Research Article

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How far are the platelet indices mirror image of mechanism of thrombocytopenia-mystery still remains?

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ABSTRACT

Background: Evaluation of thrombocytopenia requires thorough clinical history, examination, complete hemogram, including platelet indices and bone marrow study whenever indicated. The etiopathogenetic mechanism decides patient management. The aim was to study relationship between thrombocytopenia and platelet indices with respect to underlying mechanisms.

Methods: Totally 100 thrombocytopenic patients with sufficient clinico-hematological workup were included in our study. Results were confirmed by peripheral smear examination and manual platelet count wherever necessary. Similar data during the year 2012 were collected from 100 controls and compared.

Results: Patients were grouped based on mechanism-hypoproduction 15 (megaloblastic anemia 8, myelodysplastic syndrome 1, leukemia 6), hyperdestruction 4 (immune thrombocytopenic purpura), hyperspleenism 19 (chronic dengue 10, chronic malaria 6, chronic liver disease 3) and mixed 62 (chronic dengue 29, chronic malaria 24, thalassemia on regular transfusion 3, sepsis 4, disseminated intravascular coagulopathy 2).

Conclusion: (1) Platelet indices showed inverse relationship-increase (mean platelet volume [MPV] r = -0.805, platelet distribution width [PDW] r = -0.996) with decreasing platelet count in most increased destruction cases, (2) linear relationship (MPV r = 0.84, PDW r = 0.37) was seen in most hypoproduction cases. p values were also calculated, (3) variable results were obtained in hyperspleenism, mixed and few of above two groups, (4) platelet indices provide important information about platelet kinetics. However, relationship with platelet count is helpful but not always confirmative of mechanism of thrombocytopenias.

Keywords: Correlation, Platelet count and indices, Pathogenetic mechanism, Thrombocytopenia

INTRODUCTION

Thrombocytopenia is defined as platelet count below 150,000/cmm after control of pre-analytical and analytical variables.^{1,2} Platelet count is more difficult to evaluate than red cell count due to size, tendency to aggregate and potential overlap with red blood cells (RBCs).³

According to the mechanism of thrombocytopenia, the patients are categorized into groups: hyperdestruction, hypoproduction and splenic sequestration.

(Levine, 1999). Hyperdestructive thrombocytopenias are due to extramedullary platelet destruction with normal or increased bone marrow productions, e.g., immune thrombocytopenic purpura (ITP), secondary ITP and disseminated intravascular coagulopathy. Hypoproductive thrombocytopenias result from decreased bone marrow production because of primary or secondary bone marrow diseases such as aplastic anemia, megaloblastic anemia, myelodysplastic syndrome, acute leukemia, amegakaryocytic thrombocytopenic purpura, and postchemotherapy. Splenic sequestration can occur in splenic pooling, mainly due

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to chronic liver disease with portal hypertension or in congestive spleenomegaly due to homozygous sickle cell disease in children, hemoglobin C (HbC) disease, HbSC disease, thalassemia major, chronic infections, Gaucher's disease, myeloproliferative disorders, lymphomas etc.³

The evaluation and establishment of etiopathological categories is the first step towards patient management. Hence this study is undertaken to establish relationship between platelet count and platelet indices, namely mean platelet volume (MPV) and platelet distribution width (PDW) with respect to underlying mechanisms of thrombocytopenia.

METHODS

Our study included 100 thrombocytopenic patients with sufficient clinico-hematological workup along with 100 controls. Pre-analytical variables were controlled and analysis during the year 2012 was done by ABX Micros 60 counter. Results were confirmed by peripheral smear examination and manual platelet count wherever necessary. Graphs were plotted of platelet count against MPV and PDW respectively. This was done for control group and in each of the etiopathological groups. The r value and p value were calculated for all the graphs.

RESULTS

The thrombocytopenic cases are grouped as per underlying mechanism in Table 1 and Figure 1 along with comparison with study by Numbenjapon et al.⁴ The peripheral smears showing thrombocytopenia are illustrated in Figures 2-4. The graphs show relationship between platelet indices and platelet count in all etiopathological groups. MPV and PDW were found to be high in hyperdestruction category, whereas in hypoproduction group, indices were seen to be proportionately low with respect to degree of fall in platelet count. Concordant results were obtained in 66 cases (Figures 5-14).

However, we observed that in some cases in each group, discordant or variable results were obtained (34) (Figure 15).

