Original Article

Study of platelet indices and their role in evaluation of thrombocytopenia

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Abstract

Background: Thrombocytopenia may result from mechanisms such as marrow hypoplasia, increased destruction of platelets, and splenic sequestration. The gold standard method for discriminating the causes of thrombocytopenia is bone marrow examination, but it is invasive and expensive. Therefore, an alternative method should be introduced as a first-line diagnostic procedure. Of late, the automated blood cell analyzer has made it possible to assess the cause of thrombocytopenia through various machine-derived parameters, known as platelet indices, which include the mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), which are provided as a part of routine complete blood count. **Objectives:** The objectives of the present study are to study the variation and effectiveness of platelet indices in establishing the etiology of thrombocytopenia. **Method:** An observational, prospective, and comparative study was conducted on 134 patients with thrombocytopenia, and 67 cases were taken as the normal group. The study group was classified into two groups: hypo-productive and hyper-destructive. Platelet indices were recorded and compared in the two groups along with the normal group. **Results:** The mean platelet count (10^3 μL) in the normal, hypo-productive, and hyper-destructive groups was 232.03 ± 74.84, 73.00 ± 36.52, and 68.28 ± 38.24, respectively. The MPV and mean PCT in the normal, hypo-productive, and hyper-destructive groups were 9.46 ± 1.68fL, 8.99 ± 1.49fL, and 11.35 ± 1.35fL and 0.22 ± 0.06%, 0.07 ± 0.04%, and 0.08 ± 0.05%, respectively. The mean PDW in the normal, hypo-productive, and hyper-destructive groups was 15.66 ± 1.76fL, 17.63 ± 1.01fL, and 18.32 ± 1.10fL, respectively. **Conclusion:** In the present study, platelet indices such as MPV, PCT, and PDW are higher in the hyper-destructive group and may discriminate hyper-destructive from hypo-productive causes of thrombocytopenia.

Keywords: Hyper-destructive thrombocytopenia, hypo-productive thrombocytopenia, mean platelet volume, platelet distribution width, platelet indices, plateletcrit

Introduction

Platelets are the first line of defense in preventing blood loss because of micro- and macro-vascular injury by maintaining the integrity of the endothelium by aggregating and adhering to each other. A platelet count of less than 150×10^9/L is defined as thrombocytopenia. Thus, bleeding is a frequently occurring complication in a low platelet count as platelets play a vital role in primary hemostasis[1] and it may be the cause of death in thrombocytopenic patients.[2,3]

Thrombocytopenia may result from many mechanisms such as marrow hypoplasia, increased destruction of platelets, and splenic sequestration. Hypo-productive thrombocytopenia results from decreased bone marrow production because of primary or secondary bone marrow diseases such as aplastic anemia, acute myeloid leukemia (AML), megaloblastic anemia, myelodysplastic syndrome, amegakaryocytic thrombocytopenic purpura, and

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Received: 25-02-2022 **Revised:** 10-05-2022
Accepted: 25-05-2022 **Published:** 31-10-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_460_22

How to cite this article: Saran K, Vidya K, Seema K, Prasad A, Prakash J. Study of platelet indices and their role in evaluation of thrombocytopenia. J Family Med Prim Care 2022;11:6236-42.

post-chemotherapy.[4] Hyper-destructive thrombocytopenia is because of extra-medullary platelet destruction with normal or increased production of the bone marrow like disseminated intra-vascular coagulopathy (DIC), immune thrombocytopenic purpura (ITP), and secondary ITP. Splenic sequestration occurs mainly in congestive splenomegaly because of chronic infection, myeloproliferative disease, lymphomas, homozygous sickle cell disease, hemoglobin C disease (HbC), Gaucher's disease, thalassemia major, and so on.[5]

The gold standard method for discriminating the causes of thrombocytopenia is bone marrow examination, but it is invasive and expensive and carries an overt risk of bleeding diathesis. Therefore, it is not recommended as a first-line diagnostic procedure. Of late, the automated blood cell analyzer (Beckmann Coulter LH 780) has made it possible to assess the cause of thrombocytopenia through various machine-derived parameters called as platelet indices, which include the mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), which are provided as a part of routine complete blood count. These parameters form a preliminary, non-invasive mode of evaluating the cause for thrombocytopenia.[6]

