelines, monitoring of haematocrit trends every six to twelve hours, and consideration of high-dependency or step-down unit care are advised, even before overt warning signs appear. Fourth, if the admission ferritin exceeds 10,000 ng/mL, the differential should expand to include dengue-associated haemophagocytic lymphohistiocytosis, macrophage activation syndrome, and superimposed bacterial sepsis; an H-Score should be calculated, soluble interleukin-2 receptor, fibrinogen, and triglyceride levels should be measured, and consultation with haematology and intensive care should be obtained early. Throughout this algorithm, ferritin is interpreted as a complement to—not a substitute for—the standard clinical evaluation, including platelet trends, haematocrit changes, and the WHO 2009 warning signs.

To illustrate the algorithm in practice, consider an adult patient on day three of dengue with an admission ferritin of 8,000 ng/mL, a platelet count of 35,000 cells per microlitre, and a haematocrit eighteen percent above the patient's personal baseline. Each individual finding flags risk; the combination places the patient firmly in the high-risk stratum and would justify pre-emptive transfer to a high-dependency unit and structured isotonic crystalloid resuscitation pending the development of overt shock. In the absence of ferritin data, the same patient might have been observed on a standard ward until clinical decompensation; the addition of ferritin as a third axis of evaluation potentially shortens the time to escalation by several hours.

Cost-effectiveness considerations also favour ferritin in resource-constrained settings. The marginal cost of a serum ferritin assay in tertiary Indonesian hospitals is approximately fifty thousand Indonesian rupiah (roughly three United States dollars per sample), which is negligible relative to the cost of an unanticipated intensive-care admission, the cost of fluid-resuscitation complications, or the indirect costs of dengue-attributable mortality. Even a conservative estimate suggests that the additional cost of universal admission ferritin measurement in suspected adult dengue is recouped many times over by the avoidance of one or two unanticipated intensive-care admissions per hospital per outbreak season.

Future research priorities include prospective multicentre studies that report mean and standard-deviation ferritin values stratified by severity, age, and comorbidity, with particular attention to under-represented populations (Indonesian Bahasa-language studies; African dengue cohorts; pregnant women and immunocompromised adults); head-to-head comparisons against composite scoring systems such as H-Score and the dengue haemophagocytic-syndrome diagnostic criteria; harmonisation of ferritin-assay platforms across centres; and pragmatic clinical-trial work testing whether ferritin-guided decision rules improve hard outcomes such as intensive-care admission rates, dengue-attributable mortality, and length of hospital stay. The ongoing anakinra trial in Vietnam, which uses ferritin >2,000 ng/mL as an inclusion criterion, will be an important test of whether ferritin-guided immunomodulation translates a strong observational signal into clinical benefit. A formal bivariate diagnostic-test-accuracy meta-analysis, integrating sensitivity-specificity pairs across studies that report two-by-two tables, would complement the present standardised-mean-difference synthesis and is a logical next step. Paediatric severe dengue cohorts further extend the biological signal: a recent prospective Indian study reported peak ferritin values exceeding 15,000 ng/mL as a robust predictor of mortality (AUC 0.83)[33], complementing the Lakshmanan paediatric retrospective cohort. These age-extreme cohorts, although not formally pooled in the present primary analysis, reinforce the qualitative conclusion that hyperferritinemia tracks severity across the lifespan.

5. Conclusion

In this systematic review and random-effects meta-analysis of twelve observational studies enrolling 1,479 dengue-infected patients across South Asia, Southeast Asia, and Latin America, severe dengue was characterised by markedly higher serum ferritin concentrations than non-severe disease, with a pooled Hedges g standardised mean difference of 1.022 (95% confidence interval 0.494 to 1.551; p = 0.006) under the DerSimonian-Laird random-effects model with the Hartung-Knapp-Sidik-Jonkman correction. The 95% prediction interval (−0.12 to 2.17) reflects the limited number of contributing studies and signals appropriate caution about effect-size precision; nevertheless, the direction of effect was preserved across pre-specified subgroups by region and study design, remained robust under leave-one-out sensitivity analysis, and was concordant in a qualitative-synthesis review of seven additional studies that could not be quantitatively pooled. Heterogeneity was substantial but explainable by between-study differences in severity classification, sampling timing, and laboratory assay platforms. Together with the consistent diagnostic-accuracy data—area under the receiver-operating-characteristic curve typically between 0.78 and 0.95 in individual cohorts and threshold values converging around 500 to 600 ng/mL—and the well-characterised role of macrophage activation in the dengue critical phase, the present synthesis supports the use of serum ferritin as a low-cost, accessible early prognostic adjunct in adults with dengue. Clinicians practising internal medicine in tropical and subtropical regions can integrate ferritin measurement into the existing 2009 WHO warning-sign framework using the four-step structured triage algorithm presented in section 4.6, with the operational protocol of measuring ferritin at first medical contact (admission day) and re-sampling at day three or day four (around defervescence) for patients with persistent symptoms. Tomorrow morning on the ward, an internist faced with an adult dengue patient of indeterminate trajectory should obtain a ferritin value, interpret it alongside platelet trend and haematocrit change rather than in isolation, and use the integrated picture to guide the timing of escalation; this practical translation of the present synthesis is the principal contribution of the present work to the internal-medicine readership. As the dengue pandemic continues to expand its geographical footprint, the integration of biologically plausible, inexpensive, and widely available biomarkers such as serum ferritin into structured triage protocols offers a practicable strategy for reducing morbidity and mortality in resource-constrained internal-medicine settings, provided that the limitations identified in this synthesis—small evidence base, heterogeneous severity definitions, non-specificity of ferritin elevation, and imputation uncertainty—are openly communicated to readers and decision-makers.

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