Original paper

The Utility of Platelet Indices in Differentiating between Hyper-productive and Hypo-productive Thrombocytopenia in Children

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Abstract

Background: Thrombocytopenia refers to a reduction in platelet count to <150 × 10^9/L. It may occur due to decreased production) hypoproductive thrombocytopenia) such as aplastic anemia (AA) and acute leukemia (AL), or increased destruction of normally synthesized platelets (hyperproductive thrombocytopenia) such as immune thrombocytopenic purpura (ITP).
Platelet indices, namely plateletcrit (PCT), mean platelet volume (MPV), platelet distribution width (PDW), platelet –large cell ratio (P-LCR) and immature platelet fraction (IPF) .Platelet Volume Indices (PVIs) are a group of parameters which are inexpensive to measure and are derived from routine blood counts.
Objective In this study, we aimed to assess the sensitivity and specificity of these indices and set cutoff values that aid in diagnosis of thrombocytopenia causes.
Patients and Methods: We recruited 90 individuals as thrombocytopenic patients, who were divided into two groups: group I (n= 40) included newly diagnosed immune thrombocytopenic purpura (ITP) patients (hyperproductive thrombocytopenia), whereas group II(n = 50) included hypoproductive thrombocytopenia patients .The MPV and PDW were derived from automated cell counter. A comparison of the sensitivity and specificity for MPV and PDW in both conditions (hypo and hyper-production thrombocytopenia) were evaluated.
Results: All platelet indices were significantly higher in ITP than in (AA and AL), and platelet indices showed sufficient sensitivity and specificity ; the best cutoff value for MPV was greater than 10.6 fl and for PDW was greater than 16fl, with a sensitivity(90,95) and specificity(86,80) respectively.. The area under the curve (AUC) of the receiver operating characteristics curve of platelet indices was large enough to enable the diagnosis of ITP. the PDW had the larger AUCs(0.938)than MPV where AUCs (0.900) , which means that these values are very reliable for ITP.
Conclusion: Platelet volume indices can differentiate with some certainty ITP from AL and AA, and helps pediatricians to avoid the invasive bone marrow aspiration which need expert hematologist for its interpretation.
Keywords: hyperproductive thrombocytopenia hypoproductive thrombocytopenia; immune Thrombocytopenic purpura; mean platelet volume; platelet distribution width

Introduction

A low platelet count is a common entity encountered by the general pediatrician who is then faced with the dilemma of discriminating whether the low platelet count is caused by decreased production (hypoproductive thrombocytopenia) or increased destruction (hyper-productive thrombocytopenia). Bone marrow sampling is a useful tool in evaluating hematologic indices, but is invasive, expensive and not recommended as a first line diagnostic procedure and instead reserved for older patients, or patients with atypical features [(1)]. Bone marrow sampling

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also requires a trained hematologist to perform and interpret the results making it a difficult test to obtain for patients who do not live near an academic center. Noninvasive and cost effective diagnostic approaches for the evaluation of thrombocytopenia are needed to better assess pediatric patients in the community. Thrombocytopenia refers to a reduction in a platelet count of <150 x 109/L, which can occur due to a decrease in platelet production such as in aplastic anemia (AA) and acute leukemia (AL) [(2)]. Other disorders such as immune thrombocytopenia purpura (ITP) are a result of increased destruction of normally synthesized platelets [(3)]. The differentiating between these disorders is vital as the treatment plans differ. Platelet volume indices are a group of parameters, which are inexpensive to measure and are derived from routine blood counts. Advanced technology in automated blood cell analyzers has made it possible to measure various platelet indices namely, mean platelet volume (MPV) defined as a measurement of the average size of platelets in the blood; and platelet distribution width (PDW) that reflects the variability in the platelet size and increases in the presence of platelet anisocytosis [(4)]. Little is known about the usefulness of platelet indices in differentiating thrombocytopenia in children, and whether these indices are satisfactory tests for thrombocytopenia. Therefore the main objectives of this study are to: investigate the usefulness of MPV and PDW in discriminating between hyperdestructive thrombocytopenia and hypo-productive thrombocytopenia, assess the sensitivity and specificity of MPV and PDW, and obtain cutoff values in an attempt to consider the use of theses indices in the initial evaluation of thrombocytopenia in pediatric patients.

