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Use of Mean Platelet Volume as a Predictor of Bleeding Risk in Thrombocytopenia

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Abstract: ***Introduction: A low platelet count is commonly encountered in clinical practice. Life threatening haemorrhages are a risk associated with severe thrombocytopenia, though it may not be seen in all such patients. Hence, there arises a need for determining the haemostatic potential in a thrombocytopenic patient. Rationale: Immature platelets have higher MPV and are found be more active. Hence the notion, higher MPV, lesser bleeding risk. Methods: This is a cross-sectional study conducted among 260 diagnosed cases of thrombocytopenia attending General Medicine department as OP and IP in Amala Institute of Medical Sciences, Thrissur from February 2021 to February 2022. Patients were monitored daily for bleeding manifestations and daily hemogram was done with Beckman Coulter counter and Sysmex counter. Data was analysed by using SPSS software, V.22. Results: Lower platelet counts were seen to be associated with higher MPV. Around 50% of the patients with bleeding manifestation had low mean platelet volume. Also, in around 96% of patients who did not have any bleeding manifestations, MPV was found to be on the higher side. Conclusions: Mean Platelet Volume can be used for predicting bleeding manifestations in patients with thrombocytopenia as patients with a lower MPV have higher risk of bleeding. Timing of platelet transfusions in thrombocytopenia has always been a matter of conflict as the prediction of bleeding was difficult. The mean platelet volume, which is obtained along with the hemogram in automated counters can be used as cheap method of predicting bleeding risk.***

Keywords: Thrombocytopenia; bleeding; mean platelet volume

1. Introduction

The normal platelet concentration in the blood is between 150, 000 and 300, 000 per microliter. Young platelets which are recently released by megakaryocytes, are larger and denser and undergo remodelling while in circulation, in part by shedding some of their surface components. The presence of large platelets in a scenario of low platelet counts may reflect a disturbance in the steps of platelet production. The properties of large platelets may reflect unique attributes of platelets recently released from bone marrow or proplatelets produced under accelerated or abnormal production conditions (1) .

Assessment of platelet function

Bleeding risk doesn't depend on the platelet number alone (2) . It is also determined by the platelet function and turnover. A number of tests are available (3) for the evaluation of platelet function however they lack validation for bleeding risk stratification in thrombocytopenia. For example, the mean platelet volume (MPV) which can be determined by automated hematology equipment (4) is a measure of the platelet size. Invitro testing has shown that large and immature platelets appear more active than small or older platelets (5, 6) .

Platelet indices

Modern haematology analysers in routine diagnostic use, make use of impedance counting or optical light scatter counting techniques to measure platelet indices (PI) (7–9).

Platelet indices are biomarkers of platelet activation. They allow extensive clinical investigations focusing on the diagnostic and prognostic values in a variety of settings without bringing extra costs of more advanced investigations. These include plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) which are parameters determined together in automatic CBC profiles; they are related to platelets' morphology and proliferation kinetics (10, 11) .

Mean platelet volume

The volume of platelets in the bloodstream is heterogeneous, and their structures and metabolic functions differ according to their morphology. Typically, the average mean platelet cell volume is 7.2–11.7 fL in healthy subjects. The analyser-calculated measure of thrombocyte volume, the MPV, is determined directly by analysingthe platelet distribution curve, which is calculated from a log transformation of the platelet volume distribution curve, to yield a geometric mean for this parameter in impedance technology systems (12) . MPV is the mode of the measured platelet volume in some optical systems (13) .

The MPV is determined in the bone marrow megakaryocyte. The platelet volume is found to be associated with cytokines (thrombopoietin, interleukin-6 and interleukin-3) which regulate megakaryocyteploidy and platelet number and thus result in theproduction of larger platelets. When platelet production is decreased, young platelets become larger and more active, and MPV increase (5) . Increased MPV indicates production rate and platelet activation (14) . During activation, platelets' shapes change from biconcave discs to spherical, and a pronounced pseudopod formation occurs that leads to MPV increase during platelet activation.

