



The Comprehensive Systematic Review of Platelet Count and Hematocrit as Predictors of Plasma Leakage in Dengue Hemorrhagic Fever

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ABSTRACT

Introduction: Dengue hemorrhagic fever (DHF) remains a major public health concern in endemic regions, with plasma leakage being the pathognomonic feature determining disease severity. Despite widespread clinical use of platelet count and hematocrit as monitoring parameters, their predictive value for plasma leakage remains debated. This systematic review aims to comprehensively evaluate the evidence for platelet count and hematocrit as predictors of plasma leakage in DHF patients.

Methods: A systematic review of 34 sources including primary observational studies, systematic reviews, meta-analyses, and randomized controlled trials was conducted. Studies were screened based on predefined criteria including DHF population according to WHO criteria, plasma leakage assessment through clinical signs or imaging, reporting of platelet count and/or hematocrit as predictors, and adequate statistical information. Data extraction encompassed study characteristics, platelet and

hematocrit measurements, statistical findings, and confounding factors.

Results: Low platelet count demonstrated consistent association with plasma leakage across multiple meta-analyses, with pooled odds ratios ranging from 2.01 (95% CI: 1.70-2.38) to 3.21 (95% CI: 1.81-5.69). A dose-response relationship showed 33% increase in logOR per 10,000-cell decrement. Platelet count below 50,000/mm³ was identified as a significant threshold for dengue shock syndrome (OR=2.85; 95% CI: 1.25-6.47). Hematocrit showed variable predictive utility depending on measurement timing; significant during critical phase (days 4-7) but not during early febrile phase. Combined assessment of rising hematocrit with declining platelet count yielded the strongest predictive signal (OR range: 5.13-43.17).

Discussion: The apparent contradiction regarding hematocrit's predictive value is explained by temporal discordance in measurement timing. Platelet count emerges as a more reliable early predictor, with reductions detectable during febrile phase before hemoconcentration manifests. Population-specific factors, particularly age, significantly modulate predictive accuracy. The combined parameter approach captures mechanistically linked processes of capillary permeability and platelet consumption.

Conclusion: Platelet count below 50,000/mm³ and rising hematocrit (particularly >20% above baseline) are consistent predictors of plasma leakage, with combined assessment providing optimal predictive utility. Serial monitoring rather than single-point measurements is essential. Future research should focus on developing integrated predictive models incorporating clinical, laboratory, and sonographic parameters.

Keywords: Dengue hemorrhagic fever, plasma leakage, platelet

count, hematocrit, predictor, systematic review

INTRODUCTION

Dengue viral infection represents one of the most rapidly spreading mosquito-borne diseases globally, with an estimated 390 million infections annually and approximately 96 million manifesting clinically [6, 8]. The clinical spectrum ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), and the potentially life-threatening dengue hemorrhagic fever (DHF) with its extreme form, dengue shock syndrome (DSS) [3, 14]. Plasma leakage constitutes the pathognomonic feature distinguishing DHF from uncomplicated dengue, characterized by increased vascular permeability leading to hemoconcentration, pleural effusion, ascites, and hypoproteinemia [11, 14]. The World Health Organization (WHO) has promulgated classification schemes—the 1997 criteria (DF/DHF/DSS) and the 2009 criteria (dengue without warning signs, dengue with warning signs, severe dengue)—to standardize disease categorization and guide clinical management [1, 8, 14].

The identification of reliable, accessible, and cost-effective predictors for plasma leakage remains a critical priority in dengue-endemic regions where healthcare resources are often limited [2, 6]. Platelet count and hematocrit are ubiquitously available laboratory parameters routinely monitored in suspected dengue cases [7, 11]. Thrombocytopenia, resulting from bone marrow suppression, peripheral destruction, and consumption during endothelial activation, is a hallmark of dengue infection [3, 15]. Similarly, hemoconcentration due to plasma extravasation forms the basis for hematocrit monitoring as a surrogate marker of leakage severity [5, 13]. Clinical practice guidelines universally recommend serial assessment of both parameters for early detection of impending shock and guidance of fluid resuscitation [4, 27].

Despite their widespread adoption, the predictive validity of platelet count and hematocrit for plasma leakage remains contested. Several large meta-analyses have demonstrated significant associations between thrombocytopenia and severe disease outcomes [1, 2, 3], while others have reported non-significant findings or identified substantial heterogeneity across studies [6, 12]. The predictive utility of hematocrit appears particularly controversial, with some studies identifying it as

a robust predictor [2, 7] and others failing to demonstrate significant associations during early illness phases [6]. This inconsistency creates clinical uncertainty regarding optimal monitoring strategies and interpretation of laboratory trends.

The research gap encompasses several dimensions. First, existing studies exhibit substantial methodological heterogeneity in outcome definitions, measurement timing, and analytical approaches [8, 14]. Second, the majority of evidence derives from pediatric populations in Southeast Asia, limiting generalizability to adults and other geographic regions [1, 18]. Third, the interrelationship between platelet count and hematocrit as combined predictors remains incompletely characterized [5, 8]. Fourth, the temporal dynamics of these parameters across different phases of illness have not been systematically evaluated [6, 25]. Fifth, the influence of confounding factors such as dengue serotype, secondary infection status, and patient demographics on predictive accuracy requires further elucidation [3, 29, 30].

The primary objective of this comprehensive systematic review is to evaluate and synthesize the available evidence regarding platelet count and hematocrit as predictors of plasma leakage in DHF patients. Specific aims include: (1) quantifying the strength of association between these laboratory parameters and plasma leakage outcomes; (2) identifying optimal threshold values for clinical prediction; (3) examining the influence of measurement timing on predictive accuracy; (4) evaluating the combined predictive utility of both parameters; and (5) assessing population-specific factors that modify predictive relationships.

The novelty of this review lies in its comprehensive integration of evidence from 34 diverse sources encompassing multiple study designs, geographic regions, and patient populations. By systematically analyzing temporal patterns, combined parameter effects, and population-specific modifiers, this review provides a nuanced understanding that reconciles apparent contradictions in the existing literature. The findings will inform evidence-based clinical guidelines, optimize monitoring strategies, and identify priority areas for future research.

