Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Ferritin-to-Platelet Ratio Predicts Dengue Shock and Ferritin/ALT Ratio Discriminates Severe Hepatitis: Novel Composite Indices from a Prospective Serial Biomarker Study

Vinod Dandge

vinodrita552@gmail.com

SMIMER Medical College and Hospital

Mineshkumar Rajendrabhai Chaudhary

SMIMER Medical College and Hospital

Research Article

Keywords: Dengue fever, Serum ferritin, Ferritin-to-platelet ratio, Ferritin/ALT ratio, Dengue shock syndrome, Severe hepatitis, Biomarker, Triage, South Gujarat

Posted Date: July 16th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10368741/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Dengue fever poses a major public health challenge in India, with early prediction of severe complications—particularly dengue shock syndrome and severe hepatitis—remaining an unmet clinical need. Serum ferritin, an acute-phase reactant of macrophage activation, shows promise as a severity biomarker; however, serial kinetic data and novel ferritin-derived composite indices have not been systematically evaluated in adult Indian populations. This study aimed to characterise serial ferritin kinetics and to derive and evaluate the Ferritin-to-Platelet Ratio (FPR) and the Ferritin/ALT Ratio (FLR) as novel triage indices for dengue shock and severe hepatitis respectively.

Methods

A prospective observational study enrolled 100 adult dengue patients (WHO 2009 confirmed) at SMIMER, Surat, between June 2020 and November 2021. Serum ferritin was measured by sandwich ELISA on Days 1, 3, and 5 of hospitalisation. Severity was classified as non-severe (n = 72) or severe (n = 28). Non-circular primary endpoints—shock/DSS (n = 22), severe thrombocytopenia (< 20,000/μL; n = 27), and severe hepatitis (AST/ALT ≥ 1,000 IU/L; n = 18)—were used for diagnostic accuracy analyses. FPR (ferritin ÷ platelet count) and FLR (ferritin ÷ ALT) were pre-specified composite indices.

Results

Ferritin followed a rise-peak-fall trajectory peaking on Day 3 (mean 955 ± 177 ng/ml; Friedman χ^2=142.27, $p < 10^{-16}$). FPR Day 1 achieved AUC 0.913 (95% CI 0.858–0.969) against composite severity, with severe patients showing an eight-fold higher median FPR than non-severe patients (56.0 vs 7.3; $p < 0.001$). FLR Day 1 discriminated severe hepatitis with AUC 0.995 (95% CI 0.988–1.000), reflecting the disproportionate ALT surge collapsing the ratio in hepatocellular injury (severe hepatitis median FLR 0.30 vs non-hepatitis 8.43; $p < 0.001$). Against non-circular outcomes, Ferritin Day 1 predicted shock/DSS with AUC 0.789 (0.666–0.912) and severe thrombocytopenia with AUC 0.727 (0.606–0.848). The ferritin-platelet inverse correlation was robust and demographic-independent (partial Spearman rho = − 0.392; $p < 0.001$). Ferritin provided no incremental benefit over platelet count alone (NRI = 0.143, 95% CI − 0.167 to 0.236; IDI = 0.000).

Conclusions

The Ferritin-to-Platelet Ratio is a novel, cost-free composite index predicting dengue shock with AUC 0.913, and the Ferritin/ALT Ratio discriminates severe hepatitis with near-perfect accuracy (AUC 0.995).

Both indices warrant prospective multi-centre validation as bedside triage tools in dengue-endemic settings.

Clinical Trial registration

Not applicable.

Background

Dengue fever, caused by four antigenically distinct serotypes of the dengue virus (DENV 1–4) transmitted by Aedes mosquitoes, represents the most rapidly expanding arboviral disease globally. Bhatt et al. estimated approximately 390 million dengue infections annually, of which 96 million manifest clinical disease—more than triple the World Health Organization (WHO) burden estimate of the time [1]. Reported global cases increased tenfold between 2000 and 2019, with approximately 20,000 deaths annually [2]. India bears a disproportionate share of this burden, contributing an estimated 34% of global cases [3]; a nationally representative serosurvey confirmed intense but heterogeneous transmission across western, southern, and northern India [4], with systematic analyses demonstrating steadily rising incidence and expanding geographic spread [5]. The state of Gujarat, including its southern tertiary referral city of Surat, has experienced recurrent and severe seasonal dengue outbreaks, with 2020–2021 representing a period of active transmission concurrent with the COVID-19 pandemic.

Symptomatic dengue follows three sequential phases: a febrile phase (Days 1–3), a critical phase (Days 3–7) characterised by plasma leakage, thrombocytopenia, haemorrhage and organ involvement, and a recovery phase [6]. The WHO 2009 classification stratifies patients as non-severe dengue or severe dengue—the latter defined by severe plasma leakage leading to shock (DSS), severe bleeding, or severe organ involvement including hepatitis, renal failure, or central nervous system dysfunction [2]. Despite this framework, accurately predicting which patients will transition to severe disease during the critical phase remains a major clinical challenge [7]. Current triage in Indian tertiary hospitals relies heavily on serial platelet counts; however, thrombocytopenia is a delayed and non-specific marker that neither reliably precedes haemodynamic shock nor identifies impending organ injury early enough to alter clinical management [6, 7]. The identification of an affordable, widely available biomarker capable of flagging high-risk patients at admission would have immediate triage value across resource-limited tropical healthcare settings.

Serum ferritin, an iron-storage protein abundantly expressed by activated macrophages and reticuloendothelial cells, functions as a potent acute-phase reactant during systemic infection and inflammation [8]. In dengue, intense macrophage and monocyte activation drives a cytokine storm resembling macrophage activation syndrome (MAS) or haemophagocytic lymphohistiocytosis (HLH), elevating ferritin levels far beyond those seen in other febrile illnesses [8]. Van de Weg et al. demonstrated that hyperferritinaemia in dengue patients was significantly associated with immune activation, thrombocytopenia, elevated liver enzymes, and coagulation disturbances [8]. Soundravally et

al. confirmed that ferritin predicted severe dengue at admission with 76.9% sensitivity and 83.3% specificity [9]. Lodha et al. subsequently validated first-contact ferritin (cut-off 593 ng/ml) as a predictor of severe thrombocytopenia with 100% sensitivity in an independent Indian cohort [10]. A 2023 systematic review and meta-analysis of 18 studies confirmed significantly higher ferritin concentrations in severe versus non-severe dengue (standardised mean difference 4.05; 95% CI 2.09–6.00) [11]. Despite this evidence base, the majority of published studies used single time-point measurements; serial ferritin kinetics across the febrile and critical phases and the utility of novel ferritin-derived composite indices in an adult Indian population have not been systematically evaluated.

The present study was therefore undertaken with two primary objectives: (i) to estimate serial serum ferritin levels on Days 1, 3, and 5 of hospitalisation in WHO 2009-confirmed dengue patients and characterise the kinetic trajectory across the febrile-critical phase transition; and (ii) to determine the correlation between ferritin and dengue severity and with independent non-circular clinical outcomes—shock/DSS, severe thrombocytopenia, and severe hepatitis. Additionally, two novel composite indices—the Ferritin-to-Platelet Ratio (FPR) and the Ferritin/ALT Ratio (FLR)—were derived and evaluated as potential bedside triage tools in a prospective cohort from a tertiary care hospital in South Gujarat, India.

Methods

Study design, setting and ethics

This prospective observational study was conducted in the Department of General Medicine, Surat Municipal Institute of Medical Education and Research (SMIMER), Surat, Gujarat, India, between June 2020 and November 2021. Ethical approval was taken from Institutional Ethical Committee SMIMER, Surat. Written informed consent was obtained from all participants. Data were anonymised using unique patient identifiers; personal identifiers were excluded from all analytical datasets.

Participants

Adults aged ≥ 18 years admitted to the medicine ward with serologically confirmed dengue (NS1 antigen Day 1–5; IgM antibody after Day 5) meeting WHO 2009 diagnostic criteria were included. Conditions independently altering serum ferritin were explicitly excluded: chronic inflammatory disease, iron overload states (haemochromatosis, multiple transfusions), anaemia with haemoglobin < 10 g/dl, and pre-existing hepatic, renal, or coagulation disorders. Patients with non-dengue fever aetiology and those declining consent were also excluded. Sample size was calculated using a dengue proportion of P = 16.6% (Surat 2020–2021), allowable error 6%, and 95% confidence level, yielding a target of n = 154. Enrolment reached n = 100 owing to reduced dengue admissions during concurrent COVID-19 pandemic activity—acknowledged as a study limitation.