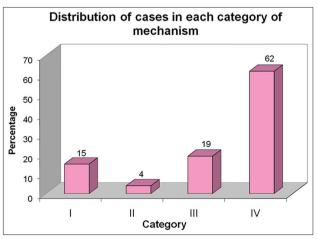


Figure 1: Etiological groups I - hypoproduction, II - increased destruction, III - hyperspleenism, IV - mixed.

This was with respect to etiology and platelet indices, due to co-existence of other diseases as follows:

- Normal platelet indices were observed in 9 cases Multiple mechanisms acting in these cases may be responsible for normalization of platelet indices.
 - Dengue 5
 - Chronic malaria 2
 - Chronic liver disease 2.
- II. High MPV and/or PDW in mild thrombocytopenia were observed in 23 patients and they were suffering from other diseases like
 - Preeclampsia 3
 - Chronic renal failure on hemodialysis 3
 - Alcoholic liver disease 3
 - Chronic hepatitis -2
 - Malignancy 2 Sarcoma thigh, carcinoma of maxillary sinus
 - Rheumatoid arthritis 3
 - Ischemic heart disease 4.

Table 1: Etiological groups with comparison study.

Etiologies	Present study	Numbenjapon et al. ⁴
Hypoproduction	15	38
Aplastic anaemia	-	12
Megaloblastic anaemia	8	-
Myelodysplastic syndrome	1	4
Leukemia	6	22
AML	1	18
CLL	3	0
CML	2	0
ALL	0	4
Increased destruction	4	53
ITP	4	53
Hyperspleenism	19	-
Chronic dengue	10	-
Chronic malaria	6	-
Chronic liver disease	3	-
Mixed	62	9
Chronic dengue	29	-
Chronic malaria	24	-
Thalassemia on regular transfusion	3	-
Sepsis	4	9
DIC	2	-
Multiple myeloma	-	2
Total	100	102

ITP: Immune thrombocytopenic purpura, AML: Acute myelogenous leukemia, CLL: Chronic lymphocytic leukemia, CML: Chronic myelogenous leukemia, ALL: Acute lymphocytic leukemia, DIC: Disseminated intravascular coagulopathy

- III. Normal or high MPV in (2) hypoproduction cases due to
 - Megaloblastic anaemias.

DISCUSSION

Recent advances in technology have made it possible to record various platelet indices, such as MPV, PDW, and platelet large cell ratio (PLCR), with an automated hematology analyzer.⁵ Bone marrow sampling is invasive and not necessary as the first-line diagnostic procedure in thrombocytopenic cases. It was recommended that it should be reserved for older patients, or patients with atypical features (George et al, 1996; Mak et al, 2000; Marsh et al, 2003). Thus, a new non-invasive diagnostic approach for thrombocytopenia is needed. There are seven parameters in approach toward the underlying mechanism of thrombocytopenia namely MPV, PDW, PLCR, plateletcrit, flow cytometry of platelet RNA content, high total platelet immunoglobulins G (IgG) concentration and sCD40L.^{1,2}

Large platelets are seen in diseases like ITP, May Hegglin anomaly and Bernard Soulier's syndrome, while small

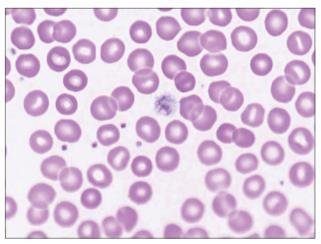


Figure 2: Peripheral smear showing thrombocytopenia with large platelets (Leishman's stain, ×40).

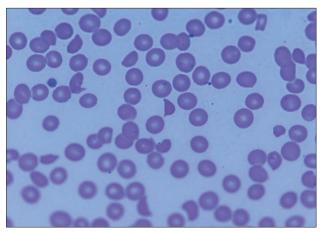


Figure 3: Peripheral smear showing thrombocytopenia with large platelets (Leishman's stain, ×40).

platelets are observed in conditions like aplastic anemia, Wiskott Aldrich syndrome, thrombocytopenia absent radii syndrome and storage pool disease.² The presence of RBC fragmentation may be measured by the Coulter counter as a large size platelet. Whenever associated with splenic sequestration, large size platelets are trapped and not released into the systemic circulation (Bessman et al., 1985; Garg et al., 1972; Karpatkin & Freedman, 1978).⁴

Elevated level of MPV is an indication of increased megakaryocyte shedding of platelets, and raised PDW indicates anisocytosis. Although MPV is raised in consumptive thrombocytopenia, platelet size is still a difficult parameter to quantitate accurately due to wide physiological variations in MPV. An indirect measure of platelet production is the flow cytometric assay for platelet RNA content. High total platelet IgG concentration is seen in patients with hyperdestruction as high platelet IgG indicates high young mean platelet age. MPV increases in raised platelet turnover or Bernard Soulier's syndrome. Normal or decreased values are noted in hypoproduction, sepsis or big spleen syndromes. In ITP, PDW is also raised

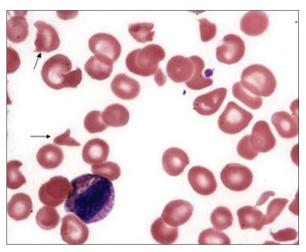


Figure 4: Peripheral smear showing thrombocytopenia with large platelets (Leishman's stain, ×40).

