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Original Research Article

TEMPORAL DYNAMICS OF PLATELET INDICES IN DENGUE: FROM ADMISSION TO RECOVERY AND DISCHARGE.

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Abstract

Background: Platelet indices such as platelet distribution width, mean platelet volume and platelecrit are the chief platelet related parameters besides platelet counts, that have been utilized as prognostic and diagnostic markers in the study of acute febrile illnesses associated with thrombocytopenia. The aim is to evaluate the role of platelet indices in dengue patients and their variation in the natural history of the disease. **Materials and Methods:** This observational hospital-based study evaluated the platelet indices of 186 dengue patients at the time of admission, clinical recovery and discharge. Patients were categorized into groups having different grades of thrombocytopenia and serial platelet indices in different groups was studied over the course of hospitalization. **Result:** Platelet count improved significantly from admission to discharge (P<0.001). The MPV and plateletcrit also increased significantly at the discharge compared to the admission levels (P<0.001). The PDW was seen to increase from 16.83fL to 17.47fL (P<0.0001) during the admission to discharge period. Platelet count was positively correlated with the mean platelet volume (R=0.20, P=0.0068) and plateletcrit levels (R=0.94, P<0.0001). Admission values of MPV and Plateletcrit were significantly lower and PDW were significantly high in patients with lowest platelet counts (less than twenty thousand/mm3) compared to patients with platelet counts>1lakh/mm3. **Conclusion:** Monitoring of platelet indices provides additional insight in early prediction of the severity of disease in terms of degree of imminent thrombocytopenia.

INTRODUCTION

Dengue fever is caused by Flavivirus transmitted by mosquitos occurring mainly in people living in subtropical and tropical regions of the world. Most of the cases have been reported from South-east Asian, American, Western Pacific regions, with Asia accounting for over 70% of the burden.[1] As an acute illness, it generally presents as a fever that lasts for 3 to 5 days, associated with excessive headache, muscle pain, retro-orbital pain, pain in joints, decreased appetite as well as a rash.[2] Patients with dengue are categorized into three severity groups as per the WHO classification of 2009, dengue fever that is accompanied by warning signs (abdominal pain, nausea, and recurrent vomiting, generalized body swelling, mucosal bleeding, tiredness, liver enlargement, rising PCV, etc), dengue not accompanied by warning signs, and severe dengue.[3]

The severity and recovery of dengue infection revolves around the platelet counts. Thrombocytopenia is synonymous with increasing severity of the disease while improved counts indicate recovery from the infection.[4] Besides the numbers, the characteristics of platelets studied as plateletcrit, platelet distribution width and mean platelet volume are also altered in dengue viral infection. These platelet indices are indicators of platelet activation.[5]

Platelet volume is a reflection of platelet activity and function and is acquired as MPV (healthy Indian individual's MPV ranges from 8.60 to 15.50 fL),[6] measured by laboratory hematology auto-analyzers. MPV is also used as an isolated predictor of bleeding and signifies bone marrow activity - low mean platelet volume signifies suppression of bone marrow and a risk of imminent bleeding, whereas a high MPV implies increased megakaryocyte activity. Upon activation, the platelets change their shape from

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biconcave disc to a more spherical structure; pseudopods are formed commonly that further lead to an increased MPV during this process of activation. Studying relationship between parameters like mean platelet volume, platelet levels and severity of illness and complications like bleeding can be utilized to foresee disease outcome.[7] Platelet distribution width (PDW) reflects variability in the platelet size and an increased PDW reflects platelet anisocytosis. The PDW reference range is from 8.3-25.0 fL.[6] PDW measures the variation in platelet volume and size. Changes that occur with activation of platelets imply the morphological diversity in platelets.[5]

Plateletcrit is a measure of total weight of platelets and the range for plateletcrit found in a healthy person is 0.22- 0.24 percent.[8] Plateletcrit is also used to detect quantitative platelet abnormalities. Plateletcrit is the total volume of blood which is occupied by platelets, measured as a percentage and is computed by the equation [plateletcrit equals platelet count multiplied by Mean platelet volume/104].