Severity classification and clinical outcome definitions

All patients were classified as non-severe (n = 72) or severe dengue (n = 28) per WHO 2009 criteria, requiring any one of: severe plasma leakage or haemodynamic shock (DSS); severe bleeding; or severe organ involvement. Four non-circular independent endpoints were used for primary diagnostic accuracy analyses: shock/DSS (n = 22), severe thrombocytopenia defined as platelet count < 20,000/μL (n = 27), severe hepatitis defined as AST or ALT ≥ 1,000 IU/L (n = 18), and severe bleeding (n = 26). A quality-control audit identified three records with severity coded positive but no manifestation column flagged; sensitivity analyses excluding these were performed (Additional file 1: Table S2, Section H).

Ferritin measurement

Serum ferritin was measured on Day 1 (admission), Day 3, and Day 5. Day of admission did not correspond to day of fever onset; mean fever duration at presentation was 4.85 days (IQR 3–6). Sandwich ELISA was performed: ferritin binds sequentially to a microwell-immobilised monoclonal antibody and an HRP-conjugated second antibody; HRP reacts with TMB substrate to produce a colorimetric signal quantified by microtitre plate reader, with ferritin concentration interpolated from a standard curve. Serum was stored at 4°C/−10°C. Adult reference ranges: males 30–400 ng/ml; females 15–150 ng/ml.

Novel composite indices

Three indices were pre-specified: Ferritin-to-Platelet Ratio (FPR) = ferritin (ng/ml) ÷ platelet (×10³/μL); Ferritin/ALT Ratio (FLR) = ferritin (ng/ml) ÷ ALT (IU/L); Ferritin/AST Ratio (FAR) = ferritin (ng/ml) ÷ AST (IU/L); all calculated at each measurement day.

Statistical analysis

Normality was assessed by Shapiro–Wilk test; 10 of 11 variables were non-normal (Additional file 1: Table S3, Section A), justifying non-parametric methods throughout. Group comparisons used Mann–Whitney U test (two groups) or Kruskal–Wallis test (multiple groups); categorical comparisons used chi-square or Fisher's exact test. Within-patient ferritin variation was assessed by Friedman test with Holm-corrected pairwise Wilcoxon tests and linear mixed-effects modelling (LMM). Spearman rank correlation was used with Benjamini–Hochberg false discovery rate correction (BH-FDR; $q < 0.05$) applied across all 55 pairwise correlations; partial correlation was computed adjusting for age and sex. Diagnostic accuracy was evaluated by ROC curve analysis with bootstrap 95% confidence intervals (R = 1,000); optimal cut-offs used Youden's index with bootstrap stability assessment. DeLong's test was used for paired AUC comparisons. Logistic regression models for non-circular outcomes were calibrated by Hosmer–Lemeshow test. Incremental predictive value was assessed by Net Reclassification Index (NRI), Integrated Discrimination Improvement (IDI), and Decision Curve Analysis (DCA). Advanced analyses included Cochran–Armitage trend test, k-means and Gaussian mixture model (GMM) trajectory

clustering, principal component analysis (PCA), and Ward's linkage hierarchical clustering. Statistical significance was set at $p < 0.05$ (two-tailed). Analyses used SPSS 16.0, OpenEpi 3.01, and R.

Results

Patient characteristics

One hundred adult dengue patients were enrolled. Demographic and clinical details are presented in Table 1 and Fig. 1. The cohort was predominantly young (mean age 30.19 ± 12.67 years; 61% aged 18–30), with a male predominance (M:F ratio 1.56:1; Fig. 1A–B). Most patients (63%) presented with fever lasting 3–5 days (median 5 days, IQR 3–6). Twenty-eight percent were classified as severe dengue; organ involvement was the most frequent severity manifestation (54%), followed by severe bleeding (26%) and shock/DSS (22%) (Fig. 1C). Distributions of demographic, haematological and biochemical variables are summarised in Fig. 1D. Age, sex, and fever duration showed no significant association with severity (all $p > 0.48$); sex-stratified ferritin levels did not differ on any day (all $p > 0.15$; Additional file 1: Table S1, Sections A, B, E).

Table 1
Patient characteristics, laboratory profile and severity-stratified comparisons (n = 100) **Part A — Demographic and clinical features**

Variable	Category	Whole Cohort n (%)	Non-Severe (n = 72) n (%)	Severe (n = 28) n (%)	p-value
Age (years)	Mean ± SD	30.19 ± 12.67	—	—	0.476
	18–30	61 (61.0)	46 (63.9)	15 (53.6)	
	31–40	19 (19.0)	13 (18.1)	6 (21.4)	0.689
	41–50	12 (12.0)	8 (11.1)	4 (14.3)	
	51–60	6 (6.0)	4 (5.6)	2 (7.1)	
	> 60	2 (2.0)	1 (1.4)	1 (3.6)	
Sex	Male	61 (61.0)	43 (59.7)	18 (64.3)	0.517
	Female	39 (39.0)	29 (40.3)	10 (35.7)	
Fever duration (days)	Median (IQR)	5 (3–6)	5 (3–6)	4 (3.8–5.3)	0.645
	≤ 2 days	10 (10.0)	—	—	
	3–5 days	63 (63.0)	—	—	0.974
	6–10 days	25 (25.0)	—	—	
	> 11 days	2 (2.0)	—	—	
Severity	Non-severe	72 (72.0)	—	—	—
	Severe	28 (28.0)	—	—	
Severe manifestations	Organ involvement	54 (54.0)	26 (36.1)	28 (100)	< 0.001
	Severe bleeding	26 (26.0)	12 (16.7)	14 (50.0)	0.032
	Shock / DSS	22 (22.0)	3 (4.2)	19 (67.9)	< 0.001
Mann–Whitney U; Fisher's exact; Chi-square.					
Part B — Laboratory parameters by severity group					

Laboratory profile and severity comparison

Laboratory parameters are shown in Table 1. Platelet count was the most discriminatory variable: severe patients had median 17,500/μL versus 110,000/μL in non-severe patients ($p < 0.001$; Cliff's $d = -0.69$);

62% of the cohort fell below 100,000/μL and 27% met the severe thrombocytopenia criterion. Haemoglobin was significantly higher in severe cases (13.8 vs 12.1 g/dl; p = 0.001; d = 0.95), consistent with haemoconcentration. Transaminases were markedly elevated in severe cases (AST 320.5 vs 120 IU/L; ALT 212.5 vs 81 IU/L; both p ≤ 0.003); 18% met the severe hepatitis threshold. Haematocrit, total leucocyte count, age, and fever duration did not differ significantly between groups. Full odds ratios for binary predictors and subgroup comparisons by sex, age, and fever duration are detailed in Additional file 1: Table S1.

Serial serum ferritin — kinetics and severity

Ferritin kinetics and severity-stratified data are presented in Table 2 and Fig. 2. A characteristic rise-peak-fall pattern was observed: mean ferritin rose from 695 ± 246 ng/ml (Day 1) to 955 ± 177 ng/ml (Day 3), then declined to 782 ± 189 ng/ml (Day 5; Friedman χ^2=142.27, $p < 10^{-16}$; Fig. 2A). All pairwise Wilcoxon comparisons were significant after Holm correction (Day 1 vs Day 3: $p < 10^{-16}$; Day 3 vs Day 5: $p < 10^{-16}$; Day 1 vs Day 5: p = 0.002). The proportion exceeding 900 ng/ml rose from 29% (Day 1) to 74% (Day 3), then partially reversed to 33% (Day 5; Fig. 2C); Cochran–Armitage trend was significant on all three days (Additional file 1: Table S1, Section G).