Platelet indices are also bio-markers of platelet activation, which give diagnostic and prognostic clues in many clinical settings. MPV is the mode of measured platelet volume and determines the progenitor cell (megakaryocytes) in the bone marrow. When platelet production is decreased, young platelets become enlarged and more active, so the MPV level increases, which indicates the increased platelet diameter, which can be used as a marker of platelet rate and platelet activation. Therefore, MPV is the parameter that measures the average platelet size as the mean corpuscular volume does for red blood cells (RBCs).[7-9].PDW directly measures the variability in platelet size and reflects the heterogeneity in platelet morphology and has shown usefulness in establishing the differential diagnosis between reactive thrombocytosis and thrombocytosis associated with the myeloproliferative disease. Therefore, it helps in establishing a differential diagnosis of thrombocytopenia because of decreased production or platelet destruction.[7,8,10-12] PCT is a measure of total platelet mass and is an effective screening tool for detecting platelet quantitative abnormality. Platelet-large cell ratio (P-LCR) is an indicator of circulating larger platelets and used to monitor platelet activity. It is the ratio of larger platelets to total platelet count, and it is inversely related to platelet count and directly related to MPV and PDW. Therefore, platelet indices have a significant role in discrimination between hypo-productive and hyper-destructive thrombocytopenia.[13,14]

Studies have shown that MPV, PDW, and P-LCR have a good diagnostic correlation which can be compared to findings from the study of the bone marrow. The present study attempts to find the usefulness of these platelet indices (MPV, PDW, and PCT) derived from the machine on the principle of impedance in discriminating between hyper-destructive or hypo-productive causes of thrombocytopenia and to assess their sensitivity and specificity and thereby help in avoiding or at least delaying a request for bone marrow examination.

Materials and Methods

Study design

The present study was an observational, prospective, and comparative study conducted on patients with thrombocytopenia and matched control getting investigated in our hospital. It was carried out during the academic period of January 2017 to June 2018, in which 201 thrombocytopenia cases were studied. After approval from the Institutional Ethics Committee, the study was registered with Clinical Trials Registry-India (CTRI/2018/03/012407). This study conformed to the Helsinki Declaration (World Medical Association, 1995). Written informed consent was obtained from all the patients and parents/guardians for children before the enrollment in the study.

Suspected or confirmed hematological patients were enrolled in the study with a platelet count below 150×10^9/L, which was confirmed by peripheral smear examination. The peripheral blood smears were stained by Leishmann's stain. The clinical details and demographics were taken from case records and by using case collecting proforma. Only those cases were included in the study whose diagnosis was established by either ancillary test or bone marrow examination. All cases of thrombocytopenia with a platelet count below 1,50,000/cu mm with or without bone marrow studies, cases with sufficient clinico-hematological work-up with an established clinical diagnosis, and only one sample of the single participant taken were included. However, pseudo-thrombocytopenia and patients who have received the blood transfusion or platelet transfusion within 7 days were excluded.

Laboratory analysis

Blood samples for complete blood count (CBC) analysis were collected into 5 ml EDTA anti-coagulant tubes, and the samples were analyzed using an automated hematology analyzer (Beckmann Coulter LH 780) between 2 and 4 hours of collection. The Beckmann Coulter measures RBC and platelet on the impedance principle. Platelets are classified as pulses representing cells from 2 to 20 fl. Pulses are sorted using the analyzer into three 64-channel size distribution histograms. The data collection was performed between 2 and 20 seconds. The data collection was stopped with collection of a minimum of 1500 cells in each of the three histograms or for 20 seconds, whichever is reached the earliest. These data were sent to the workstation of the machine where platelet count was calculated as areas filled under the histogram. Then, platelet counts were adjusted for calibration and predilute factor. MPV and PDW were derived, whereas PCT was calculated.

Three-level quality control samples were run twice daily. We were also enrolled with a Proficiency Testing Program

with Bio-Rad. All our results were satisfactory. To rule out pseudo-thrombocytopenia and fragments of cells such as schistocytes, a Leishmann's stained peripheral blood smear was reviewed.

