

Utility of Platelet Indices in Diagnosing The Underlying Cause of Thrombocytopenia Due To Accelerated Platelet Destruction

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ABSTRACT

Background: Thrombocytopenia is a common clinical manifestation of many diseases and has numerous causes, including decreased bone marrow production, increased spleen sequestration, and accelerated destruction of platelets. Among the various aetiologies, Accelerated platelet destruction is the most common cause. Distinction between the various aetiological categories of thrombocytopenia is usually made by invasive bone marrow examination. Some studies stated that Platelet indices were altered in various causes of thrombocytopenia and helpful in discriminating the causes. we aim, to know the role of platelet indices in determining the underlying cause of thrombocytopenia due to platelet destruction.

Methods: 30 Healthy controls and 145 patients (study group) with thrombocytopenia (platelet count $<150 \times 10^9$) were included in the study. Thrombocytopenia due to decreased bonemarrow production and artefactual thrombocytopenia were excluded. The study group was divided into 3groups. Group 1 includes immune thrombocytopenia, Group 2 having thrombocytopenia of non immunological causes and Group 3 includes miscellaneous causes. Clinical features, Platelet counts and platelet indices were studied and statistical analysis was performed.

Result: In all the groups of thrombocytopenia due to accelerated platelet destruction, MPV and P-LCR were significantly higher; P-LCC was significantly lower than healthy controls. There was no significant variation of PDW in NonImmune thrombocytopenia and miscellaneous groups, but PDW was significantly lower in immune thrombocytopenia than healthy controls.

Conclusion: Platelet indices should be considered in the diagnosis of thrombocytopenia due to accelerated destruction of any cause. Among the platelet indices, PDW can be useful for a positive diagnosis of immunological thrombocytopenia.

Keywords: Platelet Indices, Thrombocytopenia Due To Accelerated Destruction, Immune, Nonimmune, Miscellaneous.

Introduction

Among the various pathogenetic mechanisms of thrombocytopenia, the most common mechanism is Accelerated destruction. When the platelet destruction exceeds the compensatory increase in platelet production, thrombocytopenia develops. Platelet destruction may result from both intracorpuseular and extracorpuseular abnormalities. Intracorpuseular defects are rare. Platelet destruction most often is the result of extracorpuseular factors like immunological, non immunological and miscellaneous causes.^[1] Platelet counts below normal values define thrombocytopenia but do not reveal the underlying pathomechanism. The gold standard method for discriminating these causes is bone marrow examination. No consensus is reached regarding the necessity of a bone marrow examination in the evaluation of thrombocytopenia due to accelerated platelet destruction. Due to its invasiveness and being painful for the patients, this procedure is not recommended as first line diagnosis.^[2] Advances in automated blood cell analyzers have made it possible to measure various biomarkers of platelet activation which may provide some important information

in diagnosing the underlying condition.² The present study was conducted to demonstrate the discriminating potential of the platelet indices between Immune, Nonimmune and Miscellaneous causes of thrombocytopenia.

Materials and Methods

The present study included 30 Healthy controls and 145 patients (study group) with thrombocytopenia (platelet count $<150 \times 10^9$). Thrombocytopenia due to decreased bonemarrow production and artefactual thrombocytopenia were excluded. The study group was divided into 3groups. Group 1 includes Thrombocytopenia due to immunological causes, Group 2 having thrombocytopenia of non immunological causes and Group 3 includes miscellaneous causes. The immune thrombocytopenia group included (group I) Autoimmune thrombocytopenia due to ITP and secondary causes like drugs, SLE, infections (HIV, Hepatitis B and C, Tuberculosis, Cytomegalovirus, Infectious Mononucleosis, Varicella or Zoster), lymphoproliferative disorders and thyroid disorders. The Non immunological causes included for Group II are Acute Pancreatitis, DIC, Hemolytic uremic syndrome, septicemia, pneumonia, septic shock, burns,

snake bite, infections, hypothermia, platelet agglutinating drugs, coronary artery bypass, stenosed or artificial heart valves, cancers. Miscellaneous causes of group III included thrombocytopenias due to bacterial and viral infections such as Dengue, Malaria, Typhoid and other gram negative or gram positive infections. Assessment of complete blood count, MPV, PDW, P-LCR and P-LCC was done on Beckman Coulter. All whole-blood counts were assayed within 2 h of sample collection. Microscopic examination of a peripheral blood film stained with Leishman stain was done wherever necessary.