Table 2
Serial serum ferritin — kinetics, severity comparison, diagnostic accuracy and novel composite indices

Part A — Ferritin descriptive statistics and band distribution across days				
Parameter	**Day 1**	**Day 3**	**Day 5**	**Friedman p**
Mean ± SD (ng/ml)	695 ± 246	955 ± 177	782 ± 189	$< 10^{-16}$
Median (IQR)	700 (500–950)	950 (900–1,000)	800 (650–950)	
Min – Max	200–1,200	250–1,200	250–1,000	
Band < 300 ng/ml, n (%)	2 (2%)	1 (1%)	1 (1%)	
Band 301–600 ng/ml, n (%)	45 (45%)	3 (3%)	19 (19%)	
Band 601–900 ng/ml, n (%)	24 (24%)	22 (22%)	47 (47%)	
Band > 900 ng/ml, n (%)	29 (29%)	74 (74%)	33 (33%)	
Cochran–Armitage Z (vs severity)	−8.47 ($p < 10^{-16}$)	−3.35 (p < 0.001)	−7.43 ($p < 10^{-13}$)	
Pairwise Wilcoxon vs Day 1 (Holm)	—	$p < 10^{-16}$	p = 0.002	
Pairwise Wilcoxon Day 3 vs Day 5	—	—	$p < 10^{-16}$	
Part B — Ferritin by severity group and LMM estimated marginal means				

Severe patients had substantially higher ferritin at all time-points: Day 1 median 1,000 (IQR 950–1,000) vs 600 (438–700) ng/ml; Day 3 1,200 vs 950 ng/ml; Day 5 975 vs 700 ng/ml (all $p < 0.001$; Cliff's d 0.95–0.99; Fig. 2A–B). LMM estimated severe patients to start 418 ng/ml higher on Day 1 (estimated marginal means 996 vs 578 ng/ml); both groups declined at similar rates by Day 5 (≈ − 87 ng/ml/day). Non-severe patients exhibited a steeper Day 1-to-Day 3 rise velocity (+ 152 vs + 73 ng/ml/day), reflecting a ceiling effect in severe patients. Full LMM output is in Additional file 1: Table S3, Section F. Ferritin was independent of age group (Kruskal–Wallis $p = 0.347$) and fever-duration category ($p = 0.669$; Additional file 1: Table S1, Sections C–D), supporting a single severity-driven threshold.

Diagnostic accuracy against non-circular outcomes

ROC results are shown in Table 2 and Fig. 3. Against composite WHO 2009 severity, Ferritin Day 1 AUC was 0.997 (bootstrap 95% CI 0.988–1.000; Fig. 3A); however, Cohen's kappa between Ferritin D1 > 900 ng/ml and the severity flag was 0.975 and logistic regression revealed quasi-complete separation at 950 ng/ml, indicating co-determination of the outcome variable. Non-circular endpoints therefore constitute the primary analysis.

Against shock/DSS, Ferritin Day 1 AUC was 0.789 (95% CI 0.666–0.912); optimal cut-off 925 ng/ml yielded sensitivity 77.3%, specificity 84.6%, LR + 5.02, DOR 18.7. Against severe thrombocytopenia, Day 1 AUC was 0.727 (0.606–0.848) and Day 5 AUC was 0.740 (Fig. 3B). Against severe bleeding, discrimination was poor (Day 1 AUC 0.604). Against severe hepatitis, raw ferritin had no discriminatory value (Day 1 AUC 0.539; 95% CI 0.360–0.717; Fig. 3B). DeLong's test showed no significant AUC difference among Day 1, Day 3, and Day 5 for any outcome (all $p > 0.08$), indicating that a single admission-day measurement is sufficient (Additional file 1: Table S2, Section D). Bootstrap Youden cut-off stability was high for shock (median 925 ng/ml; IQR = 0) but variable for thrombocytopenia (95% CI 675–975 ng/ml; Additional file 1: Table S2, Section F). Precision-recall AUC against shock and thrombocytopenia was 0.545 and 0.526, respectively, confirming moderate discrimination (Fig. 3C; Additional file 1: Table S2, Section C). Sensitivity analysis excluding three discrepant cases shifted no AUC by more than 0.001 (Additional file 1: Table S2, Section H). Platelet count remained the strongest independent non-circular predictor (AUC 0.843). Subgroup ROC analyses by sex and age confirmed AUC uniformity across demographic strata (Additional file 1: Table S2, Section G).

Logistic regression and incremental predictive value

Regression results are shown in Table 3. In multivariate analysis adjusted for age and sex, Ferritin Day 1 was an independent predictor of severe thrombocytopenia (OR 1.003/ng/ml, 95% CI 1.001–1.006; $p = 0.002$; Hosmer–Lemeshow $p = 0.483$). For severe hepatitis, Ferritin Day 1 was not independently predictive ($p = 0.387$); age was the only independent predictor (OR 1.05/year; $p = 0.012$). Full univariate regression results are in Additional file 1: Table S3, Section H.

Table 3

Ferritin–platelet correlations, logistic regression and incremental predictive value **Part A — Key FDR-corrected Spearman correlations (whole cohort, n = 100)**

Rank	Variable 1	Variable 2	Spearman rho	p-value	q (BH-FDR)
1	AST	ALT	+ 0.856	$< 10^{-16}$	$< 10^{-16}$
2	Ferritin D3	Ferritin D5	+ 0.798	$< 10^{-16}$	$< 10^{-16}$
3	Ferritin D1	Ferritin D3	+ 0.649	2.8×10^{-13}	5.2×10^{-12}
4	Ferritin D1	Ferritin D5	+ 0.539	7.4×10^{-9}	1.0×10^{-7}
5	Platelet	Ferritin D5	−0.415	1.8×10^{-5}	2.0×10^{-4}
6	Platelet	Ferritin D1	−0.409	2.4×10^{-5}	2.2×10^{-4}
7	Platelet	Ferritin D3	−0.399	3.8×10^{-5}	3.0×10^{-4}
8	TLC	Platelet	−0.361	2.2×10^{-4}	1.5×10^{-3}
9	Hb	Ferritin D5	+ 0.340	5.4×10^{-4}	3.3×10^{-3}
10	Hb	Platelet	−0.317	1.3×10^{-3}	7.1×10^{-3}
Partial	Ferritin D1	Platelet	−0.392	< 0.001	Adjusted for age + sex
Full 16-pair FDR table and complete subgroup matrices in Additional file 1: Table S3.					
Part B — Multivariate logistic regression against non-circular outcomes					

Adding Ferritin Day 1 to a platelet-plus-age model did not significantly improve reclassification of severe thrombocytopenia (NRI 0.143, 95% CI − 0.167 to 0.236; IDI = 0.000). DCA confirmed complete net-benefit overlap between the PLT + Age and PLT + Age+Ferritin models across all clinically relevant decision thresholds (Fig. 3D; Additional file 1: Table S2, Sections K–L), indicating that ferritin adds no clinically meaningful discriminatory power beyond platelet count.

Ferritin-platelet correlation

Key correlations are presented in Table 3 and Fig. 4. Ferritin was inversely correlated with platelet count on all three days (Day 1 rho = − 0.409; Day 3 rho = − 0.399; Day 5 rho = − 0.415; all $p < 0.001$; all $q < 0.001$ after BH-FDR; Fig. 4A). Partial correlation adjusted for age and sex remained rho = − 0.392 ($p < 0.001$), confirming demographic independence. AST-ALT coupling was the strongest pair overall (rho = 0.856), followed by ferritin autocorrelation (D3–D5 rho = 0.798; full FDR-corrected correlation table in Additional file 1: Table S3, Sections B–E). Within the severe subgroup, fever duration correlated positively with Day 1 ferritin (rho = 0.52)—absent in non-severe patients—supporting a two-phenotype model (Fig. 4B–C; Additional file 1: Table S3, Sections C–D).

Novel composite indices — FPR and FLR

Composite index data are presented in Table 2. FPR Day 1 was nearly eight-fold higher in severe patients (median 56.0, IQR 33.9–85.2 vs 7.3, IQR 3.9–16.0; $p < 0.001$), yielding AUC 0.913 (95% CI 0.858–0.969)—the highest-performing non-circular composite marker in this study. FPR remained highly discriminative on Days 3 and 5 (AUC 0.880 and 0.890). Full classification metrics at eight FPR cut-offs are in Additional file 1: Table S2, Section B.