In physiological conditions, MPV is inversely proportional to the platelet count, which is associated with hemostasis maintenance and preservation of constant platelet mass (15) . This means that increased production of platelets is accompanied by a reduction in their mean volume. It is also suggested that large thrombocytes show a greater content of

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cell granules, display higher expression of adhesion molecules, and undergo faster activation, which results in platelet hyperactivity and increased risk of clot formation. Elevated MPV correlates with increased platelet aggregation, enhanced synthesis, and release of thromboxane TXA2 and β-thromboglobulin (13) .

Prediction of hemorrhagic diathesis in thrombocytopenia by mean platelet volume, a study conducted in the Department of Haematology, Hadassah University Hospital, Jerusalem, Israel, showed that the mean platelet volume of patients with hemorrhagic tendency was significantly lower (5.52 ± SD 0.7 fL) than that of patients without these tendencies (7.87 ± SD 1.75 fL) p<0.01). In cases of severe thrombocytopenia (<20x 10^9/l platelets) hemorrhagic episodes were frequent; however, the frequency of bleeding was considerably lower in cases in which the mean platelet volume was higher than a suggested cut-off point of 6.4 fL (16) .

In a similar study done among patients in whom gold therapy was instituted, there was no significant difference between the pre-treatment values of MPV and those of patients receiving gold therapy. One patient developed a hemorrhagic diathesis with bleeding from multiple sites and required a platelet transfusion. The MPV in this patient was significantly lower during the thrombocytopenic episode (5.6 (SD 0.1) fL) compared with the other thrombocytopenic patients without hemorrhage (11.2 (3.5) fL; p<O.001) (17) .

The relationship between MPV and bleeding risk is also evident from a study done among Dengue patients in Sudan. MPV levels were lower in dengue fever patients compared to controls and significant with bleeding (p <0.046) (18) .

The interaction of the platelets and leukocytes has also been studied and determined the role of platelets in inflammation and atherogenesis. Hence the MPV can also be used as marker for risk of atherogenesis.

2. Methodology

Diagnosed cases of thrombocytopenia, receiving treatment as inpatient and outpatient basis in the department of General Medicine at Amala Institute of Medical Sciences, Thrissur, were monitored daily for bleeding manifestations and daily hemogram done to monitor the platelet counts and mean platelet volume. The study was conducted from February 2021 to February 2022.

Patients with congenital haemorrhagic disorders, abnormal coagulation tests (PT, INR, aPTT), being treated with anticoagulant drugs or antiplatelet drugs, who were receiving platelet transfusions and those with platelet counts <20, 000/µL or whose mean platelet volume cannot be determined were excluded from the study. A total of 260 patients were included in the study.

Blood samples were collected from these patients daily and collected into EDTA in a concentration of 1mg/ml. All samples were processed in Beckman Coulter counter and Sysmex counter within 1 hour of collecting. Patients were checked daily for haemorrhagic diathesis: those exhibiting any positive signs of bleeding underwent routine coagulation studies-PT, INR, a PTT, those not exhibiting positive signs were followed up for 1 week.

Statistical analysis

P value < 0.05 was considered statistically significant. Data was entered in MS Excel and worksheet was analyzed by using SPSS software, V.22. (SPSS I. IBM SPSS Statistics Version 22 Statistical Software: Core System Users' Guide. SPSS Inc.2014.)

3. Results

A total of 260 subjects were considered into the study**.** Out of the 260 people in whom the study was done, 119 (45.77%) were males and 141 (54.23%) were females. The age of participants in the study varied from 15 years to 89 years with the mean being 48.54 years.

Table 1: Descriptive analysis of Diagnosis in the study population (N=260)

Diagnosis	Frequency	Percentage
Dengue	140	53.85%
ITP	55	21.15%
LEPTO	19	7.31%
CML	14	5.38%
SFI	9	3.46%
MDS	8	3.08%
SLE	4	1.54%
AML	2	0.77%
APLASTIC A	2	0.77%
CLL	2	0.77%
HLH	1	0.38%
MIS C	1	0.38%
MIS A	1	0.38%
HERPES ZOSTER	1	0.38%
AIHA	1	0.38%

Among the various patients under the study, the platelet counts ranged from a minimum of 25, 000/ cu mm to a maximum of 2.80 lakhs / cu mm, the mean being 72.69 x 10^3 /cu mm. The mean platelet volume (MPV) of the study population ranged from 7.29 fL to 25.97 fL with the mean being 10.44.

