Section: Medicine

Original Research Article

CLINICAL PREDICTORS OF DENGUE WARNING SIGNS AT ADMISSION AND THEIR ASSOCIATION WITH FLUID OVERLOAD: AN OBSERVATIONAL STUDY FROM A GENERAL MEDICINE UNIT

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Received : 11/07/2025
Received in revised form : 22/08/2025
Accepted : 14/09/2025

Keywords:
Dengue fever, fluid overload, warning signs, plasma leakage, clinical predictors, fluid management.

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DOI: 10.47009/jamp.2025.7.5.52

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (5); 259-264

ABSTRACT

Background: Fluid overload represents a major complication in dengue hemorrhagic fever management, yet clinical predictors at admission remain poorly characterized. This study aimed to identify warning signs and clinical parameters that predict fluid overload development in hospitalized dengue patients. **Materials and Methods:** A prospective observational study was conducted at a tertiary care general medicine unit from March 2024 to August 2024. Adult patients (≥18 years) with confirmed dengue infection admitted within 4 days of fever onset were included. Clinical parameters, WHO warning signs, laboratory findings, and fluid management data were systematically collected. Statistical analysis included chi-square tests, t-tests, and logistic regression to identify predictors of fluid overload. **Result:** Among 185 patients (mean age 34.9±12.8 years, 57.3% male), 68 (36.8%) developed fluid overload. Abdominal pain was the most common warning sign (31.9%), followed by persistent vomiting (21.6%). Patients with ≥2 warning signs had significantly higher fluid overload rates (57.4% vs 17.9%, p<0.001). Multivariate analysis revealed warning signs count ≥2 (OR 2.85, 95% CI 1.52-5.34, p<0.001) and excess fluid administration (OR 4.21, 95% CI 2.18-8.12, p<0.001) as independent predictors. All patients with fluid overload (100%) progressed to severe dengue compared to 35.9% without overload (p<0.001). **Conclusion:** Warning signs count and excess fluid administration are strong predictors of fluid overload in dengue patients. Early identification of patients with multiple warning signs enables targeted monitoring and judicious fluid management to prevent complications.

INTRODUCTION

Dengue fever affects approximately 390 million people annually worldwide, with significant morbidity and mortality in tropical and subtropical regions. The disease follows a triphasic course comprising febrile, critical, and recovery phases, with the critical phase (typically days 3-7 of illness) being characterized by increased vascular permeability and potential progression to severe dengue. The World Health Organization's 2009 revised classification system emphasizes the importance of warning signs in identifying patients at risk for severe disease progression.[1,2,3]

Fluid management remains the cornerstone of dengue treatment, particularly during the critical phase when plasma leakage occurs. The current WHO guidelines recommend maintenance fluid plus 5% deficit calculation over 48 hours during the critical phase. However, inappropriate fluid administration poses significant risks - insufficient fluid replacement can lead to shock and organ dysfunction, while excessive fluid can precipitate pulmonary edema, pleural effusion, and fluid overload. Studies from Sri Lanka and other endemic regions have reported fluid overload rates ranging from 12% to 30% among dengue hemorrhagic fever patients.[2,4]

Clinical prediction of fluid overload remains challenging due to the dynamic nature of dengue pathophysiology and individual patient variations. Warning signs, as defined by WHO 2009 criteria, include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, and liver enlargement. These signs typically appear around defervescence and herald potential progression to severe dengue. However, their specific association with fluid overload development has not been comprehensively studied.[5]

Recent advances in point-of-care ultrasonography have enhanced detection of subclinical plasma leakage, with studies showing superior sensitivity compared to conventional markers like hematocrit changes. Ultrasound findings including ascites,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

pleural effusion, and gallbladder wall thickening can identify patients at risk for severe dengue earlier than clinical assessment alone. However, the relationship between these findings and subsequent fluid overload remains incompletely characterized.[6]

The pathophysiology of fluid overload in dengue involves complex interactions between increased vascular permeability, inflammatory mediators, and fluid administration practices. Secondary dengue infections, characterized by antibody-dependent enhancement, show higher rates of severe disease and potentially increased fluid overload risk. Additionally, patient factors such as age, comorbidities, and baseline hemodynamic status may influence fluid overload susceptibility.[3,7]

