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Pathology Section

# Differentiating between Dengue Fever from Other Febrile Illnesses Using Hematological Parameters

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## ABSTRACT

**Introduction:** Dengue fever is the most common arthropod borne disease and major public health concerns in India. The clinical presentation of this disease is difficult to distinguish from other febrile illnesses like malaria and typhus fever. Correlation of hematological parameters helps to differentiate these diseases in early stage.

**Aim:** The present study aimed to identify the hematological features useful for discriminating dengue from other febrile illnesses and to evaluate the accuracy of these hematological parameters.

**Materials and Methods:** A retrospective study was done to differentiate between dengue and other febrile illnesses between January 2017 to July 2017 at Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad Karnataka. Data regarding hematological parameters were collected in 170 cases classified as dengue (D) and 170 cases classified as non dengue (ND) based on laboratory tests.

**Results:** The following parameters were significantly lower in patients with DF as compared to non dengue patients (p-value less than 0.05); WBC, Platelets, Neutrophils, Eosinophils.

The following parameters were significantly higher in patients with DF as compared to non dengue cases ($p<0.05$): Hemoglobin, PCV, RBC count, Lymphocytes, Monocytes. Multiple logistic regression model used in this study showed two hematological predictors with positive association to confirm dengue: WBC count <4000/cumm and platelet count <1 lakh/cumm (likely to be present in dengue cases).

**Conclusion:** The study helps to differentiate dengue from other febrile illnesses at an early stage and avoids a large number of other investigation to diagnose dengue from other febrile illness.

Keywords: Febrile illness, Hemoglobin, Lymphocytes, Platelet count

## INTRODUCTION

Dengue is a mosquito borne tropical disease presenting with acute febrile illness caused by an arbovirus transmitted by *Aedes aegypti* mosquito [1-5]. Dengue is a global public health problem illness caused by dengue virus and can range from non specific febrile illness to classic dengue fever ,which may then progress to dengue hemorrhagic fever and dengue shock syndrome. Average incidence rate is 21 to 50 per million population in Karnataka from 1998 to 2014 [6].

Dengue fever is caused by the dengue virus with one of the four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 [7]. WHO has estimated that about 50 million patients are infected with dengue fever annually worldwide and 2.5 billion people live in endemic areas of dengue [8]. It is a challenging workup for the clinicians to detect dengue cases in the early stage before the development of severe manifestations. Paired acute and convalescent phase samples are required to diagnose dengue in the first 3 days after symptoms onset. But Serological tests are unreliable during the early course of illness and also for under developed and developing countries, it is difficult to afford PCR testing and rapid diagnostic tests in all the public health centers [9]. It is important to differentiate dengue fever from other infectious diseases that requires management with specific anti microbial therapy [10]. Specific diagnostic laboratory tests, even when available may not be accurate in early stages of illness. Serological tests for dengue fever and typhus are frequently negative in early stages of illness. Thus, there is still a role for diagnosis based on hematological parameters.

That is why, WHO recently identified among its global research priorities the need for “clinical and laboratory indicators for early dengue” [11].

Multiple clinical and laboratory features can differentiate dengue from other febrile illness. A recent systematic literature review identified multiple clinical and laboratory features that could potentially differentiate dengue from other febrile illness [9].

Dengue diagnosis based on only clinical presentation is challenging and can lead to misdiagnosis also. In study done by Fernandez E et al., shows that less than 50% of the specimens tested in cases of suspected dengue are confirmed to be positive and the rest were negative for dengue test [8]. The present study aimed to identify the

hematological features useful for discriminating dengue from other febrile illnesses and to evaluate the accuracy of these hematological parameters. Logistic regression model is used on hematological parameters to predict laboratory confirmed dengue cases. Using these data, we built and validated logistic regression models to identify hematological parameters to predict laboratory confirmed dengue.

## MATERIALS AND METHODS

A retrospective study designed on 340 patients. Of 340 patients ,170 had laboratory evidence for dengue infection while 170 patients had other febrile illness who were admitted with infections like malaria, filariasis, typhoid, influenza, SARS and were negative for dengue test. All these patients complained about fever for 2 to 5 days. All 340 patients were admitted patients in the SDM medical hospital. Non dengue cases consisted of patient with typhoid, influenza, SARS , leptospirosis, malaria, filariasis. Severity of illness consisted of patients with body temperature above 100.4°F for more than two days.

The study period was between January 2017 and July 2017 in Department of Pathology at the SDM medical college and hospital, Dharwad. We have taken ethical committee approval to conduct the study.

Patients presenting with acute onset fever (≥38.0°C) above the age of 18 years with no other clinically definitive alternative diagnosis were eligible for inclusion in the study.