The central hypothesis posits that both platelet count and hematocrit serve as significant predictors of plasma leakage in DHF, but their predictive utility is critically dependent on measurement timing, serial monitoring, and combined assessment. Specifically, platelet count is

hypothesized to demonstrate earlier predictive value during the febrile phase, while hematocrit becomes discriminative during the critical phase of active leakage. The combined trajectory of declining platelets with rising hematocrit is expected to yield superior predictive accuracy compared to either parameter alone.

The clinical significance of this investigation derives from the potential to enhance early identification of patients at risk for severe disease, thereby facilitating timely intervention and improving outcomes. For healthcare systems in resource-limited endemic regions, validated predictors utilizing routinely available laboratory tests offer practical utility without requiring advanced diagnostic capabilities [9, 10, 32]. Furthermore, understanding the temporal dynamics of these parameters can refine monitoring protocols and discharge criteria [13, 24, 28].

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Platelet Count and Hematocrit as Predictors of Plasma Leakage in Dengue Hemorrhagic Fever.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Dengue Hemorrhagic Fever Population:** Does the study include patients with laboratory-confirmed or clinically diagnosed dengue hemorrhagic fever (DHF) according to WHO criteria or other established diagnostic guidelines?

- **Plasma Leakage Assessment:** Does the study evaluate plasma leakage as an outcome measure through clinical signs (pleural effusion, ascites, hypoproteinemia) or imaging findings?
- **Laboratory Parameters:** Does the study report platelet count and/or hematocrit values as potential predictors?
- **Study Design:** Is the study an observational study (cohort, case-control, cross-sectional), systematic review, or meta-analysis?
- **Data Sufficiency:** Does the study provide adequate statistical information (sample sizes, effect measures, confidence intervals, or raw data) to allow for meaningful interpretation of the predictive relationship?
- **Hemorrhagic Manifestations:** Does the study include patients with hemorrhagic manifestations rather than focusing solely on uncomplicated dengue fever?
- **Study Size and Type:** Is the study NOT a case report or case series with fewer than 10 patients?
- **Plasma Leakage Definition:** Does the study clearly define and measure plasma leakage as an outcome?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Dengue Hemorrhagic Fever	Platelet Count	Combined Markers	Plasma Leakage

Keyword 2	Dengue Infection	Blood Platelets	Dual Markers	Vascular Permeability
Keyword 3	Dengue with warning signs	Hematocrit	Concurrent Assessment	Capillary Leak
Keyword 4	Severe Dengue	Low Platelet	Parallel Monitoring	Hemoconcentration

The Boolean MeSH keywords inputted on databases for this research are: (*"Dengue Hemorrhagic Fever"* OR *"Dengue Infection"* OR *"Dengue with warning signs"* OR *"Severe Dengue"*) AND (*"Platelet Count"* OR *"Blood Platelets"* OR *"Hematocrit"* OR *"Low Platelet"*) AND (*"Combined Markers"* OR *"Dual Markers"* OR *"Concurrent Assessment"* OR *"Parallel Monitoring"*) AND (*"Plasma Leakage"* OR *"Vascular Permeability"* OR *"Capillary Leak"* OR *"Hemoconcentration"*)

Data extraction

- **Study Population:**

Extract details about the study population specifically related to dengue hemorrhagic fever patients, including:

- Total number of DHF patients
- Age range and demographics of DHF patients
- Inclusion/exclusion criteria for DHF patients
- How DHF was diagnosed or classified
- Setting (hospital, outpatient, community)
- Geographic location and time period

- **Plasma Leakage Definition:**

Extract how plasma leakage was defined, detected, or measured in the study, including:

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- Clinical criteria used (e.g., ascites, pleural effusion, shock)
- Diagnostic methods (ultrasound, physical exam, chest X-ray)
- Specific thresholds or cutoffs used
- Timing of assessment relative to illness onset
- Whether WHO classification criteria were used

- **Platelet Count Data:**

Extract all data on platelet count as a predictor of plasma leakage in DHF patients, including:

- Mean/median platelet counts for patients with vs. without plasma leakage
- Platelet count ranges, quartiles, or cutoff values
- Timing of platelet measurement (day of illness)
- Statistical measures (odds ratios, sensitivity, specificity, p-values)
- Any platelet trends or trajectories described
- Normal reference ranges used

- **Hematocrit Data:**

Extract all data on hematocrit as a predictor of plasma leakage in DHF patients, including:

- Mean/median hematocrit values for patients with vs. without plasma leakage
- Hematocrit ranges, percentage increases, or cutoff values
- Baseline vs. peak hematocrit levels
- Timing of hematocrit measurement (day of illness)
- Statistical measures (odds ratios, sensitivity, specificity, p-values)
- Criteria for significant hematocrit rise (e.g., >20% increase)

- **Statistical Findings:**

Extract the main statistical results regarding platelet count and hematocrit as predictors of plasma leakage in DHF, including:

- Univariate and multivariate analysis results
- Odds ratios, risk ratios, or correlation coefficients with 95% CIs
- P-values for significance testing
- Area under ROC curves for predictive accuracy
- Sensitivity and specificity values
- Any predictive models developed or validated

- **Study Design:**

Extract study methodology details relevant to assessing predictive relationships, including:

- Study design (cohort, case-control, cross-sectional, RCT)
- Sample size and power calculations
- Follow-up duration and timing of assessments
- Blinding of outcome assessors
- Statistical methods used for analysis
- How missing data was handled

- **Confounding Factors:**

Extract information about other factors that may influence the relationship between platelet count/hematocrit and plasma leakage in DHF patients, including:

- Other laboratory parameters studied (albumin, liver enzymes, etc.)
- Clinical variables adjusted for in analysis
- Demographics or comorbidities that modified effects
- Dengue serotype or secondary infection status

