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The impact of platelet indices in the evaluation of different causes of platelet count disorder

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Abstract:

BACKGROUND: Some of the platelet count disorders have no single clinical or laboratory diagnostic finding and bone marrow examination may be required which is invasive, time consuming. Platelet indices are readily available parameters by recent hematology autoanalyzers and could provide some important information and can differentiate between several mechanisms of platelet disorders.

AIM OF STUDY: To evaluate and interpret different platelet indices (plateletcrit, mean platelet volume [MPV], platelet distribution width [PDW], platelet-large cell ratio [P-LCR]) in patients with quantitative platelet disorders.

PATIENTS AND METHODS: A prospective cross-sectional study was carried out from November 2019 to September 2020 in different Iraqi hematology centers and conducted on 160 adult patients from 3 hematology centers, from November 2019 to September 2020, 80 patients have thrombocytopenia, and 80 patients with thrombocytosis. Platelet count and indices (MPV, P-LCR, PDW) were determined using automated analyzers. For each hematological parameter, two measurements were taken at different time interval and the mean value of these two records was relied on.

RESULTS: A significant increase in all platelet indices (MPV, PDW, P-LCR) with cutoff values of 7.9 femtoliters (fl), 15.3%, and 12.6%, respectively, $P = 0.000$ was observed in primary thrombocytosis, with 90% sensitivity for MPV and 50% specificity for PDW. In immune thrombocytopenia (ITP), all platelet indices (MPV, PDW, and P-LCR) were significantly higher than in hypoproductive thrombocytopenia with cutoff values of 7.9fl, 15.3%, and 12.9%, respectively. MPV has a sensitivity of 97% and specificity of 50%, P-LCR had a sensitivity of 100%, and PDW had a sensitivity and specificity of 77% and 70%, respectively.

CONCLUSIONS: These abnormalities in platelet indices are of value for differentiation of platelet quantitative disorders, higher value in ITP in comparison with other causes of thrombocytopenia, and for primary thrombocytosis, the value is higher than reactive thrombocytosis.

Keywords:

Autoanalyzer, platelet indices, thrombocytopenia, thrombocytosis

Background

Complete blood count (CBC) tests with automated hematology analyzers are one of clinical laboratories most widely ordered tests in practice. Modern hematology analyzers in routine diagnostic use, which measure platelet indices, based on impedance counting or optical light scatter counting techniques.[1]

Platelet indices are platelet activation biomarkers. They facilitate extensive clinical investigations focusing on the diagnostic and prognostic values in a variety of settings without causing unnecessary costs. Among these platelet indices, plateletcrit (PCT), mean platelet volume (MPV), platelet-large cell ratio (P-LCR), and platelet distribution

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width (PDW), as they are related to platelets' morphology and proliferation kinetics.[2,3]

MPV is a measure of thrombocyte volume with normal range (7.2–11.7 femtoliters [fL]). PDW platelet volume distribution width is an indicator of platelet volume variability with normal range 8.3%–56.6%. PCT is a volume occupied by platelets in the blood with a range of 0.22%–0.24%. P-LCR is an indicator of larger (>12 fL) circulating platelets which represents normally as 15%–35%.[3]

It has been suggested that large platelets may be an indication of activation of the platelets and increased platelet volume represents increased production of platelets leading to larger circulating reticulated platelets released from the bone marrow (BM) into the bloodstream.[4] Thus, platelet indices including (MPV), (PCT), and (PDW) can provide crucial information for megakaryopoietic activity. In addition, platelet indices can help distinguish between hyperdestructive or hypoproductive thrombocytopenia. Among the platelet indices, MPV was shown to associate with both megakaryocyte ploidy and the percentage of reticulated platelets in circulation. PDW measures variability of platelet size and reflects platelet heterogeneity, both of them have been used to differentiate platelet disorders, including essential thrombocythemia (ET) and reactive thrombocytosis.[5]

Aim of the study

To evaluate and interpret different platelet indices (PCT, MPV, PDW, P-LCR) in patients with quantitative platelet disorders.

Patients and Methods

Study design and setting

A prospective cross-sectional study was conducted in the hematology center in Baghdad medical city, hematology department in Al-Imamain Al-Kadhimian medical city, and National center of hematology/Almustansiriyh university over 11 months from November 2019 to September 2020.