The current study was undertaken to study the effect of dengue virus infection on qualitative parameters of the platelets at the time of hospitalization, clinical recovery and prior to discharge and compare the indices at the various stages of the natural history of the disease. The larger aim of the study was to evaluate if these qualitative changes could be used to pre-empt the clinical recovery.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in a tertiary referral centre of north Indian state of Uttarakhand. All adults patients with dengue fever diagnosed on the basis of WHO clinical criteria (1) over a period of 12 months (August 2019 - August 2020) after obtaining an informed written consent from the patients and ethical clearance from the institutional ethics committee. Excluded were those with prior history of thrombocytopenia, patients of cirrhosis or any chronic liver disease, positive diagnostic tests for other etiologies of febrile thrombocytopenia viz. scrub typhus, enteric fever, malaria, etc., evidence of DIC/ sepsis, those with present or past history of malignancy and/ or chemotherapy, and those receiving drugs that affect the platelets viz. aspirin, heparin.

Demographic data, history, clinical examination and details of investigations such as Dengue serology for NS1 antigen, IgM, IgG by Rapid card test and/or IgM using IgM capture ELISA technique, complete hemogram, platelet indices, scrub typhus serology, WIDAL test, malaria by rapid card test, and relevant biochemistry and radiological investigations, etc. were recorded in the case recording forms. Parameters such as day of presentation after the onset of fever, pulse rate, blood pressure, pulse pressure, temperature, evidence of severe symptoms, evidence of capillary leak, bleeding events, etc were recorded at the time of hospital admission. On admission and clinical recovery (defined as defervescence and subsidence of warning symptoms and signs, if present earlier), platelet count and platelet indices were determined by Beckman Coulter LH 750 Analyzer.

Statistical analysis : The data was compiled and analyzed using MS Excel (R) office 365, GraphPad prism 8.4.2 and SPSS version 25. Descriptive statistics were presented as percentages or proportions for categorical variables and mean and standard deviation for continuous data variables. Fisher Exact test/Chi square test was used for the comparison of proportions (Categorical variables). Continuous variables were analyzed using the Mann Whitney test/student T test (Independent group/Unpaired data) and Wilcoxon sign rank test/Paired T test (for paired data) based on the normality of the data. Multigroup comparison for continuous variables like platelet indices and platelet counts was done using repeat measure ANOVA with a mixed effects model (for normally distributed data) or Friedman test for the non-parametric data. Pearson correlation coefficient [R] and coefficient of determination [R2] were calculated for platelet indices with respect to the platelet count and liver function parameters. P value of <0.05 was considered significant.

RESULTS

A total of 186 patients of dengue fever were included in the study. The patients' average age was 39.2 ±15.2 years (median age 35 years; range 15-80 years). There was a male preponderance (n=118; 63.44%) in the study.

The main co-morbidities (n=13) were type 2 diabetes mellitus (n= 4), COPD (n=4) and hypertension (n=3). Two patients had both hypertension and diabetes, whereas 1 patient had CHF and hypothyroidism as comorbidities.

The main presenting complaints were fatigue (n=120, 64.5%) and myalgia (n=74, 39.7%). The average duration of fever at time of presentation was 4.4 days (range 1-15 days). Rash (n=;%), hepatomegaly (n=18, 9.6%) and splenomegaly (n=11, 5.9%) were the most prominent signs.

Bleeding events were reported in 22 (11.8%) patients, in the form of - melena (n=14), gum bleeding (n=2), epistaxis (n=1), hematuria (n=1), whereas four patients reported a combination of hematemesis with epistaxis, hematemesis with gum bleed, hematemesis with melena and melena with epistaxis respectively. Platelets were transfused in 18 patients (9.6%) with major bleeding events during hospital stay.

