Clinicohematological parameters during Acute Febrile Illness- A tool for early prediction of Dengue fever

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Abstract

Background: Dengue infection presents with Acute Febrile Illness (AFI) and can range from mild illness to severe forms such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Its early diagnosis by Non-Structural Protein 1 (NS1) antigen test is crucial to prevent severe complications. However, this test can be costly and may not be readily accessible in peripheral healthcare settings. Therefore, identifying clinico-hematological parameters that can aid in the early prediction of dengue fever is essential for timely intervention.

Objective: To evaluate the clinico-hematological parameters in patients with AFI as predictive indicators for early diagnosis of dengue fever, prior to the availability of serological results.

Material & Methods: Patients with AFI lasting less than 10 days and undergoing dengue serology testing (NS1 antigen) were included. Clinical and hematological parameters were recorded on days 0, 3, and 7. The data were divided into two groups: NS1 positive and NS1 negative. The clinical features and hematological findings of each parameter on Complete Blood Count (CBC) for the two groups were compared.

Results: Among 364 patients with AFI, the mean age was 31.13 years; 59.6% were male. Common symptoms included myalgia (26.9%), abdominal pain (24.2%), chills (20.1%), and arthralgia (15.4%). Hematological abnormalities were prevalent: thrombocytopenia (89.6%), leukopenia (37.9%), anemia (34.3%), neutrophilia (21.4%), and eosinophilia (6.6%). Dengue was confirmed by NS1 testingin 171 patients (47.0%), while 62 (17.0%) tested negative. NS1 antigen status was unavailable for 131 patients due to non-availability of NS1 test reports in medical record department at time of data extraction. These patients were retained in the overall descriptive analysis of AFI cases but were excluded from the comparative analysis between NS1-positive and NS1-negative groups to avoid classification bias.Serial CBC analysis showed a slight decline in hemoglobin and hematocrit, with platelet counts increasing over time. Neutrophil percentage decreased, while lymphocyte percentage increased during the study period.

Conclusion: The clinico-hematological parameters can aid in early dengue detection, especially in resource-limited settings.

Keywords: Dengue fever, Acute febrile illness, Clinico-hematological parameters, Thrombocytopenia, NS1 antigen.

Introduction:

Acute Febrile illness (AFI) is defined as fever for at least 2 successive days with a body temperature >38˚C. Malaria (Plasmodium), Dengue (Dengue virus), Urinary tract infection (E coli), Chikungunya fever, Typhoid (Salmonella) are the chief causes of AFI[1]. Dengue fever is known to occur in tropical, subtropical and temperate areas with a worldwide annual incidence of 50 million cases[2,3,4].AFI is the most emergent public health disease among the patient's attending hospital[5]. Patients with Dengue infection present with AFI[3]. Clinical features of Dengue infection are variable and can range from early asymptomatic disease that often resembles other febrile illnesses to lethal life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[5,6,7]. Though, usually a self-resolving disease, it may prove to be lethal if not diagnosed or treated at an early stage[2].

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From January 2021 to October 2021, a total number of 123,106 cases of Dengue have been reported in India with mortality of 0.073%. The incidence of Dengue in Uttar Pradesh in the same period has been reported to be 21,687 with a mortality of 0.032%[8].

Serological tests for definitive diagnosis of dengue are costly and inaccessible in peripheral hospitals/primary health care centres. Utilizing clinical and hematological parameters, complete blood count (CBC), which can distinguish Dengue infection from other causes of AFI will help bridge this gap. It has been documented in the literature that CBC parameters like hemoglobin (Hb), Packed cell volume (PCV)/Hematocrit (Hct), Total Leucocyte Count (TLC), Differential Leucocyte count (DLC) and Thrombocyte/Platelet count changes each day in a case of Dengue infection. CBC is a routine, easy and affordable blood test[5]. This study aims to analyse clinico-hematological parameters during AFI as a tool for early prediction of Dengue fever, before positive serology report is available.

This study underscores the diagnostic value of routinely available hematological parameters in facilitating the early recognition of dengue fever at the stage of AFI, prior to serological confirmation. The serial evaluation of CBC indices across the disease course reveals characteristic patterns, particularly the evolution of thrombocytopenia with relative hematocrit stability, aiding differentiation from other febrile conditions. By addressing a dengue-endemic, resource-constrained setting, the study offers a pragmatic and cost-effective framework for early clinical decision-making.