Table 2: Comparison MPV with Platelet Counts (N=260)

Platelet Counts (x10^3/µL)	MPV (fL)	Kruskal Wallis Test (P Value)
25-50 (N=60)	8.03 (7.64 to 8.52)	<0.001
50-75 (N=77)	10.92 (10.92 to 11.23)	
75-100 (N=78)	11.46 (11.36 to 11.54)	
100-125 (N=27)	11.16 (10.33 to 11.63)	
125-150 (N=14)	11.41 (10.27 to 11.71)	
150-175 (N=3)	10.53 (10.19 to 10.59)	
275-300 (N=1)	11.56 (11.56 to 11.56)	

On comparing the platelet counts and the MPV, it was found that the lower platelet counts had lower MPV, and as the counts increased the MPV also increased.

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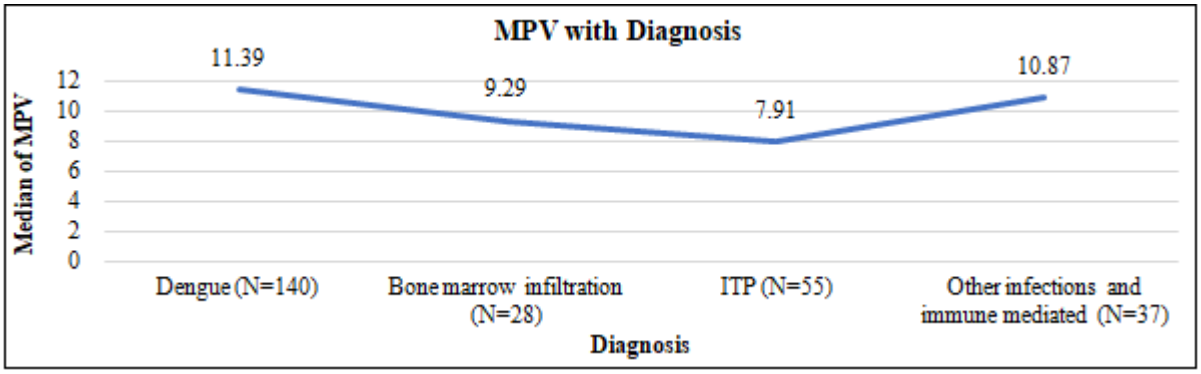

Figure 1: Comparison of MPV with Diagnosis (N=260)

Patients with ITP were found to have the lowest mean platelet volume and those with Dengue fever had the highest mean platelet volume.

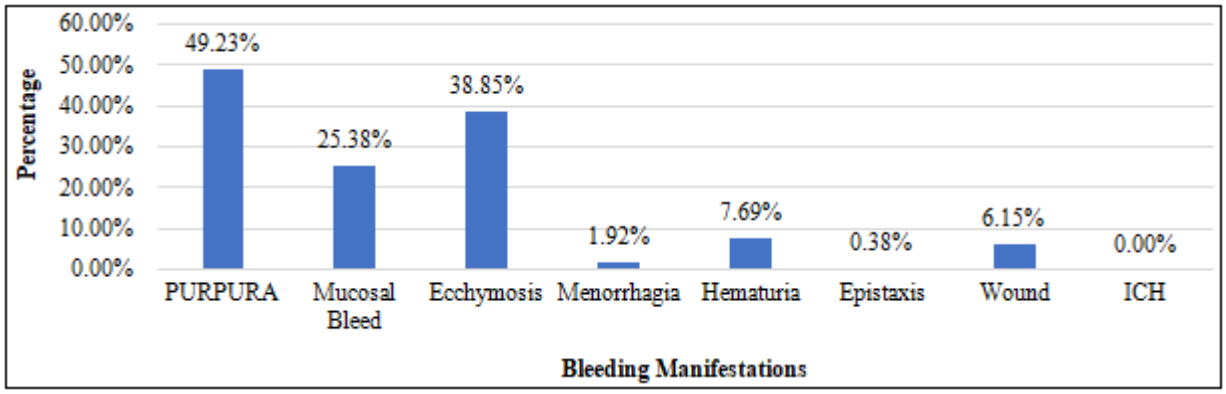

Figure 2: Bleeding Manifestations in the study population (N=260)

The most common bleeding manifestation observed in the population was purpura (49.23%), followed by ecchymosis (38.85%) and mucosal bleeds (25.38%).

