

## Evaluation of Neutrophil-lymphocyte Ratio as a Predictor of Complications in Dengue Infection

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### Abstract

**Introduction:** Dengue is an endemic infection in Bangladesh with frequent outbreaks. Severe dengue including dengue shock syndrome (DSS), severe haemorrhage and expanded dengue syndrome (EDS), is the major contributor of morbidity and mortality in dengue infection. This study aimed to assess the association of neutrophil-lymphocyte ratio (NLR) with severe dengue, DHF, DSS, severe haemorrhage and EDS in dengue fever.

**Methods:** This prospective study was conducted on 250 randomly selected dengue patients admitted under the Department of Medicine in Shaheed Monsur Ali Medical College Hospital, Dhaka, Bangladesh from July to December 2023. The study participants were divided into two groups – with  $NLR \geq 2$  and  $NLR < 2$ , on the third day of fever. Frequencies severe dengue, dengue haemorrhagic fever (DHF), DSS, severe haemorrhage and EDS were compared between the two groups.

**Results:**  $NLR \geq 2$  on the third day of fever was associated with a statistically significant higher frequency of DHF, DSS, EDS and severe dengue.

**Conclusion:** NLR can be used as a predictor of complications in dengue infection. Dengue patients with  $NLR \geq 2$  on the third day of fever possess a higher risk of developing complications, and hence need close monitoring.

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## Introduction

Dengue infection is reported in 125 countries across the globe, affecting approximately 400 million people with 40,000 deaths annually.<sup>1</sup> Nearly half of the dengue infections occur in South Asia.<sup>2</sup> Dengue fever is an endemic infection in Bangladesh with frequent outbreaks. Since 2008, 82% of outbreaks have occurred between July and November.<sup>3</sup> The 2023 dengue outbreak was the biggest one in Bangladesh with 2,77,801 cases and 1393 deaths (mortality rate 0.5%).<sup>4</sup>

Major causes of death in dengue infection is severe dengue that includes severe haemorrhage, dengue shock syndrome (DSS) and expanded dengue syndrome (EDS) with major organ damage (myocarditis, acute hepatic failure and encephalitis). Total count of WBC <5,000/cumm and platelet <1,00,000/cumm are regarded as high risk of dengue haemorrhagic fever (DHF) and subsequent DSS.<sup>5</sup>

Recent studies have identified the neutrophil-lymphocyte ratio as a predictor of severe dengue. Both high and low NLR were found to be associated with poor outcomes in different studies.<sup>5-9</sup> However, there is no published study in Bangladesh on the prognostic value of NLR in dengue infection.

### Objective

This study aimed to find the association of NLR with DHF, DSS, severe haemorrhage, EDS and severe dengue in dengue infection.

### Methods

This prospective study was conducted on 250 randomly selected patients admitted under the Department of Medicine of Shaheed Monsur Ali Medical College Hospital, Dhaka, Bangladesh from July to December 2023.

Confirmed cases of dengue infection with positive NS1 antigen and/or Anti-Dengue

IgM tests,<sup>10</sup> admitted in the hospital within five days of fever onset were included as study participants, after taking their informed consent. Dengue patients found to have DHF, DSS, haemorrhagic manifestations or EDS on admission were excluded from the study. Dengue patients with co-infections, pregnancy or comorbidities like ischaemic heart disease, heart failure, chronic kidney disease and chronic liver disease, and on any hepatotoxic or nephrotoxic drugs were also excluded.

A complete blood count (CBC) report on day three of all participants was collected. The third day was chosen as the majority of the participants were admitted from the third day of fever onwards, and hence the data on the first two days were not readily available. The neutrophil-lymphocyte ratio was calculated from the CBC. Development of DHF, DSS, severe haemorrhage, EDS and severe dengue was recorded.

DHF was defined as dengue infection with one or more of: 1. Pleural effusion, 2. Ascites and 3. Rise of haematocrit by 20% of baseline<sup>10</sup>. DSS was defined as dengue infection any of: 1. Narrow pulse pressure ( $\leq 20$  mmHg), 2. Systolic blood pressure (SBP) <90 mmHg and/or diastolic blood pressure (DBP) <60 mmHg with low volume pulse and/or cold extremities and 3. Unrecordable blood pressure.<sup>10</sup> Severe haemorrhage (Dengue fever with haemorrhage - DFH) was defined as a significant haemorrhage assessed by the clinician,<sup>10</sup> Dengue infections with organ involvement, that did not fall into the categories of DHF or DSS were termed as EDS,<sup>11</sup> Severe dengue (SD) was defined as dengue infections with any of 1. DSS, 2. Severe haemorrhage, 3. Severe organ dysfunction (SGPT>1000 U/L, encephalopathy, myocarditis, acute kidney injury, pancreatitis or cholecystitis).<sup>10</sup> Participants who did not

develop any of DHF, DSS, DFH or EDS were termed as dengue fever (DF).