Material and Methods:

A retrospective observational study was conducted from January 1 to December 31, 2021, at our institute. The study aimed to analyse the clinico-hematological parameters of patients admitted with AFI, characterized by fever lasting less than 10 days and who underwent Dengue serology testing (NS1 antigen). Clinical data, including fever, chills, headache, myalgia, skin rash, arthralgia, abdominal pain and loss of appetite were recorded. Hematological parameters such as hemoglobin, PCV/Hct, platelet count, TLC and DLC comprising of neutrophils, lymphocytes, monocytes and eosinophils were also collected from the medical record department. The data was divided into two groups: NS1 positive and NS1 negative.

Patients with previously documented anaemia (Hemoglobin <13 g/dL in males and <12 g/dL in females), leukopenia (TLC <4000/mm3), thrombocytopenia (platelet count <150,000/mm3) or thrombocytosis (platelet count >450,000/mm3), chronic liver disease (CLD), chronic kidney disease (CKD), malignancies or incomplete medical records were excluded from the study.

Patients were initially enrolled based on the presence of AFI with clinical suspicion of dengue infection and were labeled as clinically suspected dengue cases. Cases were subsequently categorized according to NS1 antigen test results into dengue confirmed cases (NS1 positive) and non-confirmed cases (NS1 negative).Cases where NS1 antigen status was unavailable were retained in the overall descriptive analysis of AFI cases but were excluded from the comparative analysis between NS1-positive and NS1-negative groups to avoid classification bias. Statistically, missing NS1 data were handled by complete-case analysis. Comparative analyses involving NS1 status were performed only on patients with documented NS1 results. No imputation method was applied for missing NS1 values, and the missing data were acknowledged as a limitation of the retrospective study design.

Definitions for various abnormalities on CBC are as follow: Leukopenia is TLC <4000 cells/mm3, Anaemia is Hemoglobin <13 g/dL in males and <12 g/dL in females; Thrombocytopenia is platelet count <150,000/mm3; Neutrophilia was defined as Neutrophil percentage >70%; Monocytosis was defined as monocyte percentage >10%; and Eosinophilia was defined as eosinophil percentage >6% of the Total leukocyte count.

The clinical features and hematological findings of each parameter on CBC for the two groups were compared. Serological test for the detection of NS 1 antigen for Dengue was documented. CBC values were recorded on the day of admission (day 0), followed by day 3 and day 7 and subsequently analysed.

Statistical analysis was done using the Chi-square test to assess associations, with a significance level set at 5% ($p<0.05$). Mean ± standard deviation was used to assess continuous variables of CBC over the three successive readings. SPSS version 21.0 software was utilized for statistical analysis. The study was approved by the Institutional Ethics Committee.

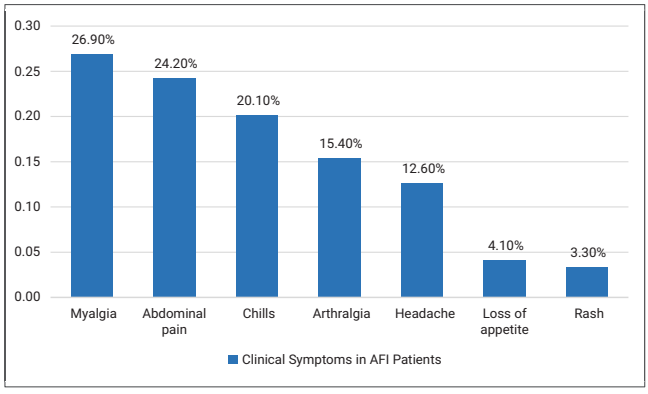
Results:

A total of 364 patients presenting with AFIwere included in the present study.