- Day of illness when measurements were taken
- Any interaction effects reported

- **Key Conclusions:**

Extract the authors' main conclusions specifically about platelet count and hematocrit as predictors of plasma leakage in DHF, including:

- Whether each parameter was found to be a significant predictor
- Clinical utility or recommendations made
- Optimal cutoff values proposed
- Limitations acknowledged regarding these predictors
- Comparison to other predictive factors
- Clinical implications for DHF management

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Dengue Hemorrhagic Fever") AND ("Platelet Count" AND "Plasma Leakage" OR "Vascular Permeability" OR "Capillary Leak" OR "Hemoconcentration")</i>	154
Semantic Scholar	<i>("Dengue Hemorrhagic Fever" OR "Dengue Infection" OR "Dengue with warning signs" OR "Severe Dengue") AND ("Platelet Count" OR "Blood Platelets" OR "Hematocrit" OR "Low Platelet") AND ("Combined Markers" OR "Dual Markers" OR "Concurrent Assessment" OR "Parallel Monitoring") AND ("Plasma Leakage" OR "Vascular Permeability" OR "Capillary Leak" OR "Hemoconcentration")</i>	212
Springer	<i>("Dengue Hemorrhagic Fever") AND ("Platelet Count" AND "Plasma Leakage" OR "Vascular Permeability" OR "Capillary Leak" OR "Hemoconcentration")</i>	539
Google Scholar	<i>("Dengue Hemorrhagic Fever" OR "Dengue Infection" OR "Dengue with warning signs" OR "Severe Dengue") AND ("Platelet Count" OR "Blood Platelets" OR "Hematocrit" OR "Low Platelet") AND ("Combined Markers" OR "Dual Markers" OR "Concurrent Assessment" OR "Parallel Monitoring") AND ("Plasma Leakage" OR "Vascular Permeability" OR "Capillary Leak" OR "Hemoconcentration")</i>	3
Wiley Online Library	<i>("Dengue Hemorrhagic Fever" OR "Dengue Infection" OR "Dengue with warning signs" OR "Severe Dengue") AND ("Platelet Count" OR "Blood Platelets" OR "Hematocrit" OR "Low Platelet") AND ("Combined Markers" OR "Dual Markers" OR "Concurrent Assessment" OR "Parallel Monitoring") AND ("Plasma Leakage" OR "Vascular Permeability" OR "Capillary Leak" OR "Hemoconcentration")</i>	2

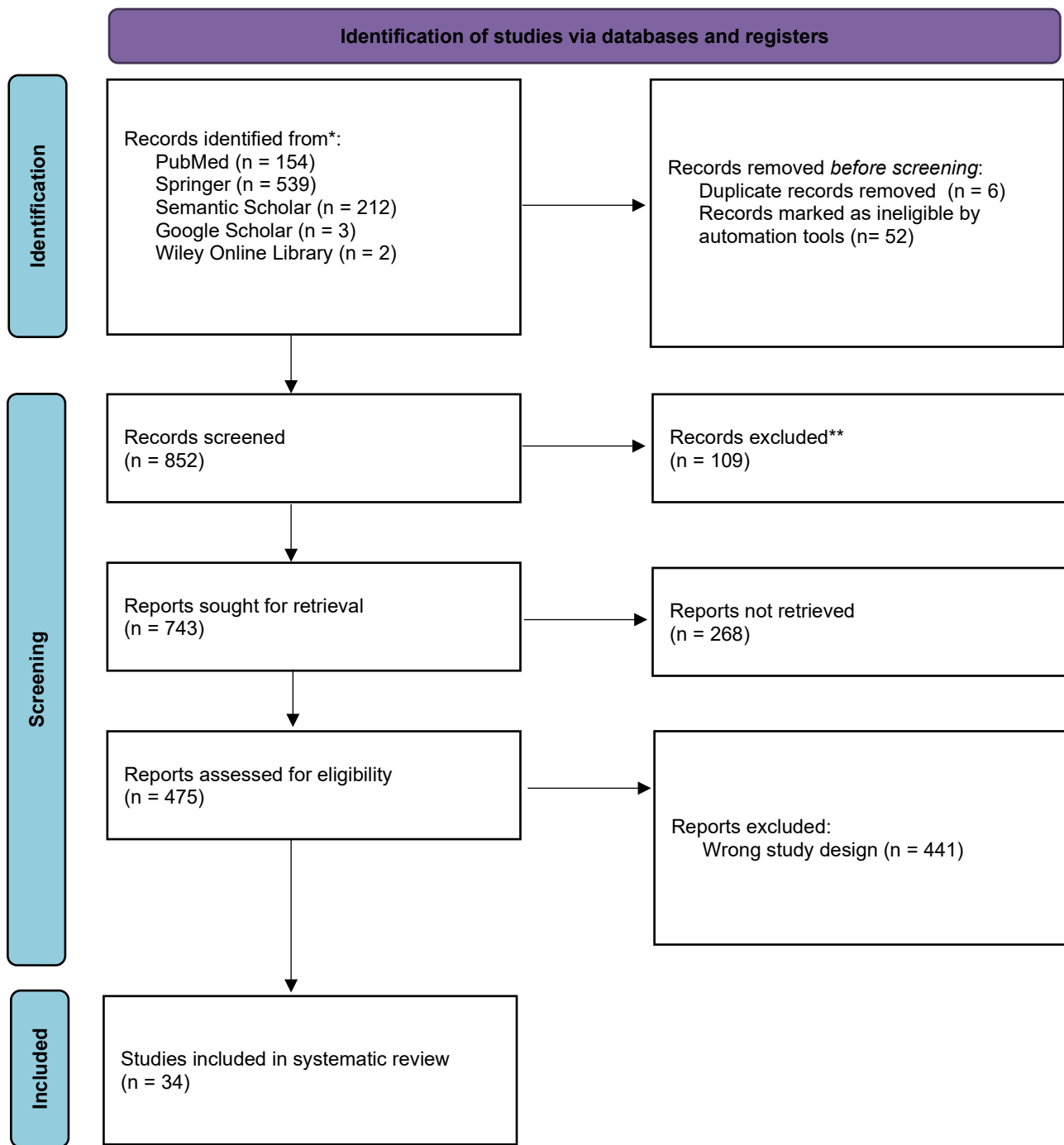


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The 34 sources encompassed a broad range of study designs, geographic settings, and populations. The majority originated from South and Southeast Asia, with additional contributions from Latin America, the Caribbean, and the Middle East. Studies included primary observational studies (cross-sectional, cohort, case-control), randomized controlled trials, and etc.