Study patients

Based on clinical and laboratory information, including preceding and follow-up laboratory data, the cases were broadly classified into two groups on the basis of the cause of thrombocytopenia because of peripheral hyper-destruction (immune thrombocytopenic purpura, infections such as malaria, dengue, etc.) and a hypo-proliferative bone marrow (megaloblastic anemia, acute leukemia, aplastic anemia, myelodysplastic syndrome, multiple myeloma, marrow infiltration, chronic leukemia). Patients with a platelet count below 150×10^9/L were followed up to 2 to 3 weeks or depending upon the case scenario with respect to clinical response to the treatment. In a few patients, the diagnosis was made on bone marrow examination. An automated CBC including platelet count and platelet indices (MPV, PWD, and PCT) were recorded.

The sample size was calculated by estimating the difference between two means from the literature in a study by Negash *et al.*[15] The mean standard deviation (SD) in group I is 3.2, the SD in group II is 2.3, and the estimated difference between means is 1 with CI (confidence interval) = 95%. We estimated that we would need a sample size of around 60 for a study with 80% power at the 5% level of confidence.

Statistical analysis

The data were analyzed by statistical methods using SPSS version 21. The descriptive variables were expressed in frequency and percentage. The correlation test was to be used to see the association between continuous variables. The Student t-test was used for comparison of both groups. The ANOVA test was used for comparing the groups with the control. A *P* value of < 0.05 was considered statistically significant.

Results

In the present study, a total of 201 were studied and the age range of patients was between 3 yr and 80 yr. Each group (hypo-productive, hyper-destructive, and control) has 67 cases with a similar age and sex. The mean age of the patients was 41.56 ± 18.11, 28.54 ± 10.81, and 32.22 ± 10.86, respectively. The most common age groups for thrombocytopenia in hypo-productive groups were 41–50 years, and those in the hyper-destructive group were between 21 and 30 years. A slight male preponderance was seen in the overall three groups, and the overall male to female ratio was 2.14:1 [Table 1].

Comparison of platelet count and platelet indices between study patients

The platelet count and the platelet indices were compared between hypo-productive, hyper-destructive and healthy controls groups. The platelet count, MPV, PCT, and PDW between the groups were statistically significant [Table 2]. On comparing among the groups, the platelet count, PCT, and PDW in normal versus hypo-productive and normal versus hyper-destructive were statistically significant ($p < 0.05$), whereas in hypo-productive versus hyper-destructive, they were statistically not significant ($p > 0.05$). However, MPV in normal versus hypo-productive was statistically not significant, whereas those in normal versus hyper-destructive and hypo-productive versus hyperdestructive were statistically significant. All the platelet indices were higher in hyper-destructive thrombocytopenia as compared to hypo-productive thrombocytopenia except platelet count, whereas PCT in healthy controls was higher than that in hypo-productive and hyper-destructive thrombocytopenia patients.

Correlation between platelet and platelet indices among all groups [Table 3] shows that PCT in all three groups was statistically significant, whereas PDW was statistically significant in the hypo-productive group and MPV was statistically significant the in normal and hyper-destructive groups. Overall, correlation between platelet and platelet indices (MPV, PCT, and PDW) was statistically significant.

Platelet indices under various clinical conditions

Platelet indices were analyzed under various clinical conditions [Table 4], and it was observed that the platelet count was lower in acute leukemia, whereas it was higher in the hypo-cellular marrow. Other platelet indices such as MPV were higher in ITP and lower in acute leukemia. PCT was higher in CLL and lower in acute leukemia. PDW was higher in CLL and lower in lymphoproliferative disorder. However, the number of samples was only one in CLL and the hypo-cellular marrow.