Table 1: Demographic character of AFI patients

Character	Number (%) of Patients
Age (years)	
Mean±SD	31.13 ±12.38
Median (IQR)	28 (21-38)
Age Group (years)	
18-29	201 (55.2)
30-39	83 (22.8)
40-49	46 (12.6)
≥ 50	34 (9.3)
Gender	
Male	217 (59.6)
Female	147 (40.4)

The mean age of participants was 31.13 years (SD ±12.38), with a median age of 28 years (IQR 21-38). The majority (55.2%) of patients were between 18 and 29 years of age, followed by 22.8% aged 30-39 years, 12.6% aged 40-49 years and 9.3% aged 50 years and older. Males comprised 59.6% (n=217) of the study population while females accounted for 40.4% (n=147). [Table 1]



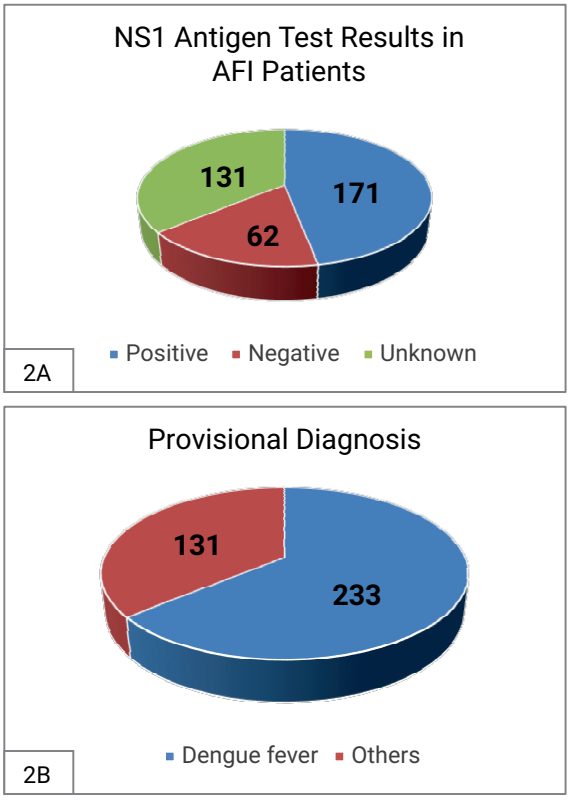
Graph 1: Clinical Symptoms in AFI Patients

Common clinical symptoms observed among patients included myalgia (26.9%), abdominal pain (24.2%), chills (20.1%) and arthralgia (15.4%). Less frequent symptoms were headache (12.6%), rash (3.3%) and loss of appetite (4.1%). [Graph 1]

Table 2: Hematological Findings in AFI Patients

Parameter	Percentage (%)	Frequency
Anaemia (Hb<12g/dL for females, <13g/dL for males)	34.3	125
Leukopenia (<4000/mm3)	37.9	138
Monocytosis (>10%)	5.5	20
Neutrophilia (>70%)	21.4	78
Eosinophilia (>6%)	6.6	24
Thrombocytopenia (<1.5 X109/L)	89.6	326
Hct/PCV >46%	14.6	53

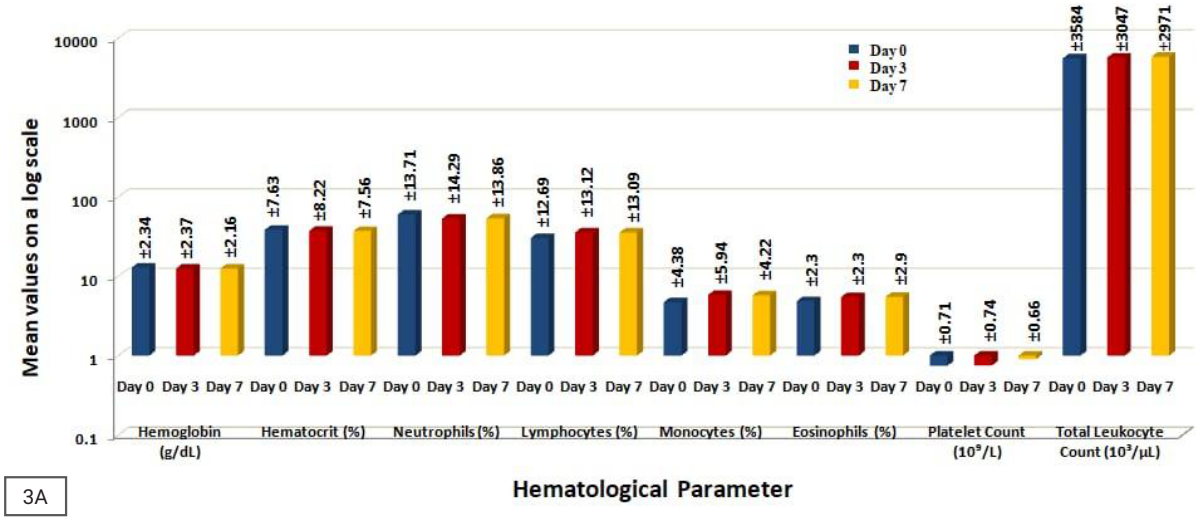
Hematological abnormalities were frequently noted among AFI patients. Thrombocytopenia (platelet count <1.5 x 10^9/L) was the most prevalent, affecting 89.6% of individuals. Leukopenia was present in 37.9% and anaemia in 34.3% of patients. Neutrophilia and eosinophilia were seen in 21.4% and 6.6% of cases, respectively, while monocytosis (>10%) was relatively uncommon (5.5%). Elevated hematocritvalue (>46%) was documented in 14.6% of the study population. [Table 2]