Selection criteria of study sample

Based on clinical and laboratory information, 160 adult patients >18-year-old who's randomly selected were enrolled in this study and divided into two groups according to the diagnosis of platelet count disorders, 80 patients with thrombocytopenia (Plt <150 × 109) and further 80 patients with thrombocytosis (Plt >450 × 109).[6] Each group is subdivided further according to the pathogenesis of etiology of platelet disorder.

Thrombocytopenia group is subdivided into 40 cases with hypoproliferative thrombocytopenia, including any condition that interfere with the production capacity of BM, e.g., (aplastic anemia, acute leukemia, metastasis, and postchemotherapy), and 40 cases with hyperproliferative/destructive thrombocytopenia for those mechanisms outside the BM like Immune induced thrombocytopenia.

Similarly, pathogenesis mechanism had categorized for 80 cases of thrombocytosis into– 40 cases with reactive thrombocytosis to indicate high platelet count secondary to iron deficiency anemia (IDA), inflammatory response, splenectomy, malignancy and 40 cases with primary thrombocytosis for conditions attributed to over productive BM proliferative capacity (like ET, polycythemia vera [PRV], chronic myelogenous leukemia [CML]).

For each record of platelet count for any of the above conditions, it was designed that at least 2 reading in different time table that persistently showed these variations in platelet counts.

The study was approved by the Ethical Committees of Iraqi board for medical specialties committee.

All patients were informed about enrollment of their record in this research and a verbal consent taken for their agreement in addition to keep all records under confidentiality.

The following conditions were excluded from the study: congenital platelet disorders, microangiopathic hemolytic anemia associated thrombocytopenia and patients on plasmapheresis.

Data collection

For any patient with platelet count disorder, the demographic data were collected including, age, sex, occupation, also diagnosis of the underlying platelet count disorder, duration of the disease, method of diagnosis, in addition to the main clinical manifestation like history of bleeding or thrombotic event.

Subsequently, laboratory data were also reported to register the following parameters after at least two measurements at different time interval and taking the mean values of these two records including CBC, as well as platelet indices like MPV, PDW, P-LCR. A new venous blood sample of 3–5 ml was taken from each patient under aseptic technique into EDTA tube to be interpreted by automated blood cell analyzer within 1 h from collection at different standardized lab inside a hospital or private labs. The autoanalyzers used in this study are:

1. Mythic 18 3-part differential hematology auto-analyzer (Switzerland) by Orphee company

2. MEK 9100 autoanalyzer by NIHON KODHEN company (JAPAN)
3. MEK-6510K autoanalyzer by NIHON KODHEN company (JAPAN).

Statistical analysis

It was carried out using the Statistical Packages for the Social Sciences version 24 (SPSS Inc, Chicago, USA). Data were presented in measures of mean, standard deviation, and range for the numerical data, while frequency, and percentages were used for the categorical data. The significance of association was tested using Pearson Chi-square test and independent samples *t*-test. Receiver operating curve was used to predict the sensitivity and specificity parameters at different cutoff points for the diverse tests. Statistical significance was considered with $P \leq 0.05$.

Results

The sample consists of a total of 160 patients; mean age was 43.95 ± 12.36 years while the minimum and the maximum ages were 18 and 70 years old, respectively. The mean age for the thrombocytosis group is 48.73 years, while for the thrombocytopenia group, it is 39.16 years. Patients distributed in term of gender percent in relation to underlying mechanism pf platelet count disorders are shown in Table 1.

Regarding the thrombocytosis group, patients who have in reactive etiology of thrombocytosis have mean age of 41.6 years, while those with BM diseases have 55.87 years as mean age which is of high statistical significance as in Table 2.

Patients who have hypoproductive causes of thrombocytopenia are presenting with a mean age of 38.97 years, along with 39.35 years representing the mean age for those patients with destructive causes of thrombocytopenia but with no statistical significance as in Table 3.

Analyses of platelet indices in thrombocytosis patients group show that Platelets (PLTS), PCT, MPV, PDW, PCLR, and hemoglobin (HB) were significantly higher in patients with BM disease than those with reactive causes of thrombocytosis ($P = 0.000$) [Table 2].

Mean PCT, MPV, PDW, PLCR, and HB were significantly higher in patients with destructive causes than those with hypo-productive causes of thrombocytopenia ($P = 0.000$) [Table 3].

Table 4 illustrates that about 55% of the patients with reactive causes of thrombocytosis are diagnosed with IDA, while 55% of patients who have BM diseases as a cause of thrombocytosis are diagnosed with ET.

About 47.5% of the patients with hypo-productive causes of thrombocytopenia are diagnosed with acute myeloid leukemia, along with 100% of patients who have destructive causes of thrombocytopenia are diagnosed with immune thrombocytopenia (ITP) [Table 5].