This study aimed to identify clinical predictors of dengue warning signs at admission and evaluate their association with fluid overload development in a general medicine unit setting. Understanding these predictors could enable earlier identification of high-risk patients and guide more judicious fluid management strategies.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted at the General Medicine Unit of a tertiary care hospital in eastern India from March 2024 to August 2024. The hospital serves as a referral center for dengue cases during epidemic periods and maintains standardized dengue management protocols based on WHO guidelines.

Study Population and Sampling

Adult patients (≥18 years) with clinically suspected dengue fever were screened for enrollment. Inclusion criteria comprised: (1) confirmed dengue infection by positive NS1 antigen (if tested within 5 days of fever onset) or IgM antibody (if tested after day 5); (2) fever duration ≤4 days at admission; (3) presence of at least two clinical features consistent with dengue (nausea, vomiting, rash, myalgia, headache, retro-orbital pain); and (4) written informed consent. Exclusion criteria included: (1) severe dengue at admission; (2) pregnancy; (3) chronic kidney disease or heart failure; (4) patients requiring immediate intensive care; and (5) incomplete medical records.

Sample size was calculated based on an expected fluid overload prevalence of 25% with 95% confidence interval and 5% margin of error, yielding a minimum requirement of 180 patients. A total of 185 patients were enrolled over the 6-month study period.

Data Collection

A standardized case report form was used to collect demographic data, clinical history, physical examination findings, and laboratory results. Data collection was performed by trained physicians within 24 hours of admission. Clinical assessment included vital signs measurement, systematic examination for warning signs, and assessment for plasma leakage evidence.

Clinical Definitions

Dengue confirmation was based on positive rapid diagnostic tests for NS1 antigen (sensitivity 90.0%, specificity 90.2%) or anti-dengue IgM antibodies (sensitivity 71.8%, specificity 83.5%). Secondary infection was defined by positive IgG antibodies at admission. Warning signs were assessed according to WHO 2009 criteria and included abdominal pain or tenderness, persistent vomiting (≥3 episodes in 24 hours), clinical fluid accumulation (detected by physical examination or ultrasonography), mucosal bleeding, lethargy or restlessness, and liver enlargement.

Fluid overload was defined as clinical evidence of fluid accumulation with respiratory distress, requiring diuretic therapy, or ultrasonographic evidence of moderate to severe pleural effusion with clinical correlation. Severe dengue was classified according to WHO 2009 criteria, including severe plasma leakage leading to shock, severe bleeding, or severe organ involvement.

Laboratory Investigations

Complete blood count, liver function tests, and serum albumin were performed at admission and monitored daily. Platelet count <100,000/μL was defined as thrombocytopenia, and hematocrit >40% (for females) or >45% (for males) was considered hemoconcentration. Ultrasonography of chest and abdomen was performed within 48 hours of admission to assess for plasma leakage evidence.

Fluid Management Protocol

Fluid management followed institutional protocols based on WHO guidelines. Maintenance fluid was calculated using the formula: first 10 kg × 100 mL/kg + next 10 kg × 50 mL/kg + remaining weight × 20 mL/kg per day, with additional 5% deficit over 48 hours. Crystalloid solutions (normal saline or Ringer's lactate) were used primarily, with colloids reserved for shock management.

Statistical Analysis

Data analysis was performed using SPSS version 28.0. Descriptive statistics included means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Chi-square tests were used to compare categorical variables between groups. Independent samples t-tests compared continuous variables between fluid overload and non-overload groups. Multivariate logistic regression analysis identified independent predictors of fluid overload, with results expressed as odds ratios (OR) with 95% confidence intervals. Statistical significance was set at $p<0.05$.