Patients and Methods

The study population consisted of thrombocytopenic patients seen in the Karbala Teaching Hospital for Children and the Hematology/Oncology Clinic in the period between January 2014 and January 2015. Patient demographics and consent were obtained, followed by a detailed history and physical examination. An automated CBC including platelet count, MPV and PDW were recorded, in addition to a bone marrow aspirate was done on each patient included in the study. The differentiation between hyperproductive thrombocytopenia and hypo-thrombocytopenia was confirmed using peripheral blood smear and bone marrow aspiration/ biopsy. A total of 90 patients were recruited, female and male, with ages ranging from 1-14 years. These patients were divided into two groups, hyper-productive thrombocytopenia (N= 40) and hypo-productive thrombocytopenic (N= 50). Thrombocytopenia of other causes or unknown origin was not included in this study. The automated cell counter (CELL-DYN RUBY: 35863BG) with quality control and established reference ranges, was used to measure platelet count, MPV and PDW. The sensitivity and specificity of MPV and PDW were calculated under various cutoff ranges for both thrombocytopenic conditions. The receiver operating characteristic (ROC) curves was obtained by plotting sensitivity against 1-specificity for the complete range of decision thresholds. The performance of each test was assessed by the area under the ROC curves. This area gives the probability that a patient with the ITP disease has a higher value of MPV and PDW in comparison to patients with other causes of thrombocytopenia (AA or AL). A test that perfectly differentiates between the two patient groups would begin in the lower left corner, go straight up to the upper left corner, and then to the upper right corner of the plot. All statistical analysis were completed by using SPSS 20 software package. Statistical significance was defined as a *p* value of less than 0.5.

Results

This study included 90 patients with thrombocytopenia, who were studied as (40) had a diagnosis of ITP of which (36) patients had MPV > 10.6 fL, (3) patients had normal MPV (6.9-10.6)fL; and (1) patient had low MPV(< 6.9 fL) and for PDW (38) patients had PDW > 16 fL,(2) patients had normal PDW(11-16)fL; and no one had low PDW(< 11 fL).

On the other hand 50 patients had thrombocytopenia due to decreased platelet production (hypoproductive thrombocytopenia). Of them 35 patients had acute leukemia, and 15 had aplastic anemia. (15) patients from all the hypoproductive thrombocytopenic patients had low MPV, (28) patients had normal MPV; and (7) had MPV>10.6fL and for PDW (10) had PDW >16 , (26) with in normal range(11-16) and (15) patient had low PDW (< 11 fL), as shown in table (1,2) The platelet count and platelet indices were compared between hyper-productive and hypo-productive thrombocytopenia as shown in Table 3. Platelet indices were significantly higher in ITP patients compared to AA or AL group (p<0.001).

ROC curve of MPV to distinguish hyperproductive from hypoproductive thrombocytopenic patients was shifted to the upper left of the graph, which indicates that this parameter is sufficient to distinguish the two types of thrombocytopenia as apparent from figure (1). The area under the curve (AUC) of the MPV was 0.900 which mean that a newcut off point for MPV value is 10.6(MPV value giving best specificity and sensitivity).

ROC curve of PDW to distinguish hyperproductive from hypoproductive thrombocytopenic patients was shifted to the upper left of the graph, which indicates that this parameter is sufficient to distinguish the two types of thrombocytopenia as apparent from figure (2). The area under the curve (AUC) of the PDW was very large 0.938 which mean that a new cut off point for PDW value is 16 (PDW value that giving the best specificity and sensitivity). The sensitivity, specificity positive predictive value (PPV), and negative predictive value (NPV) of (MPV and PDW) were calculated under various cut-off ranges as shown in table (4, 5).