Statistics: Patient data were tabulated and processed using SPSS (17.0; SPSS Inc., Chicago, Illinois, USA) for Windows XP. Quantitative variables were expressed as mean, SD, and range and analyzed using Student's unpaired *t*-test. Qualitative data were expressed as frequency and percentage and were analyzed using the χ^2 -test. *P*-value less than 0.05 were considered statistically significant.

Result

A total of 145 thrombocytopenic patients and 30 healthy controls were reviewed in this study. These thrombocytopenic patients were divided into three categories based on the underlying cause. Group 1 includes 7 patients with thrombocytopenia due to immunological causes, Group 2 includes 14 patients with nonimmunological thrombocytopenia, Group 3 consists of 124 patients having thrombocytopenia due to miscellaneous causes.

The age of the patients ranged from 2 days to 80 years. The oldest case (78 years) was having nonimmune thrombocytopenia due to chronic kidney disease and pneumonia and the youngest (2 days) was diagnosed as neonatal thrombocytopenia due to respiratory distress syndrome. Maximum numbers of thrombocytopenia cases were reported in second to third decades. Healthy controls were also considered in third to fifth decades. Female patients comprised 68 and male patients 77 of total cases.

The aetiological distribution revealed, most of the thrombocytopenia cases (85.5%) were due to miscellaneous causes. The different causes of thrombocytopenia were analyzed for the three patient groups along with the respective platelet count and platelet indices. The main causes of thrombocytopenia in immune thrombocytopenia are ITP, Viral Hepatitis, Tuberculosis and Thyroid disease. Nonimmune thrombocytopenia is due to Sepsis, septic shock, pneumonia, effusions, meningitis, drugs and toxins, snake bite and Acute Pancreatitis. Most common aetiology in the present study is Infections. Infections contribute 124 cases (85.5%). Miscellaneous causes for thrombocytopenia in the present study are Infections like Malaria, Dengue, Typhoid and viral, Hypersplenism, chronic liver disease, chronic kidney disease or Diabetes Mellitus. (Table 1)

The platelet count and the platelet indices were compared between the three groups and healthy controls. In healthy controls, MPV Values are 9.74 ± 1.106 , PDW is 12.16 ± 2.015 , P-LCR is 33.88 ± 11.88 and P-LCC is 74.53 ± 20.59 . In all the three groups of individuals; MPV and P-LCR are significantly higher than healthy controls with the mean of 17.43 ± 3.69 and 36.86 ± 27.39 (Group 1), 17.57 ± 4.89 and 37.57 ± 15.45 (Group 2), 15.09 ± 3.51 and 33.88 ± 11.88 (Group 3) respectively. P-LCC values are lower than controls with the mean of 17.10 ± 15.74 (Group 1), 20.36 ± 6.640 (Group 2) and 18.71 ± 10.18 (Group 3). But PDW is significantly decreased (8.86 ± 6.122) in Immune Thrombocytopenia (ITP) than the other two groups. In other two groups no significant decrease noted-

Platelet count, MPV and P-LCR were significantly higher ($P < 0.0001$) in all the three groups as compared to healthy controls. P-LCC is significantly lower than healthy controls. There is no significant variation of PDW in NonImmune thrombocytopenia and miscellaneous groups, but PDW is significantly lower in immune thrombocytopenia than healthy controls. (Tables 2-4)

Table 1: Distribution of Thrombocytopenia cases based on underlying pathogenetic mechanism .