Graph 2- Provisional diagnosis and NS1 antigen status in AFI patients

Among the 364 patients, 171 (47.0%) tested positive for Dengue NS 1 antigen while 62 (17.0%) tested negative. The NS1 antigen status was unavailable for 131 (36%) patients primarily due to incomplete serological records in this retrospective study and/or non-availability of NS1 test reports in the medical record department at the time of data extraction. These patients were retained in the overall descriptive analysis of acute febrile illness (AFI) cases but were excluded from the comparative analysis between NS1-positive and NS1-negative groups to avoid classification bias. Statistically, missing NS1 data were handled by complete-case analysis. Comparative analyses involving NS1 status were performed only on patients with documented NS1 results (171 NS1-positive and 62 NS1-negative cases).

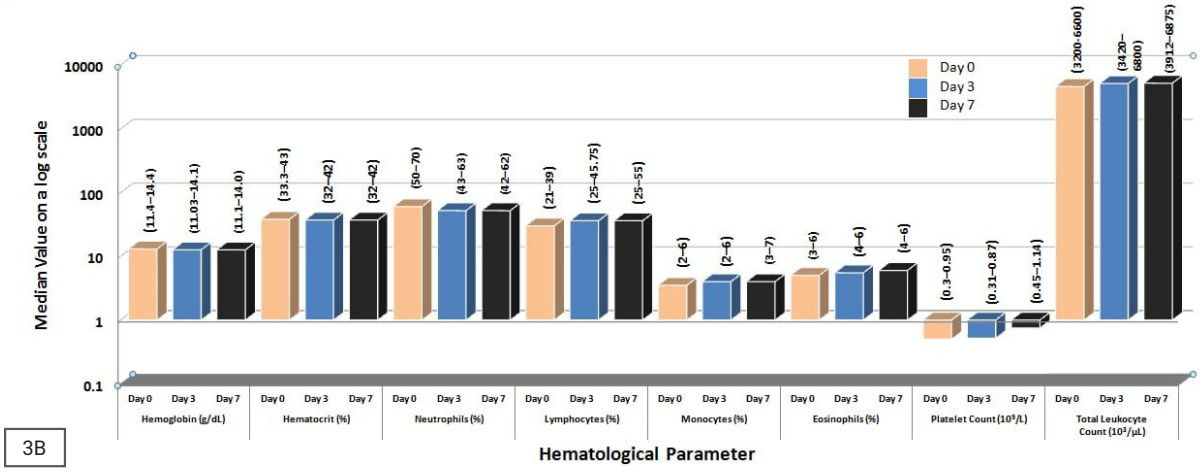
[Graph 2A] Based on the clinical assessment and preliminary investigations, 233 patients (64%) were provisionally diagnosed with Dengue while 131 (36 %) were classified under other febrile illnesses. [Graph 2B]



3A

Graph 3A: Mean and Median values of Hematological parameters over time

Serial hematological values taken on Days 0, 3 and 7 revealed several trends. Mean hemoglobin levels declined slightly from Day 0 (12.87 ± 2.34 g/dL) to Day 3 (12.48 ± 2.37 g/dL), remaining stable thereafter. Similarly, hematocrit values decreased marginally over time. Platelet counts were initially low (0.745 ± 0.71 x 10^9/L on Day 0) but showed gradual recovery by Day 7 (0.900 ± 0.666 x 10^9/L). [Graph 3A]