Table 6 indicates that platelet count with cutoff value 501 000/ml has the highest sensitivity and specificity in the diagnosis of reactive causes of reactive thrombocytosis (sensitivity 74%, specificity 70%) as well as BM disease thrombocytosis (sensitivity 92%, specificity 75%), than the others including; PCT, PDW, and PLCR apart from MPV cutoff value 7.95 fl in BM thrombocytosis (sensitivity 90%, specificity 48%).

As well as the highest sensitivity and specificity in the diagnosis of destructive thrombocytopenia for MPV cutoff value 7.95 fl (sensitivity 97%, specificity 50%) compared

Table 1: Comparison between two study groups in gender distribution

Variables	Gender		Total, *n* (%)
	Male, *n* (%)	Female, *n* (%)	
Thrombocytosis			
Reactive	16 (40)	24 (60)	40 (100)
Bone marrow disease	30 (75)	10 (25)	40 (100)
Thrombocytopenia			
Hypo-productive	23 (57.5)	17 (42.5)	40 (100)
Destructive	9 (22.5)	31 (77.5)	40 (100)
Total	78 (48.8)	82 (51.3)	160 (100)

Table 2: Comparison between two causes of thrombocytosis in mean age, platelet indices, and other parameters

Variables	Reactive (secondary) (*n*=40)		Bone marrow diseases (primary) (*n*=40)		*P*
	Mean±SD	Range	Mean±SD	Range	
Age (years)	41.6±12.83	48 (18-66)	55.87±8.22	32 (38-70)	0.000
PLTS	659.77±213.83	771 (454-1225)	884.97±303.81	1572 (490-2062)	0.000
PCT	0.45±0.14	0.58 (0.30-0.88)	0.9±0.19	0.91 (0.53-1.44)	0.000
MPV	6.87±0.82	4.10 (4.8-8.9)	9.21±1.007	4 (7-11)	0.000
PDW	13.61±1.83	7.6 (10.4-18)	14.85±0.92	4.3 (12.8-17.1)	0.000
PLCR	11.39±2.18	12 (4.6-16.6)	25.02±4.54	25.5 (8.5-34)	0.000
HB	8.94±2.33	9.3 (4.7-14)	12.72±4.2	15.2 (7.8-23)	0.000

SD=Standard deviation, MPV=Mean platelet volume, PDW=Platelet distribution width, PLCR=Platelet large cell ratio, PCT=Plateletcrit, PLTS=Platelets, HB= Hemoglobin

Table 3: Comparison between two causes of thrombocytopenia in mean age, platelet indices, and other parameters

Variables	Hypo-productive (central) (*n*=40)		Destructive (peripheral) (*n*=40)		*P*
	Mean±SD	Range	Mean±SD	Range	
Age (years)	38.97±11.44	49 (18-67)	39.35±7.87	34 (26-60)	0.865
PLTS	34.4±20.92	94 (6-100)	39.27±19.89	99 (15-114)	0.289
PCT	0.02±0.01	0.07 (0.01-0.08)	0.04±0.01	0.07 (0.01-0.08)	0.000
MPV	7.84±0.88	3.5 (6.5-10)	12.05±1.07	6.2 (7.8-14)	0.000
PDW	14.47±2.88	10.2 (8.1-18.3)	16.48±1.79	6.8 (11.9-18.7)	0.000
PLCR	16.12±4.82	17.7 (9.7-27.4)	38.41±8.14	41.6 (12.8-54.4)	0.000
HB	8.89±1.57	7 (5-12)	11.85±0.97	4.5 (9.5-14)	0.000

SD=Standard deviation, MPV=Mean platelet volume, PDW=Platelet distribution width, PLCR=Platelet large cell ratio, PCT=Plateletcrit, PLTS=Platelets, HB= Hemoglobin

Table 4: Distribution of the patients with thrombocytosis according to the diagnosis, *n*=80

Thrombocytosis (*n*=80)	Diagnosis	*n* (%)
Reactive (secondary causes), *n*=40	IDA	22 (55)
	Infection	8 (20)
	Postsplenectomy	6 (15)
	Underlying malignancy	2 (5)
	IBD	1 (2.5)
	Connective tissue disease	1 (2.5)
	Total	40 (100)
Bone marrow diseases (primary causes), *n*=40	ET	22 (55)
	PRV	9 (22.5)
	CML	8 (20)
	PMF	1 (2.5)
	Total	40 (100)

IDA=Iron deficiency anemia, IBD=Inflammatory bowel diseases, ET=Essential thrombocythemia, PRV=Polycythemia vera, CML=Chronic myeloid leukemia, PMF=Primary marrow fibrosis

with BM hypoproductive thrombocytopenia (sensitivity 47%, specificity 34%) and similarly PDW cut off 15.35% with (sensitivity 77%, specificity 70%) and *P* LCR cutoff (sensitivity 100%, specificity 35%) for destructive causes [Table 7].

