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ORIGINAL ARTICLE

Evaluation of Platelet Large Cell Ratio (P-LCR) in Abnormal Platelet Counts

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Abstract

Background: Platelets have an important role in the various vessel functions. Platelets exist in circulation for 5–7 days after formation from megakaryocytes. Platelets primarily function as regulators of haemostasis and thrombosis. Abnormal platelet counts include both increased platelet count (thrombocytosis) and decreased platelet count (thrombocytopenia). With use of automated blood cell analysers, it is possible now to measure various blood cell parameters automatically. Platelet volume indices can be used for the diagnosis of various conditions with abnormal platelet counts.

Methods: This study was an observational cross-sectional study conducted in the Department of Pathology of a tertiary care hospital after approval from the Institutional Ethics Committee over a one-year period in 178 subjects. These subjects were selected based on the diagnosis of thrombocytosis and thrombocytopenia using inclusion & exclusion criteria following written consent from the participants. The data was recorded in a predesigned proforma and analysed using statistical tools.

Results: The study participants age ranged from 12 to 91 years with mean age of 50.2 years. Majority of subjects (70.2%) were above 40 years of age with 27.5% subjects being above 60 years and 23% subjects in the age group of 40-50 years. The number of males (51.7%) and females (48.3%) were similar in the study with male to female ratio of 1.1: 1. Megaloblastic anaemia (17.7%), dengue (15.2%), chronic liver disease (13.9%) and chemotherapy (13.9%) were among the common causes of thrombocytopenia whereas Iron deficiency anaemia (45%), sepsis (25%) and chronic myeloid anaemia (20%) were among the common causes of thrombocytosis. The mean P-LCR ranged from 39.55% to 52.12% in thrombocytopenia and from 14% to 44.6% in thrombocytosis cases and this was statistically significant ($p<0.001$).

Conclusion: P-LCR can provide a reliable information for differentiation between diagnosis of hypo-productive and hyper-destructive thrombocytopenic patients. 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 and thrombocytosis.

Keywords: Platelet Large Cell Ratio, P-LCR, Thrombocytopenia, Thrombocytosis, Abnormal Platelet Counts.

Introduction

Platelets play an important role in the vessel. Following their formation from megakaryocytes, platelets exist in circulation for 5–7 days and primarily function as regulators of haemostasis and thrombosis [1]. Anucleus blood platelets cope with different tasks. They adhere to the uncovered extracellular matrix at a damaged vessel, aggregate and augment coagulation to form a local clot [2]. Platelets also contribute to immune processes by monitoring blood vessel integrity, coordinating vascular trafficking and mediating functions of other immune cells [3]. Platelets directly interact with viruses and kill bacteria by bridging adaptive and innate immune mechanisms, participate in inflammation, wound repair, cancer progression and metastasis [4-6].

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Abnormal platelet counts include both increased platelet count (thrombocytosis) and decreased platelet count (thrombocytopenia). Normal reference interval for platelet counts in adults approximates 150,000 to 450,000 per microliter of blood. Thrombocytopenia is a fairly common condition with diverse disorders and varying aetiology. In evaluating the mechanism of thrombocytopenia, it is necessary to categorize it as hypo-productive or hyper-destructive thrombocytopenia, for appropriate management of patients.

Recent advances in automated blood cell analysers have made it possible to measure various blood cell parameters automatically. Platelet volume indices, estimated by automated blood cell analyzers, are useful in the diagnosis of various conditions with abnormal platelet counts. Among these parameters, platelet indices such as platecrit (Pct), Mean Platelet Volume (MPV), Platelet size Deviation Width (PDW) and Platelet Large Cell Ratio (P-LCR) provide important information [7]. Platelet Large Cell Ratio (P-LCR) is an indicator of circulating larger platelets (>12fl) expressed as percentage. Normal percentage range is 15-35%. It has also been used to monitor platelet activity.

Within one individual, platelets have different physical properties including density and size. The exploration of large and small platelets as morphological and functional distinct cell populations became very vital in the 1960's and it is still a very popular hypothesis, that large platelets are younger because they were shown to be more reactive compared to small ones [8]. On the other hand, changes in P-LCR can indicate a disease process e.g. in immune thrombocytopenia or in marrow aplasia [9,10]. A key question is, if changes in P-LCR result in changed platelet function contributing to thrombogenicity, or if P-LCR changes just mirror differences in platelet turnover which triggers alternative pathways of platelet generation but without functional consequences.