Discussion

The most important function of a clinical test in evaluating thrombocytopenia is not solely to be sensitive enough to capture the vast majority of hyper-productive state as in ITP, but to be specific enough to essentially rule out hypo-productive cases, such as acute leukemia or aplastic anemia. It is also important to know whether a low platelet count in a patient is caused by decreased production or increased platelet destruction. Bone marrow examination, which is an invasive test, is necessary for aplastic anemia, but there is no agreed consensus regarding its necessity for ITP diagnosis, especially given it's invasive nature and cost [(5)]. Thus, a new non-invasive, cost effective and easier approach for thrombocytopenia in children is needed to better evaluate these platelet disorders [(6)].

Table 1. MPV category in etiology of thrombocytopenia

PDW category	etiology of thrombocytopenia		P
	ITP	aplastic anemia or acute leukemia	
low <16 fL	00	10	
High >16 fL	38	14	
Normal(11-16)fL	2	26	< 0.001
Total	40	50	

Table 2: PDW category in etiology of thrombocytopenia

MPV category	etiology of thrombocytopenia		P
	ITP	aplastic anemia or acute leukemia	
Low < 6.9 fL	1	15	< 0.001
High >10.6 fL	36	7	
Normal(6.9-10.6)fL	3	28	
Total	40	50	

Table 3. Comparison of platelet count and platelet indices between hypoproductive and hyperproductive thrombocytopenic patients.

	ITP Mean ± SD	AA +AL Mean ± SD	P
Plat. Count ($\times 10^3$/ml)	25.6 ± 20.7	40.6±34.5	0.001
MPV fL	12.7±2.5	8.2±2.3	<0.001
PDW fL	19.4±1.8	13.1±3.3	<0.001

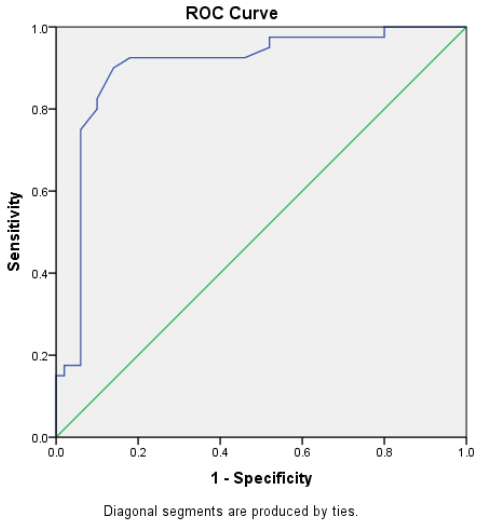

Figure 3. Receivers operating characteristic (ROC) curves of MPV to distinguish hyperproductive from hypoproductive thrombocytopenic patient

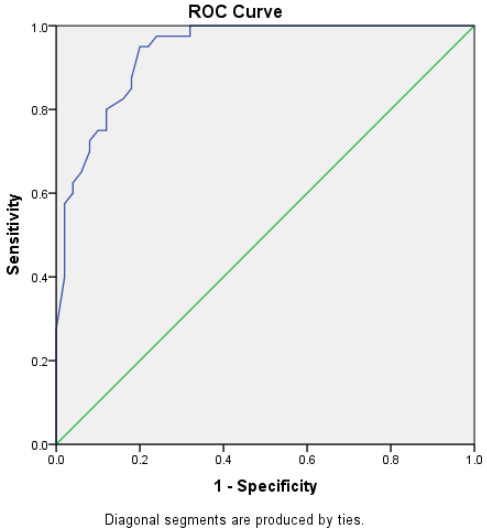

Figure 4. Receivers operating characteristic (ROC) curves of PDW to distinguish hyperproductive from hypoproductive thrombocytopenic patient

Table 4. Sensitivity, specificity, Ppv, and Npv for the diagnosis of hyperproductive and hypoproductive thrombocytopenia under various cut-off ranges of MPV.