Discussion

In the present study, the main cause of hyperproliferative (destructive) thrombocytopenia was ITP with higher incidence in females which is corresponding to Schoonen *et al*.,[7] while the main cause of hypoprilferative thrombocytopenia is acute leukemia and aplastic anemia.

Patients with thrombocytosis are divided into reactive thrombocytosis that is found to be secondary to IDA followed by infection then postsplenectomy in this study unlike Rose, Rose *et al*. report who find that the most common causes of reactive thrombocytosis in general population as infection followed by inflammatory reaction due to tissue damage like (trauma, bone fracture, surgery) then malignancy and IDA.[8]

The other group of thrombocytosis is primary thrombocytosis due to BM diseases, including ET, PRV, CML, and PMF in order. These causes are comparable to Griesshammer *et al*.[9]

These differences can be attributed secondary to variation in sample size and population.

In thrombocytopenia

It seems that PLT indices are statistically significantly higher in hyperproliferative (destructive) thrombocytopenia group compared to hypoproductive group ($P = 0.000$), which is in correspondence to Negash *et al*. findings.[10]

MPV has the highest sensitivity and specificity, 97% and 50%, respectively, in the diagnosis of the destructive causes of platelet disorders than other platelet indices with a cutoff value of 7.9 fl, similar to Numbenjapon *et al*. cutoff MPV value that gave a sensitivity of 82.3% and a specificity of 92.5% and therefore; MPV is a reliable diagnostic test to differentiate between the two conditions.[11] Other previous researchers such as Ntaios *et al*., Shah *et al*. reported also that MPV is higher in ITP patients compared with hypoproliferative thrombocytopenic patients, which reflected an increase in the production rate, but their cutoff values ranged from >9 fl to >11 fl, respectively.[12,13] This variation in the cutoff values of MPV in different studies can be attributed to the difference in the selection of patients or difference in the type of the hematological analyzer used, as some old automated analyzers, cannot discriminate PLTs from other similarly sized particles such as fragmented red or white blood cells, cell debris, and immune complexes, Furthermore, since giant PLTs cannot be distinguished from red blood cells, they are not counted properly by some autoanalyzer devices. Besides this, several studies have found that MPV is affected by a variety of factors, including the time of study after venipuncture, the anticoagulant used, the temperature of the specimen storage status, and counter technologies.[14]

PDW is significantly higher in hyperproliferative thrombocytopenia than in hypoproliferative group,

Table 5: Distribution of the patients with thrombocytopenia according to the diagnosis, *n*=80

Thrombocytopeia, *n*=80	Diagnosis	*n* (%)
Hypo-productive (central causes), *n*=40	AML	19 (47.5)
	ALL	10 (25)
	AA	5 (12.5)
	CLL	2 (5)
	NHL	1 (2.5)
	MCL	1 (2.5)
	HL	1 (2.5)
	BL	1 (2.5)
	Total	40 (100)
Destructive (peripheral causes), *n*=40	ITP	40 (100)
	Total	40 (100)

AML=Acute myeloid leukemia, ALL=Acute lymphoblastic leukemia, AA=Aplastic anemia, CLL=Chronic lymphcytic leukemia, NHL=NonHodgkin's lymphoma, MCL=Mantle cell lymphoma, HL=Hodgkin's lymphoma, BL=Burkitt lymphoma, ITP=Immune thrombocytopenia

Table 6: PLTS, plateletcrit, mean platelet volume, platelet distribution width, platelet large cell ratio indices to predict the reactive causes, and bone marrow diseases of thrombocytosis

Indices	Cutoff values	Reactive causes		Bone marrow diseases	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
PLTS	501.000	74	70	92	75
PCT	0.5150	30	66	-	-
PDW	15.3500	17	50	-	-
MPV	7.9500	____-	-	90	48

PCT=Plateletcrit, MPV=Mean platelet volume, PDW=Platelet distribution width, PLTS=Platelets