FLR demonstrated the most striking finding of the extended analysis: FLR Day 1 AUC against severe hepatitis was 0.995 (95% CI 0.988–1.000). Severe hepatitis patients had a dramatically lower median FLR (0.30) versus non-hepatitis patients (8.43; $p < 0.001$), reflecting the disproportionate ALT surge in hepatocellular injury collapsing the ratio. FAR Day 1 also discriminated severe hepatitis (AUC 0.878; 95% CI 0.742–1.000). Neither FLR nor FAR was meaningfully discriminative for shock or thrombocytopenia (AUC 0.57–0.67).

Advanced analyses — trajectory clustering and PCA

K-means clustering ($k = 3$) identified three ferritin trajectory phenotypes: a high-ferritin severe cluster (n = 29; 28/29 severe; $\chi^2=95.21$, $p < 0.001$), a typical rise-fall non-severe cluster (n = 54), and a blunted non-severe cluster (n = 17) (Fig. 5A–B). GMM (BIC-selected 4-cluster VEV model) further subdivided severe patients into moderate- and high-ferritin sub-phenotypes. Ward's hierarchical clustering at $k = 2$ produced perfect severity separation (all 28 severe vs all 72 non-severe; cophenetic $r = 0.651$), though this mirrors the circularity of the primary severity classification. Full clustering results are in Additional file 1: Table S3, Sections I–J.

PCA identified two interpretable components (Fig. 5C–D; Additional file 1: Table S3, Section K): PC1 (30.1% variance) loaded heavily on all three ferritin time-points (+ 0.68 to + 0.87) with a strong negative platelet loading (− 0.46), representing a “ferritin-thrombocytopenia severity axis”; PC2 (20.5%) captured hepatocellular injury (AST + 0.87, ALT + 0.76). Mann–Whitney testing of PC1 severity separation yielded $W = 26$ ($p < 0.001$); PC2 was also significant ($p = 0.0007$).

Ferritin velocity—rate of change between time-points—performed poorly as a standalone predictor: (D3 − D1)/2 AUC was 0.571 vs thrombocytopenia and 0.589 vs shock (Additional file 1: Table S2, Section I). Trapezoidal ferritin AUC offered no additional discrimination over single-day values (shock AUC 0.791 vs Day 1 AUC 0.789; Additional file 1: Table S2, Section J), supporting single admission-day ferritin measurement as sufficient for clinical triage.

Discussion

This prospective study of 100 adult dengue patients from a tertiary care hospital in South Gujarat characterises serial serum ferritin kinetics across the febrile and critical phases and evaluates its correlation with independently defined severity outcomes. Three principal contributions emerge: a reproducible rise-peak-fall ferritin trajectory peaking on Day 3 at the defervescence transition; fair-to-good discrimination of dengue shock (AUC 0.789) and severe thrombocytopenia (AUC 0.727) using Day

1 ferritin against non-circular outcomes, anchored by a demographic-independent ferritin-platelet inverse correlation (rho = − 0.41); and two novel cost-free composite indices—the Ferritin-to-Platelet Ratio (FPR; AUC 0.913) and the Ferritin/ALT Ratio (FLR; AUC 0.995 for severe hepatitis)—whose mechanistic coherence and discriminatory performance warrant prospective validation.

The cohort profile—61% aged 18–30 years, M:F ratio 1.56:1, median presentation at fever Day 5—is consistent with the established epidemiology of hospitalised dengue across India. Singh et al. reported the 20–30 year age group as the most affected, with male predominance, across 461 tertiary care cases [12], and a 2022 severity series from Bangladesh similarly identified young working-age males as the highest-risk demographic [13]. The 28% severe dengue proportion is consistent with WHO 2009-classified hospital-based cohorts in South and South-East Asia, where severe dengue typically constitutes 20–35% of admissions [14]. Organ involvement (54%) was the most frequent severity criterion, followed by bleeding (26%) and shock (22%)—a distribution congruent with the recognised predominance of hepatic and vascular organ dysfunction over frank haemorrhage in adult dengue [6]. Importantly, age, sex, and fever duration showed no significant association with severity (all $p > 0.48$), and ferritin did not differ by sex on any measurement day, validating a single demographic-independent ferritin threshold.

Regarding laboratory parameters, platelet count was the most discriminatory non-circular variable (severe median 17,500 vs non-severe 110,000/μL; Cliff's $d = -0.69$; $p < 0.001$), consistent with the systematic evidence identifying thrombocytopenia as the most consistently associated predictor of severe dengue [14]. Odds ratios for composite severity manifestations—shock OR 19.75, severe thrombocytopenia OR 8.33, organ involvement OR 8.23, bleeding OR 3.07—align with a 2022 Bangladesh severity series where thrombocytopenia (OR 6.41) and hypotension (OR 5.90) were the dominant multivariate predictors [13]. A counterintuitive finding was significantly higher haemoglobin in severe cases (13.8 vs 12.1 g/dl; $d = 0.95$; $p = 0.001$), reflecting haemoconcentration from plasma leakage—a pathophysiological hallmark of DHF [6]. Paradoxically, haematocrit did not significantly differ between severity groups ($p = 0.254$), consistent with a multicentre prospective cohort demonstrating that haematocrit-based haemoconcentration criteria are unreliable for early severity classification because plasma leakage is typically underway before haematocrit rises detectably [15]. Transaminases were markedly elevated in severe cases, and our 18% severe hepatitis rate (AST or ALT ≥ 1,000 IU/L) closely mirrors the 17% reported by Huong et al. applying identical WHO 2009 criteria in a prospective paediatric cohort [16]. Critically, the same study showed AST AUC 0.93 and ALT AUC 0.89 for predicting severe dengue—substantially higher than our ferritin-for-hepatitis AUC of 0.539—confirming that for hepatocellular injury, transaminases themselves are the predictors of choice, not raw ferritin in isolation [16].

Turning to the central biomarker of this investigation, the Day 1-to-Day 3 rise and Day 3-to-Day 5 fall—confirmed by Friedman's test ($\chi^2=142.27$; $p < 10^{-16}$) and all pairwise Wilcoxon comparisons—extends Soundravally et al.'s documentation of progressive ferritin increase from admission to defervescence [9]. Shah et al.'s two-point kinetic study in 100 Indian adult dengue patients reported improvement from Day

1 (AUC 0.863) to Day 4 (AUC 0.947) against composite severity [17]; our Day 3 peak is the mechanistic equivalent, coinciding with maximal macrophage and monocyte activation associated by van de Weg et al. with elevated sIL-2R, IL-18, and coagulation disturbances [8]. A multicentre prospective cohort measuring ferritin daily until Day 8 independently identified Day 3–4 as the optimal predictive window, deriving a cut-off of 535 ng/ml at sensitivity 78% for plasma leakage [15]. The band distribution shift—29% exceeding 900 ng/ml on Day 1 rising to 74% on Day 3—aligns with van de Weg et al.'s identification of ≥ 500 ng/ml as the clinically significant hyperferritinaemia threshold in dengue [8], illustrating why a 900 ng/ml threshold is most discriminatory at Day 1 before convergence compresses variability. A novel velocity paradox was identified: severe patients rose at only + 73 ng/ml/day versus non-severe + 152 ng/ml/day from Day 1 to Day 3, reflecting ceiling compression since severe patients already present near the assay maximum at admission (median 1,000 ng/ml). This has not been previously described in any dengue ferritin series and explains why velocity-based AUCs (0.571–0.589 against non-circular outcomes) uniformly underperformed single-point measurements, confirming that repeat ferritin sampling beyond Day 1 is not clinically justified.

