

## Do Hematocrit Levels Differentiate between Complicated and Uncomplicated Dengue Fever?

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### ABSTRACT

**Objective:** To compare mean hematocrit levels in patients with uncomplicated and complicated Dengue Fever and evaluate the role of hematocrit in differentiating uncomplicated and complicated Dengue Fever.

**Study Designs:** Prospective longitudinal study.

**Place and Duration of Study:** Department of Infectious Diseases, Holy Family Hospital, Rawalpindi Pakistan, from Oct 2019 to Sep 2020.

**Methodology:** Around 240 dengue patients were enrolled. Hematocrit level at presentation was measured using an automated haematology analyzer. The patients were then followed for the development of complications (Dengue hemorrhagic fever and Dengue shock syndrome).

**Results:** Of 240 patients, 183(76.2%) were male, and 57(23.8%) were female. Dengue Fever was present in 96(40%) patients, whereas 144(60%) patients developed complications (Dengue Hemorrhagic Fever and Dengue Shock Syndrome). The mean hematocrit level at presentation significantly differed among the groups ( $p=0.012$ ). Following the ROC curve analysis, for the cut-off value of 42.6% of hematocrit Group II had a sensitivity of 56.25% and a specificity of 62.5% at an Area under the curve of 0.589.

**Conclusion:** The mean hematocrit levels were significantly higher in patients with complicated versus uncomplicated Dengue Fever. Hematocrit could not be projected as a predictor of Dengue Fever severity.

**Keywords:** Dengue fever, Dengue Shock Syndrome, Dengue Hemorrhagic Fever, Hematocrit.

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### INTRODUCTION

Dengue fever (DF) is a major public health concern and affects more than 100 countries worldwide. Annually, 390 million infections and around 20,000 deaths around the globe highlight the gigantic challenge posed by the dengue virus.<sup>1,2</sup> A vast majority of dengue infections remain sub-clinical. The clinical spectrum of dengue infection varies from mild febrile illness to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).<sup>3</sup> The development of shock characterizes dengue shock syndrome. Dengue hemorrhagic fever and DSS are both severe illnesses with greater fatality rates.<sup>4,5</sup> Different biochemical and clinical parameters have been studied as predictors of severe dengue infection. White blood cell count, platelet indices, coagulation profile, hepatic aminotransferases, and hematocrit levels have been investigated as markers of the severity of dengue infection.<sup>6,7</sup> Red blood cell volume about total blood volume is measured by hematocrit. Hematocrit monitoring is a vital part of the management of DF. Increasing

hematocrit in DF usually indicates plasma leakage, whereas decreasing hematocrit can be due to bleeding.<sup>8,9</sup>

Previously many national and international studies have reported changes in hematocrit during DF.<sup>10</sup> However, the data specifically looking at the hematocrit levels on presentation as a marker of severity is scarce, especially in the Pakistani medical literature. Early detection of DHF and DSS is extremely important as these severe forms of DF warrant strict monitoring and prompt treatment. Hematocrit, a cheap and widely available option, can be very useful. Therefore, this study was proposed to compare the mean hematocrit levels at the presentation of DF patients with DHF and DSS patients and evaluate the importance of hematocrit in differentiating classical DF from DHF and DSS.

### METHODOLOGY

The prospective longitudinal study was conducted at the Department of Infectious Diseases, Holy Family Hospital, Rawalpindi Pakistan, from October 2019 to September 2020, after approval from Rawalpindi Medical University Research and Ethical Committee (R-61/RMU dated 12 Oct 2019).

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**Inclusion criteria:** The study comprised patients over the age of twelve, with proven DF as defined by the Dengue Expert Advisory Group, Punjab, Pakistan.

**Exclusion criteria:** The study excluded patients with polycythemia, haematological malignancies, or a known chronic obstructive airway disease history.

Dengue fever was defined as pyrexia that lasted for two to twelve days and included at least two of the following symptoms: a headache, retro-orbital pain, myalgias, arthralgias, abdominal pain, rash, bleeding, and decreased urine output, as well as low leucocyte count (4,000/ $\mu$ L) or low platelet count (100,000/ $\mu$ L) and either a positive non-structural protein 1 (NS1) or a positive dengue Ig M antibodies.<sup>11</sup> Classical DF was defined as DF without evidence of plasma outflow or shock. The term DHF was used to describe DF that included signs of plasma leakage, such as ascites, pleural effusion, thickened gallbladder walls or pericholecystic fluid, or a hematocrit that increased or decreased by more than 20% from baseline. Dengue shock syndrome was defined as having DF together with any of the symptoms of shock, such as hypotension (blood pressure less than 90/60 mmHg, pulse less than 20 mmHg, urine output less than 0.5 ml/kg/hr, or capillary refill time shorter than 2 seconds), or any combination of these symptoms.<sup>12</sup>

Demographics, the day of the sickness at the presentation, and every other pertinent information were recorded. With an automated haematology analyzer, Hematocrit upon presentation was measured. Patients were followed throughout their hospital stay for the development of DHF and DSS. Patients were split into two groups: those with DF were in Group-I, i.e. group with patients without warning signs, and those with DHF and DSS were in Group-II, i.e. group containing patients with warning signs and/or complications.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Median and interquartile ranges were reported for quantitative variables and qualitative variables were expressed as frequency and percentages. Independent sample t-test was applied to explore the inferential statistics for normally distributed data. The *p*-value of  $\leq 0.05$  was considered statistically significant. The accuracy of the haematological ratios was characterized and compared using a Receiver Operating Characteristic (ROC) curve. AUC, or the area under the ROC curve, showed how well the marker distinguished between Group-I and Group-II. Hematocrit cut-off value, sensitivity,

