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Evaluating Relationship between Platelet Count, Leukocytes and Platelet Indices in Dengue Fever in a Tertiary Care Hospital in Bangladesh: A Retrospective Study

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Abstract

Dengue fever is public health concerns in Bangladesh, where it occurs in epidemics and has a high mortality in the advanced stages. Clinical features are nonspecific and diagnosis is supported by lab features. Common lab tests include Platelet count, leucocyte count and platelet indices are useful in small rural set ups for early diagnosis and prognosis of dengue. The aim of this study is to evaluate relationship between platelet count, leukocytes and platelet indices. This retrospective cross-sectional study was conducted at Department of Laboratory Medicine in collaboration with Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2019 to September 2019. Clinical records of 260 cases were preserved in a structured Clinical Record Form (CRF). Only those, with antigen/antibody supported cases was enrolled in the study. Mean neutrophil (%), mean lymphocyte (%) and mean eosinophil (%) count were statistically significant difference among different platelet count groups ($p<0.05$). There was significant negative correlation between PDW and platelet count ($r= -0.228$, $p<0.001$). MPV was also negatively correlated with platelet count but not significant ($r= -0.106$, $p= 0.088$). Beside Platelet count and leukocyte count, Platelet indices such as PDW and MPV are also useful to monitor dengue fever.

Keywords: Dengue Fever, Platelet count, Leukocyte, Platelet Indices.

1. INTRODUCTION

Dengue is emerging as a serious public health problem globally. It is estimated to occur annually in over 100 endemic countries, putting almost half of the world's population at risk [1, 2]. The incidence and geographical distribution of dengue infections have significantly increased in the past few decades and a large number of cases remain undiagnosed and underreported. The overall incidence of dengue having increased 30-fold over the past 50 years [3]. Most of the cases are reported from Southeast Asia and the western Pacific regions. Southeast Asian region together with Western Pacific region bears nearly 75% of current global disease burden [4]. Dengue fever is the most common arthropod borne disease caused by dengue virus. It is a vector borne arboviral disease transmitted by predominantly by Aedes aegypti and Aedes albopictus mosquito. Man and mosquito are reservoir of the infection [5]. Increases in the incidence of dengue outbreaks are seen during the monsoon and post-monsoon seasons. Children and young adults are the population that are most affected [6]. Early, accurate diagnosis and an accurate assessment of the stage and condition of the patient are very important factors in determining the patient's prognosis. The more severe the patient's disease, the worse the prognosis [7, 8]. Bleeding is usually caused by thrombocytopaty and thrombocytopenia, therefore it is necessary to check

platelets [9]. World Health Orgnization (WHO) criterion for clinical degree of dengue do not provide a definite value from the results of the examination of platelets, hematocrit and leukocytes for each clinical degree. The medical staff determines the degree of the clinic only based on clinical signs and symptoms, even though the examination of platelets, hematocrit and leukocytes plays an important role in helping diagnose dengue, especially if there is a plasma leak which can trigger shock [10]. One of the most common laboratory findings in dengue is thrombocytopenia [11]. The complex mechanism of thrombocytopenia remains unclear. Possible mechanisms of thrombocytopenia could be, direct bone marrow suppression by the virus; antidengue antibody-mediated platelet destruction, peripheral consumption of platelets and isolated viral replication in the platelet. Recently, novel platelet indices such as Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Platelet to Large Cell Ratio (PLCR) have been investigated as prospective platelet activation markers [12]. Platelet volume, a marker of platelet function and activity is measured as mean platelet volume (MPV) by hematology analyzers. MPV can be used as independent predictors of bleeding. It is surrogate marker of bone marrow activity; a high MPV indicates increased megakaryocyte activity. A low MPV indicates marrow suppression and increased risk of bleeding. Correlation of platelet count and MPV with bleeding and severity of the disease can potentially predict outcome [13]. PDW directly measures variability in platelet size, changes with platelet activation, and reflects the heterogeneity in platelet morphology. It is an indicator of platelet anisocytosis. PDW is increased in the presence of platelet anisocytosis. There is a direct relation between MPV and PDW, that is, a high PDW is associated with a high MPV [14]. Leucopenia, defined as total leucocyte count $<4x10^9$ /l is a prominent and supposedly the second most common feature in dengue [15, 16]. It gives enough clue for diagnosis of Dengue and helps in differentiation from other febrile illnesses thus aiding in reducing its morbidity and mortality [17-19]. Some studies have observed that total leucocyte counts/leucopenia could serve as a prognostic factor for dengue severity while others dispute it [20-27]. A few studies have observed that there is a progressive decline in white cell counts with sudden platelet drop which precedes plasma leakage and hence it could be the earliest prognosticator of severe dengue [28]. Our study focuses on the significance and patterns of one such simple, routine test the total white cell count in diagnosis of dengue. Based on this data, the study aimed to see the relationship between the examination of the platelet, leukocytes and platelet indices in dengue fever.

2. MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at Department of Laboratory Medicine in collaboration with Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2019 to September 2019. Patients admitted in the dengue cell of BSMMU in the year 2019 from July to September was comprised our study population. Among them, clinical records of 260 cases were preserved in a structured Clinical Record Form (CRF). Only those, with antigen/antibody supported cases was enrolled in the study. A structured CRF was maintained during the management of dengue cases admitted in dengue cell BSMMU during 2019 outbreak. This CRF contains socio-demography, clinical presentation, laboratory reports and management given during that period. Dengue cases were diagnosed as per diagnostic criteria given by the National guideline of management of dengue fever. Severity of illness were categorized accordingly. Disease complications were noted and management given was directed by following the National guideline. After ethical clearance from Institutional Review Board (IRB), form clinical records of 260 cases which are preserved in a structured CRF patients who fulfilled the inclusion and exclusion criteria was selected as study population. All dengue cases with antigen/antibody confirmation was included in this study. Cases with incomplete data was discarded from the analysis. In this study patient's complete blood counts were measured by haematology auto analyzer Sysmex XN-2000, rechecked manually in the Department of Laboratory Medicine, BSMMU. Statistical analysis were carried out by using the Statistical Package for Social Sciences version 26.0. The mean values were calculated for continuous variables. ANOVA test was used to compare the groups and Pearsons's correlation co-efficient test was done to assess the relationship.

3. RESULTS

This retrospective cross-sectional study was carried out to explore platelet indices in Dengue Fever. From clinical records of 260 cases were analyzed. Table-1 shows the age distribution of the patients among five platelet groups. Out of 206 patients, maximum cases 76(36.9%) of the patients platelet range 51,000 to 1,0000, 73(35.4%) patients within 1,0000 to 1,50000, 64(31.1%) platelet group more than 1,50000, 35(17.0%) patients had 21,000 to 50,000 and minimum percentage 12(5.8%) in platelet count less than 20,000. The mean age of the patients among five platelet groups were not statistically difference.

Table-1: Comparison of age among different platelet groups of the study patients (N=260)

Age group (years)	Platelet					p-value
	<20 (n=12) No. (%)	**21-50 (n=35) No. (%)**	**51-1 lac (n=76) No. (%)**	**1-1.5 lac (n=73) No. (%)**	**>1.5 lac (n=64) No. (%)**	
<20	2(16.7%)	8(22.9%)	22(28.9%)	23(31.5%)	19(29.7%)	
21-30	4(33.3%)	11(31.4%)	23(30.3%)	22(30.1%)	25(39.1%)	
31-40	3(25.0%)	6(17.1%)	13(17.1%)	17(23.3%)	11(17.2%)	
41-50	1(8.3%)	5(14.3%)	12(15.8%)	5(6.8%)	5(7.8%)	
51-60	1(8.3%)	3(8.6%)	3(3.9%)	4(5.5%)	2(3.1%)	
>60	1(8.3%)	2(5.7%)	3(3.9%)	2(2.7%)	2(3.1%)	
Total	12(100.0%)	35(100.0%)	76(100.0%)	73(100.0%)	64(100.0%)	
Mean±SD	35.8±15.6	31.9±16.8	30.8±15.4	28.9±14.8	27.5±13.2	0.333^{ns}

Data were expressed as frequency and percentage and mean±SD, ANOVA test was performed to compare among groups
ns = not significant

Table-2 shows the sex distribution on basis of platelet count. Maximum patients 171(65.8%) were male and rest 89(34.2%) were female. The prevalence was found to be high in males. No significant difference of sex among different platelet indices (p>0.05).