| | Group 1 (Immunological) | Group 2 (Non Immunological) | Group 3 (Miscellaneous) | Total |
|-----------|---|---|---|-------|
| Aetiology | ITP, Viral Hepatitis, Tuberculosis, Thyroid disease | Sepsis, septic shock, pneumonia, effusions, meningitis, Acute pancreatitis, drugs and toxins, snake bite, Acute Pancreatitis | Infections like Malaria, Dengue, and Typhoid, viral. Hypersplenism, chronic liver disease, chronic kidney disease or Diabetes Mellitus | |
| Number | 7 | 14 | 124 | 145 |
| (%) | 4.8 | 9.7 | 85.5 | 100 |

Table 2: comparison of platelet count and platelet indices between Group 1 and control group.

| Platelet count and indices | Group 1 | Control group | p- value |
|----------------------------|--------------|---------------|----------|
| Platelet count (mean± SD) | 36.71± 13.66 | 303.53± 22.18 | <0.0001 |
| MPV(mean± SD) | 17.43±3.69 | 9.74±1.106 | <0.0001 |
| PDW(mean± SD) | 8.86±6.122 | 12.16±2.015 | =0.0167 |
| P-LCR(mean± SD) | 36.86±27.39 | 24.87±7.196 | =0.0360 |
| P-LCC(mean± SD) | 17.10±15.74 | 74.53±20.591 | <0.0001 |

Table 3: comparison of platelet count and platelet indices between Group 2 and control group.

| Platelet count and indices | Group 2 | Control group | p- value |
|----------------------------|--------------|---------------|----------|
| Platelet count (mean± SD) | 46.71± 19.37 | 303.53± 22.18 | <0.0001 |
| MPV(mean± SD) | 17.57±4.89 | 9.74±1.106 | <0.0001 |
| PDW(mean± SD) | 11.14±4.44 | 12.16±2.015 | =0.2966 |
| P-LCR(mean± SD) | 37.57±15.45 | 24.87±7.196 | =0.0005 |
| P-LCC(mean± SD) | 20.36±6.640 | 74.53±20.591 | <0.0001 |

Table 4: comparison of platelet count and platelet indices between Group 3 and control group.

| Platelet count and indices | Group 3 | Control group | p- value |
|----------------------------|--------------|---------------|----------|
| Platelet count (mean± SD) | 54.74± 29.17 | 303.53± 22.18 | <0.0001 |
| MPV(mean± SD) | 15.09±3.506 | 9.74±1.106 | <0.0001 |
| PDW(mean± SD) | 11.86±4.834 | 12.16±2.015 | =0.7401 |
| P-LCR(mean± SD) | 33.88±11.88 | 24.87±7.196 | =0.0002 |
| P-LCC(mean± SD) | 18.71±10.18 | 74.53±20.591 | <0.0001 |

Discussion

Platelet indices are biomarkers of platelet activation. Platelet indices (PI) — Mean platelet volume (MPV) and platelet distribution width (PDW), Platelet – Large cell ratio (P-LCR), Platelet- Large cell coefficient (P-LCC) — are a group of derived platelet parameters obtained as a part of the automated complete blood count. Emerging evidence suggests that PIs may allow extensive clinical investigations focusing on the diagnostic and prognostic values in a variety of settings without bringing extra costs.^[3]

The volume of platelets in the bloodstream is heterogeneous, and their structures and metabolic functions differ. Typically, the average mean cell volume is 7.2–11.7 fL in healthy subjects.^[4,5] MPV is determined in the progenitor cell, the bone marrow megakaryocyte. When platelet production is decreased, young platelets become bigger and more active, and MPV levels increase. 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. MPV changes are complex, and are not only related to the PLT count, but also related to the method of laboratory analysis

used.^[6,7] In a study by Akarsu et al, a MPV >9.5 fl was considered above normal range,^[8] and in another study, MPV elevation was defined >10.4 fl, both of which were commonly found in our study. The normal range of MPV from our laboratory was 9–17 fl.^[3]