Study	Population	Geographic Setting	Sample Size	Severity Classification
M. Z. Hossain et al., 2021	Adults >18 years [11]	Dhaka, Bangladesh [11]	199 [11]	National guideline (DF, DHF, DSS) [11]
T. Tsheten et al., 2021	Children and adults [8]	Multiple WHO regions [8]	143 articles [8]	WHO 1997 and 2009 [8]
N. Huy et al., 2013	Infants, children, adults [3]	Primarily Southeast Asia [3]	198 studies (203 data sets) [3]	WHO 1997 [3]
A. Manggala et al., 2025	Children [2]	Indonesia [2]	19 studies, 3086 children [2]	Not specified [2]
I. Sandinirwan et al., 2023	Pediatric [1]	Asia and Latin America [1]	49 studies, 93,628 patients [1]	WHO 1997 or 2009 [1]

Study	Population	Geographic Setting	Sample Size	Severity Classification
F. Chowdhury et al., 2024	Adults >16 years [12]	Dhaka, Bangladesh [12]	1978 [12]	National guideline (Group B, C) [12]
Rika Bur et al., 2024	Adults 18-60 years [13]	Jakarta and Banten, Indonesia [13]	84 randomized [13]	WHO 2011 [13]
C. Rodrigo et al., 2021	Children and adults [14]	18 countries [14]	43 studies, 15,794 patients [14]	WHO 1997 and 2009 [14]
Sorawat Sangkaew et al., 2021	Children and adults [6]	Multiple countries [6]	150 articles [6]	WHO criteria [6]
T. Htun et al., 2021	Children and adults [15]	Asia, Brazil, Germany, Mexico, Spain [15]	39 articles [15]	WHO 2009 [15]
Sorawat Sangkaew et al., 2020	Not specified [16]	Multiple countries [16]	98 studies [16]	WHO criteria [16]

Study	Population	Geographic Setting	Sample Size	Severity Classification
K. Aung et al., 2013	Adults [7]	Bangkok, Thailand [7]	323 [7]	WHO 1997 and 2009 [7]
Wendell Paiva Vita et al., 2009	Not specified [17]	Rio de Janeiro, Brazil [17]	26 deaths [17]	Serological confirmation [17]
I. Sandinirwan et al., 2023a	Pediatric [18]	Asia and Latin America [18]	49 studies, 93,628 patients [18]	WHO 1997 or 2009 [18]
N. Zakariah et al., 2020	Adults [19]	Not specified [19]	9 articles [19]	Not specified [19]
F. Djossou et al., 2016	All ages [20]	Cayenne, French Guiana [20]	806 [20]	Confirmed dengue [20]
M. Kaagaard et al., 2022	Children and adults [21]	Not specified [21]	84 studies, 12,448 patients [21]	WHO criteria [21]

Study	Population	Geographic Setting	Sample Size	Severity Classification
S. Kalayanarooj et al., 2008	Children (mean age 8.6 years) [22]	Not specified [22]	104 [22]	Not specified [22]
R. Tunjungputri et al., 2022	Adults ≥ 16 years [23]	Central and West Java, Indonesia [23]	70 [23]	NS1 or acute serology [23]
Ing-Kit Lee et al., 2010	Adults >18 years [24]	Southern Taiwan [24]	49 [24]	WHO criteria [24]
P. Dussart et al., 2020	Children 2-15 years [25]	Cambodia [25]	243 [25]	WHO 1997 and adapted 2009 [25]
A. Ahmad et al., 2018	Not specified [26]	Lahore, Pakistan [26]	200 [26]	Not specified [26]
Tiwawan Piyakulmal a et al., 2015	Not specified [27]	Kalasin, Thailand [27]	247 [27]	WHO criteria [27]

Study	Population	Geographic Setting	Sample Size	Severity Classification
Suryadi N. N. Tatura et al., 2009	Children (mean age ~7 years) [28]	Indonesia [28]	50 [28]	Clinical diagnosis [28]
A. Dinkar et al., 2023	Not specified [29]	North India [29]	220 [29]	Serology (IgG) [29]
S. Moallemi et al., 2023	Not detailed [30]	South/Southeast Asia, Latin America [30]	37 studies, 5925 patients [30]	WHO 1997 and 2009 [30]
Gerald C. D. Podung et al., 2021	Children >5 years [5]	Not specified [5]	10 articles reviewed [5]	Not specified [5]
R. Chandran et al., 2018	Not specified [10]	India [10]	140 [10]	Ultrasound-based [10]
F. Rasool et al., 2022	Adults (mean age 28 years) [31]	Karachi, Pakistan [31]	248 [31]	Not specified [31]

Study	Population	Geographic Setting	Sample Size	Severity Classification
A. Shahsavan d Davoudi et al., 2025	Adults and mixed [32]	Asia and South America [32]	19 studies [32]	WHO criteria (various years) [32]
M. Kaagaard et al., 2023	Children and adults (mean age 24 years) [33]	Southeast Asia [33]	85 studies, 12,800 patients [33]	WHO 1997 and 2009 [33]
V. Vaz et al., 2025	Adults [9]	Not specified [9]	21 studies, 3214 patients [9]	WHO 1997 and 2009 [9]
K. Deawwattanawiwat et al., 2013	Pediatric [4]	Phichit, Thailand [4]	151 (116 DHF, 35 DSS) [4]	WHO criteria [4]
Thang Dao Phuoc et al., 2019	Not applicable [34]	Not applicable [34]	Not applicable [34]	Not applicable [34]

The included sources reflect substantial heterogeneity in study design, population, and classification system. Fourteen sources are systematic reviews or meta-analyses, providing synthesized evidence from hundreds of underlying studies. Primary studies range from large cross-sectional investigations (n = 1978) [12] to small RCTs (n = 50) [28]. Classification of dengue severity varied across the WHO 1997 scheme (DF/DHF/DSS), the WHO 2009 scheme

(dengue/dengue with warning signs/severe dengue), and national guidelines, which complicates direct comparisons. Full texts were available for 20 of the 34 sources. The geographic concentration in South and Southeast Asia reflects the epidemiological burden but limits generalizability to other endemic regions.