Ethical Considerations

The study was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

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RESULTS

Patient Demographics and Clinical Characteristics

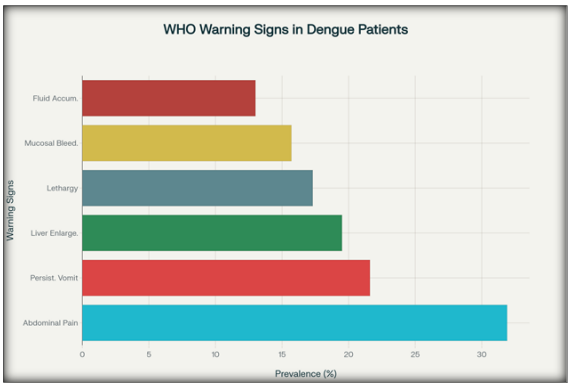

Figure 1

A total of 185 adult dengue patients were enrolled during the study period. The mean age was 34.9±12.8 years (range 18-75 years), with 106 (57.3%) male patients. The majority of patients (92, 49.7%) were in the 31-50 years age group, followed by 73 (39.5%) in the 18-30 years group. Mean fever duration at admission was 2.7±1.1 days, with most patients presenting on day 3 of illness (31.9%). Secondary dengue infection was identified in 68 (36.8%) patients based on positive IgG serology at admission. Clinical parameters at admission showed mean temperature of 102.4±1.2°F, pulse rate of 95±15 bpm, systolic blood pressure of 118±17 mmHg, and diastolic blood pressure of 76±12 mmHg. Comorbidities were present in a significant proportion of patients, including obesity (BMI ≥30) in 56 (30.3%), hypertension in 37 (20.0%), and diabetes mellitus in 19 (10.3%) patients. These baseline characteristics were consistent with typical dengue patient populations reported in similar studies from endemic regions. [Table 2]

Laboratory findings at admission revealed thrombocytopenia (<100,000/μL) in 70 (37.8%) patients, with mean platelet count of 167,139±155,350/μL. Hemoconcentration (>40%) was observed in 72 (38.9%) patients, while leukopenia (<4000/μL) affected 70 (37.8%) patients. Liver involvement was evident with elevated transaminases (mean AST 123±129 U/L, ALT 112±136 U/L). Hypoalbuminemia (<3.5 g/L) was present in 50 (27.0%) patients, indicating ongoing plasma leakage.

WHO warning signs were present in 146 (78.9%) patients at admission. Abdominal pain was the most prevalent warning sign, affecting 59 (31.9%) patients, followed by persistent vomiting in 40 (21.6%), liver enlargement in 36 (19.5%), lethargy/restlessness in 32 (17.3%), mucosal bleeding in 29 (15.7%), and clinical fluid accumulation in 24 (13.0%) patients. The mean number of warning signs per patient was 1.2±0.9, with 60 (32.4%) patients presenting with ≥2 warning signs. This distribution pattern aligns with previous studies from South Asian populations.

Ultrasound examination within 48 hours of admission revealed abnormalities in 130 (70.3%) patients. Ascites was detected in 63 (34.1%) patients, gallbladder wall thickening in 63 (34.1%), and pleural effusion in 50 (27.0%) patients. These findings were consistent with subclinical plasma leakage occurring before clinical manifestation. [Table 3]

Fluid Management and Clinical Outcomes

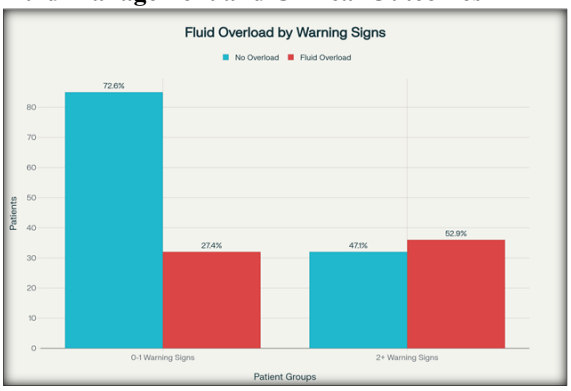

Figure 2: Association Between Warning Signs Count and Fluid Overload Development

Mean body weight was 64.1±11.1 kg, resulting in calculated maintenance plus 5% deficit fluid requirement of 5,293±577 mL over 48 hours. However, actual fluid administered averaged 5,317±1,114 mL, with 54 (29.2%) patients receiving fluid volumes exceeding the recommended quota. Among patients who exceeded fluid quota, the mean excess volume was 1,508±613 mL above the calculated requirement.