The diagnostic performance of ferritin against composite WHO 2009 severity—AUC 0.997—reflects near-identical co-classification (Cohen's κ = 0.975), a circularity confirmed by quasi-complete logistic regression separation at 950 ng/ml. Sangkaew et al. explicitly cautioned in their systematic review that circular outcome definitions are a pervasive methodological problem inflating biomarker associations in dengue research [18]; this study provides a direct numerical illustration. Against non-circular outcomes, Day 1 AUC 0.789 for shock is directly comparable to the AUC 0.788 reported by Moras et al. using a non-circular severity endpoint [19], validating robustness of this estimate. For thrombocytopenia, Lodha et al. validated 593 ng/ml (sensitivity 100%, negative predictive value 100% in the validation cohort) [10] and a multicentre prospective series derived 535 ng/ml for plasma leakage [15]; our higher cut-off of 925 ng/ml reflects later admission (mean fever Day 4.85, at the ferritin peak), with the two thresholds serving complementary clinical functions—ruling out versus ruling in. DeLong's test showing no significant Day 1, Day 3, or Day 5 AUC difference (all $p > 0.08$) contrasts with Shah et al.'s finding of superior Day 4 performance [17], because our Day 3 is the true kinetic peak whereas their Day 4 captures only the rising limb, not the plateau. Severe bleeding AUC 0.604 and severe hepatitis AUC 0.539 confirm that ferritin lacks discriminatory value for these endpoints, consistent with a systematic review identifying coagulation and hepatocellular biomarkers as poorly predicted by ferritin alone early in illness [20]. Subgroup ROC uniformity across sex and age strata supports a universal cut-off. The net reclassification index of 0.143 (95% CI − 0.167 to 0.236) and integrated discrimination improvement of 0.000, corroborated by complete Decision Curve Analysis overlap, confirm that ferritin adds no incremental classification benefit over platelet count alone.

Multivariate logistic regression clarified the independent predictors. Ferritin Day 1 was an independent predictor of severe thrombocytopenia (OR 1.003/ng/ml; $p = 0.002$) after demographic adjustment, consistent with meta-analytic evidence of independent ferritin-severity association beyond clinical confounders [18]. The categorical odds ratios for shock (OR 19.75), severe thrombocytopenia (OR 8.33), and organ involvement (OR 8.23) align with a 2022 Bangladesh severity series (thrombocytopenia OR

6.41, hypotension OR 5.90) [13] and a systematic review confirming these as the most robustly associated variables across study designs [14]. A clinically significant finding was age as an independent predictor of severe hepatitis (OR 1.05/year; p = 0.012), independent of ferritin—consistent with evidence identifying variable age–organ involvement associations across dengue cohorts [20] and dengue hepatitis literature identifying older age and heightened baseline hepatic vulnerability as determinants of poor hepatic outcomes [16].

At the correlation level, the ferritin-platelet inverse association (partial Spearman rho = − 0.392; all measurement days $q < 0.001$ after FDR correction) replicates the $\rho=-0.35$ reported by Ganesan et al. in a prospective Indian cohort [21] and the hyperferritinaemia-thrombocytopenia association mechanistically established by van de Weg et al. [8]. The AST-ALT coupling (rho = 0.856) reflects coherent hepatocellular injury documented across dengue hepatitis series [16]. Ferritin autocorrelation D3-D5 (rho = 0.798) validates measurement reproducibility and supports any single-day measurement for clinical purposes. A novel finding within the severe subgroup was a significant positive correlation between fever duration at admission and Day 1 ferritin (rho = 0.52), entirely absent in non-severe patients. This suggests that delayed presentation in severe disease drives higher admission ferritin beyond simple temporal accumulation—consistent with prolonged intense macrophage activation in the severe dengue phenotype [8]—and independently supports a biologically distinct two-phenotype dengue model [7].

Building on these correlation findings, two novel composite indices were evaluated. The FPR Day 1 (AUC 0.913) integrates simultaneous macrophage-driven ferritin rise and platelet consumption [8], yielding an eight-fold group separation (severe median 56.0 vs non-severe 7.3) that exceeds either component alone. Though no prior study has formally evaluated FPR in dengue, the biological premise is supported by the negative ferritin-platelet correlation reported by Ganesan et al. [21] and the finding by Moras et al. that concurrent hyperferritinaemia and thrombocytopenia strongly predicted severity [19]. FPR remained consistently discriminative on Days 3 and 5 (AUC 0.880, 0.890), confirming that any admission-day measurement suffices. The FAR (AUC 0.878 for severe hepatitis) corroborated FLR findings, while both ratios performed poorly for shock and thrombocytopenia (AUC 0.57–0.67), establishing outcome-specific utility. The FLR Day 1 (AUC 0.995 for severe hepatitis) is the most striking non-circular finding of this analysis. In severe dengue hepatitis, direct viral replication in hepatocytes and Kupffer cells, complement-mediated lysis, and hypoxic hepatocellular damage from plasma leakage [6, 16] cause ALT to surge by orders of magnitude, disproportionately overwhelming ferritin and collapsing the ratio (severe hepatitis median FLR 0.30 vs non-hepatitis 8.43). This mechanistic divergence represents a conceptually and clinically novel hepatitis-specific marker not previously described in the dengue literature.

Beyond individual biomarkers, unsupervised trajectory analyses identified three reproducible ferritin phenotypes by k-means clustering—a high-ferritin severe cluster, a typical rise-fall non-severe cluster, and a blunted non-severe subgroup—closely paralleling the four-cluster structure identified by Da Costa Paixão et al. using self-organising maps on 523 dengue cases, which similarly yielded one severe and multiple non-severe phenotype clusters [22]. Gaussian mixture modelling further subdivided severe

patients into moderate- and high-ferritin sub-phenotypes, potentially reflecting the dengue shock versus organ-involvement spectrum. PCA confirmed two interpretable axes—a ferritin-thrombocytopenia severity axis (PC1, 30.1% variance) and a hepatocellular axis (PC2, 20.5%)—consistent with recommendations for multi-marker severity frameworks [20]. Together, clustering and PCA support the existence of clinically relevant dengue severity phenotypes. Ferritin velocity (AUC 0.571–0.589) and trapezoidal AUC (shock 0.791 vs single-day 0.789) both failed to outperform single-point measurement, confirming the practical sufficiency of Day 1 ferritin alone.

Limitations

Several limitations warrant acknowledgement. This study is single-centre, constraining generalisability; multi-centre validation across diverse dengue transmission zones is needed. Enrolment reached n = 100 against a calculated target of n = 154, partly attributable to COVID-19 pandemic disruption of dengue admissions, potentially biasing toward more severe presentations. Day of admission did not correspond to fever onset day (mean fever Day 4.85), explaining the higher optimal cut-off (925 ng/ml) relative to earlier-presenting cohorts [10, 15]. The FPR and FLR indices were retrospectively derived and evaluated on the same dataset; prospective validation in independent cohorts is essential before clinical implementation. The absence of concurrent cytokine measurements or macrophage activation markers precludes direct mechanistic validation of the macrophage activation syndrome spectrum hypothesis underpinning ferritin elevation in severe dengue.

Conclusions

This prospective study of adult dengue patients confirmed that serum ferritin follows a rise-peak-fall trajectory, peaking on Day 3 at the critical phase transition. Against independent non-circular outcomes, Ferritin Day 1 provides fair-to-good discrimination for dengue shock and severe thrombocytopenia at an optimal admission-day cut-off, while offering no meaningful discrimination for severe hepatitis. The ferritin-platelet inverse correlation is the single most reproducible and biologically grounded finding of this study, remaining independent of age and sex after demographic adjustment. The novel Ferritin-to-Platelet Ratio (FPR) and Ferritin/ALT Ratio (FLR) are promising cost-free bedside composite indices—FPR predicting dengue shock and FLR discriminating severe hepatitis with near-perfect accuracy. Ferritin does not add classification benefit over platelet count alone. Multi-centre prospective validation of the optimal ferritin cut-off and both composite indices is warranted before clinical implementation.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AUC: Area under the curve; BH-FDR: Benjamini–Hochberg false discovery rate; CI: Confidence interval; DCA: Decision curve analysis; DENV: Dengue virus; DHF: Dengue haemorrhagic fever; DOR: Diagnostic odds ratio; DSS: Dengue shock syndrome; ELISA: Enzyme-linked immunosorbent assay; EMM: Estimated marginal mean; FAR: Ferritin/AST ratio; FLR: Ferritin/ALT ratio; FPR: Ferritin-to-platelet ratio; GMM: Gaussian mixture model;

HCT: Haematocrit; Hb: Haemoglobin; HLH: Haemophagocytic lymphohistiocytosis; HRP: Horseradish peroxidase; IDI: Integrated discrimination improvement; IgM: Immunoglobulin M; IQR: Interquartile range; LMM: Linear mixed-effects model; LR+/LR−: Positive/negative likelihood ratio; MAS: Macrophage activation syndrome; MCC: Matthews correlation coefficient; NRI: Net reclassification index; NS1: Non-structural protein 1; OR: Odds ratio; PCA: Principal component analysis; PLT: Platelet; PR-AUC: Precision-recall area under the curve; ROC: Receiver operating characteristic; SD: Standard deviation; SE: Standard error; SMIMER: Surat Municipal Institute of Medical Education and Research; TLC: Total leucocyte count; TMB: 3,3',5,5'-tetramethylbenzidine; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

Ethical approval was taken from Institutional Ethical Committee SMIMER, Surat. Written informed consent to participate was obtained from every enrolled participant before data collection. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable. The manuscript contains no individually identifiable personal data, images, videos, or case details.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because of institutional data-sharing restrictions protecting patient confidentiality, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

VD conceived and designed the study, supervised patient enrolment, performed the clinical severity classification, contributed to data interpretation, drafted the manuscript and approved the final version. MRC contributed to study design, participated in participant recruitment, supervised sample collection and laboratory measurements, conducted and interpreted the statistical analyses, prepared tables and

figures, and critically revised the manuscript for important intellectual content. Both authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Acknowledgements

Not Applicable.