Table 7: PLTS, plateletcrit, mean platelet volume, platelet distribution width, platelet large cell ratio indices to predict the hypo-productive, and destructive causes of thrombocytopenia

Indices	Cutoff values	Hypo-productive		Destructive	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
MPV	7.9500	47	34	97	50
PDW	15.3500	47	60	77	70
PLCR	12.6000	__-	-	100	35

MPV=Mean platelet volume, PDW=Platelet distribution width, PLCR=Platelet large cell ratio, PLTS=Platelets

with a cut-of value of 15.35 fl (sensitivity 47% and specificity 60%) in the diagnosis of the hypoproliferative causes of platelet disorders than other indices but it may reach to a sensitivity 77% and specificity 70% in the diagnosis of hyperdestructive thrombocytopenia. Kaito *et al*. suggested a cutoff value of >17 fl for PDW to differentiate ITP from hypoproductive thrombocytopenia, with 71.8% diagnostic sensitivity and 95% specificity.[5] Similarly, Ntaios *et al*. suggested a cutoff value between 15 and 17 fl, with 100% sensitivity and specificity.[12]

P-LCR was significantly higher in hyperproliferative (destructive) thrombocytopenia group with mean value of 38.41 ± 8.14% (P = 0.000) compared to mean value of 16.12 ± 4.82% for hypoproliferative group. A cutt-off value of 12.6% has a sensitivity and specificity of 100% and 35% for detecting hyperdestructive thrombocytopenia. These results are similar to Ntaios *et al*. and Kaito *et al*. P-LCR was significantly higher in ITP, indicating increased platelet activity and BM productivity of more large PLTs measuring more than 12 fl in volume.[5,12]

In thrombocytosis

It is found that all platelet indices are significantly higher in patients with BM disease (primary thrombocytosis) than in reactive thrombocytosis (P = 0.000). Platelet count in primary thrombocytosis group was significantly higher than the reactive group and platelet count has the highest sensitivity and specificity, 92% and 75%, respectively, than other platelet indices. A cutt-off platelet count value of 501 × 10^9/L is considered as demarcation to differentiate between the two mechanisms.

MPV in patients with primary thrombocytosis is significantly higher than in patients with reactive thrombocytosis (9.21 fl vs. 6.87fl, P = 0.000), with a cutt-off value of 7.95 fl carries a sensitivity 90% and specificity 48% in favor of primary thrombocytosis in similar to Saeed *et al*.[15]

This is in approximation to others who suggested a MPV a cutoff points of <8.33 fL to have a sensitivity of 65% and specificity of 89% for ET.[16,17] An inverse relationship between platelet count and MPV had been observed in reactive thrombocytosis in different inflammatory conditions to maintain hemostasis by preserving a constant platelet mass and the release of different cytokines such as interleukin-1 (IL-1), tumor necrosis factor, IL-6 with enhanced thrombopoiesis leading to release of highly reactive large size platelets, when migrate to inflammatory sites they are intensely consumed resulting in low MPV. Whereas in clonal thrombocytosis, increased megakaryopoiesis in response to continued thrombopoietic stress with the resultant increased synthesis of platelet granular component, higher rate of megakaryocyte cytoplasmic maturation led to production of large platelet with high MPV.[18]

Regarding PDW, a high statistical significant differences (P = 0.000) between mean PDW in primary thrombocytosis (14.85fl) than in reactive thrombocytosis (13.61fl), similar to Saeed *et al*. and Syed *et al*. observation.[15,19] A cutt-off value of 15.3 fl demonstrated low sensitivity 17% but good specificity 50% in differentiation of the underlying causes. Therefore, low MPV and PDW in patients with high platelet counts strongly suggest reactive aetiology.[19]

P-LCR was also significantly higher in primary thrombocytosis patients, with mean value of 25.02% than in reactive thrombocytosis with mean value of 11.39%, corresponding with Babu and Basu who suggested that it can be utilized as a helpful measure in the differential diagnosis of conditions associated with abnormal platelet counts.[20]

Conclusions

Platelet indices are useful in clinical differentiation between different platelet count disorders. In immune thrombocytopenia, all platelet indices (MPV, PDW, and P-LCR) are higher than other BM causes of thrombocytopenia with cutoff values of 7.9fl, 15.3%, and 12.6%, respectively.

While primary thrombocytosis is associated with higher values in all platelet indices (MPV, PDW, and P-LCR) with cutoff values of 7.9fl, 15.3%, and 12.6%, respectively.

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Conflicts of interest
There are no conflicts of interest.

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