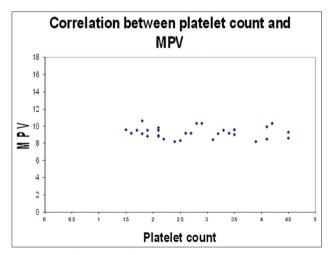


Figure 5: Control - Correlation between platelet count and mean platelet volume.

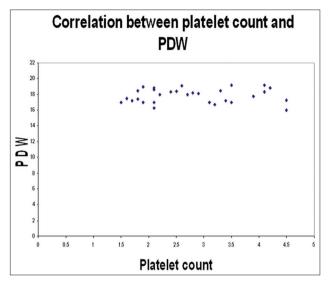


Figure 6: Control - Correlation between platelet count and platelet distribution width.

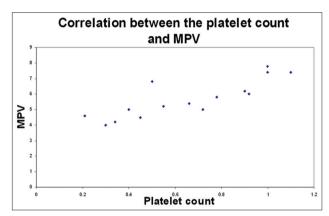


Figure 7: Hypoproduction cases - Correlation between platelet count and mean platelet volume. Foot notes linear r = 0.84 p < 0.0001.

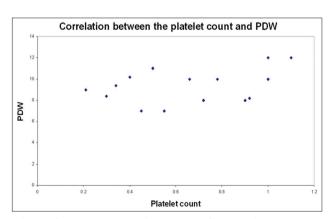


Figure 8: Hypoproduction cases - Correlation between platelet count and platelet distribution width. Foot notes linear r = 0.37 p > 0.05.

in addition to MPV and inversely related to platelet count. Low values of MPV are obtained in hyperspleenism, myeloproliferative disorders, sepsis and postchemotherapy.¹ PLCR is percentage of platelets with size of more than 12 fl.

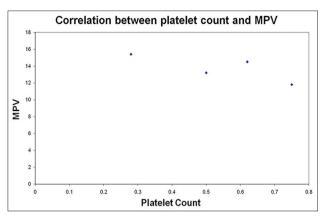


Figure 9: Hyperdestruction cases - Correlation between platelet count and mean platelet volume. Foot notes inverse r = -0.805 p > 0.05.

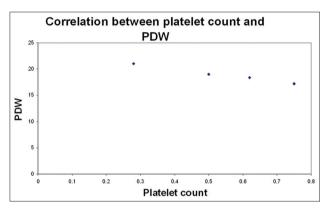


Figure 10: Hyperdestruction cases - Correlation between platelet count and platelet distribution width. Foot notes inverse $r = -0.996 \ p < 0.004$.

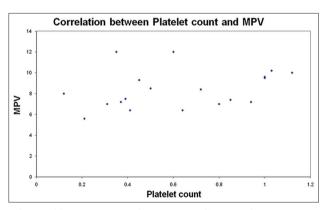


Figure 11: Hypersplenism cases - Correlation between platelet count and mean platelet volume. Foot notes r = 0.299 p > 0.05.

Together with MPV and PDW; it is also significantly raised in ITP than in aplastic anaemia.⁵

It is observed that MPV and PDW variation is directly proportional to platelet count in hypoproduction and inversely proportional in hyper destructive categories. A majority of patients with hyperdestructive thrombocytopenia had significantly higher MPV values than those with

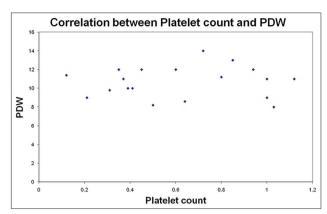


Figure 12: Hypersplenism cases - Correlation between platelet count and platelet distribution width. Foot notes r = 0.043 p > 0.05.