Exclusion criteria included 1) patients age <18years

2) lab results for dengue which are indeterminate.

Demographic, clinical and epidemiological information were recorded on a proforma and consent of the patient was taken. A full blood count was performed on anticoagulated whole blood collected at all time points. EDTA blood were analysed to determine the complete blood count using Sysmex XN – 1000. Calibration by internal and external QC controls was also performed on a regular basis.

The following parameters were listed by the haematology analyser-RBC count, Hemoglobin (Hb), Haematocrit (Hct), Platelet count, WBC count, Neutrophil, Monocytes, Lymphocyte and Eosinophils counts, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC).

Dengue can be diagnosed in laboratories using different methods. In the present study, Nonstructural protein 1 (NS1) antigen detection was performed from day 0 to day 5, and indirect diagnosis based on the detection of specific anti-dengue immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies in patients' sera after day 3. If one of the antibodies (either IgG or IgM) is positive, the sample is designated as positive for dengue infection. All these data were retrieved from the patients and the computer records.

## STATISTICAL ANALYSIS

Normal distribution of continuous data was determined using the Kolmogorov-Smirnov test. Continuous variables were categorized following laboratory or usual cut-off values. Cut-off values for the parameters were as follows-WBCs <4000/µL, Neutrophils <40%, Lymphocytes <10%, Monocytes <2% Eosinophils <1%, RBCs <4×$10^6$/µL, Hb <11 g/dL and Platelets <1,00,000/µL were considered lower than cut-off values. Hematocrit >40%, MCV >80 fL, MCH > 25 pg/cell, MCHC > 33 g/dL, were considered higher than cut-off values. Mann–Whitney U test was used to compare the continuous variables [7]. Categorical variables were analyzed using the Fisher's exact test or chi-square test.Statistical significance was set at p-value less than 0.05. Variables found to be statistically significant in univariate analyses were entered into multivariate analysis using a logistic regression model to identify independent risk factors for outcomes of interest. All statistical computations were performed using the SPSS version 20.0 software.

## RESULTS

The 340 patients who were investigated in this study had a mean age of 26.75 years (SD age 14.36) and in non dengue cases it was 41.66 years (SD age 14.64) .

There were more men 101 cases (59.41%) in the dengue group and more men 102 cases (60%) in the Non dengue group. A significant difference relating to gender between the two groups was observed (p = 0.001).

Out of 170 patients infected with dengue, 54.71% were positive with NS1 antigen , 52.94% were positive with dengue Ig M antibody and 44.71% were positive for dengue Ig G antibody.

The following parameters were significantly lower in patients with DF as compared to Non dengue patients (p-value less than 0.05): WBC, Platelets, Neutrophils, Eosinophils. The following parameters were significantly higher in patients with DF as compared to Non dengue cases (p<0.05): PCV, Hemoglobin, RBC count, Lymphocytes, Monocytes. The following parameters show no significant difference in patients with DF compared to patients with non dengue cases (p>0.05): MCV, MCH, MCH [Table/Fig-1].

Multiple logistic regression analysis of prediction of dengue cases by different parameters was done using independent variables [Table/Fig-2].

**The following variables were independently associated with dengue in multivariable analysis:** RBC count (OR = 0.47, 95% CI 0.22,1.00) WBC count (OR = 3.94, 95% CI 1.91,8.11), Platelet count (OR = 6.94, 95%CI 3.46,13.90) lymphocyte (OR= 0.47, 95% CI 0.22, 1.02 ), Eosinophils (OR=3.67, 95% CI 1.9,6.89 ), MCHC (OR = 0.47, 95% CI 0.25, 0.88)

In the present study, multivariate analysis showed two hematological predictors with positive association to confirm dengue: WBC count <4000/cumm and platelet count <1 lakh/cumm. The study also revealed negative association with respect to RBC count <4 million/cumm, Lymphocytes <10%, Eosinophils <2% and MCHC >33 g/dL [Table/Fig-2].