Anemia (n=40; 21.5%), leucopenia (n=86; 46.2%), leucocytosis (n=7; 3.7%) were seen in patients at presentation The hematocrit was reduced in 36 (19.35%) patients while 12 (6.45%) patients had raised hematocrit at admission. The main haematological parameters and platelet indices at the

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time of hospitalisation and at clinical recovery are shown in [Table 1]. [Table 2] demonstrates the platelet indices as per the platelet counts at the time of admission. [Table 3] depicts correlation of platelet indices with platelet counts at the time of admission.

Table 1: Hematological parameters and platelet indices in dengue patients at the time of admission, on clinical recovery and at the time of discharge

Hematological parameters	Admission (Mean ± SD)	Clinical recovery (Mean ± SD)	Discharge (Mean ± SD)	P Value
TLC Count (x 10^3 /µl)	5.04±3.23	5.65±2.79	6.00±3.04	0.0002
Red blood cell count (x 10^3 /µl)	4.52±0.85	4.30±0.70	4.31±0.66	<0.0001
Hemoglobin(g/dl)	13.55±2.45	12.87±2.02	12.85±1.98	<0.0001
Hematocrit (%)	40.70±7.06	38.73±5.84	38.83±5.57	<0.0001
MCV (in fL)	90.18±8.77	90.02±8.39	89.95±8.25	0.2533
Platelets (x 103 /µl)	52.65±44.56	76.51±42.15	109.41±88.70	<0.0001
MPV (in fL)	10.95±1.60	11.26±1.59	11.42±1.52	<0.0001
Plateletcrit (%)	0.05±0.05	0.08±0.05	0.11±0.06	<0.0001
Platelet distribution width (fL)	16.83±0.99	17.43±1.01	17.47±0.96	<0.0001

Table 2: Platelet count based distribution and platelet indices in dengue patients at admission

Platelet count (x 10^3 /µl) and indices	More than 150 (x 10^3 /µl)	100-150 (x 10^3 /µl)	20-100 (x 10^3 /µl)	Less than 20 (x 10^3 /µl)	P Value
Mean MPV (fL)	9.13±0.96	12.11±1.68	11.26±1.51	9.96±1.05	<0.0001
Mean Plateletcrit (%)	0.17±0.03	0.14±0.02	0.05±0.03	0.01±0.01	<0.0001
Mean PDW (fL)	16.32±0.81	16.72±0.57	16.81±1.08	17.00±0.90	0.0048

Table 3: Platelet count correlation with the platelet indices (at baseline/admission level)

Platelet count correlation with	MPV- Admission	Plateletcrit- Admission	PDW- Admission
Pearson Coefficient	0.2	0.94	-0.12
95% CI	0.056 to 0.33	0.92 to 0.96	-0.26 to 0.020
R squared	0.039	0.89	0.015
P (two-tailed)	0.0068	<0.0001	0.0922

DISCUSSION

The values of platelet indices increased significantly over the course of illness along with an increase in platelet counts. Mean platelet volume (MPV) and plateletcrit (PCT) were positively correlated with the platelet count. Plateletcrit had a correlation coefficient of 0.94 and was the best amongst the indices studied.

The prevalence of thrombocytopenia can be as high has 89% in cases of dengue fever.[9] Several causes for dengue related thrombocytopenia have been hypothesized, including virus-mediated marrow suppression, platelet destruction because of dengue antibodies, platelet depletion peripherally, and isolated viral multiplication in platelets. Newer platelet indices such as the mean platelet volume, platelet distribution width and platelet large cell ratio have lately been employed as markers of activation of platelets.

In our study, the MPV and plateletcrit increased significantly at the time of discharge compared to the admission levels. It was observed that the platelet indices values such as MPV and Plateletcrit were substantially lower in patients with severe thrombocytopenia, while the PDW levels were the highest. Our results are concordant with another study from central India.[10]

A research comparing platelet indices in dengue patients with control group found that the average MPV and platelets were seen to be noticeably lesser in test population compared with control population and mean platelet distribution width was seen to be substantially higher in test category.[11] A study from previous year on dengue patients observed that the mean MPV was 7.28fL and average white cell count was 3446 cells/cumm. The mean platelet volume showed a decreasing trend with reducing platelet counts in dengue fever patients,[12] a finding which resembled our results and which helped in predicting the severity of dengue infection in the study population.