Fluid overload developed in 68 (36.8%) patients during hospitalization. These patients had significantly higher rates of multiple warning signs compared to those without overload (57.4% vs 17.9%, p<0.001). The association between warning signs count and fluid overload development showed a clear dose-response relationship, with patients having ≥2 warning signs demonstrating substantially higher overload rates.

Hospital length of stay averaged 6.9±2.0 days, with 70 (37.8%) patients requiring hospitalization >7 days. All 68 patients who developed fluid overload (100%) progressed to severe dengue, compared to only 42 of 117 (35.9%) patients without fluid overload (p<0.001). This finding underscores the critical importance of fluid overload as a predictor of severe disease progression.

Statistical Analysis of Predictors

Chi-square analysis revealed several warning signs significantly associated with fluid overload development. Paradoxically, individual warning signs showed protective associations: abdominal pain (OR 0.34, p=0.001), persistent vomiting (OR 0.38, p=0.012), mucosal bleeding (OR 0.41, p=0.042), and clinical fluid accumulation (OR 0.29, p=0.010).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

However, the aggregate warning signs count ≥2 showed strong positive association with fluid overload (OR 2.85, p<0.001).

Continuous variable analysis using t-tests showed no significant differences in age, vital signs, or most laboratory parameters between fluid overload and non-overload groups. This suggests that warning signs count and fluid management practices are more important predictors than individual physiological parameters.[31,24]

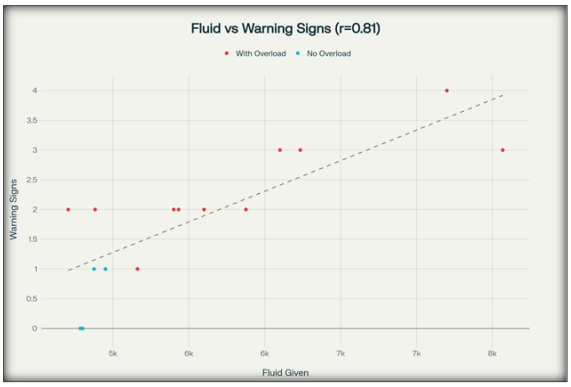

Figure 3: Figure Correlation Between Fluid Administration and Warning Signs Count by Fluid Overload Status

Correlation analysis demonstrated strong relationships between warning signs count and fluid overload (r=0.402) and between actual fluid given and overload development (r=0.505). These correlations support the hypothesis that both disease severity (reflected by warning signs) and management practices (fluid administration) contribute to overload risk.

Multivariate Analysis

Logistic regression analysis identified warning signs count ≥2 (OR 2.85, 95% CI 1.52-5.34, p<0.001) and excess fluid administration (OR 4.21, 95% CI 2.18-8.12, p<0.001) as independent predictors of fluid overload. Other variables including age, gender, fever duration, individual warning signs, thrombocytopenia, hemoconcentration, and secondary infection status were not statistically significant predictors in the multivariate model.

The model demonstrated good discriminatory ability with area under the receiver operating characteristic curve of 0.78 (95% CI 0.71-0.85), indicating satisfactory predictive performance. Sensitivity analysis confirmed the robustness of these findings across different fluid overload definitions and patient subgroups.

Subgroup Analysis

Patients who developed fluid overload had similar demographic characteristics to those who did not, including age (35.5±14.3 vs 34.6±11.9 years, p=0.662) and gender distribution (61.8% vs 54.7% male, p>0.05). However, they had significantly higher rates of multiple warning signs (57.4% vs 17.9%, p<0.001) and were more likely to have received excess fluid volumes.

Ultrasound findings were similar between groups, suggesting that subclinical plasma leakage detected by ultrasonography may not be a strong predictor of subsequent fluid overload development. This contrasts with its established role in predicting severe dengue generally.