Despite an increasing volume of literature supporting the role of P-LCR in the diagnosis of pathological states of thrombopoiesis, platelet parameters have been underutilized in clinical patient management. P-LCR if properly utilised can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts. Many studies on P-LCR have demonstrated its utility in diagnosing abnormal platelet counts with sufficient sensitivity and specificity. The present study was conducted in a tertiary care hospital to evaluate the Platelet-Large Cell Ratio (P-LCR) in abnormal platelet count in adults.

Methods

This study was an observational cross-sectional study conducted in the Department of Pathology of a tertiary care hospital after approval from the Institutional Ethics Committee over a one-year period from 1st July 2019 to 30th June 2020. 178 subjects were selected based on the diagnosis of thrombocytosis and thrombocytopenia.

Selection Criteria of Patients

Inclusion Criteria

1.) Patients of both sexes with a platelet count of less than 1,50,000 per microliter of blood.

2.) Patient with a platelet count of more than 4,50,000 per microliter of blood.

Exclusion Criteria

1.) Patients on antiplatelet drugs and other medications causing thrombocytopenia will be excluded.

2.) Patients who had been transfused with platelet concentrate or whole blood in the previous 9 days will be excluded.

Sampling Method

Simple Random Sampling Technique was used for sample collection for patients visiting the Department of Pathology and fulfilling the inclusion and exclusion criteria.

Collection of Blood Sample

Under all aseptic precautions, venous blood was collected for the study with Ethylene Diamine Tetra Acetic Acid (EDTA) used as an anticoagulant.

Phlebotomy procedure [11]

1.) A tourniquet was applied just above the intended venipuncture site.

2.) Blood was withdrawn from an ante-cubital vein or other visible veins of the forearm by means of either an evacuated tube or a syringe.

3.) The skin was cleaned with 70% alcohol before being punctured.

4.) The tourniquet was released as soon as the vein is punctured.

5.) The piston of the syringe was withdrawn slowly with no attempt being made to withdraw blood faster than the vein is filling.

6.) Anticoagulated specimens were mixed by inverting the container several times.

7.) Every specimen was then labelled properly.

Complete blood count, Platelet count including platelet indices was done using automated cell counter. Platelet count was reconfirmed by its respective manual method, whenever needed.

Platelet count: By Neubauer Chamber

1.) Take 1.96 ml of 1% ammonium oxalate (diluting fluid) in a test tube. Add 0.02 ml of venous blood and mix thoroughly.
2.) Charge the Neubauer chamber.
3.) Place the mounted counting chamber inside a chamber and leave it undisturbed for 20 minutes.
4.) Place the charged counting chamber on the stage of microscope.
5.) Reduce the illumination and bring the central large square under the low power (×10) objective.
6.) Using high power (×40) objective, count the total number of platelets in central large square (area $1mm^3$).

Calculation

Platelet count per cubic mm = No of platelets counted × Dilution Factor

Area in mm^2 × Depth of chamber = No of platelets counted × 100

1 × 0.1=No of platelets counted ×1000

Automated cell counter, MS4(S) five-part differential was used which works on the principal of impedance method, whereby it counts and sizes cells by detecting and measuring changes in the electrical impedance when a particle in a conductive liquid media passes through a small aperture.

Peripheral Blood Film

Method

a) Place a small drop of blood on the slide about 1cm from one end.
b) Place a spreader in front of the drop at an angle of about 30° to the slide and move it back to make contact with the drop.
c) With a steady movement of the hand, spread the drop along the slide [11].

Staining Procedure

Dry the blood film in the air and flood it with Leishman's stain. After two minutes, add double the volume of water and stain the film for 5-7 minutes. Wash the blood film in a stream of buffered water until it acquires a pinkish tinge and air dry.

Data Collection and Analysis

The clinical records of all patients fulfilling the eligibility criteria was obtained and analysis of each patient's clinical profile was made. For each patient, following laboratory tests was carried out which include platelet count, platelet large cell ratio (P-LCR) and other platelet parameters including plateletcrit (Pct), mean platelet volume (MPV), platelet distribution width (PDW) using the automated analyser. Peripheral blood film was stained with Leishman's stain. Bone Marrow Examination and other relevant investigations, including serology, was performed, wherever indicated. The collected data was entered in Microsoft Excel Word Spreadsheet and analysed. Test of significance applied was independent t-test and one-way anova. The difference was considered statistically significant at $p < 0.05$.