Our study showed that Platelet count, MPV and P-LCR were significantly higher ($P < 0.0001$) in all the three groups as compared to healthy controls. P-LCC is significantly lower than healthy controls. There is no significant variation of PDW in NonImmune thrombocytopenia and miscellaneous groups, but PDW is significantly lower in immune thrombocytopenia. Borkatoky *et al.*^[9] found no significant difference in the MPV between the destructive thrombocytopenia groups and the control group. Similarly, previous work by researchers such as Kaito *et al.*^[10], Ntaios *et al.*^[11] and Shah *et al.*^[12] reported that MPV was higher in ITP patients, which reflected an increase in the production rate, and they established cutoff values ranging from greater than 9 fl to greater than 11 fl. Although Numbenjapon *et al* reported that MPV could be used in distinguishing hyperdestructive from hypoproductive thrombocytopenia; they proposed a cutoff value of 7.9 fl, which is lower than the previously reported cutoff values.^[13] PDW is an indicator of volume variability in platelets size and is increased in the presence of platelet anisocytosis

.The PDW reported varies markedly, with reference intervals ranging from 8.3 to 56.6% .^[4,6-7] PDW directly measures variability in platelet size, changes with platelet activation, and reflects the heterogeneity in platelet morphology.^[5,7] Under physiological conditions, there is a direct relationship between MPV and PDW; both usually change in the same direction.^[5] Meanwhile, there are conflicting reports in the literature about the relationship between platelet volume and numbers, which suggests that they are affected by different mechanisms.^[3] In our study also, we observed that MPV and PDW changed in same direction.

Platelet larger cell ratio (P-LCR) is an indicator of circulating larger platelets (> 12 fL), which is presented as percentage. The normal percentage range is 15–35%. It has also been used to monitor platelet activity. Platelet large cell ratio, PLCR, is often correlated to MPV but is more sensitive to changes in platelet size. Babu et al has shown its level is inversely related to the platelet counts and directly related to MPV and PDW, and is an aid for the differentiation of thrombocytopenia.^[14]

Platelet large cell Coefficient (P-LCC) means number of platelets larger than 12 fl and smaller than 30 fl. P-LCR is calculated in automated blood analyzers using this formula- P-LCC/ PLT. Another explanation for the differences in the cutoff values of Platelet indices in different studies can be the difference in the type of the hematological analyzer used. Moreover, they do not count large or giant platelets because they cannot be differentiated from red blood cells. Furthermore, many papers in the literature have shown that MPV is dependent on a number of variables, including the time of analysis after venipuncture, the anticoagulant used, the specimen storage temperature, and counter technologies. In the present study, the P-LCR was significantly higher in in all the three groups of thrombocytopenia when compared with the control group. Similarly, Ntaios *et al.* ^[11] and Kaito *et al.* ^[10] reported nearly similar cutoff value of greater than 30%, with diagnostic sensitivities of 90.4 and 91.4%, respectively. In addition, Babu and Basu ^[15] and Borkataky *et al.* ^[9] reported that the P-LCR was increased in destructive thrombocytopenia patients compared with healthy controls and they concluded that the P-LCR can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts. With regard to PDW, there was no significant difference between the two patient groups or between the patient groups and the control group in our study. In contrast, Shah *et al.*^[12] and Borkataky *et al.* ^[9] found that the PDW was higher in ITP patients compared with acute myeloid leukemia patients and nonmegaloblastic hypoproliferative

patients, respectively. In addition, Kaito *et al.* ^[10] suggested a cutoff value of greater than 17 fl for PDW to distinguish ITP from hypoproductive thrombocytopenia, with 71.8% diagnostic sensitivity and 95% specificity. Similarly, Ntaios *et al.* ^[11] suggested a cutoff value between 15 and 17 fl, with 100% sensitivity, specificity, positive predictive value, and negative predictive value. In our study, PDW values are significantly lower in Immune thrombocytopenia (ITP) than Nonimmune and miscellaneous groups in whom there is no significant variation. In the future, improved research designs and standardized measurements for platelet indices may significantly increase the diagnostic predictive power of platelet indices in the differential diagnosis of thrombocytopenia.

Conclusion

Platelet indices should be considered in the diagnosis of thrombocytopenia due to accelerated destruction of any cause. No significant variation in the MPV, P-LCR, P-LCC in all the three groups. The PDW can be useful for a positive diagnosis of immunological thrombocytopenia (ITP).

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