Table-2: Association of sex among different platelet type of the study patients (N=260)

Sex	Platelet					p-value
	<20 (n=12) No. (%)	**21-50 (n=35) No. (%)**	**51-1 lac (n=76) No. (%)**	**1-1.5 lac (n=73) No. (%)**	**>1.5 lac (n=64) No. (%)**	
Male	7(58.3%)	24(68.6%)	49(64.5%)	44(60.3%)	47(73.4%)	0.537^{ns}
Female	5(41.7%)	11(31.4%)	27(35.5%)	29(39.7%)	17(26.6%)	
Total	12(100.0%)	35(100.0%)	76(100.0%)	73(100.0%)	64(100.0%)	

Figures in the parentheses indicate corresponding percentage, Chi-squared Test (χ^2) was done to analyze the data,
ns = not significant

Table-3 showed the comparison of differential platelet count and total and differential count (%) of leukocytes, platelet indices. Mean neutrophil (%), mean lymphocyte (%) and mean eosinophil (%) count were statistically significant difference among different platelet count groups (p<0.05). Platelet indices such as MPV and PDW were statistically significant difference (p<0.05).

Table-3: Comparison of differential count among different platelet type of the study patients (n=260)

Differential count	Platelet					p-value
	<20 (n=12) Mean±SD	21-50 (n=35) Mean±SD	51-1 lac (n=76) Mean±SD	1-1.5 lac (n=73) Mean±SD	>1.5 lac (n=64) Mean±SD	
WBC count	6.25±2.41	8.24±3.27	6.69±4.07	6.51±3.39	6.36±2.68	0.086^{ns}
Neutrophil(%)	52.33±9.91	42.94±13.68	50.61±16.80	50.40 ±16.14	54.25±13.99	0.015^{s}
Lymphocyte(%)	40.42±9.80	51.37±14.03	43.83±16.02	42.77±15.66	38.05±12.91	0.001^{s}
Monocyte (%)	4.92±2.19	3.94±2.14	3.58±2.05	3.96±1.87	4.44±2.14	0.074^{ns}
Eosinophil (%)	2.33±2.02	1.83±1.10	1.99±1.92	2.88±3.37	3.27±3.73	0.038^{s}
Neut : Lymp ratio	1.44±0.71	1.02±0.72	2.18±4.52	1.57±1.24	1.87±1.65	0.276
MPV	11.75±1.72	11.10±1.61	11.82±1.62	11.78±1.32	11.01±1.31	0.003^{ns}
PDW	67.80±17.82	64.59±11.33	62.48±12.70	61.32±6.68	57.63±7.49	0.002^{s}

Data were expressed as mean±SD, ANOVA test was performed to compare among groups, s= significant, ns = not significant