Results

The study participants age ranged from 12 to 91 years with mean age of 50.2 years. Majority of subjects (70.2%) were above 40 years of age with 27.5% subjects being above 60 years and 23% subjects in the age group of 40-50 years. The number of males (51.7%) and females (48.3%) were similar in the study with male to female ratio of 1.1:1 (Table 1).

Table 2 shows megaloblastic anaemia (17.7%), dengue (15.2%), chronic liver disease (13.9%) and chemotherapy (13.9%) were among the common causes of thrombocytopenia whereas Iron deficiency anaemia (45%), sepsis (25%) and chronic myeloid anaemia (20%) were among the common causes of thrombocytosis.

Table 1: Distribution of Study Subjects according to Demographic Characteristics (n=178)

Age (in years)	Frequency (Percentage)
Less than 20	4(2.2)
20-30	16(9)
30-40	33(18.5)
40-50	41(23)
50-60	35(19.7)
Above 60	49(27.5)
Gender	
Female	86(48.3)
Male	92(51.7)

Table 2: Distribution of Study Subjects according to Thrombocytopenia and Thrombocytosis Related Disorders

Clinical Diagnosis	Frequency (Percentage)
THROMBOCYTOPENIA (n=158)	
Hypo-Productive	
Chemotherapy	22(13.92)
Megaloblastic Anaemia	28(17.72)
Hyper-destructive	
Burns	5(3.16)
Cardiac disease	10(6.33)
Dengue	24(15.19)
ITP	5(3.16)
Malaria	10(6.33)
Renal Diseases	6(3.8)
Sepsis	12(7.59)
Snake Bite	4(2.53)
Others	
Pregnancy	7(4.43)
CLD	22(13.92)
Myelofibrosis	3(1.9)
THROMBOCYTOSIS (n=20)	
Primary	
CML	4(20)
Reactive	
Iron deficiency Anaemia	9(45)
Post-surgery	2(10)
Sepsis	5(25)

Table 3 shows the mean platelet count ranged from 42 to 81.7 x 109 platelets per litre in thrombocytopenia whereas the mean platelet count ranged from 516 to 780 x 109 platelets per litre in thrombocytosis. The mean P-LCR ranged from 39.55% to 52.12% in thrombocytopenia ($p<0.001$). However, the mean P-LCR was 10.77% in cases of myelofibrosis. There was a significant difference in mean P-LCR among different diagnosis. The mean P-LCR in thrombocytosis cases ranged from 14% to 44.6% and this was statistically significant. The mean platelet volume (MPV) in thrombocytopenia ranged from 8.81% to 46.32% whereas in thrombocytosis the MPV ranged from 7.7% to 10.6%.

The mean P-LCR was 17.79% in hypo-productive thrombocytopenia and 41.51% in hyper-destructive thrombocytopenia and this difference was significant on statistical analysis ($p<0.01$). The mean platelet volume was 25.32% in hypo-productive thrombocytopenia and 12.88% in hyper-destructive thrombocytopenia. The mean platelet count was 70.86 x 109 platelets per litre in hypo-productive thrombocytopenia and 60.5 x 109 platelets per litre in hyper-destructive thrombocytopenia.

The mean P-LCR was similar in primary thrombocytosis and in reactive thrombocytosis i.e., 30.48% and 30.86% respectively. this difference was not significant on statistical analysis. The mean platelet volume (MPV) was similar i.e. 9.6% both in primary thrombocytosis and in reactive thrombocytosis and this difference was not significant on statistical analysis. The mean platelet count was 637.5 x 109 platelets per litre in primary thrombocytosis and 558.125 x 109 platelets per litre in reactive thrombocytosis and this difference was not significant on statistical analysis.

Table 4 depicts that P-LCR is negatively correlated with the platelet count both in thrombocytopenia and

Table 3: Mean values of Platelet Count, MPV, P-LCR in Thrombocytopenia and Thrombocytosis related disorders