Table 3: Comparison of MPV with Bleeding Manifestations (N=260)

	Bleeding Manifestations		Mann Whitney U Test (P Value)
MPV (fL)	Yes (N=145)	No (N=115)	
	9.78 (7.91 to 11.17)	11.46 (11.17 to 11.81)	<0.001

Bleeding manifestations were seen with a lower MPV

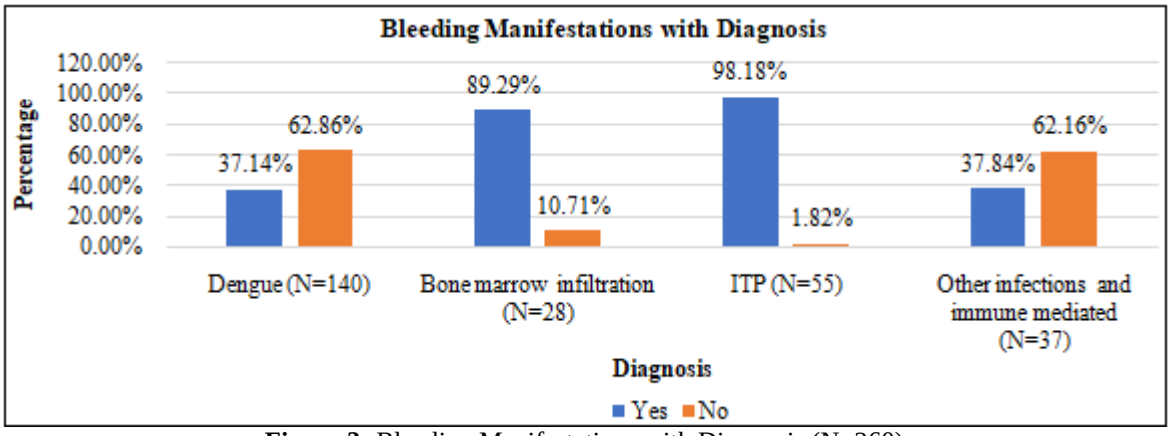

Figure 3: Bleeding Manifestations with Diagnosis (N=260)

More bleeding manifestations were observed in patients with bone marrow disorders like AML, CML, CLL, MDS and those with ITP.98.18% of the patients with ITP had bleeding manifestations, whereas dengue fever despite constituting more than half of the diagnosis had only 37.14% patients with bleeding manifestations.

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Table 4: Comparison of MPV with Bleeding Manifestations in Dengue fever (N=140)

	Bleeding Manifestations		Mann Whitney U Test (P Value)
MPV (fL)	Yes (N=52)	No (N=88)	
	10.92 (10.92 to 11.23)	11.46 (11.38 to 11.81)	<0.001

Bleeding manifestations in dengue fever were seen in those patients with lower MPV, reflecting the general population trend.

Table 5: Comparison of MPV with Bleeding Manifestations in ITP (N=55)

	Bleeding Manifestations		Mann Whitney U Test (P Value)
MPV (fL)	Yes (N=54)	No (N=1)	
	7.84 (7.57 to 8.11)	8.94 (8.94 to 8.94)	0.0459

Bleeding manifestations were seen in patients with lower MPV in ITP patients.

4. Discussion

The study was done to determine whether the Mean Platelet Volume can be used as predictor of hemorrhagic diathesis in patients with thrombocytopenia. This was achieved by comparing the said parameter with the platelet counts and the bleeding manifestations observed.

The lowest platelet count noted was 25, 000/µL and highest was 280 x 10^3/µL, with the mean value being 72.69 ±33.26 x 10^3/µL. The mean MPV in the study population was 10.44±1.82 fL.

A study was conducted in 945 healthy individuals, age ranges from 18 to 64 years coming for voluntary blood donation in a tertiary care hospital in Gurgaon, India. In the study, the normal range for mean platelet volume (MPV) was found to be 8.6-15.5 fL, (19) , which was comparable to the findings in our study.