Effects

Platelet Count as a Predictor of Plasma Leakage and Severe Dengue

Source	Platelet Measure	Effect Size (OR or SMD)	95% CI	p-value	Population
M. Z. Hossain et al., 2021	Median: DHF/DSS 43,500 vs DF 65,000 [11]	Not computed	Not applicable	p = 0.01 [11]	Adults, Bangladesh
T. Tsheten et al., 2021	Increased HCT with concurrent platelet decrease [8]	OR = 5.13 [8]	1.61–16.34 [8]	Not specified	Mixed, global
N. Huy et al., 2013	Thrombocytopenia [3]	OR = 2.64 [3]	1.95–3.59 [3]	Not specified	Mixed, Southeast Asia
A. Manggala et al., 2025	Thrombocytopenia [2]	OR = 3.21 [2]	1.81–5.69 [2]	p < 0.001 [2]	Children, Indonesia

Source	Platelet Measure	Effect Size (OR or SMD)	95% CI	p-value	Population
I. Sandinirwan et al., 2023	Low platelet count [1]	OR = 2.01 [1]	1.70–2.38 [1]	Not specified	Children, Asia/Latin America
T. Htun et al., 2021	Thrombocytopenia (<150,000/m ³) [15]	OR = 2.70 [15]	1.60–4.55 [15]	p < 0.001 [15]	Mixed, global
Sorawat Sangkaew et al., 2021	Low platelet (first 4 days) [6]	SMD = -0.34 [6]	-0.54 to -0.15 [6]	Not specified	Mixed, global
Gerald C. D. Podung et al., 2021	<50,000 cells/mm ³ [5]	OR = 3.78–19.8 [5]	Not specified	p < 0.05 [5]	Children
K. Deawwattana wiwat et al., 2013	<50,000 cells/mm ³ [4]	OR = 2.85 [4]	1.25–6.47 [4]	p = 0.012 [4]	Pediatric, Thailand
A. Shahsavand Davoudi et al., 2025	Thrombocytopenia [32]	OR = 2.65 [32]	Not specified	Not specified	Mixed, global

Across the evidence base, low platelet count is consistently associated with severe dengue, plasma leakage, and dengue shock syndrome. Pooled odds ratios from multiple meta-analyses range from 2.01 [1] to 5.13 [8], though the highest estimate (OR = 5.13) represents the combined effect of rising hematocrit with concurrent platelet decline rather than platelet count alone [8]. The meta-analysis by Huy et al. demonstrated a linear dose-response relationship: logOR increased by 33% for every 10,000-cell decrement in platelet count [3]. This finding is mechanistically consistent with a progressive consumptive process associated with endothelial activation during plasma leakage.

Specific cutoff values were proposed by several primary studies. A platelet count below 50,000 cells/mm³ was identified as a risk factor for DSS in pediatric cohorts in Thailand (OR = 2.85) [4] and in the literature review by Podung et al. [5]. Rasool et al. reported that platelet counts below 40,000/mm³ were associated with sonographic features of capillary leak syndrome, whereas counts above 150,000/mm³ were associated with no ultrasonographic abnormalities [31]. The Sangkaew et al. meta-analysis noted that non-severe dengue groups generally maintained platelet counts above 100,000 cells/dL, though no robust single cutoff was established [6].

However, the Sandinirwan et al. meta-analysis in children flagged high heterogeneity (I² = 90%) and publication bias (Egger's test $p < 0.001$) for platelet count as a predictor [1], and a sensitivity analysis reduced the pooled OR from 2.01 to 1.47 [1]. A meta-regression within that study showed age as a significant moderator, with logOR decreasing by 22% for each 1-year increment in age [1]. Notably, Chowdhury et al. did not find platelet count to be a significant differentiator between Group B (warning signs) and Group C (severe) dengue in their large Bangladeshi cohort ($p = 0.6563$) [12].

Hematocrit as a Predictor of Plasma Leakage and Severe Dengue

Source	Hematocrit Measure	Effect Size (OR or other)	95% CI	p-value	Population
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Source	Hematocrit Measure	Effect Size (OR or other)	95% CI	p-value	Population
M. Z. Hossain et al., 2021	Median HCT: 41% in both DF and DHF/DSS [11]	Not significant [11]	Not applicable	Not significant [11]	Adults, Bangladesh
T. Tsheten et al., 2021	Increased HCT + decreased platelet [8]	OR = 5.13 [8]	1.61–16.34 [8]	Not specified	Mixed, global
N. Huy et al., 2013	Hemoconcentration [3]	20.5% increase in logOR per 1% HCT increment [3]	4.65–36.36 [3]	Not specified	Mixed, Southeast Asia
A. Manggala et al., 2025	Increased hematocrit [2]	OR = 4.65 [2]	2.95–7.34 [2]	$p < 0.001$ [2]	Children, Indonesia
I. Sandinirwan et al., 2023	Elevated hematocrit [1]	OR = 1.76 [1]	1.50–2.07 [1]	Not specified	Children, Asia/Latin America
F. Chowdhury et al., 2024	Group C: 39% vs Group B: 40.1% [12]	Not computed	Not applicable	$p = 0.006$ [12]	Adults, Bangladesh