Table 1: Socio-demographic characteristics of patients and controls

Variable	Number	Sex		Age in years (Mean±SD)
		Male	Female	
Hypo-productive	67	49	18	41.56±18.11
Hyper-destructive	67	47	20	28.54±10.81
Control	67	41	26	32.22±10.86
Total	201	137	64	

Values are presented as mean±SD. SD - standard deviation

Table 2: Comparison of mean platelet count and mean platelet indices between hypo-productive, hyper-destructive, and healthy controls

Variables	Hypo-productive	Hyper-destructive	Control	*P*
Platelet count (10^3 µL)	73.00±36.52	68.28±38.24	232.03±74.84	<0.001
MPV (fl)	8.99±1.49	11.35±1.35	9.46±1.68	<0.001
PCT (%)	0.07±0.04	0.08±0.05	0.22±0.06	<0.001
PDW (fl)	17.63±1.01	18.32±1.10	15.66±1.76	<0.001

Values are presented as mean±SD. Data were analyzed using Student's t-test. SD - standard deviation. MPV - mean platelet volume, PCT- plateletcrit, PDW - platelet distribution width

Distribution of platelet indices in the ITP and megaloblastic marrow

Distribution of MPV, PCT, and PDW among cases in the study groups of ITP and the megaloblastic marrow is shown in Table 5. The mean values of MPV and PDW were higher in ITP in comparison to the megaloblastic marrow. PCT was similar in both groups, whereas the platelet count was higher in the megaloblastic marrow. The mean value of MPV in the ITP group showed a higher value than the megaloblastic marrow, which was statistically significant, but the mean value of PCT and PDW was statistically non-significant.

Distribution of platelet indices among cases in ITP and dengue

Table 6 shows the distribution of MPV, PCT, and PDW among cases in the study groups of ITP and dengue. The mean values of MPV and PDW were almost similar in both groups; however, PCT was higher in dengue, whereas the platelet count was mildly increased in dengue. The mean values of MPV, PCT, and PDW in both the groups were statistically non-significant on comparison of both the ITP and dengue groups.

Table 3: Correlation of platelet and platelet indices among all groups

Correlations				
Group	**Variable**	**Platelet (10^3 µL)**		
		r	***P***	***n***
Normal	MPV	-0.297**	0.015	67
	PCT	0.862**	0.000	67
	PDW	-0.197	0.110	67
Hypo-productive	MPV	0.193	0.118	67
	PCT	0.932**	0.000	67
	PDW	0.321**	0.008	67
Hyper-destructive	MPV	0.313**	0.010	67
	PCT	0.975**	0.000	67
	PDW	-0.094	0.447	67
Correlations				
Variable		**Platelet (10^3 µL)**		
		r	***P***	***n***
MPV		-0.184**	0.009	201
PCT		0.958**	<0.001	201
PDW		-0.556**	<0.001	201

Data were analyzed using ANOVA test. SD - standard deviation. MPV - mean platelet volume, PCT - plateletcrit, PDW - platelet distribution width, **significant

Discussion

Platelets play a vital role in the primary hemostasis. A recent development in technology has made it possible to know platelet indices such as MPV, PCT, and PDW with an automated hematology analyzer.[15]

Bone marrow examination is an invasive procedure, so it is not necessary to use it as a first-line diagnostic procedure in thrombocytopenia. The complete blood counts generated by automated analyzer values for platelet indices are also given along with the platelet counts.[16] These platelet indices vary according to platelet production and activation. Therefore, platelet indices can be used to categorize the cause of the thrombocytopenia so that the treatment is started at the earliest.

In our study, to know the diagnostic predictive capacity in different patients of thrombocytopenia, three platelet indices, MPV, PCT, and PDW, were analyzed. The important function of a clinical test in our study was to know whether a low platelet count in patients was caused by either decreased production or increased destruction of platelets and to identify the causes of thrombocytopenia.

The mean age group of the present study in hypo-productive thrombocytopenia and hyper-destructive thrombocytopenia was similar to that in the previous study.[15] Male predominance in our study was similar to that in other studies;[17] on the other hand, because of uneven distribution of sex among the study group, females were predominant;[15,18] however, males were predominant in the hypo-productive group. This may be explained by the fact that epidemiological differences in the prevalence of chronic ITP are more common in females and chronic myeloid leukemia (CML) is more common in males and also in old age groups.[19-22]

Platelet counts were higher in the hypo-productive group than in the hyper-destructive group in previous studies,[18,23] which is similar to our study. However, in a few studies,[15,24,25] the mean platelet count in the hyper-destructive group was more than that in the hypo-productive group.