The model had a sensitivity of 77.65% and specificity of 81.76% with positive predictive value of 80.98% and negative predictive value of 78.53% .

| Variables | Groups | Mean | SD | Median | p-value | Non dengue vs Dengue |
|---|---|---|---|---|---|---|
| HB g/dL | Non dengue | 12.16 | 2.97 | 12 | 0.0001* | p=0.0003* |
| | Dengue | 13.32 | 2.63 | 13 | | |
| PCV%or HCT | Non-dengue | 37.22 | 8.22 | 38 | 0.0001* | p=0.0001* |
| | Dengue | 40.67 | 8.52 | 42 | | |
| RBC | Non-dengue | 4.13 | 1.16 | 4 | 0.0001* | p=0.0001* |
| | Dengue | 4.74 | 1.08 | 5 | | |
| WBC | Non-dengue | 9737.59 | 4798.05 | 8720 | 0.0001* | p=0.0001* |
| | Dengue | 5449.67 | 3231.87 | 4540 | | |
| Platelets | Non-dengue | 276477.65 | 131975.64 | 268500 | 0.0001* | p=0.0001* |
| | Dengue | 114223.53 | 93663.05 | 90000 | | |
| Neutrophils | Non-dengue | 66.16 | 15.84 | 66 | 0.0001* | p=0.0001* |
| | Dengue | 56.15 | 20.47 | 58 | | |
| Lymphocytes | Non-dengue | 23.84 | 13.04 | 24 | 0.0001* | p=0.0001* |
| | Dengue | 33.66 | 19.92 | 32 | | |
| Monocytes | Non-dengue | 7.81 | 4.24 | 7 | 0.1260 | p=0.0479* |
| | Dengue | 8.45 | 4.27 | 8 | | |
| Eosinophils | Non-dengue | 2.12 | 3.51 | 1 | 0.0001* | p=0.0001* |
| | Dengue | 1.14 | 2.16 | 0 | | |
| MCV | Non-dengue | 85.81 | 9.59 | 86 | 0.5570 | p=0.6125 |
| | Dengue | 85.60 | 6.98 | 86 | | |
| MCH | Non-dengue | 27.95 | 3.74 | 29 | 0.3060 | p=0.0952 |
| | Dengue | 27.68 | 3.10 | 28 | | |
| MCHC | Non-dengue | 32.34 | 2.01 | 32 | 0.0030* | p=0.5706 |
| | Dengue | 39.39 | 46.00 | 32 | | |

**[Table/Fig-1]:** Pair wise comparisons by Mann-Whitney U test

| Independent variables | Odds Ratio | p-value | 95% CI for OR | |
|---|---|---|---|---|
| HB <11g/dl | 0.53 | 0.1680 | 0.21 | 1.31 |
| PCV% or HCT>40% | 0.97 | 0.9380 | 0.50 | 1.89 |
| RBC<4x10$^6$/uL | 0.47 | 0.0500* | 0.22 | 1.00 |
| WBC<4000/µL | 3.94 | 0.0001* | 1.91 | 8.11 |
| Platelets<100000/µL | 6.94 | 0.0001* | 3.46 | 13.90 |
| Neutrophils<2800/µL | 1.56 | 0.3460 | 0.62 | 3.95 |
| Lymphocytes<800/µL | 0.47 | 0.0500* | 0.22 | 1.02 |
| Monocytes<80/µL | 1.18 | 0.7980 | 0.34 | 4.15 |
| Eosinophils<40/µL | 3.67 | 0.0001* | 1.97 | 6.83 |
| MCV>80fL | 1.01 | 0.9790 | 0.38 | 2.72 |
| MCH>25pg/cell | 1.06 | 0.9110 | 0.36 | 3.10 |
| MCHC>33g/dL | 0.47 | 0.0190* | 0.25 | 0.88 |

**[Table/Fig-2]:** Multiple logistic regression analysis of prediction of dengue cases by different parameters.
*p<0.05

## DISCUSSION

The present study confirmed that socio-demographic characteristics differ between patients with DF and those with non dengue fever patients.

Firstly, patients with DF tended to be younger than non dengue patients, however, no significant difference between the two groups and age were observed (mean age DF = 26.75, ND = 41.66 years old). This was in concordance to another study conducted by Kotepui M et al., which, indicated that patients with DF were younger [12]. Another study done by Gregory CJ et al., showed that laboratory positive dengue cases were older than patients who were laboratory negative for dengue [9].

Secondly, males were infected more in dengue cases in the present study. This was in concordance with the study done by Fernandez E et al., and Daumas P et al., in which males accounted for 59% and 65.1% in cases respectively [8,13].

However, in study done by Hammond SN et al., females were more affected than males [14]. In the present study, hematological parameters were more severe and

abnormalities were more frequent in patient with dengue than those with non dengue.

The following parameters were significantly lower in patients with DF as compared to non dengue patients (p-value less than 0.05): WBC, Platelets, Neutrophils, Eosinophils. Transient marrow suppression is the cause of Neutropenia in DF [15]. Platelet survival time is shortened due to multiple mechanisms leading to platelet destruction [15]. In initial stages of dengue illness there is hypocellularity of bone marrow and attenuation of megakaryocytes maturation [16].