The study participants were divided into two groups based on NLR on the third day of fever. Participants with  $NLR \geq 2$  and  $NLR < 2$  were categorized into group A and group B, respectively. NLR 2 was taken as the cut-off value as used in the majority of the previous studies.<sup>5-9</sup> The frequencies of DHF, DSS, DFH, EDS and severe dengue were compared between the two groups, using relative risk to assess the association. The quantitative variables were expressed in terms of median and interquartile range (IQR) due to the skewness of data, and compared with Mann-Whitney *U* test. The qualitative variables were compared with Chi-square test or Fisher's exact test, as appropriate. A p-value  $< 0.05$  was considered as significant. Statistical Package for the Social Sciences

(SPSS) version 26.0 and Microsoft Excel were used for statistical analyses.

#### *Ethical consideration*

The study was conducted with the formal approval of the Institutional Ethical Review Board (IERB) of Shaheed Monsur Ali Medical College Hospital (Ref: SMAMC/04/2023/1789, dated 04/10/2023). Informed written consent was taken from every study participant.

#### **Results**

A total of 250 study participants were included in the study, 148 (59.2%) were males, and 102 (40.8%) were females. The median (IQR) age of the study subjects was 30(24-40) years, the youngest and the oldest being 13 and 75 years of age, respectively. A detailed age distribution is shown in Figure 1.

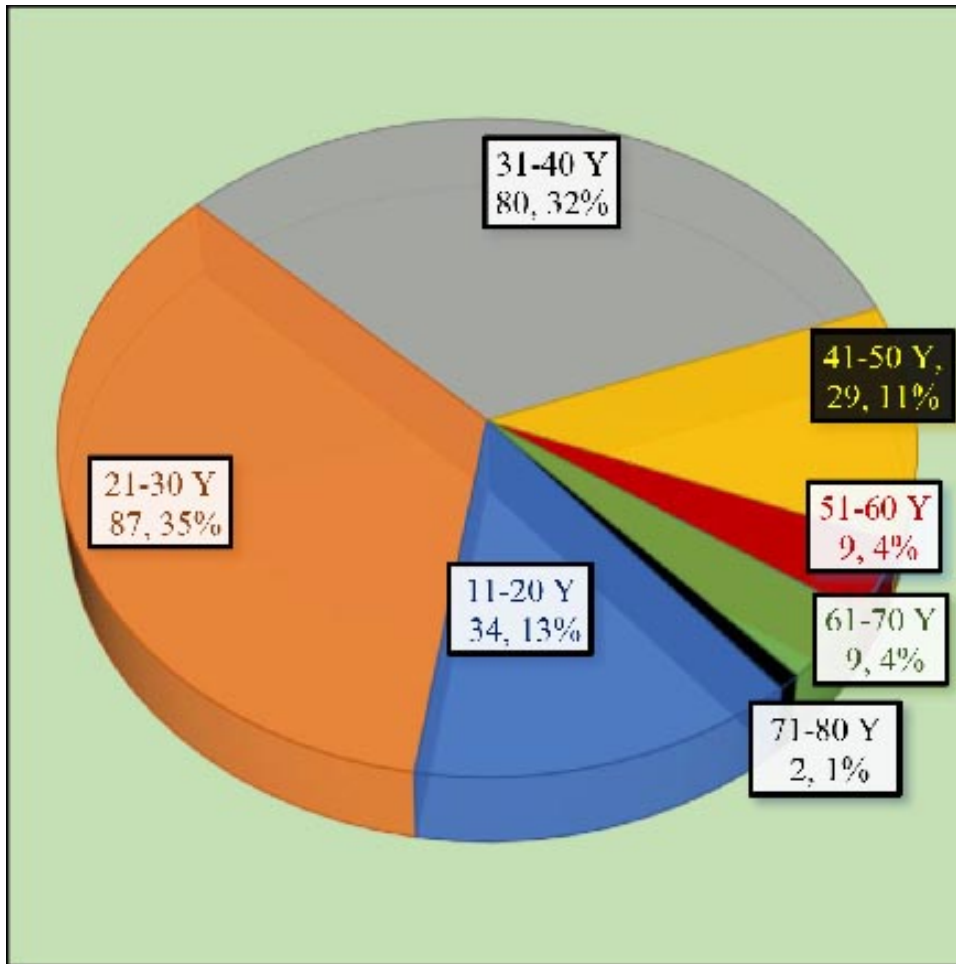


Figure 1. Age distribution of the study participants (n=250).