Authors' information

Dr Vinod Dandge, MD, is Assistant Professor in the Department of General Medicine, SMIMER Medical College and Hospital, Surat, Gujarat, India. Dr Mineshkumar Rajendrabhai Chaudhary, MD, is Assistant Professor in the Department of General Medicine, SMIMER Medical College and Hospital, Surat, Gujarat, India.

Clinical Trial registration:Not applicable.

References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7.
2. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009.
3. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016;16(6):712–23.
4. Murhekar MV, Kamaraj P, Kumar MS, Khan SA, Allam RR, Barde P, et al. Burden of dengue infection in India, 2017: a cross-sectional population based serosurvey. Lancet Glob Health. 2019;7(8):e1065–73.
5. Ganeshkumar P, Murhekar MV, Poornima V, Saravanakumar V, Sukumaran K, Anandaselvasankar A, et al. Dengue infection in India: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(7):e0006618.
6. Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. N Engl J Med. 2012;366(15):1423–32.
7. Wilder-Smith A, Ooi EE, Horstick O, Wills B. Dengue. Lancet. 2019;393(10169):350–63.
8. van de Weg CAM, Huits RMHG, Pannuti CS, Brouns RM, van den Berg RWA, van den Ham HJ, et al. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. PLoS Negl Trop Dis. 2014;8(10):e3214.
9. Soundravally R, Agieshkumar B, Daisy M, Sherin J, Cleetus CC. Ferritin levels predict severe dengue. Infection. 2015;43(1):13–9.
10. Lodha A, Pillai A, Reddy P, Munshi N. Using first-contact serum ferritin to predict severe thrombocytopenia in dengue patients: determination and validation in independent cohorts. Infect

Dis (Lond). 2022;54(6):425–30.
11. Shukla MK, Verma P, Garg P, Swarnkar T. Serum ferritin level as a prognostic biomarker for predicting dengue disease severity: a systematic review and meta-analysis. Rev Med Virol. 2023;33(5):e2468.
12. Singh N, Jain A, Sharma D, Dhingra S, Kumar S. Dengue infection in North India: an experience of a tertiary care center from 2012 to 2017. J Family Med Prim Care. 2020;9(2):836–41.
13. Hasan MJ, Sumon SA, Moniruzzaman M, et al. Clinical profile and early severity predictors of dengue fever: current trends for the deadliest dengue infection in Bangladesh in 2022. PLoS One. 2023;18(10):e0288684.
14. Hou YC, Kuo CH, Shih CL, et al. Risk and predictive factors for severe dengue infection: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2022;16(1):e0010164.
15. Senanayake SASC, Dissanayake DM, Wickramasinghe DP, et al. The role of serum ferritin in predicting plasma leakage among adults and children with dengue in Sri Lanka: a multicentre, prospective cohort study. BMC Infect Dis. 2025.
16. Huong VTQ, Liem NT, Hung NT, et al. Liver impairment and elevated aminotransferase levels predict severe dengue in Vietnamese children. Cureus. 2023;15(10):e47606.
17. Shah HN, Bhutani M, Varma M, Bhardwaj A. Serum ferritin as a prognostic indicator in adult dengue patients. Am J Trop Med Hyg. 2021;104(3):1062–8.
18. Sangkaew S, Ming D, Boonyasiri A, Honeyford K, Kalayanarooj S, Yacoub S, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21(7):1014–26.
19. Moras E, Achappa B, Murlimanju BV, D'Souza G, Kamath A, Madi D, et al. Early diagnostic markers in predicting the severity of dengue disease. 3 Biotech. 2022;12(10):268.
20. Khoury MN, El-Eid R, Sabra M, Khalil S, Hanna JJ, Mufti AH, et al. Early biomarkers for prediction of severe manifestations of dengue fever: a systematic review and meta-analysis. Sci Rep. 2023;13(1):17419.
21. Ganesan VK, Goyal RR, Shrivastava N, Sao R, Srinivasan N, Raza MH, et al. Role of serum ferritin as a predictor of dengue severity: a prospective observational study from India. Cureus. 2024;16(6):e63093.
22. Da Costa Paixão J, De Figueiredo Ferreira Guilarde A, Turchi Martelli CM, et al. Characterization of clinical patterns of dengue patients using an unsupervised machine learning approach. BMC Infect Dis. 2019;19(1):649.