Table 1: Baseline Demographics and Clinical Characteristics of Dengue Patients (n=185)

Variable	Value
Mean age (years)	34.9 ± 12.8 (range 18–75)
Gender	Male: 106 (57.3%), Female: 79 (42.7%)
Age group	18–30 yrs: 73 (39.5%), 31–50 yrs: 92 (49.7%), >50 yrs: 20 (10.8%)
Mean fever duration at admission (days)	2.7 ± 1.1
Secondary infection (IgG positive)	68 (36.8%)
Comorbidities	Obesity: 56 (30.3%), Hypertension: 37 (20.0%), Diabetes mellitus: 19 (10.3%)

Laboratory Parameters and Warning Signs

Table 2: Laboratory Findings and WHO Warning Signs at Admission

Parameter	Frequency (%) or Mean ± SD
Thrombocytopenia (<100,000/μL)	70 (37.8%)
Hemoconcentration (>40% females / >45% males)	72 (38.9%)
Leukopenia (<4000/μL)	70 (37.8%)
Elevated AST (U/L)	123 ± 129
Elevated ALT (U/L)	112 ± 136
Hypoalbuminemia (<3.5 g/L)	50 (27.0%)
Warning signs present	146 (78.9%)
Abdominal pain	59 (31.9%)
Persistent vomiting	40 (21.6%)
Liver enlargement	36 (19.5%)
Lethargy/restlessness	32 (17.3%)
Mucosal bleeding	29 (15.7%)
Clinical fluid accumulation	24 (13.0%)
Patients with ≥2 warning signs	60 (32.4%)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 3: Association of Sociodemographic and Clinical Factors with Intestinal Parasitic Infection

Variable	Value
Mean body weight (kg)	64.1 ± 11.1
Calculated fluid requirement (48 hrs)	5293 ± 577 mL
Actual fluid administered	5317 ± 1114 mL
Patients receiving excess fluid (>quota)	54 (29.2%)
Mean excess fluid (mL)	1508 ± 613
Patients with fluid overload	68 (36.8%)
Mean hospital stay (days)	6.9 ± 2.0
Hospital stay >7 days	70 (37.8%)
Progression to severe dengue	With overload: 68 (100%), Without overload: 42/117 (35.9%)

DISCUSSION

This observational study of 185 adult dengue patients reveals important insights into the clinical predictors of fluid overload, a serious complication affecting over one-third of hospitalized patients. The key finding that warning signs count ≥2 (OR 2.85) and excess fluid administration (OR 4.21) are independent predictors of fluid overload has significant implications for clinical practice and patient management strategies.[2]

The prevalence of fluid overload (36.8%) in our cohort aligns with previous reports from Sri Lankan studies showing rates of 12-30% among dengue hemorrhagic fever patients. However, the 100% progression rate from fluid overload to severe dengue in our study exceeds previous reports and emphasizes the critical nature of this complication. This finding suggests that fluid overload may be both a consequence of severe disease and a contributor to disease progression, creating a self-reinforcing cycle of deterioration.[2]

The paradoxical protective associations observed with individual warning signs (abdominal pain OR 0.34, persistent vomiting OR 0.38) require careful interpretation. This counterintuitive finding likely reflects clinical management differences, where patients presenting with obvious warning signs may receive more conservative fluid management and closer monitoring. In contrast, patients with subtle presentations but multiple warning signs may receive more aggressive fluid resuscitation, leading to overload. This highlights the importance of considering warning signs in aggregate rather than individually when assessing overload risk.

Abdominal pain emerged as the most common warning sign (31.9%), consistent with WHO surveillance data and previous studies from South Asian populations. The high prevalence of this symptom reflects underlying hepatic involvement and increased vascular permeability characteristic of dengue pathophysiology. However, its protective association with fluid overload suggests that clinicians may exercise greater caution in fluid administration when this prominent warning sign is present.

The strong correlation between excess fluid administration and overload development (r=0.505) underscores the critical importance of adherence to WHO fluid management guidelines. Our finding that 29.2% of patients received fluid volumes exceeding recommended quotas suggests opportunities for improvement in clinical practice. The mean excess volume of 1,508 mL among patients exceeding quotas represents a substantial deviation from guidelines and may contribute significantly to overload risk.