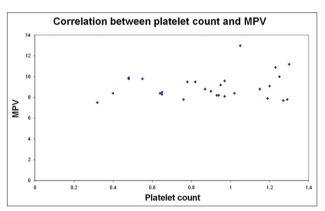


Figure 13: Mixed mechanism cases - Correlation between platelet count and mean platelet volume. Foot notes r = 0.18 p > 0.05.

hypoproductive thrombocytopenia, in accordance with previous studies (Bowles et al., 2005; Kaito et al., 2005).⁴

Kaito et al. established the relationship of platelet indices with platelet count in two etiopathological categories of thrombocytopenia namely idiopathic thrombocytopenic purpura ITP (no significant correlation) and aplastic anemia (significant inverse relationship) categories. Our study reveals significant linear correlation between platelet count and MPV in hypoproduction group (p < 0.0001) and significant inverse relationship between platelet count and PDW in hyperdestruction group (p < 0.004). In hypersplenism and mixed mechanism group too, linear relationship was observed between platelet count and indices respectively.

Discordant results were obtained in 34 cases due to coexistent conditions as described: normalization of platelet indices in dengue was due to other mechanisms involved in thrombocytopenia like splenomegaly with splenic sequestration of platelets and bone marrow suppression by dengue virus. 1.2 According to Funahara et al, there are three possible triggers to induce thrombocytopenia in dengue virus infection as: (1) dengue virus (DV) antigen attached to platelets without immune mediated reaction, (2) a decrease in platelet count was more markedly demonstrated by

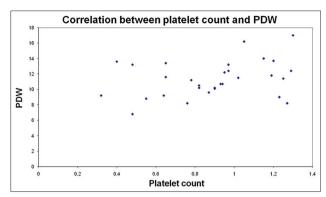


Figure 14: Mixed mechanism cases - Correlation between platelet count and platelet distribution width. Foot notes r = 0.32 p > 0.05.

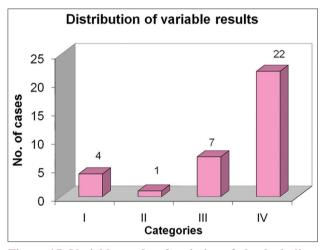


Figure 15: Variable results of variation of platelet indices with thrombocytopenia I - hypoproduction, II - increased destruction, III - hyperspleenism, IV - mixed.

binding of anti DV antibodies on the DV antigen associated with platelets than by the binding of antigen antibody complex on platelets.⁶ In malaria, spleenic pooling is well-known cause of thrombocytopenia. However Coelho et al. analyzed cytokine profile in healthy subjects and malaria patients and found that levels of interleukin (IL) 6, IL 10 and interferon gamma were elevated in malaria patients. Collectively indicating that platelet phagocytosis may contribute to thrombocytopenia. Hence contributing to variable platelet indices.⁷ Chronic alcohol consumption has direct toxic effect on bone marrow-in this context on platelet production, survival and function.⁸

Recently it is found that MPV is increased in myocardial infarction and cerebrovascular accident. It is widely used surrogate marker of platelet function and shown as sign of inflammation in ulcerative colitis, Crohn's disease, rheumatoid arthritis, chronic renal and liver disease, hepatitis B, pre-eclampsia, metabolic syndromes like diabetes mellitus and nonalcoholic fatty liver.⁹

The activation of coagulation, angiogenesis and inflammatory cytokines are considered to be related with tumor growth and metastasis. Kim et al. investigated

and found that plasma levels of platelet microparticles, vascular endothelial growth factor, IL 6,T cell expression and secretion were significantly raised in cancer patients. ¹⁰ We too observed high MPV and thus variable result in two cases of thrombocytopenia associated with malignancy.

In two patients with megaloblastic anemia, MPV was raised and hence leading to variable results. One patient was in impending sepsis and other had high fever and severe productive cough. The inflammatory mediators like IL 6 may be responsible as it raises in fever and sepsis as per the literature.¹¹ Moreover, IL 6 is responsible for inducing platelet production by interfering megakaryopoeisis with subsequent release of big platelets from bone marrow and causing a rise in MPV.⁹

CONCLUSION

In this study, platelet indices showed linear relationship i.e., decrease (MPV < 6 fl, PDW < 10) with decreasing platelet count in most hypoproduction group. Whereas, inverse relationship i.e., Increase (MPV > 10 fl, PDW > 16) with decreasing platelet count was observed in most cases of hyperdestruction group. However, we observed interesting findings in our study that many thrombocytopenic patients showed variable and discordant results. This was observed in all the etiopathological groups due to co-existent diseases. We are documenting this study as there are very few studies of this kind in the literature.

To conclude, though the platelet indices provide important information about platelet kinetics, their relationship with platelet count is not always confirmative of underlying mechanism of thrombocytopenia.

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