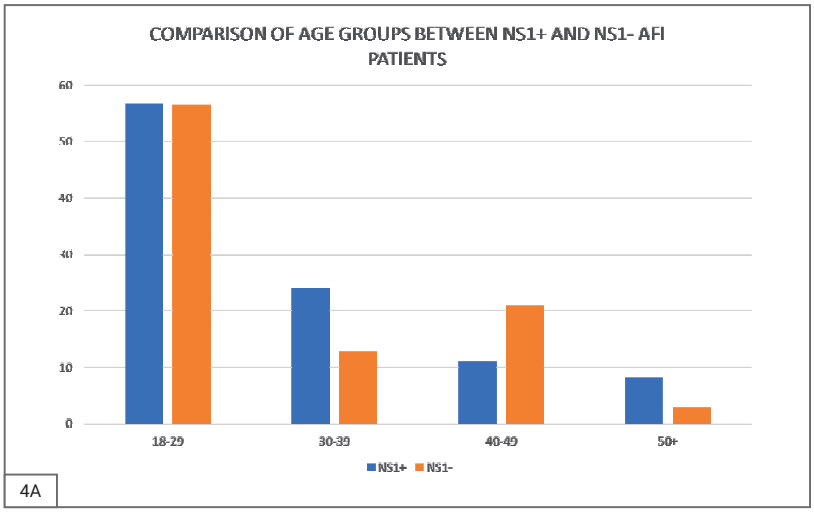
3B

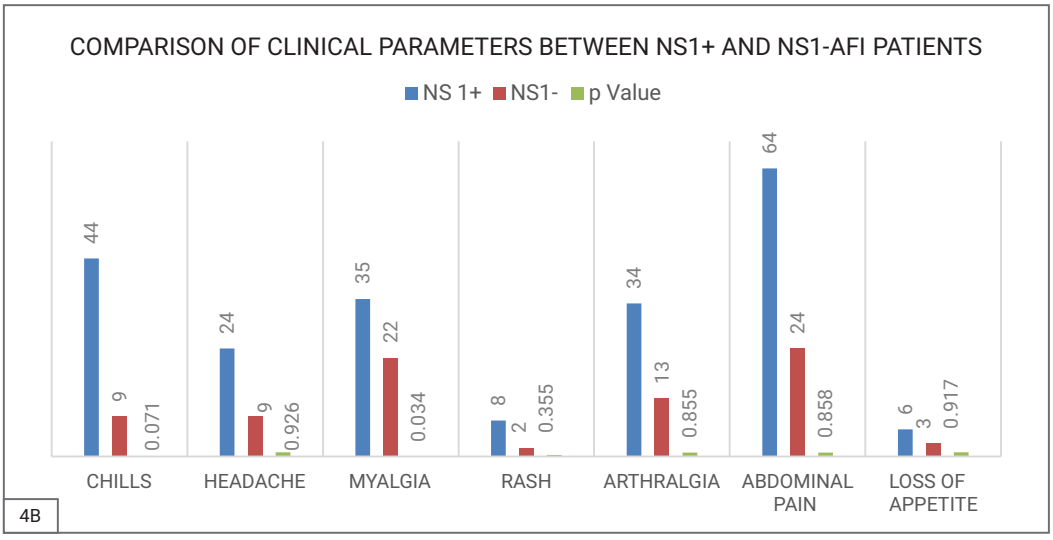
Graph 3B: Mean and Median Values of Hematological Parameters over time