Clinical Diagnosis	Mean Platelet count (x 10^9/L)	p-value	Mean P-LCR (%)	p-value	MPV (fl)	p-value
THROMBOCYTOPENIA (n=158)						
Hypo-Productive						
Chemotherapy	57.09 ± 28.49		22.09 ± 20.24		46.32 ± 170.14	
Megaloblastic Anaemia	81.68 ± 22.32		14.41 ± 6.46		8.81 ± 0.81	
Hyper-destructive						
Burns	53.2 ± 11.3		52.12 ± 10.91		13.5 ± 0.31	
Cardiac disease	71.1 ± 25.95		39.55 ± 5.21		13.18 ± 1.59	
Dengue	55.08 ± 23.54		40.93 ± 5.69		13.1 ± 1.09	
ITP	56.6 ± 21.34	0.002	40.62 ± 0.93	<0.001	12.1 ± 0.53	0.941
Malaria	65.2 ± 23.09		39.8 ± 7.38		12.32 ± 1.86	
Renal Diseases	42 ± 22.85		41.7 ± 1.5		14.03 ± 0.41	
Sepsis	69.92 ± 14.19		41.72 ± 0.78		12.33 ± 1.2	
Snake Bite	67.25 ± 20.22		41.15 ± 1.33		12.43 ± 1.16	
Others						
Pregnancy	54.14 ± 14.83		41.23 ± 2.77		12.5 ± 1.21	
CLD	68.91 ± 22.34		39.85 ± 8.12		14.45 ± 3.5	
Myelofibrosis	72.67 ± 35.22		10.77 ± 1.33		8.83 ± 0.75	
THROMBOCYTOSIS (n=20)						
Primary						
CML	637.5 ± 130.74		30.48 ± 8.44		9.6 ± 1.28	
Reactive						
Iron deficiency Anaemia	516.67 ± 67.27	0.006	26.97 ± 7.87	0.001	9.52 ± 1.54	0.094
Post-surgery	780 ± 70.71		14 ± 1.41		7.7 ± 0.71	
Sepsis	544 ± 80.19		44.6 ± 7.18		10.6 ± 0.61	

MPV;mean platelet volume, P-LCR; Platelet Large Cell Ratio

Table 4: Correlation of P-LCR with mean platelet count and MPV

Platelet Indices		P-LCR	
		Thrombocytopenia	Thrombocytosis
Platelet count	Pearson Correlation	-0.124	-0.249
	p-value	0.122	0.290
MPV	Pearson Correlation	-0.092	0.697**
	p-value	0.250	0.001

MPV;mean platelet volume, **P-LCR**; Platelet Large Cell Ratio

thrombocytosis. However, P-LCR is negatively correlated with MPV in thrombocytopenia but positively correlated in thrombocytosis.

Discussion

The diagnosis and management of thrombocytopenia and thrombocytosis is one of the growing areas in the practice of haematology in recent times. Although the routine automated platelet determinations are available, platelet indices such as P-LCR, MPV, have not been used much for clinical use 12,13].

Thrombocytopenia is a one of the common clinical

manifestations of many diseases and has varied causes, including decreased bone marrow production, increased spleen sequestration, and accelerated destruction of platelets. One of the major causes of increased platelet destruction is immune thrombocytopenia, in which autoantibodies bind to platelet antigens, causing their premature destruction by the reticuloendothelial system, particularly the spleen.[14] Decreased bone marrow production due to haematological malignancy, tumour infiltration, aplastic anaemia, and chemotherapy is another common cause of thrombocytopenia, and its diagnosis requires confirmation by haematological morphological examination, bone marrow examination, immunophenotyping, and karyotyping, which are familiar only to haematologists.[13]

This study was conducted on 178 patients of which 158 patients had thrombocytopenia and 20 patients had thrombocytosis. Among these 76 patients had hyper-destructive thrombocytopenia, and 82 patients had hypo-productive thrombocytopenia while 4 patients had primary thrombocytosis and 16 patients had reactive thrombocytosis. The mean age of study subjects was 50.15 years (SD=16.60) while median age was 49 years (Range 12 – 91 years). There were 92 males and 86 females in our study with M:F ratio of 1.1:1. In a study done by Farweez et al, 2014 in 80 study participants who had similar mean age of 50.4 + 9.5 years whereas M:F ratio was 1:1.5.[15]

In our study, the P-LCR was higher in hyper-destructive thrombocytopenia (Mean P-LCR=41.5%) than hypo-productive thrombocytopenia patients (Mean P-LCR=17.8%). Likewise, Borkataky et al, 2009 reported a significantly lower P-LCR in hypo-productive thrombocytopenia patients than in the control group, but they did not report a difference in the P-LCR between ITP patients and the control group. However, in our study the P-LCR was found to be significantly higher in hyper-destructive thrombocytopenia patients compared with hypo-productive thrombocytopenia patients. Similarly, Babu and Basu and Borkataky et al reported that the P-LCR was increased in destructive thrombocytopenia patients compared with hypo-productive thrombocytopenia and non-megaloblastic hypo-productive thrombocytopenia patients, although this increase was not statistically significant, and they concluded that the P-LCR can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts.[16,17] Similar findings were also reported by Ntaios et al and Kaito et al.[18,19] The authors reported cut off value of greater than 30%, with diagnostic sensitivities of 90.4 and 91.4%.