Source	Hematocrit Measure	Effect Size (OR or other)	95% CI	p-value	Population
Rika Bur et al., 2024	Hemoconcentration at 4, 12, 24 h [13]	Not computed	Not applicable	p = 0.002, 0.001, 0.003 [13]	Adults, Indonesia
K. Aung et al., 2013	HCT >2% above reference [7]	OR = 3.235 [7]	1.807–5.793 [7]	Not specified	Adults, Thailand
I. Sandinirwan et al., 2023a	Elevated hematocrit [18]	OR = 1.76 [18]	1.50–2.07 [18]	Not specified	Children, Asia/Latin America
Gerald C. D. Podung et al., 2021	HCT $\geq$ 42%; >20% rise with platelets <50,000 [5]	OR = 0.3–23.4 (HCT $\geq$ 42%); OR = 43.17 (combined) [5]	Not specified	p = 0.003 [5]	Children
Tiwawan Piyakulmala et al., 2015	Hemoconcentration >22% from baseline [27]	Not computed	Not applicable	Not specified	Not specified, Thailand
Sorawat Sangkaew et al., 2021	Not significant predictor [6]	Not applicable	Not applicable	Not applicable	Mixed, global

The evidence for hematocrit as an independent predictor of plasma leakage is more nuanced than that for platelet count. In the largest febrile-phase meta-analysis, Sangkaew et al. (2021) found that hematocrit was not significantly associated with progression to severe disease [6], while in the same analysis platelet count was significant. In contrast, multiple other studies and meta-analyses found hematocrit to be a significant predictor. The meta-analysis by Huy et al. demonstrated a continuous relationship in which logOR increased by 20.5% for every 1% increment in hematocrit [3]. Manggala et al. reported a strong association in Indonesian children (OR = 4.65; 95% CI: 2.95–7.34) [2], and Aung et al. found that hematocrit more than 2% above the reference range was independently associated with DHF grades II–IV on multivariate analysis (OR = 3.235) [7].

Proposed cutoff values for significant hematocrit rise varied: a greater than 20% increase from baseline was widely used per WHO criteria [5, 11], while the Bur et al. RCT used a greater than 10% increase or reaching 50% as thresholds for plasma leakage [13]. Piyakulmala et al. identified hemoconcentration exceeding 22% from baseline as a risk factor for DSS [27]. Aung et al. applied a lower threshold of greater than 2% above the reference range in their multivariate model [7].

The combined effect of rising hematocrit with concurrent platelet decline appears to be a more potent predictor than either parameter alone. Tsheten et al. reported an OR of 5.13 (95% CI: 1.61–16.34) for this combined marker [8], and Htun et al. described the concurrent increase in hematocrit with rapid platelet decline as predictive of severe plasma leakage [15]. Podung et al. reported a strikingly high OR of 43.17 for hematocrit increase exceeding 20% combined with platelet count below 50,000 cells/mm³ [5].

Other Laboratory and Clinical Predictors

Several studies contextualized platelet count and hematocrit within a broader panel of predictors. Serum albumin was consistently lower among patients progressing to severe disease during the febrile phase (SMD = -0.5) [6], and low albumin was identified as a biomarker for DHF in the Moallemi et al. meta-analysis [30]. Elevated aminotransferases (AST and ALT) were significant predictors across multiple meta-analyses [1, 6, 30], with AST showing a particularly

strong association in Indonesian children (OR = 7.42) [2]. Secondary dengue infection was consistently associated with severe disease progression (OR = 2.26–3.23) [3, 6, 8], and DENV-2 serotype was specifically linked to severe disease in children [1, 6].

Sonographic markers offered complementary diagnostic value. Gallbladder wall thickening showed a pooled sensitivity of 0.83 and specificity of 0.70 for severe dengue (AUC = 0.80) [9], while ascites had a sensitivity of 0.60 and specificity of 0.89 [9]. Pleural effusion was present in approximately one-third of dengue patients overall, increasing to 48% in complicated dengue [33], and was detected more frequently by lung ultrasound than by chest X-ray [21, 33]. Chandran et al. argued that ultrasound findings are more clinically useful than hematocrit for detecting plasma leakage, noting that hematocrit is "rarely of clinical benefit" as a laboratory marker [10].

Intervention Studies Relevant to Plasma Leakage Parameters

Three RCTs provided data on how interventions affect hematocrit and platelet trajectories during plasma leakage. Bur et al. demonstrated that early 5% albumin intervention in DHF grade I and II patients produced significantly lower hemoconcentration at 4, 12, and 24 hours ($p = 0.002$, 0.001 , 0.003) and higher platelet counts at 4 hours ($p = 0.036$) compared to Ringer's Lactate [13]. Tunjungputri et al. found that oseltamivir phosphate had no effect on platelet recovery kinetics or plasma leakage parameters including hematocrit [23]. Tatura et al. showed that gelatin solution produced a greater hematocrit decrement ($p = 0.017$) and lesser platelet decline ($p = 0.018$) than plasma at four hours in DSS resuscitation [28]. These findings illustrate that hematocrit and platelet trajectories are responsive to fluid management choices and can serve as treatment monitoring parameters.

Synthesis

The apparent contradiction between studies that find hematocrit to be a strong predictor of plasma leakage and those that do not can be largely explained by measurement timing and analytical approach. The Sangkaew et al. (2021) meta-analysis, which found hematocrit non-significant, restricted analysis to measurements obtained during the first four days of illness (febrile phase) [6], when hemoconcentration may not yet have peaked. In contrast, studies reporting

significant associations—such as the Huy et al. meta-analysis spanning 40 years of data [3] and the Aung et al. retrospective study [7]—did not restrict to this early window and likely captured measurements during the critical phase (days 4–7), when plasma leakage is maximal. This temporal discordance means both sets of findings may be valid: hematocrit has limited predictive value during the early febrile phase but becomes a strong marker once plasma leakage is actively occurring.

The role of hematocrit as a predictor versus a diagnostic marker also differs conceptually. A rising hematocrit is part of the WHO definition of DHF itself [11, 14], introducing circularity when used as a "predictor." Hossain et al. found no significant difference in median hematocrit between DF and DHF/DSS groups (both 41%) [11], but this likely reflects that hematocrit was measured at a single time point (admission) rather than tracked serially. Serial monitoring, as performed in the Bur et al. RCT [13] and the Dussart et al. prospective study [25], is necessary to capture the dynamic rise that signals ongoing leakage.