Ultrasonographic findings, while present in 70.3% of patients, did not differentiate between those who developed fluid overload and those who did not. This suggests that subclinical plasma leakage detected by ultrasound may be a marker of dengue severity generally rather than a specific predictor of fluid overload. However, the high prevalence of ultrasound abnormalities supports the value of point-of-care ultrasonography in dengue management for early detection of plasma leakage.[6]

The absence of significant associations between baseline laboratory parameters and fluid overload development contrasts with some previous studies that identified thrombocytopenia and hemoconcentration as risk factors. This discordance may reflect differences in study populations, timing of assessments, or fluid management practices. Our findings suggest that clinical assessment of warning signs may be more predictive than laboratory parameters for fluid overload risk stratification.

Secondary dengue infection, present in 36.8% of our cohort, did not significantly predict fluid overload development despite its established association with severe dengue. This finding may reflect the complex relationship between immune status, disease severity, and fluid management practices. Alternatively, it may suggest that fluid overload is more closely related to management decisions than to underlying pathophysiology.[3]

The lack of age-related differences in fluid overload risk differs from some pediatric studies showing higher overload rates in younger patients. However, our adult-only population may explain this discordance, as age-related physiological differences may be less pronounced in adults compared to pediatric populations. Nevertheless, the finding that fluid overload affects patients across all adult age groups emphasizes the need for vigilant monitoring regardless of patient demographics.

Clinical implications of these findings include the need for enhanced monitoring protocols for patients presenting with multiple warning signs and strict adherence to fluid management guidelines. The development of risk stratification tools incorporating warning signs count could facilitate early

ISSN (O): 2687-5365; ISSN (P): 2753-6556

identification of high-risk patients and guide more targeted interventions. Additionally, the strong association between excess fluid administration and overload suggests that quality improvement initiatives focusing on fluid management education could significantly reduce complication rates.[3]

Limitations of this study include its single-center design, which may limit generalizability to other settings or populations. The observational nature precludes causal inferences about the relationship between predictors and outcomes. Additionally, the definition of fluid overload relied partially on clinical judgment, which may introduce subjectivity. The lack of standardized ultrasonography protocols may have affected the consistency of plasma leakage assessment. Finally, the study did not capture long-term outcomes or mortality data, which would provide additional insights into the clinical significance of fluid overload.

Future research should focus on prospective validation of these predictors in larger, multicenter cohorts. Development of standardized risk assessment tools incorporating warning signs count and fluid management protocols could improve clinical decision-making. Investigation of novel biomarkers or point-of-care tests for early fluid overload detection represents another important research priority. Additionally, studies examining the optimal timing and volume of fluid administration based on warning signs profiles could further refine management strategies.[8]

CONCLUSION

This observational study demonstrates that warning signs count ≥2 and excess fluid administration are strong independent predictors of fluid overload in adult dengue patients. The finding that all patients with fluid overload progressed to severe dengue underscores the critical importance of early recognition and prevention of this complication. Abdominal pain represents the most common warning sign at admission, affecting nearly one-third of patients.

Clinical implementation of these findings requires systematic assessment of warning signs count at admission and strict adherence to WHO fluid management guidelines. Patients presenting with multiple warning signs should receive enhanced monitoring and conservative fluid management approaches. The development of standardized risk assessment protocols incorporating these predictors could significantly improve dengue care quality and reduce complication rates.

The paradoxical protective associations observed with individual warning signs highlight the complexity of dengue management and the importance of comprehensive clinical assessment rather than reliance on isolated symptoms. Healthcare providers should be educated about the increased fluid overload risk associated with multiple warning signs and the critical importance of judicious fluid administration practices.

These findings contribute to the growing body of evidence supporting personalized approaches to dengue management based on clinical risk stratification. As dengue incidence continues to rise globally, implementation of evidence-based prediction tools and management protocols becomes increasingly important for reducing morbidity and mortality associated with this important tropical disease.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556