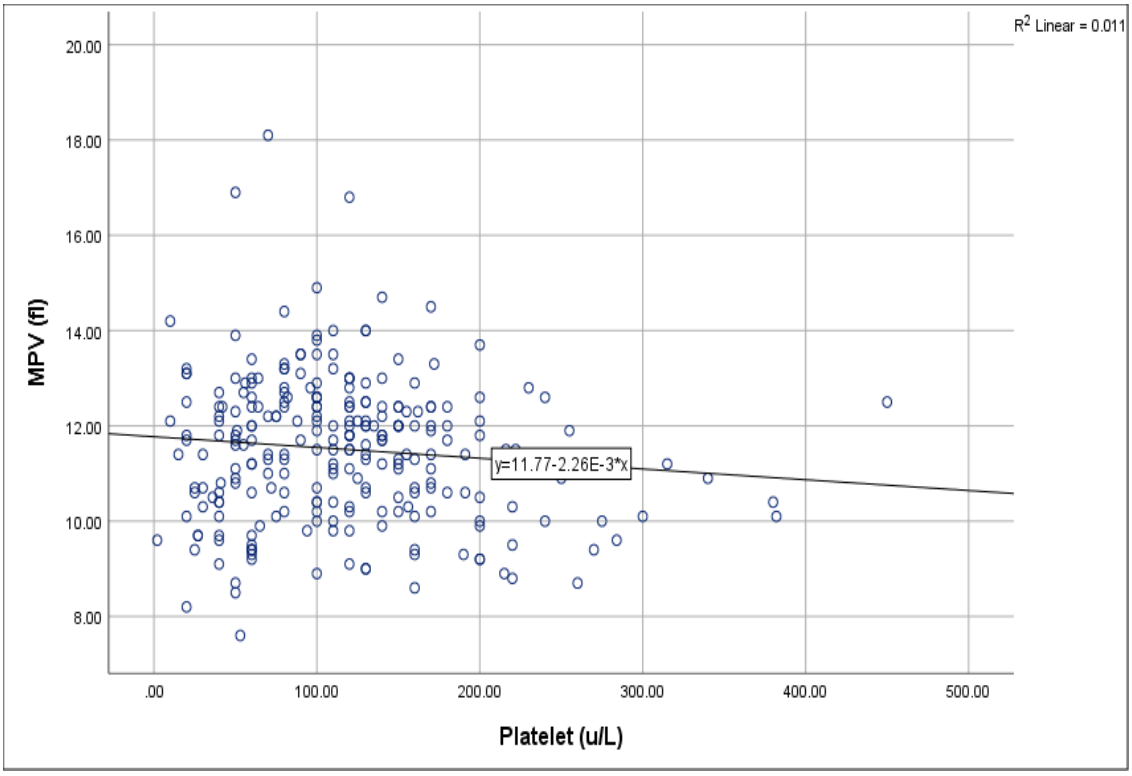

Figure-1: Shows that there was negative correlation between platelet and MPV (r= -0.106). It was observed that the Pearsons's correlation was not statistically significant (p= 0.088)

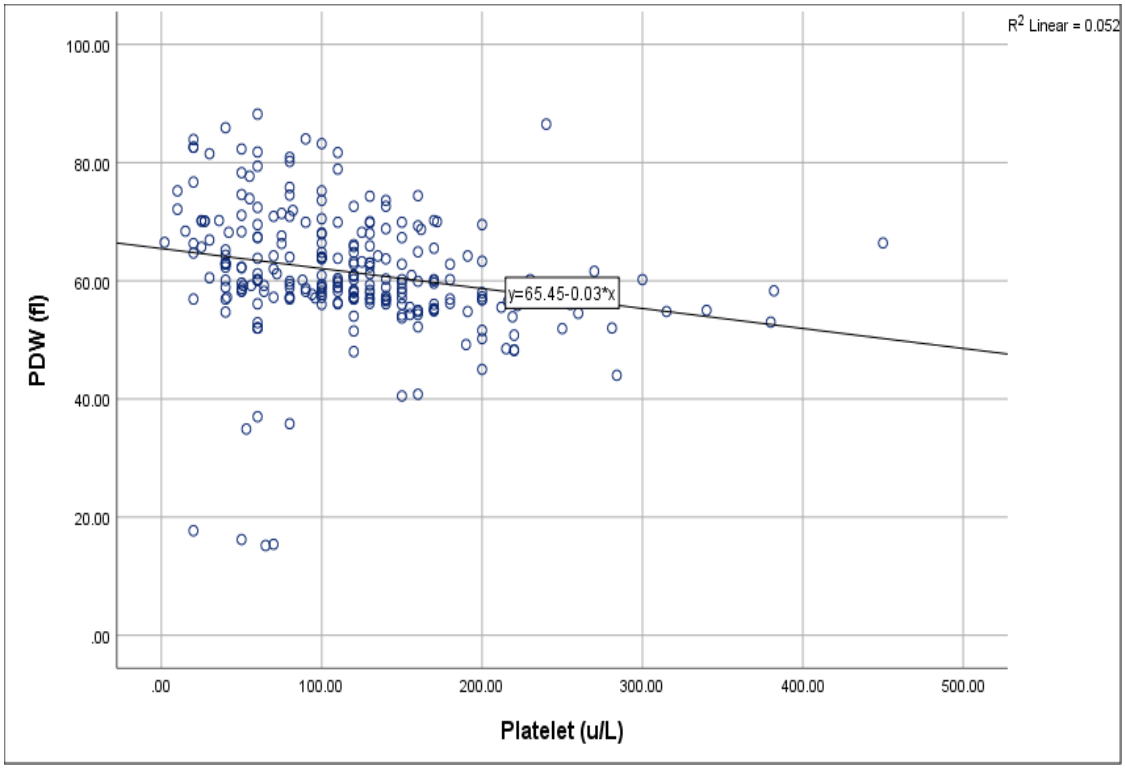

Figure-2: Shows that there was negative correlation between platelet and PDW (r= -0.228). It was observed that the Pearsons's correlation was statistically significant (p <0.001)