In study done by Kalyanarooj S et al., Platelet count, Total WBC, Neutrophils and Monocytes were significantly lower in DF than OFI [17].

The following parameters were significantly higher in patients with DF as compared to non dengue cases ($p<0.05$): PCV, Hemoglobin, RBC count, Lymphocytes, Monocytes. Higher values of PCV vascular leakages are one of the causes for increase in PCV leading to haemo concentration [18]. 0ne study showed that lymphocyte count was within normal limits during the course of dengue illness [16]

Rising values of hematocrit and rapid decrease of platelet count indicates plasma leakage in dengue patient [19].

In study done by Kotepui M et al., RBC, Hb, PCV, MCV, MCH, MCHC were significantly higher in patients with dengue. Parameters with significantly lower values were WBC, Neutrophils, Monocytes, Eosinophils. In another study done by Daumas P et al., Platelet and Leucocytes counts were significantly lower in dengue than in non dengue groups [13].

Our logistic regression model found that five hematological parameters helped differentiate dengue from other febrile illness:

1) WBC count; 2) Platelet count; 3) RBC count;

4) Lymphocytes; 5) Eosinophils.

Of these, the association was positive for the WBC count and Platelet count (likely to present in dengue cases) and association was negative for the RBC count, Lymphocytes, Eosinophils, MCHC consistent with being less likely to be present in dengue cases.

Platelet count has a higher odds ratio than other predictors followed by WBC count. Therefore, low platelet count and low WBC count are strong positive predictors in dengue cases. In study done by Gregory CJ et al., low platelet count had a odds ratio of 2.1 (95% CI 1.3, 3.4) [9]

Hammond SN et al., showed that platelet count less than 150,000/$mm^3$, 100,000/$mm^3$ and 50,000/$mm^3$ having positive laboratory diagnosis for dengue. Platelet was significantly lower in DF than OFI and Hematocrit were significantly higher in DF than in OFI [14].

The platelet cut-off of <140,000/$mm^3$ is shown to be predictors in distinguishing dengue from other febrile illnesses [20].

One study showed that Leucopenia, Neutropenia, Monocytopenia and increased AST levels can be used as predictors of dengue in early stage before plasma leakage developed thus help in close monitoring of patient [17].This study also showed that Hematocrit and Thrombocytopenia are critical features that distinguish DF from DHF [17].

In a study done by Wilder Smith A et al., the multivariate analysis showed that predictors of dengue from other febrile illnesses were low platelet count and low WBC count and elevated AST level and these three parameters had high odds ratio [21].

In a study done by Low LG et al., platelet count was significantly lower in DF than OFI. And lymphocyte counts were significantly higher. But Neutrophil, PCV, WBC were not significant [22].

However, Deparis X et al., mentions in his study that these laboratory measures are not specific for dengue in early stage of disease as the study showed low odds ratio for the parameters [23].

Chadwick D et al., showed that WBC count lower than 5000/cumm was the only laboratory parameter which was predictive of dengue fever [24] .

In a study done by La Russa VF et al., showed that dengue infected bone marrow stromal cells and dengue specific T cells produce few cytokines which cause bone marrow suppression [25].

## LIMITATION

The limitations of the study are, since it is a retrospective study, we could not assess the variation in the clinical and laboratory features that took place during the course of illness. Secondly the data is from only one region that is north Karnataka region. So generalisation of results is difficult and samples from other parts of the state need to be studied. Thirdly, serologically negative dengue cases were not considered in dengue case group as we considered sero positivity as diagnostic criteria for dengue case.

This study suggests that simple laboratory investigation like CBC can be used to identify early dengue infection from other febrile illness in adults.

The study implicates that an algorithm is needed to identify the patients with dengue early in illness. So that unnecessary hospitalisation is avoided.

The study highlights that many more prospective studies are required so as to set up a clinical and laboratory algorithm that can validate and generalise between dengue fever and other febrile illnesses.

The study broadens the horizon in the literature of dengue illness that leucopenia especially affecting Neutrophils and Monocyte lineage is helpful to differentiate dengue from other febrile illnesses.

## CONCLUSION

Dengue will continue to increase and spread day by day until a safe and effective vaccine is available and a viable and unending mosquito control practice takes place.

This study helps the clinicians to make an empirical diagnosis when diagnostic tools and efficient trained personnel are not

available. And also helps to start treatment in emergency cases of these diseases when the reports are awaited in endemic areas.

The present study also finds a way to avoid a large number of other investigations to diagnose dengue from other febrile illnesses. However, the rising availability of rapid tests for dengue and other illness may diminish the interest of platelet count and WBC count to differentiate febrile illnesses.

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