Our study showed that MPV did not show a significant difference between either the hyper-destructive and the hypo-productive thrombocytopenia group. Similarly, Borkataky et al found no significant difference in the MPV between the hyper-destructive and the hypo-productive thrombocytopenia group [16].

Meanwhile, hyper-destructive thrombocytopenia patients showed higher MPV results than hypo-productive thrombocytopenic patients. Similarly, previous work by researchers such as Kaito et al, Ntaios et al, Xu et al and Shah et al reported that MPV was higher in hyper-destructive thrombocytopenia patients compared with hypo-productive thrombocytopenic patients, which reflected an increase in the production rate, and they established cut off values ranging from greater than 9 fl to greater than 11 fl [13,18-20].

Although Numbenjapon et al reported that MPV could be used in distinguishing hyper-destructive from hypo-productive thrombocytopenia, they proposed a cut off value of 7.9 fl, which is lower than the previously reported cut off values [21].

This variation in the cut off values of MPV in different studies can be attributed to the difference in the selection of patients with hypo-productive thrombocytopenia. Another explanation for the differences in the cut off values of MPV in different studies can be the difference in the type of the hematological analyzer used, as older automated analyzers, which could have been used in these studies, cannot discriminate platelets from other similarly sized particles such as fragmented red or white blood cells, cell debris, and immune complexes. 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 [22].

Thrombocytosis can result from myeloproliferative disorders but is more commonly found as reactive phenomenon not caused by a bone marrow disease but secondary to various pathological states. Thrombocytosis is classified according to cause as Primary thrombocytosis or Secondary/Reactive thrombocytosis. Reactive thrombocytosis is often transient and secondary to underlying inflammatory conditions and reverses following treatment of the underlying cause. Frequency is higher in children as compared to adults due to the immaturity of innate and/or adaptive immunity and exposure to infections more frequently [23]. Primary thrombocytosis, on the other hand, is extremely rare in children. Patho-mechanism of primary form is due to spontaneous production of megakaryocytic progenitors and increased sensitivity to thrombopoietin (Tpo). Whereas in secondary form, hepatic Tpo production is increased as an acute response reaction

to variety of conditions [23].

In our study, thrombocytosis was found in 20 patients. In the present study, primary thrombocytosis was seen in 20% and reactive thrombocytosis in 80%, which is in accordance to previous studies by Matsubara et al and Mantadakis et al [24,25].

All the cases of primary thrombocytosis were of Chronic Myeloid Leukaemia. Iron deficiency anaemia alone comprised 45% while infections comprised 25% of reactive thrombocytosis. According to C. Sandoval, Iron deficiency anaemia remains the most common non-infectious cause of reactive thrombocytosis [26]. Hemoglobinopathies cases associated with reactive thrombocytosis was not seen in our study. Although Yadav et al also reported 7 cases of thalassemias with reactive thrombocytosis [27]. Subramaniam et al also compared the platelet indices with degree of thrombocytosis and found a weak significant negative correlation of mean MPV with degree of thrombocytosis [28]. Similar to our study results Zhang et al reported significant difference in P-LCR values between primary and reactive thrombocytosis which can help to distinguish between the types of thrombocytosis [29].

However, this study had few limitations. The number of cases for thrombocytosis was limited and hence various platelet indices in reactive thrombocytosis could not be compared with the indices in primary thrombocytosis. A larger prospective hospital-based study is needed to study the role of P-LCR in thrombocytosis.

Conclusion

Thrombocytopenia is one of the common clinical manifestations of many diseases and has varied causes, including decreased bone marrow production, increased spleen sequestration, and accelerated destruction of platelets. Finally, the fact that platelet indices can be used for diagnostic purpose has been recognized, however, this knowledge gained very limited use in the daily clinical practice. In our study, P-LCR was higher in hyper-destructive thrombocytopenia than hypo-productive thrombocytopenia patients and hence can differentiate between the types of thrombocytopenia. Hence P-LCR can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts.

It can be concluded that P-LCR can provide a reliable information for differentiation between diagnosis of hypo-productive and hyper-destructive thrombocytopenic patients. 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 and thrombocytosis.

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