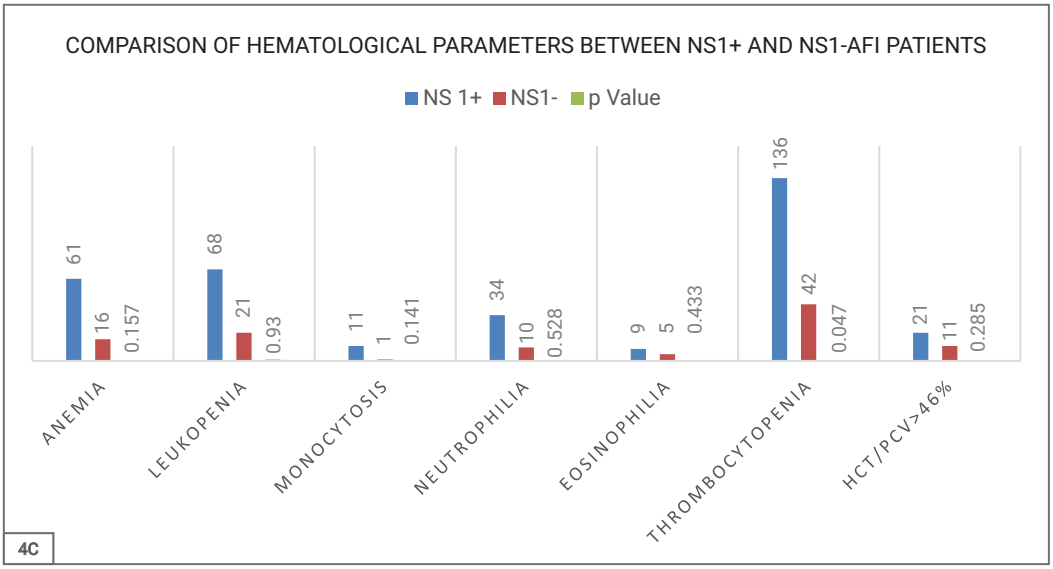
Platelet count hits lowest around day 0 to day 3 with median remaining flat at 50000 to 52000 cells/µL. Between day 3 and day 7, it showed a clear upward trend, increasing median to 75000cells/µL. The interquartile range representing the middle 50% of patient data, are wide throughout. The spread is roughly symmetric, and the range from the 25-50% to the 50-75% consistently includes critically low values, especially during the acute phase.

The median hematocrit is 38.05% upon admission. It shows a slight decrease from Day 0 to Day 3 (38.05% to 36.85%) followed by stabilization around 37.00% by Day 7. The interquartile range show a relatively consistent spread across all days.

WBCcounts showed a modest upward trend from Day 0 to Day 7. A corresponding shift in differential counts was also observed: the proportion of neutrophils decreased from 59.67% on Day 0 to 53.45% on Day 7 while lymphocytes increased from 30.32% to 35.48% over the same period. Monocyte and eosinophil percentages rose slightly but remained within expected ranges. [Graph 3B]







Graph 4- Comparison between NS1 positive and negative cases based on clinic-hematological parameters

Demographic distribution between NS1-positive and NS1-negative groups was broadly similar, with both groups having a predominance of younger adults (18-29 years). However, some clinical and hematological differences were noted. [Graph 4A]

Myalgia was significantly more common in NS1-negative patients (33.9%) compared to NS1-positive individuals (20.5%; p=0.034). Thrombocytopenia was notably more frequent in the NS1-positive group (79.5%) compared to NS1-negative patients (62.7%; p=0.047). No statistically significant differences were observed in other clinical symptoms such as chills, headache, arthralgia or abdominal pain. [Graph 4B] Likewise, the prevalence of anaemia, leukopenia and other hematological abnormalities did not differ significantly between the two groups.[Graph 4C]

Discussion:

Patients presenting with AFI in tropical countries such as India predominantly exhibit infectious etiologies.A study by Bhatnagar et al[9] identified the following distribution of common diseases presenting as AFI: dengue (45%), malaria (22%), septicaemia (15%), others (10%) and undetermined etiology (8%). Our study corroborates these findings, with a significant number of cases attributed to Dengue infection. This contrasts with earlier studies by Dash et al[10] and Kumar et al[11],which reported different distributions. Such discrepancies may be attributable to geographical and climatic variations influencing regional disease patterns.

The most affected cohort in our study was young adult males aged 18-29 years, aligning with previous researches. Among the NS 1-positivegroup, the majority were also young adult males in the 18-29years agegroup, followed by those aged 30-39 years. Similar observations were made by Makroo et al[12] This age and gender distribution may be influenced by increased outdoor activities and sleeping habits, leading to higher exposure to mosquito vectors.