The highest and lowest total count of WBC was 1,700/cumm and 12,700/cumm, respectively, with a Median (IQR) of 3400(2700-3900)/cumm. The median(IQR) of NLR was 2.7(1.5-5.2), with the range of 0.4-14.7.

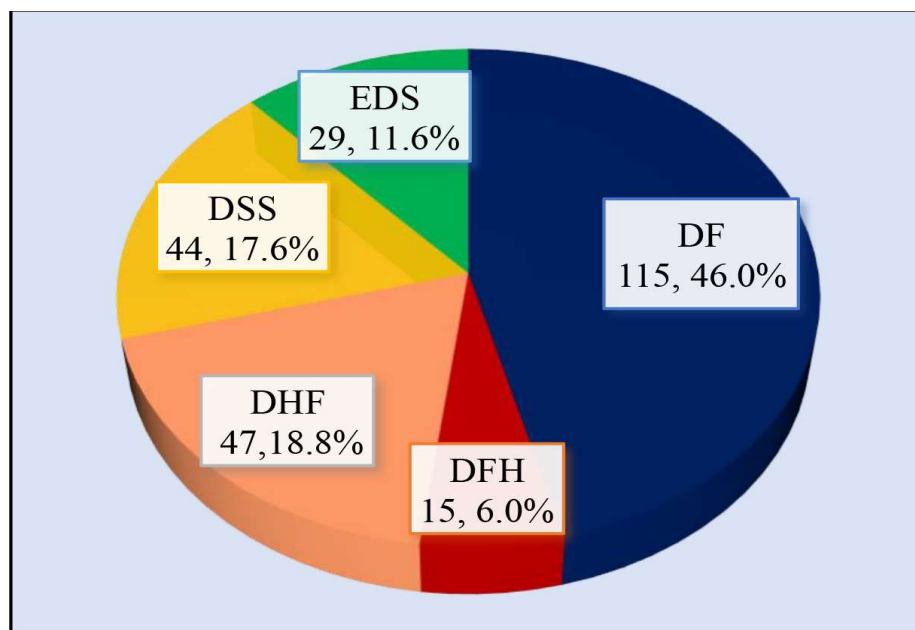


Figure 2. Distribution of clinical subtypes of dengue infection in the participants (n=250). DF –Uncomplicated dengue fever, DHF – Dengue haemorrhagic fever without shock, DSS – Dengue shock syndrome, DFH – Dengue infection with severe haemorrhage, EDS – Expanded dengue syndrome.

Figure 2 shows the distribution of clinical subtypes of dengue infection among the participants. Among 250 study participants, 115(46.0%) fell into the uncomplicated dengue fever (DF) category. DHF occurred in 91(36.4%), among whom 44(48.4% of DHF and 17.6% of total) developed DSS subsequently. DFH developed in 15 (6.0%) participants, none leading to DSS. Eighty (32.0%) study participants developed major organ involvement. Among these 80 cases 47, 24 and 4 fell in the categories of DHF, DSS and DFH, respectively. That made the number of EDS cases 29 (11.6%). Severe dengue (SD) was found in 84(33.6%) participants. No mortality occurred among the study participants.

The median (IQR) age of group A was 30(23-39) years and group B was 32(25-40) years. The number of males and females in group A and group B were 97(57.7%) and 71(42.3%); and 51(62.2%) and 31(37.8%), respectively. There was no statistically significant difference in age and gender distribution between the two groups (Table I).

Table I: Age and gender distribution in the two groups

Category	Total (n=250)	Group A (n1=168)	Group B (n2=82)	p-Value
Age (Years) <sup>1</sup>	30(24-40)	30(23-39)	32(25-40)	0.5 <sup>a</sup>
Gender <sup>2</sup>				
▪ Male	148(59.2)	97 (57.7)	51 (62.2)	0.5 <sup>b</sup>
▪ Female	102 (40.8)	71 (42.3)	31 (37.8)	
1– Median (Inter-quartile range)			Mann-Whitney U test – a	
2– n(%)			Chi-square test – b	

Table II compares the frequency of complications between the two groups. The frequency of DF, DHF, DSS, DFH and EDS in group A was 63(37.5%), 69(41.1%), 34(20.2%), 11(6.6%) and 25(14.8%), respectively. In group B; DF, DHF, DSS, DFH and EDS were found in 52(63.4%), 22(26.8%), 10(12.1%), 4(4.9%) and 4(4.9%) participants, respectively. Group A showed a higher frequency of DHF, DSS and EDS (relative risk 1.8, 2.2 and 2.1, respectively) which was statistically significant (p-value<0.01, 0.02 and 0.02, respectively). Severe dengue (SD) was also more frequent in group A (relative risk 1.7, p-value <0.01). The frequency of severe haemorrhage (DFH) was slightly higher in group A (relative risk 1.3), but this was not statistically significant.