Etiology of Thrombocytopenia	MPV value	Sn%	Sp%	PPV	NPV
Hyperproductive (ITP)	>12.6	50	94	88	72.3
	>11.6	60	94	89.6	77
	>10.6	90	86	83.7	91.4
Hypoproductive (AL or AA)	≤10.6	86	90	91.4	83.7
	<8.6	64	92.5	91.4	62.7
	<6.9	28	97.5	93.3	48

Table 5. Sensitivity, specificity,Ppv,and Npv for the diagnosis of hyperproductive and hypoproductive thrombocytopenia under various cut-off ranges of PDW.

Etiology of Thrombocytopenia	PDW value	Sn%	Sp%	PPV	NPV
Hyperproductive (ITP)	>20	40	98	94.1	32.8
	>18	75	92	88.2	82.1
	> 16	95	80	79.1	95.2
Hypoproductive (AL or AA)	≤16	80	95	95.2	79.1
	<14	66	97.5	97	69.6
	<11	38.8	100	100	52.6

Our results demonstrate that platelet indices are significantly higher in ITP patients compared to patients with hypo-productive thrombocytopenia. We also found that calculated MPV with a cutoff of >10fL detects 90% of the cases of ITP and excluding 86% of the hypo-productive situations. While PDW with a cutoff of >16fL is able to detect 95% of the ITP conditions and excluding 80% of the hypo-productive cases. Therefore, theses indices are effective in distinguishing these two types of thrombocytopenia and are consistent with a previous findings of Borkataky et al [(7)], Katio et al[(8)], Alsweedan et al[(9)], Woong et al[(10)] and Ntaios et al[(11)] where platelet indices were found to be useful in the differential diagnosis of ITP and hypo-productive thrombocytopenia in adult patients. Our study shows that the sensitivity and specificity of platelet indices are also sufficient to enable a diagnosis of ITP. ROC curves of MPV and PDW were shifted to the upper left of the graph, indicating that the area under the curve was large enough to enable the diagnosis of ITP and are correctly classify the two types of thrombocytopenia. Previous findings by Kaito et al[(7)] has indicated that platelet size deviation and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia and PDW and are a reliable marker for distinguishing hyper-productive thrombocytopenia from hypo-productive thrombocytopenia in adult patients. In comparing the sensitivity and specificity between MPV and PDW in the two thrombocytopenic groups, we found that PDW is more sensitive than MPV in detecting ITP, but less specific in a cut off above the normal range (>16). These values can be used to help clinician to stratify their differential diagnoses making ITP less likely in patients when PDW is in normal range (11-16) and to strongly reduce the likelihood of ITP when PDW is below normal range (<11). This can be valuable tool for the general pediatrician in stratifying the severity of disease in thrombocytopenic patients and more efficiently referring patients for further work-up. It is important to be aware that some limitations are encountered in our study. 1) In severe thrombocytopenia and in the presence of red cell fragmentation, a

platelet histogram cannot be adequately drawn, and the indices cannot be recorded 2) Although automated cell counters are fairly accurate in determining platelet count, the possibility of instrumental artifacts at low platelet count cannot be ruled out.

Conclusion

Our results suggest that platelet indices are significantly higher in ITP patients compared to patients with hypo-productive thrombocytopenia. Comparing the sensitivity and specificity between MVP and PDW for both groups, PDW is more sensitive to detect the ITP patient than MVP but less specific in a cutoff above the normal range. Platelet volume indices can differentiate with some certainty ITP from AL and AA which helps pediatricians to avoid the invasive bone marrow aspiration, which needs the assistance of a hematologist for diagnosis and result interpretation.

Recommendation

1. Comments on MPV and PDW should be part of haematological report especially if thrombocytopenia is present.

2. Further studies are needed to evaluate the utility of platelet indices in diagnosis the other causes of thrombocytopenia.

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