Table 4: Platelet indices under various clinical conditions

Disease Category	No. of cases	Platelet (10^3 µL) (Mean±SD)	MPV (Mean±SD)	PCT (Mean±SD)	PDW (Mean±SD)
ITP	10	63.90±34.93	11.65±1.32	0.07±0.04	18.34±0.95
Dengue	47	68.43±40.41	11.26±1.35	0.08±0.05	18.27±1.03
Malaria	10	72.00±33.49	11.48±1.51	0.08±0.05	18.55±1.56
Acute leukemia	18	55.50±40.31	7.98±1.10	0.04±0.03	17.50±1.00
Megaloblastic marrow	25	83.04±32.26	9.448±1.39	0.08±0.03	17.72±1.09
Plasma cell dyscariasis	15	78.80±36.46	9.35±1.37	0.07±0.04	17.49±0.86
Lymphoproliferative disorder	2	58.00±42.43	8.10±0.28	0.05±0.04	18.25±0.35
Myelodysplastic syndrome	5	56.80±25.52	9.58±2.28	0.06±0.04	17.28±1.34
Chronic lymphocytic leukemia (CLL)	1	112.00	9.90	0.11	19.40
Hypo-cellular marrow	1	122.00	8.40	0.10	17.70

Variables are presented as mean±SD. *n* - number of patients; SD - standard deviation. ITP - immune thrombocytopenic purpura

Table 5: Distribution of platelet indices among cases in ITP and megaloblastic marrow

Disease Category	Platelet (10^3 µL)	MPV	PCT	PDW
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
ITP	63.90±34.93	11.65±1.32	0.07±0.04	18.34±0.95
Megaloblastic marrow	80.78±36.19	9.07±1.10	0.07±0.03	17.57±1.19
P	0.24	<0.001	0.96	0.09

Values are presented as mean±SD. Data were analyzed using Student's *t*-test. SD - standard deviation. ITP - immune thrombocytopenic purpura. MPV - mean platelet volume, PCT - plateletcrit, PDW - platelet distribution width

Table 6: Distribution of platelet indices among cases in ITP and dengue

Disease Category	Platelet (10^3 µL)	MPV	PCT	PDW
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
ITP	63.90±34.93	11.65±1.32	0.07±0.04	18.34±0.95
Dengue	68.42±39.98	11.30±1.33	0.08±0.05	18.30±1.02
P	0.74	0.52	0.77	1.0

Values are presented as mean±SD. Data were analyzed using Student's *t*-test. SD - Standard deviation. ITP - immune thrombocytopenic purpura. MPV - mean platelet volume, PCT - plateletcrit, PDW - platelet distribution width

Previous studies showed[4,7,10] a significant difference in MPV among hypo-productive and hyper-destructive thrombocytopenia. However, PCT and PDW also had significant differences with better discriminating potential among the two groups. In our study, the cutoff value of MPV was 8.99 fl in the hypo-productive group and 11.35 fl in the hyper-destructive group, which was less than those in previous studies,[8,14,15] ranging from more than 9 fl to more than 11 fl. In these studies, they reported that the value of MPV was significantly different between the hypo-productive and hyper-destructive groups. It could be because of automated hematology analyzers which may not be able to discriminate platelets from other similarly sized fragmented red or white blood cells, immune complexes, or cell debris.

MPV is a marker of bone marrow activity and platelet activation and also a surrogate marker of bleeding. An elevated level of MPV is an indicator of increased megakaryocyte shedding of platelets; however, MPV is increased in consumptive or destructive thrombocytopenia. A low MPV is associated with bone marrow suppression and an increased risk of bleeding.[26] On literature search, it was found that MPV depends upon a number of variables such as the anti-coagulant used, the temperature of specimen storage, counter technologies, and time lag after venipuncture. Numbenjapon *et al.*[4] proposed a cutoff value of 7.9 fl for MPV, which was lower than that previously reported, and also reported that MPV can be used to distinguish hypo-productive from hyper-destructive thrombocytopenia.