Table II: Comparison of frequencies of complications between the two groups

Category	Total (n=250)	Group A (n1=168)	Group B (n2=82)	RR <sup>1</sup>	95% CI	p-value
DF <sup>2</sup>	115 (46.0)	63 (37.5)	52 (63.4)			
DHF <sup>2</sup>	91 (36.4)	69 (41.1)	22 (26.8)	1.8	1.2-2.6	<0.01 <sup>a</sup>
DSS <sup>2</sup>	44 (17.6)	34 (20.2)	10 (12.2)	2.2	1.2-4.0	0.02 <sup>a</sup>
DFH <sup>2</sup>	15 (6.0)	11 (6.6)	4 (4.9)	1.3	0.5-4.1	0.88 <sup>b</sup>
EDS <sup>2</sup>	29 (11.6)	25 (14.8)	4 (4.9)	2.1	1.1-8.5	0.02 <sup>b</sup>
SD <sup>2</sup>	84 (33.6)	63 (37.5)	21 (26)	1.7	1.2-2.6	<0.01 <sup>a</sup>

1 - Relative risk  
2— n(%)

Chi-square test – a Fisher's exact test – b

## Discussion

This prospective study was conducted on 250 hospital-admitted dengue patients of both genders, covering a wide range of ages. The study participants were 59.2% males and 40.8% females with 67% within the 21-40 years age group. A recent study in Dhaka, Bangladesh found similar gender and age distribution in dengue.<sup>12</sup>

Complications occurred in 54% of study participants, while 46 % went uneventful. This is consistent with the findings of a study on 542 hospital-admitted dengue patients in Dhaka, Bangladesh during the 2019 outbreak.<sup>12</sup> Dengue haemorrhagic fever was developed in 36.4% of participants, which is similar to that found by Rahman et al.<sup>13</sup>

25% frequency of DSS was found among 747 dengue cases admitted in a tertiary level teaching hospital in Dhaka, Bangladesh in 2019.<sup>14</sup> An Indian study reported a 30% incidence of DSS<sup>15</sup>. DSS developed in 17.6% of participants in this study.

EDS was found in 11.6% of participants. A recent study in Brazil found a 15% frequency of EDS.<sup>16</sup> Severe dengue was found in 33.6% of participants. A recent study in a government teaching hospital in Dhaka found a 64% frequency of severe dengue.<sup>17</sup> The majority of the complicated cases from the primary and secondary level hospitals are referred to the government tertiary level hospitals. This fact may be the reason for the relatively lower frequency of severe dengue in this study.

Severe haemorrhage was found in a small number of cases (6%) in this study, which is lower than that observed in 2019 in Jharkhand, India<sup>18</sup> The downward trend of bleeding manifestations in dengue fever since the first outbreak in 2001 might explain this difference.<sup>12</sup>

There were contradictory results among different studies on the prognostic value of NLR in dengue infection. Most of the recent studies found a lower NLR associated with poor outcomes in dengue infection.<sup>5-8</sup> One

study indirectly concluded  $\text{NLR} \geq 2$  as a bad prognostic indicator.<sup>9</sup> A neutrophil-lymphocyte ratio  $\geq 2$  was associated with a higher frequency of DHF, DSS, EDS and severe dengue in the participants of this study. The results of this study bring a new insight into the prognostic value of NLR in dengue infection.

### Limitations

Acute kidney injury (AKI) was diagnosed on the basis of serum creatinine only, without using urine volume criteria. That might have underscored the frequency of AKI, with subsequent lower frequency of EDS and severe dengue.

### Conclusion

NLR can be used as a predictor of complications in dengue infection. Dengue patients with  $\text{NLR} \geq 2$  on the third day of fever possess a higher risk of developing severe dengue, DHF, DSS, EDS and severe dengue. These patients should receive strict monitoring at the hospital and be discharged after complete recovery.

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