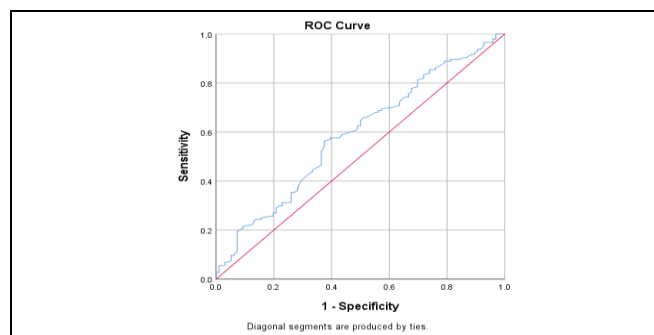
specificity, positive and negative predictive values, and 95% confidence interval were all computed.

**RESULTS**

There were 240 patients, 183(76.2%) of whom were men and 57(23.8%) of whom were women. The median age was 31 years (IQR:21), aged 13-87 years. Ninety-six patients (40%) had classic DF, whereas 136(56.7%) went on to develop DHF, and 8(3.3%) went on to develop DSS. None of the study participants passed away. The median length of stay in the hospital was three days (IQR:1;range: 2-30 days). Hematocrit levels at presentation in Groups 1 and 2 were normally distributed since the Shapiro-Wilk test had a *p*-value of 0.623. The mean hematocrit level upon presentation was  $42.53 \pm 5.24$  %. Hematocrit levels at presentation in patients with Group-I and Group-II are displayed in the Table. Following the ROC curve analysis (Figure), for the cut-off value of 42.6% of hematocrit, Group-II had a sensitivity of 56.25, a specificity of 62.5%, a negative likelihood ratio of 0.70, a positive likelihood ratio of 1.50, a 95% confidence interval of 0.524 to 0.652 at AUC of 0.589 which showed that the discriminative ability of the test was not significant statistically.

**Table: Hematocrit at Presentation of Patients with Classical Dengue Fever, Dengue Hemorrhagic Fever, and Dengue Shock Syndrome (n=240)**

Parameters	Study Groups		<i>p</i> -value
	Group I: Classical Dengue Fever(n=96) Mean (SD)	Group II: Dengue Hemorrhagic Fever and Dengue Shock Syndrome (n=144) Mean(SD)	
Hematocrit Levels(%)	41.49 $\pm$ 5.06	43.23 $\pm$ 5.27	0.012



**Figure: ROC Curve Analysis for the Hematocrit levels**

**DISCUSSION**

Our study showed that the mean hematocrit level at presentation for all the dengue patients was  $42.53 \pm 5.24$ %. According to studies by Wisanuvej *et al.*<sup>7</sup> Riswari *et al.*<sup>10</sup> Triana *et al.*<sup>12</sup> Sahassananda *et al.*<sup>13</sup>

Nandwani *et al.*<sup>14</sup> Ralapnawa *et al.*<sup>15</sup> Kularatne *et al.*<sup>16</sup> and Adil *et al.*<sup>17</sup> DF patients had hematocrit levels of 41.6%, 41.5%, 40.3%, 40.3%, 39.01%, 42.9%, 39.69%, and 41% respectively. Thus, the mean hematocrit level observed in our study corresponds to the mean hematocrit levels reported by different regional studies.

Using the ROC curve for the checking validity of hematocrit to differentiate between Group-I (uncomplicated DF) and Group-II (DF with complications), the calculated cut-off value was 42.6%, which, however, did not have a statistically significant value of area under the curve (0.589). There are very few other studies in recent times,<sup>18</sup> that have tried to estimate the predictive ability of hematocrit in differentiating Group-I and Group-II patients as defined by us in this study. Pongpan *et al.*<sup>19</sup> favoured our assumption and suggested that a hematocrit value of  $\geq 40\%$  (OR=1.34, 95% CI=1.10-1.64,  $p=0.003$ ) is a significant clinical predictor of DF severity.

Fluid leakage through the blood arteries induces plasma concentration, which increases haemoglobin weight in a unit volume of blood. It can be used to explain why patients with DHF and DSS have much higher hematocrit levels during the acute phase. Hematocrit value is anticipated to increase when plasma leaks through blood capillaries. Thus, an increase in the hematocrit can be considered evidence of increased vascular permeability, plasma leakage, and higher gravity of DF. Hemoconcentration with an increase of 20% or more in the hematocrit is generally considered definitive evidence of plasma leakage. Traditionally, in clinical practice, a change of 10% in the hematocrit value usually signals the need for the proper therapy of dengue patients. Our study was designed to look at the utility of hematocrit levels at the presentation to assess the severity of dengue infection. It has been shown that hematocrit levels at presentation are significantly higher in patients who develop DHF and DSS.

### LIMITATIONS OF STUDY

The exclusion of the juvenile population, and the use of automated haematology analyzers to calculate haematocrit were major limitations. Large multicenter studies could be designed to evaluate the various haematological and biochemical parameters on admission to forecast the development of DHF and DSS.

### CONCLUSION

Individuals with greater hematocrits upon presentation need close monitoring for the development of plasma leakage. This policy can be very useful for resource-poor

settings where resources can be diverted to other patients who are more likely to develop DHS and DSS.

**Conflict of Interest:** None.

### Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MF & SBA: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

FA & FR: Concept, study design, drafting the manuscript, data interpretation, approval of the final version to be published.

SA & FUR: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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