PCT was less in the hypo-productive group in comparison to the hyper-destructive group in a study[24] which was similar to our study. We observed in our study that PCT in the hyper-destructive group was mildly higher than that in the hypo-productive group. However, Khaleel KJ *et al.*[23] found that PCT was equal in both hyper-destructive and hypo-productive groups.

In view of PDW, we found in our study that there was no significant difference between hypo-productive and hyper-destructive groups and also between both groups and the control group. However, the previous study[8,17] reported that PDW was higher in patients with ITP when compared with AML patients and non-megaloblastic patients, respectively. Kaito *et al.*[7] suggested a cutoff value of more than 17 fl for PDW with 71.8% sensitivity and 95% specificity, and Ntaios *et al.*[10] suggested a cutoff value between 15 fl and 17 fl with 100% sensitivity, specificity, and positive and negative predictive values to distinguish ITP from hypo-productive thrombocytopenia. Because of variation in types of study participants, differences in sensitivity, specificity, and predictive values exist.

The majority of the cases in our study were of dengue (n = 47), followed by ITP (n = 10) and malaria (n = 10), in the hyper-destructive thrombocytopenia group, which was similar to the study of Katti *et al.*[13] and Parveen S *et al.*,[24] in which the majority of the cases were of dengue, followed by malaria. The anti-dengue virus antibody binds to the dengue antigen associated with platelets, leading to their immune-mediated destruction.[27] Malaria is also a common cause of thrombocytopenia in our setting. It is imperative to know the etiology of thrombocytopenia for correct patient management and to maintain a strategic distance from pointless techniques, transfusions, and potentially harmful medications. Thus, new non-invasive diagnostic approaches for thrombocytopenia are needed.

The distribution of MPV, PCT, and PDW among cases in the study groups of ITP and dengue and the mean values of MPV and PDW were slightly increased in ITP than in the dengue cases, but PCT was higher in dengue cases, which may be because of hemoconcentration as PCT is a representation of the volume percent of platelets. The mean values of MPV, PCT, and PDW were statistically non-significant on comparison of both the ITP and dengue groups.

On comparison among the groups between ITP and megaloblastic marrow, the present study shows that the mean values of MPV and PDW were higher in ITP than in megaloblastic marrow; however, PCT was similar in both the groups. The mean value of MPV in the ITP group was higher than that in megaloblastic marrow, which was statistically significant, but no statistically significant difference was seen in the mean value of PCT and PDW. Rajashekar RB *et al.*[25] found in their study that the mean of platelet indices was significantly higher ($p < 0.05$) in the hyper-destructive group [PDW (16.6fl), MPV (12.1fl), P-LCR (42.3%)] as compared to the hypo-productive group [PDW (11.8fl), MPV (10.9fl), P-LCR (31.5%)] and the mean values of PDW (14.7fl) and MPV (11.6fl) in the megaloblastic group showed a significantly higher value ($p < 0.05$) than the hypo-productive group, but no statistically significant difference was seen compared to the hyper-destructive group ($p > 0.05$). However, megaloblastic anemia has been classified as hypo-productive thrombocytopenia. Therefore, we would like to recommend the division of hypo-productive thrombocytopenia into megaloblastic and

non-megaloblastic categories. The limitations of our study were that the sample size would have been large in order to establish statistical significance, splenic sequestration was not included as a cause of thrombocytopenia, and bone marrow examination was not performed in the cases of dengue and malaria.

Conclusion

Platelet indices such as MPV, PCT, and PDW are significantly higher in hyper-destructive causes of thrombocytopenia and may discriminate hyper-destructive from hypo-productive causes of thrombocytopenia. In the majority of patients, it may help in delaying or avoiding unnecessary, invasive bone marrow examination. MPV stands as a better parameter, which is statistically significant and can be used to segregate the hyper-destructive and hypo-productive causes of thrombocytopenia. Thus, in all cases of thrombocytopenia, the clinicians need to look into platelet indices which are akin to RBC indices, which can help in arriving at probable pathophysiology of thrombocytopenia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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