4. DISCUSSION

Our study analyzing age was in consistent with others with most cases in the younger ages with male predominance probably due to occupational exposure and increased recreational activity in men. In present study, comparison of differential platelet count and total and differential count (%) of leukocytes, platelet indices were done. Mean neutrophil (%), mean lymphocyte (%)

and mean eosinophil (%) count were statistically significant difference among different platelet count groups ($p<0.05$). A few studies of the total and differential leucocyte count patterns have observed mild initial leucocytosis accompanied by neutrophilia followed later by leucopenia and lymphocytosis with atypical lymphocytes [20, 27]. These results are consistent with our study. Leucopenia is caused by bone marrow suppression by virus in acute phase and is due to decrease in polymorphs [16, 19, 25, 29, 30]. Neutropenia is also attributed to marked degeneration of mature neutrophils in febrile phase with shift to left [26]. Stress accompanied with shock may be the cause of mild initial leukocytosis [20]. One of the theories implicated in the causation of thrombocytopenia is the viral induction of bone marrow hypoplasia by affecting the bone marrow progenitor cells. A significant derangement in the plasma-kinin system, disseminated intravascular coagulation, increased apoptosis resulting in platelet destruction, lysis by the complement system and the formation of anti-platelet antibodies are crucial factors [31]. In addition, direct infection of megakaryocytes by dengue virus could lead to an increased destruction of platelets [32]. Platelets are involved in hemostasis, tissue repairing, and infection. To our knowledge, there are only few studies investigating changes in platelet indices during dengue infection. In this study, it was found that there was significant negative correlation between platelet count and PDW ($r=-0.228$, $p<0.001$). A recent study reported that significant negative correlation between platelet count and PDW ($r=-0.267$, $p<0.001$) [33]. Another study found similar result ($r=-0.3097$, $p=0.0017$) [34]. These results were consistent with our result. It was reported that platelet count was negatively correlated with MPV ($r=-0.106$) which was not statistically significant ($p=0.088$). A previous study also found no signifant correlation between platelet count and MPV which was consistent with our study [35]. Another study found significant negative correlation between platelet count and MPV ($r=-0.247$, $p=0.004$) [33]. MPV has been evaluated as a diagnostic tool in different conditions with thrombocytopenia with contradictory results. It has been demonstrated that MPV has sufficient sensitivity and specificity to discriminate aplastic anemia, bone marrow disease, hypoproductive thrombocytopenia, and bone marrow metastasis of solid tumor [13, 36, 37]. However, it has been reported that although MPV may be used as an initial suggestion of bone marrow disease in thrombocytopenic patient, it has limited sensitivity and specificity [38]. Serially observing the MPV and platelets may guide a clinician in an important subset of patients in DF and severe dengue where the mechanism of thrombocytopenia is largely marrow suppression-initial MPV significantly low and the thrombocytopenia recovery following the MPV. Increased MPV indicates increased platelet diameter, which can be used as a marker of production rate and platelet activation. During activation, platelets' shapes change from biconcave discs to spherical and a pronounced pseudopod formation occurs that leads to MPV increase during platelet activation [39]. Platelets with increased number and size of pseudopodia differ in size, possibly affecting platelet distribution width (PDW) which increases during platelet activation. PDW is higher in hyper-destructive patients when compared with hypo-productive thrombocytopenic patients. The high PDW in platelet destruction could be explained by the fact that newly produced platelets are larger than circulating platelets, which tend to decrease in size with age in circulation similar to reticulocytes with respect to red blood cells. As a result, in patients with thrombocytopenia secondary to peripheral destruction, the PDW is increased reflecting active bone marrow compensation with the release of young platelets [40]. These platelet indices show sensitivity to dengue fever thus reflecting a predictive marker for diagnosing dengue fever in endemic area.

5. CONCLUSION

Platelet count and leukocyte count are useful parameters in dengue infection. Platelet indices such as PDW and MPV are also useful to monitor dengue fever. Decrease MPV and increase PDW are also significant in thrombocytopenia and Platelet indices plays significant role in early predictive diagnosis and severity of dengue in endemic area.

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