Another team of researchers observed that when the platelet count fell less than 20 thousand/cumm, mean MPV was considerably lower on the previous day (p value < 0.00010) compared to the mean of MPVs of all the patients. Henceforth, they concluded that serial measuring of MPV could be used a reliable tool in pre-empting thrombocytopenia.[13]

A low MPV was reported in more than two thirds of dengue patients by a study from the Indian subcontinent.[14] In another research, it was observed that MPV indicating platelet activation, can be utilized as a marker in severe dengue due to its substantial association with other markers such as PCV, atypical lymphocytosis and thrombocytopenia, and could further help to guide transfusion therapy.[15]

A risk-based study found a positive association between platelet distribution width and mean platelet volume (p= 0.066; r= 0.185), in low-risk (based on the level of thrombocytopenia) group. The moderate-risk group exhibited a negative association between

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MPV and PDW (p= 0.201; r= -0.686).[16] In our study, significantly low MPV and plateletcrit levels and high PDW were observed for the group of patients with the lowest platelet counts (defined as high risk category according to this study).

Similar association of plateletcrit has been observed in children with dengue fever with fluctuating platelet counts.[17]

Other studies have also compared the platelet distribution width (57.0±13.80 vs. 55.40±6.90, p value 0.0010) and mean platelet volume (9.20±0.09 vs. 13.80±1.30fL, p value <0.0010) and various ratios of platelet indices such as the Platelet index (MPVxPDW\PLCxPCT), MPV\PLC, MPV\ Plateletcrit, PDW\PLC and PDW\Plateletcrit in patients with dengue fever with platelet counts < 20 thousand/mm3 or > one lakh/mm3 platelet counts. It was concluded that low platelet counts, low plateletcrit and high PDW could predict severe dengue infection.[18]

Hardeva RN et al compared the platelet counts and the indices in patients with dengue fever, dengue hemorrhagic fever patients and control. Dengue hemorrhagic fever had lower platelet counts (P<0.001) and plateletcrit (<0.016) and higher PDW (P<0.001) compared to dengue fever. High platelet large cell ratio, high platelet distribution width, low plateletcrit and low mean platelet volume were labelled as sensitive and specific pointers for dengue fever in an endemic area. They concluded that low platelet count when combined with low plateletcrit and high platelet distribution width could reliably be used to predict severity of infection.[19]

A few studies concentrated on recovery of thrombocytopenia due to dengue and its effects on the platelet indices. The possible implications of recognizable effects on platelet indices include the reduced need for transfusions and the approach of watchful wait. Low mean platelet volume (<9fL) was found to have a strong association with low platelet count and a rising level of mean platelet volume could indicate an imminent recovery of platelets.[20]

The strength of our study lies in the serial evaluation of the platelet counts and indices during the natural course of the infection. However, there were certain limitations to the present study. The values of platelet indices vary in relation to race, ethnicity, country and gender. Variability may also occur depending upon the auto-analyzers used for their determination. As bleeding manifestations were reported in very few patients, the variation in trends of platelet indices among patients who bled compared with those who did not bleed, could not yield useful results. Being a single centre study, its results may not be replicable on a larger population due to various factors mentioned above.

CONCLUSION

The improvement in platelet counts was accompanied by an unidirectional variation in all the major platelet indices in our study. MPV and plateletcrit were positively correlated with the platelet count at admission. This suggests that plateletcrit and MPV can be used as markers for early identification of likely thrombocytopenia. Therefore, monitoring of platelet indices along with other routine parameters provides an additional insight in early prediction of the severity of disease and disease outcome.

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