Figures

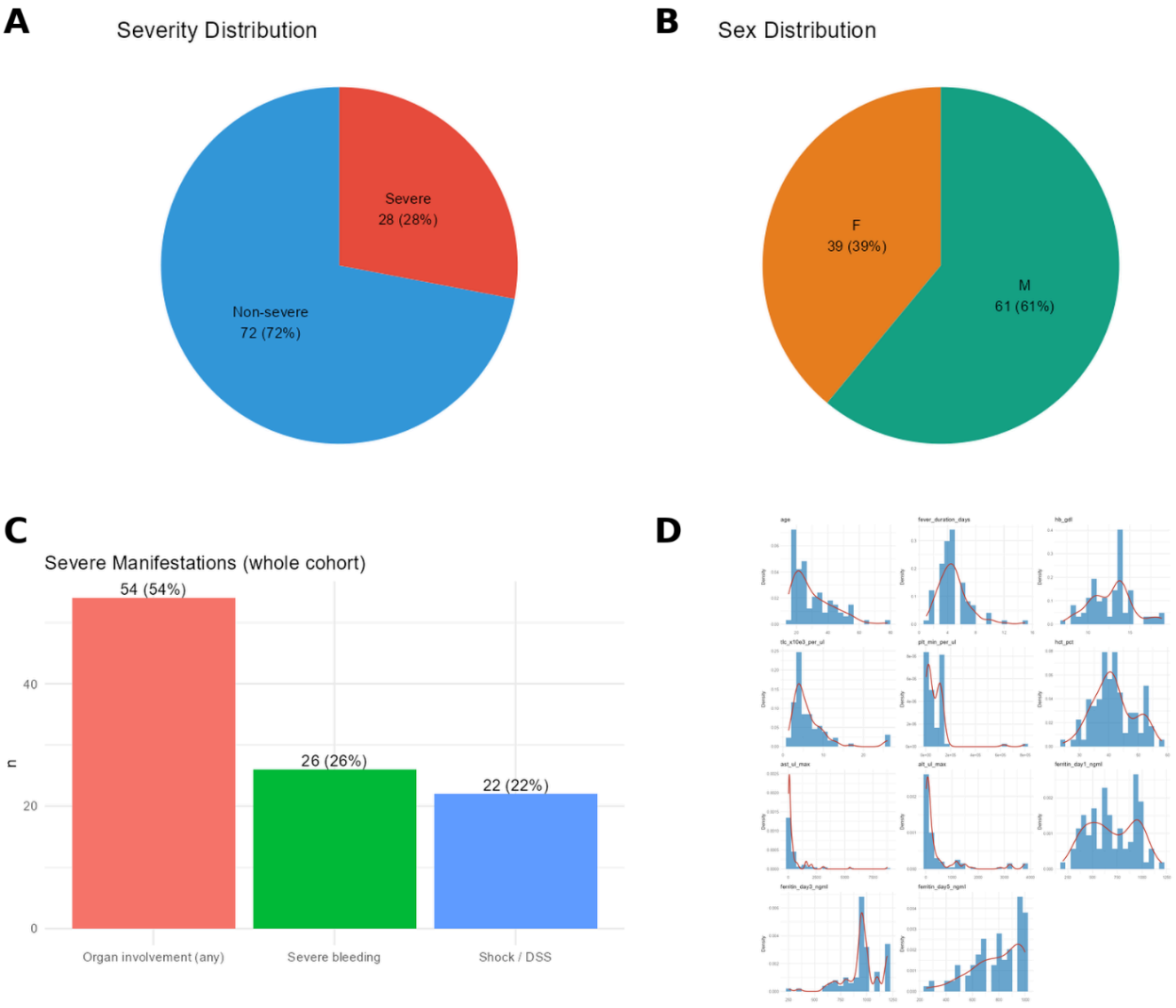


Figure 1

Cohort profile and baseline distributions. (A) Severity distribution of the 100 adult dengue patients (non-severe n=72, severe n=28 per WHO 2009 criteria). (B) Sex distribution (male n=61, female n=39; M:F 1.56:1). (C) Absolute and relative frequencies of severe manifestations in the whole cohort: organ involvement (n=54, 54%), severe bleeding (n=26, 26%) and shock/DSS (n=22, 22%). (D) Density histograms of age, fever duration, haemoglobin, total leucocyte count, platelets, haematocrit, AST, ALT and serum ferritin on Days 1, 3 and 5, with kernel-density overlays (red curves). Ten of eleven variables were non-normal by Shapiro-Wilk testing, justifying non-parametric methods throughout.

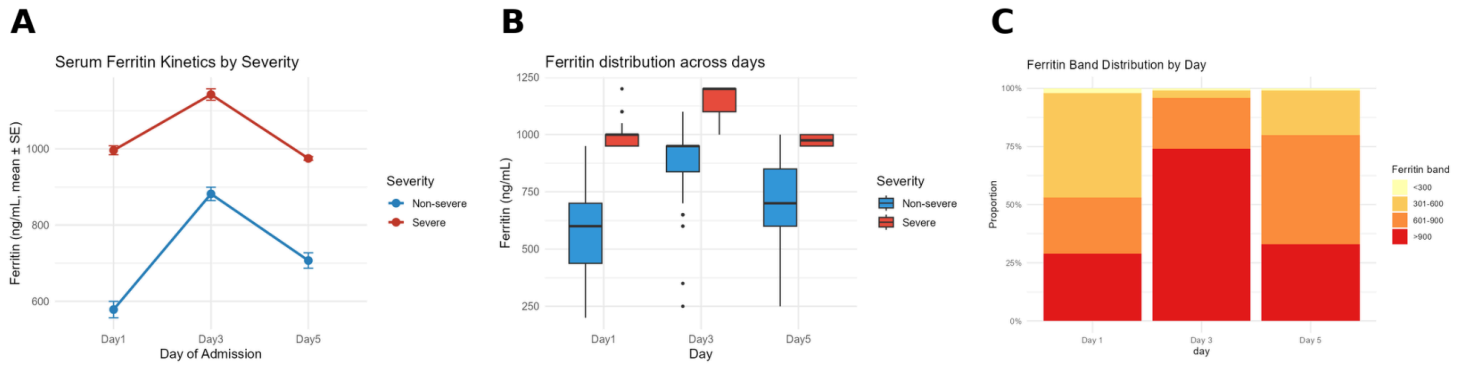


Figure 2

Serum ferritin kinetics across illness days by dengue severity. (A) Mean +/- SE ferritin trajectories on Day 1, Day 3 and Day 5 of admission, stratified by severity (non-severe, blue; severe, red). The characteristic rise-peak-fall pattern peaks on Day 3; severe patients remain substantially higher at all time-points. (B) Box-and-whisker distributions by day and severity showing median, interquartile range, whiskers (1.5xIQR) and outliers. (C) Stacked bar chart of ferritin-band proportions (<300, 301-600, 601-900, >900 ng/ml) on each day. The proportion exceeding 900 ng/ml rose from 29% (Day 1) to 74% (Day 3) and partially reversed to 33% (Day 5), significant by Cochran-Armitage trend.

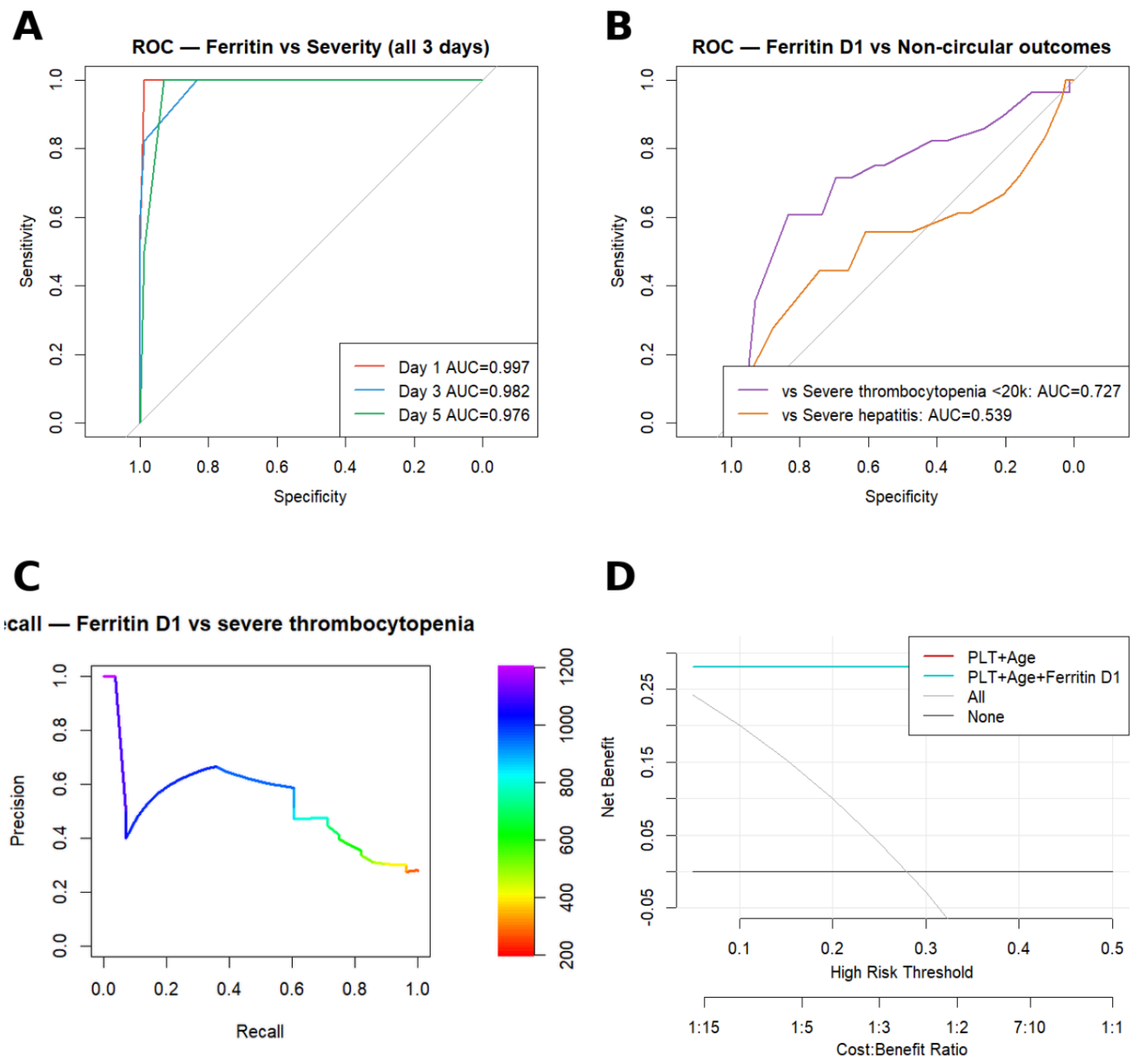


Figure 3

Diagnostic performance of ferritin against severe outcomes. (A) Receiver-operating-characteristic (ROC) curves of raw ferritin against WHO 2009 composite severity on Day 1 (AUC 0.997), Day 3 (AUC 0.982) and Day 5 (AUC 0.976). These near-perfect AUCs reflect circularity, since ferritin is correlated with platelet count, an element of the WHO severity definition. (B) Non-circular ROC curves of Day 1 ferritin against severe thrombocytopenia (<20,000/uL; purple, AUC 0.727) and severe hepatitis (AST or ALT >=1,000 IU/L; orange, AUC 0.539). Ferritin discriminates thrombocytopenia modestly but adds no value for hepatitis. (C) Precision-recall curve for Day 1 ferritin against severe thrombocytopenia, colour-graded by raw ferritin value. (D) Decision Curve Analysis (DCA) comparing a PLT+Age model with and without

Day 1 ferritin, relative to treat-all (grey) and treat-none (black) reference strategies. Net-benefit curves for the two models are superimposed across the clinically relevant 0.05-0.35 threshold range, confirming that ferritin adds no incremental clinical utility over platelet count.