Clinical manifestations in our study included myalgia (26.9%), abdominal pain (24.2%), chills (20.1%), arthralgia (15.4%), headache (12.6%), loss of appetite (4.1%) and rash (3.3%). These findings are consistent with those reported by Bhatnagar et al[9] and a Malaysian study by Tong et al[13]. However, they differ from study by Kumar et al[14] in Uttar Pradesh, which reported varying symptoms prevalence. In the NS1-positive cohort abdominal pain (57.4%), chills (25.7%), myalgia (20.5%), arthralgia (19.9%), headache (14.0%), rash (4.7%) and loss of appetite (3.5%) were prevalent. These symptoms align with those observed in previous studies[6,15,16,17].

Hematologicalabnormalities were notable, with thrombocytopenia observed in 89.6% of cases, consistent with previous studies[2,6,18]. The NS1-positive group also exhibited significant thrombocytopenia ($p < 0.05$). Leucopenia and anaemia were present in AFI and NS1-positive patients, potentially due to bone marrow suppression during the acute phase of viral infection. Over the disease course (day 0 to day 7), an increase in platelet count and white blood cell count were noted, mirroring observations by Sharma et al[19].

Hemoconcentration, defined as an increase in hematocrit of 20% or more, is indicative of increased vascular permeability and plasma leakage. In our retrospective study, we observed hematocrit levels >46% in 14.6% of AFI patients and 12.3% of NS1-positivc patients. A study by Sharma et al[19] reported hematocrit levels >48% in 6.12% of cases and increase in hematocrit by >20% in 14.28% of cases during an epidemic of dengue hemorrhagic fever in Delhi in 1996. In our study, median hematocrit remained stable (Day 0: 38.05% vs. Day 7: 37.00%), suggesting minimal evidence of plasma leakage or severe hemorrhage. Conversely, the median platelet count confirmed profound thrombocytopenia at presentation but demonstrated a clear recovery trend by Day 7. This dynamic shift in platelets, coupled with hematocrit stability, strongly aligns with the typical course of a self-limiting viral illness, such as dengue, where the platelet count nadir (lowest point) typically occurs around Days 4-7, followed by an upward rebound marking the recovery phase. Critically, the stability of the hematocrit is a favorable prognostic sign, as a rapid increase in HCT concurrent with a falling platelet count is the primary warning sign for plasma leakage and progression to severe dengue[20]. Therefore, these trends suggest a typical, uncomplicated recovery course for the majority of patients in this cohort. Similar findings were noted in study by Faridah et al[20] and Nayar et al[21].

Monocytosis, neutrophilia, and eosinophilia were noted in a small percentage of patients in our study. These findings contrast with those of Chaloemwong et al[3], who identified monocytosis as a parameter to predict the severity of dengue infection. Neutrophilia tended to resolve with disease progression, accompanied by a concurrent increase in lymphocyte count, leading to a reversal in the neutrophil-to-lymphocyte ratio.

A study by Kalyanarooj et al[22] found that platelet count, total WBC, neutrophils and monocytes were significantly lower in dengue fever compared to other febrile illnesses. Additionally, early-stage predictors of Dengue infection, such as leucopenia, neutropenia, monocytopenia and increased AST levels, have been identified to aid in close monitoring of patients.

Limitations:

This study's retrospective design limits the availability of comprehensive data, which could have enhanced the diagnostic accuracy and comparison of dengue infections. The single-centre nature of the study

may not reflect the broader spectrum of AFI cases. Furthermore, serologically negative dengue cases were excluded from the dengue cohort, potentially underrepresenting the true incidence. Missing NS1 antigen reports in a subset of patients limited comparative analysis and may have introduced selection bias due to exclusion of these cases from NS1-based subgroup comparisons.

Conclusion:

This study provides regional validation of clinico-hematological markers for early dengue prediction in a North Indian population. By analyzing serial trends in complete blood count parameters from Day 0 to Day 7, the study highlights dynamic hematological changes that may aid early recognition and monitoring of dengue infection. The findings further emphasize the practical utility of routinely available and cost-effective CBC parameters in resource-limited healthcare settings where advanced serological testing may not be readily accessible. Prospective studies are essential to develop and validate clinical and laboratory algorithms that can accurately differentiate between dengue fever and other febrile illnesses. Such tools would be invaluable in resource-limited settings, especially in tropical regions with high disease burden.

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