Very low platelet counts were associated with low MPV which slowly rose as the platelet counts increased and came towards the normal range when the counts were normalised. In a study conducted by Ana M Sanz et al among dengue patients, in 2016, it was found that MPV increased from the first blood count until day six. On the sixth day, MPV hit a high peak that suggests an inverse relationship with a platelets decrease. MPV increased with thrombocytopenia during the critical period and its decline precedes platelet count recovery (20) .

Prevalence of bleeding manifestations in patients with thrombocytopenia

Out of the 260 patients studied, 145 had bleeding manifestations in various forms. These ranged from purpura, which was the most common bleeding manifestation, followed by ecchymoses, mucosal bleeds, menorrhagia, wound bleeds, epistaxis. Intracranial bleed was not observed any of the study population. The hemorrhagic manifestations were seen more in those with a lower platelet count, mostly less than 60, 000/µL. An important study that describes the relationship between severe thrombocytopenia and bleeding was from 1977, which described a number of thrombocytopenic patients with a variety of disorders. Significant bleeding rarely occurred with platelet count levels >30 x109/L, and major bleeding only occurred when platelet count levels were<10x109/L (21) .

Diagnosis and bleeding manifestations

Majority of the study population (>50%) had been diagnosed with Dengue fever and ITP and a few hematological malignancies and hyper destructive conditions. However considering each condition individually, the proportion of patients with bleeding manifestations were much higher in ITP (98.18%) and bone marrow infiltrative conditions (89.29%) when compared to Dengue fever (37.14%).

Determinants of bleeding manifestations

It was obvious that bleeding manifestations were seen with lower platelet counts. However, there were other factors adding to this. As evidenced by the analysis, a lower mean platelet volume was associated with increased risk of bleeding. The mean MPV for the patients with bleeding manifestations was found to be 9.78fL (p <0.001) as opposed to 11.46fL (p <0.001) in those without bleeding manifestations. On comparing individual diagnosis, the patients with ITP had bleeding at much lower mean MPV of 7.84fL (p=0.0459) than those with dengue (10.92fL; p <0.001). The proposed normal value of MPV is 7.2 to 11.7 fL.6 in immune thrombocytopenia, when the platelets gets destroyed in the spleen, the new platelets that are being formed in the bone marrow are larger ones than the normal and thus the MPV increases in immune thrombocytopenia. (22) However, certain other studies showed a conflicting pattern. In a cross-sectional study conducted in 83 thrombocytopenic patients, All Platelet indices were significantly higher in ITP patients ($n = 33$) than in hypoproductive thrombocytopenic patients ($n = 50$) ($p < 0.0001$). The indices were significantly higher in ITP patients compared to 42 healthy controls ($p < 0.0001$). Also, there was significant negative correlation between platelet count and platelet indices in ITP patients, ($p < 0.001$). (23)

'Prediction of hemorrhagic diathesis in thrombocytopenia by mean platelet volume', a study conducted in the Department of Haematology, Hadassah University Hospital, Jerusalem, Israel, showed that the mean platelet volume of patients with hemorrhagic tendency was significantly lower (5.52 ± SD 0.7 fL) than that of patients without these tendencies (7.87 ± SD 1.75 fL) p<0.01). In another similar study, conducted among patients receiving gold therapy, one patient developed a hemorrhagic diathesis with bleeding from multiple sites and required a platelet transfusion. The MPV in this patient was significantly lower during the thrombocytopenic episode (5.6 (SD 0.1) fL) compared with the other thrombocytopenic patients without hemorrhage (11.2 (3.5) fL; p<O.001) (24) .

Overall, around 50% of the patients with bleeding manifestations had a low MPV whereas higher MPV was noted in 96% of patients without any bleeding manifestations.

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5. Conclusions

1) Around 50% of the patients with bleeding manifestation had low mean platelet volume. Also, in around 96% of patients who did not have any bleeding manifestations, MPV was found to be on the higher side.
2) MPV is inversely proportional to the platelet count. Lower platelet counts are seen to be associated with higher MPV, which gradually decrease as platelet counts improve.
3) The relationship of MPV with bleeding manifestations observed in the general population is applicable to the subpopulation of Dengue fever patients.

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