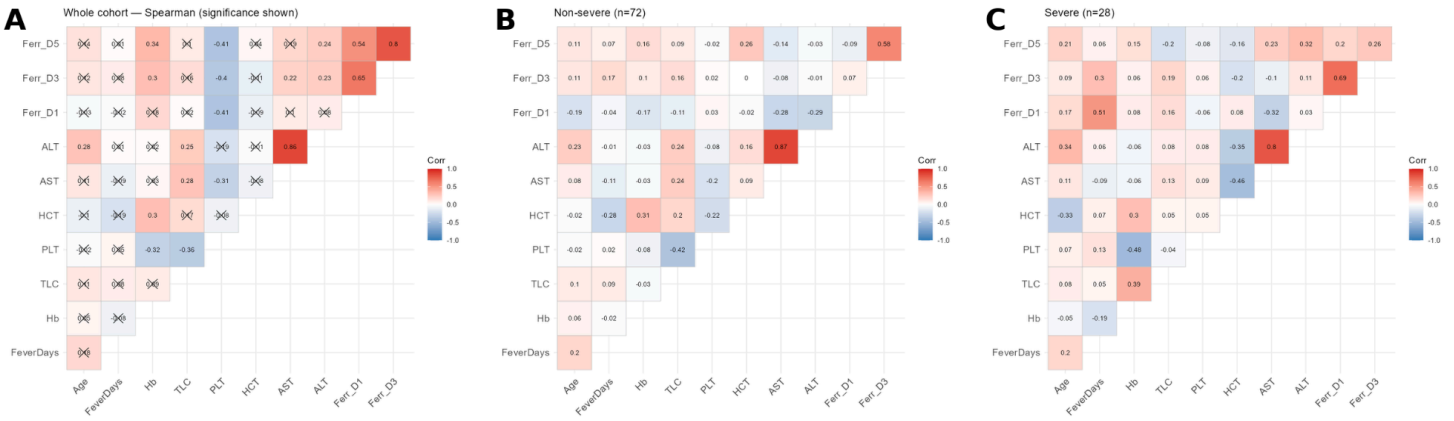


Figure 4

Spearman correlation matrices with Benjamini-Hochberg FDR correction (q<0.05). (A) Whole cohort (n=100). Non-significant pairs after FDR are crossed out. The ferritin-platelet inverse correlation is significant on all three days (rho=-0.41 on Days 1 and 5; rho=-0.40 on Day 3). (B) Non-severe subgroup (n=72). The ferritin-platelet anti-correlation is absent within this stratum. (C) Severe subgroup (n=28). Fever duration shows a positive correlation with Day 1 ferritin (rho=0.51) that is absent in non-severe patients, supporting a two-phenotype interpretation. AST-ALT coupling remains strong in all strata (rho ~ 0.80-0.87).

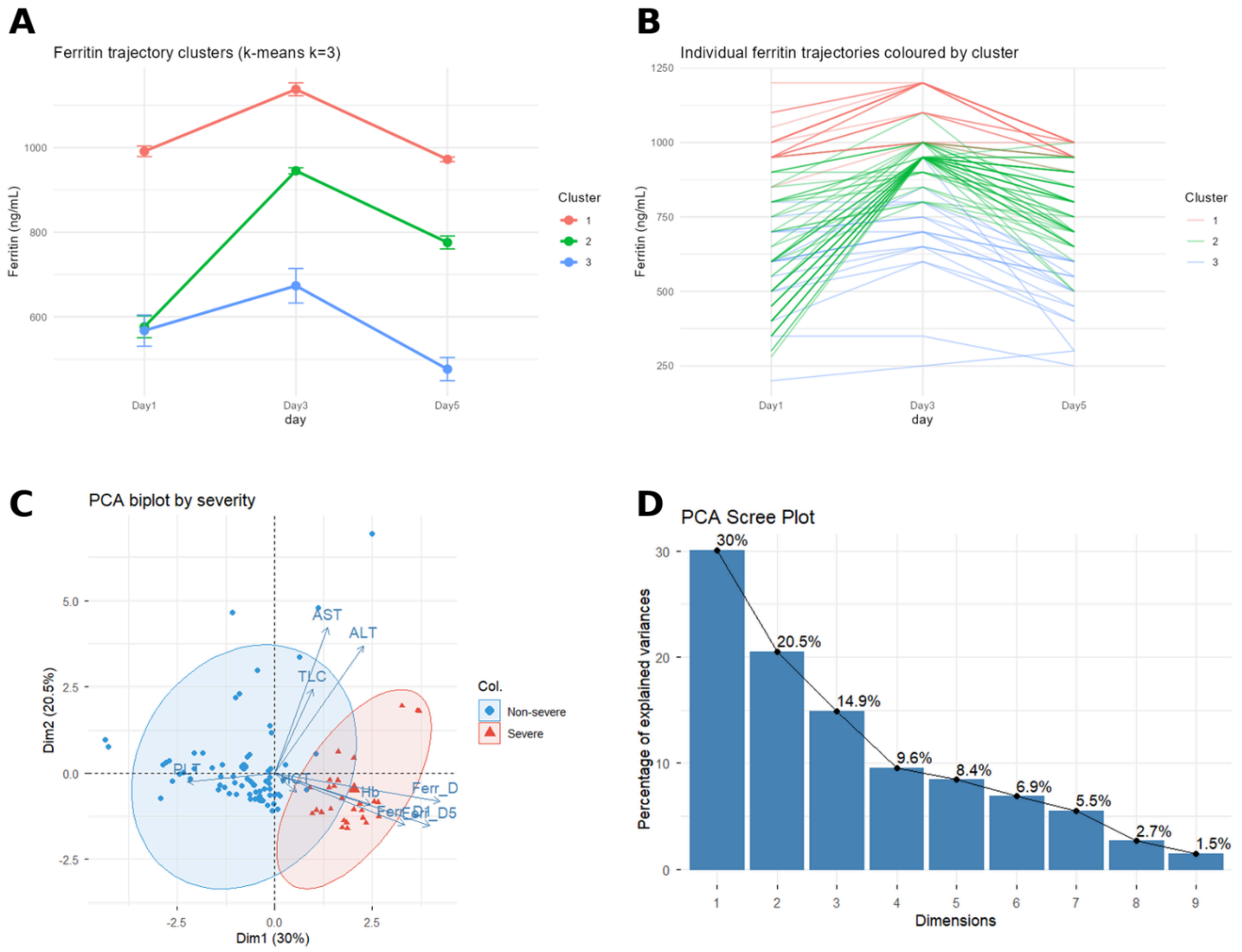


Figure 5

Ferritin trajectory phenotypes and multivariate structure. (A) K-means cluster centroids (k=3, mean +/- SE) derived from the three ferritin time-points: a high-ferritin severe cluster (n=29, salmon; 28/29 severe), a typical rise-fall non-severe cluster (n=54, green), and a blunted low-ferritin cluster (n=17, blue). (B) Individual patient ferritin trajectories coloured by cluster membership. (C) Principal Component Analysis (PCA) biplot on standardised lab variables with 95% confidence ellipses by severity. Non-severe patients cluster in the negative PC1 region (high platelets); severe patients in the positive PC1 region (high ferritin, low platelets). (D) Scree plot showing the two-component solution captures ~50% of variance (PC1 30.0%, PC2 20.5%); components 3-9 contribute diminishing variance.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SUPPLEMENTARYTABLES.docx