Platelet count appears to be a more reliable early predictor than hematocrit. The Sangkaew et al. meta-analysis demonstrated significant platelet reductions during the first four days of illness among those who progressed to severe disease (SMD = -0.34) [6], at a time when hematocrit had not yet differentiated the groups. The dose-response relationship documented by Huy et al. (33% increase in logOR per 10,000 platelet decrement) [3] and the consistent identification of platelet counts below 50,000/mm³ as a threshold for shock risk [4, 5, 27] support its utility as an early warning parameter. However, the Chowdhury et al. study—the largest single-site primary study (n = 1978)—found no significant platelet difference between warning-sign and severe groups [12], possibly reflecting that their classification distinguished severity grades within an already hospitalized population where thrombocytopenia was near-universal.

The combined assessment of rising hematocrit with declining platelet count consistently emerges as a more powerful predictor than either parameter alone, with ORs ranging from 5.13 [8] to 43.17 [5]. This dual marker captures two mechanistically linked processes: capillary permeability producing hemoconcentration and platelet consumption through endothelial activation and immune-

mediated clearance. The clinical implication is that serial monitoring of both parameters in parallel, rather than reliance on single-point measurements of either one, optimizes early detection of patients at risk for plasma leakage and shock.

Population-specific differences further modulate predictive value. The meta-regression by Sandinirwan et al. demonstrated that the association between low platelet count and severe dengue weakens with increasing age (22% decrease in logOR per year of age) [1], suggesting that platelet-based prediction is stronger in younger children. Geographic variation in study populations—largely Asian with limited representation from the Americas—constrains generalizability, especially given that serotype distribution, population immunity, and genetic susceptibility differ across endemic regions [14, 30]. Pre-existing comorbidities (diabetes, renal disease, hypertension) independently increase the risk of severe dengue [6, 8] and may confound the apparent predictive power of hematological markers in adult populations where comorbidity prevalence is high. Studies using multivariate models that adjusted for such confounders, like Aung et al., retained hematocrit as an independent predictor (OR = 3.235) [7], supporting its predictive value beyond confounding.

In summary, platelet count below 50,000/mm³ and a rising hematocrit (particularly exceeding 20% above baseline) are consistent predictors of plasma leakage and severe dengue, though their predictive utility depends on timing of measurement, serial monitoring, and population characteristics. Their combined assessment yields the strongest predictive signal. Ultrasound-based markers such as gallbladder wall thickening and serosal fluid collections offer complementary objective evidence of plasma leakage, particularly in settings where serial laboratory monitoring is impractical [9, 10, 32].

DISCUSSION

The findings of this comprehensive systematic review elucidate the complex relationship between platelet count, hematocrit, and plasma leakage in dengue hemorrhagic fever, revealing that both parameters serve as significant predictors but with important qualifications regarding measurement timing, combined assessment, and population characteristics.

The consistent association between thrombocytopenia and severe dengue outcomes across multiple meta-analyses [1, 2, 3, 15] establishes platelet count as a robust predictor of plasma leakage. The pooled odds ratios ranging from 2.01 to 3.21 demonstrate clinically meaningful effect sizes, while the dose-response relationship documented by Huy et al. [3]—a 33% increase in logOR per 10,000-cell decrement—provides strong evidence for a causal gradient supporting biological plausibility. This progressive relationship aligns with the pathophysiological understanding of dengue pathogenesis, wherein endothelial activation and immune-mediated platelet consumption parallel the severity of vascular leakage [3, 8]. The identification of platelet count below 50,000/mm³ as a significant threshold for DSS in multiple studies [4, 5, 27] offers a practical, easily remembered cutoff for clinical application, though the meta-regression finding by Sandinirwan et al. [1] demonstrating attenuation of predictive strength with increasing age (22% decrease in logOR per year) cautions against uniform application across all age groups.

The contrasting findings regarding hematocrit's predictive value represent one of the most instructive insights from this review. The apparent contradiction between studies finding strong associations [2, 3, 7] and those reporting non-significance [6, 11] is substantially resolved by considering measurement timing. The Sangkaew et al. meta-analysis [6], which restricted analysis to the first four days of illness (febrile phase), found hematocrit non-predictive, while studies capturing measurements during the critical phase (days 4-7) demonstrated significant associations [3, 7]. This temporal discordance reflects the underlying pathophysiology: plasma leakage begins after defervescence, with hemoconcentration manifesting only after clinically significant fluid extravasation has occurred [14, 25]. Consequently, hematocrit functions more effectively as a diagnostic marker of established leakage rather than an early predictor of impending deterioration. This distinction carries important clinical implications, suggesting that platelet count should be emphasized for early warning during the febrile phase, while hematocrit trends guide management once critical phase begins.

The superior predictive performance of combined assessment—rising hematocrit with declining platelet count—represents a particularly important finding with direct clinical

applicability. The odds ratios ranging from 5.13 [8] to 43.17 [5] substantially exceed those for either parameter alone, indicating synergistic predictive value. This combined marker captures two mechanistically linked processes: endothelial permeability producing hemoconcentration and platelet consumption through activation and immune clearance [5, 15]. The biological coherence of this dual parameter approach strengthens causal inference and provides a compelling rationale for serial monitoring of both parameters in parallel rather than reliance on isolated values. Podung et al.'s [5] finding of exceptionally high OR (43.17) for the combination of >20% hematocrit rise with platelet count <50,000/mm³ suggests that concurrent abnormalities in both parameters identify a particularly high-risk subset meriting intensive monitoring and intervention.

Population-specific differences modulating predictive accuracy warrant careful consideration in clinical application. The age-dependent attenuation of platelet-based prediction documented by Sandinirwan et al. [1] likely reflects developmental differences in hematopoietic reserve, endothelial function, and immune responses. Younger children, with their smaller blood volumes and developing immune systems, may manifest more dramatic platelet responses to dengue infection, enhancing discriminatory power. Conversely, adults with greater physiological reserve and higher prevalence of comorbidities [6, 8] may exhibit blunted platelet responses or confounding effects from other conditions. Geographic variation in study populations—predominantly Asian with limited representation from the Americas [14, 30]—constrains generalizability, particularly given documented differences in circulating serotypes, population immunity, and genetic susceptibility across endemic regions. The independent contribution of secondary dengue infection to severe outcomes [3, 6, 8, 29] further complicates predictive modeling, as immune status fundamentally alters disease pathogenesis and laboratory trajectories.

The comparison of laboratory predictors with sonographic markers [9, 10, 32] provides important context for clinical decision-making. Ultrasound findings such as gallbladder wall thickening (sensitivity 0.83, specificity 0.70), ascites (sensitivity 0.60, specificity 0.89), and pleural effusion offer direct visualization of plasma leakage with acceptable diagnostic accuracy [9, 32]. Chandran et al.'s [10] assertion that ultrasound findings are more clinically useful than hematocrit

reflects the advantage of direct leakage visualization over indirect laboratory surrogates. However, ultrasound requires trained personnel and equipment, limiting availability in resource-constrained settings where simple laboratory tests retain practical advantages. The higher frequency of pleural effusion detection by lung ultrasound compared to chest X-ray [21, 33] suggests that point-of-care ultrasonography could enhance leakage detection where available, potentially complementing rather than replacing laboratory monitoring.

Evidence from intervention studies [13, 23, 24, 28] demonstrates that platelet and hematocrit trajectories are modifiable by therapeutic interventions, confirming their utility as monitoring parameters. Bur et al.'s [13] demonstration that early albumin infusion produces significantly lower hemoconcentration and higher platelet counts compared to Ringer's lactate establishes these parameters as responsive endpoints for evaluating fluid resuscitation strategies. Tatura et al.'s [28] finding that gelatin solution produces greater hematocrit decrement and lesser platelet decline than plasma in DSS resuscitation similarly illustrates parameter responsiveness. These intervention effects reinforce the biological relevance of these markers and support their use in guiding and monitoring treatment.

Several limitations merit acknowledgment. The substantial heterogeneity across included studies ($I^2 = 90\%$ for platelet analyses in some meta-analyses [1]) indicates significant between-study variability limiting precision of pooled estimates. Publication bias documented by Egger's test ($p < 0.001$) [1] suggests possible overestimation of effect sizes due to preferential publication of positive findings. The predominance of observational study designs limits causal inference, though the inclusion of randomized trials [13, 23, 28] partially mitigates this concern. Variable application of WHO classification schemes (1997 vs. 2009) and national guidelines complicates direct comparisons across studies [8, 14, 25]. Limited representation from the Americas, Africa, and other endemic regions restricts global generalizability [14, 30]. Finally, the paucity of studies systematically evaluating optimal cutoff values through rigorous methodology (e.g., ROC curve analysis with validation cohorts) limits evidence-based threshold recommendations.

CONCLUSION AND RECOMMENDATIONS

This comprehensive systematic review establishes that both platelet count and hematocrit serve as significant predictors of plasma leakage in dengue hemorrhagic fever, though their predictive utility is critically dependent on measurement timing, serial monitoring, and combined assessment. Platelet count emerges as a more reliable early predictor, with significant reductions detectable during the febrile phase before hemoconcentration manifests, and counts below 50,000/mm³ consistently associated with increased shock risk. Hematocrit demonstrates variable predictive value depending on timing—limited during early febrile phase but significant during critical phase—functioning effectively as a diagnostic marker of established leakage rather than an early warning indicator. The combined assessment of rising hematocrit with declining platelet count yields substantially superior predictive performance compared to either parameter alone, capturing mechanistically linked processes of capillary permeability and platelet consumption.

The apparent contradictions in the literature regarding hematocrit's predictive value are largely resolved by considering temporal dynamics, with measurement timing explaining discrepant findings across studies. Population-specific factors, particularly age and geographic region, significantly modulate predictive accuracy and must inform clinical application. The responsiveness of both parameters to therapeutic interventions confirms their utility for treatment monitoring and endpoint assessment in clinical trials.

Recommendations:

1. **Clinical Practice:** Implement serial monitoring of both platelet count and hematocrit in all hospitalized DHF patients, with particular attention to concurrent trends rather than isolated values. Platelet count below 50,000/mm³ warrants increased vigilance, while the combination of declining platelets with rising hematocrit (>20% above baseline or >2% above reference range) should trigger intensified monitoring and consideration of prophylactic interventions.

2. **Risk Stratification:** Develop and validate integrated predictive models incorporating platelet count, hematocrit, and additional predictors (age, secondary infection status, comorbidity burden, sonographic findings) to enhance early identification of high-risk patients.
3. **Timing Considerations:** Emphasize platelet count for early warning during febrile phase (days 1-4) and hematocrit trends for monitoring during critical phase (days 4-7), with transition based on defervescence rather than fixed time points.
4. **Future Research:** Conduct prospective multicenter studies across diverse geographic regions with standardized outcome definitions, systematic measurement timing, and rigorous statistical methodology including validation cohorts. Investigate optimal cutoff values through ROC analysis with external validation. Evaluate integrated predictive models combining laboratory, clinical, and sonographic parameters. Assess cost-effectiveness of different monitoring strategies in resource-limited settings.
5. **Guideline Development:** Update clinical practice guidelines to incorporate nuanced recommendations reflecting temporal dynamics and combined parameter assessment, moving beyond simple threshold-based approaches to emphasize trend monitoring and integrated risk stratification.

The global burden of dengue hemorrhagic fever demands evidence-based approaches to early detection and management of plasma leakage. This review provides a foundation for optimizing the use of routinely available laboratory parameters to identify at-risk patients, guide clinical decisions, and ultimately improve outcomes in dengue-endemic regions worldwide.

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