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

Al-Musawi Z.[1], Al-Kabi, M.,[1] Alnoor M.[2], Alnoor, S.[2]
[1]School of Medicine, University of Karbala
[2]Directlabconsulting, Houston, Texas

Abstract

This is a prospective study with the goal of assessing the sensitivity and specificity of platelet indices and setting cutoff values that aid in diagnosis of thrombocytopenia in children. Platelet indices were evaluated in thrombocytopenic patients seen in Karbala Teaching Hospital and the Hematology/Oncology Clinic for Children between January 2014 and January 2015. In this study 90 patients were recruited and divided into two groups: Group 1 Hyper-productive thrombocytopenic patients (n=40) included newly diagnosed immune thrombocytopenic purpura (ITP). Group 2 Hypo-productive thrombocytopenic patients (n=50) included cases with aplastic anemia and acute leukemia.
Mean Platelet Volume (MPV) and platelet distribution width (PDW) were derived from an automated cell counter. Receiver Operating Characteristic (ROC) curves were constructed and the accuracy of the tests was measured by the area under the ROC curve (AUC). The sensitivity and specificity of MVP and PDW were calculated under various cutoff ranges, and used to differentiate the thrombocytopenia diagnoses between Group 1 and Group 2 patients.
Platelet indices were significantly higher in ITP patients compared to patients with hypo-productive thrombocytopenia. The best cutoff range for MPV was greater than 10.6fL (femtoliter) and for PDW was greater than 16fL; with a sensitivity of (90%) and (95%) and specificity of (86%) and (80%) respectively. The area under the curve of ROC of platelet indices was large enough to correctly classify, differentiate and diagnose of ITP patients. In addition, PDW had the larger area under the curve (0.938) than MVP where AUC is (0.900), which means that these values are reliable for ITP diagnosis.
Our results indicate that laboratory findings of platelet volume indices can differentiate ITP from hypo-productive thrombocytopenia and be used as a screening tool for the diagnosis of ITP in children. This will help pediatricians to avoid the invasive bone marrow aspiration which requires the expertise of a hematologist for the examination and interpretation of results.

Background

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 (hypo-productive 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 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. Non-invasive 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 $<150 \times 10^9$/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 hyper-destructive 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 hyper-productive 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

Table. 1 MPV ranges and patients distribution

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 2. PDW ranges and patients distribution

PDW category	Etiology of Thrombocytopenia		P
	ITP	Aplastic Anemia or Acute Leukemia	
low <11 fL	00	10	< 0.001
High >16 fL	38	14	
Normal(11-16)fL	2	26	
Total	40	50	

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).

Table 3. Comparison of platelet count and platelet indices between ITP and AA and AL patients

	ITP Mean ± SD	AA +AL Mean ± SD	P-value
Platelet 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

The sensitivity and specificity of platelet indices were calculated under various cut off ranges. The MPV with a cutoff of >10.6fL detects 90% of the cases of ITP while excluding 86% of the hypo-productive situations. When the chosen cutoff for MPV is greater than 12.6fL, detection rate was 50% of the ITP cases while excluding 94% of the hypo-productive cases (Table 4).

Table 4. Sensitivity and specificity for diagnosis of ITP and AA or AL under various cutoff 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 and specificity for diagnosis of ITP and AA or AL under various cutoff 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

The PDW with a cutoff of 16fL detects 95% of the cases of ITP while excluding 80% of hypo-productive thrombocytopenic patients. When the chosen cutoff for PDW is greater than 20fL, detection rate is only 40% of the cases of ITP while excluding 97% of the hypo-productive conditions (Table 5).

The selected ranges for MPV and PDW was 10.6 and 16 respectively. Under these cut-off ranges, platelet indices especially PDW showed favorable sensitivity and specificity (Table 5).

The ROC curves of MPV and PDW were shifted to the upper left border of the graph as apparent from figure (1 and 2). The area under the curve of the MPV was 0.900 and for PDW was 0.938, which indicates that a cutoff point of 10.6fL of MPV and 16fL of PDW gives the highest sensitivity and specificity.

Figure 1: ROC for MPV

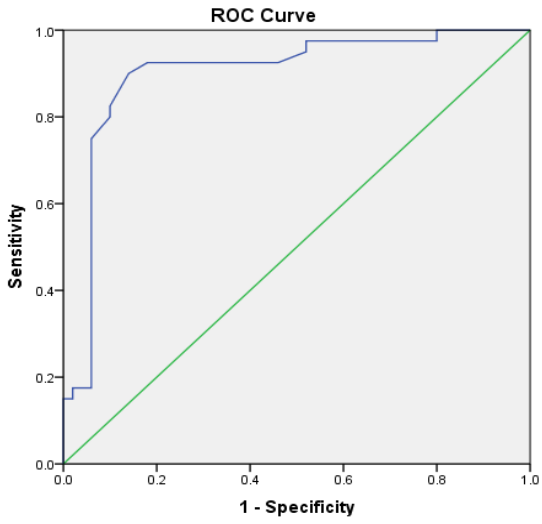
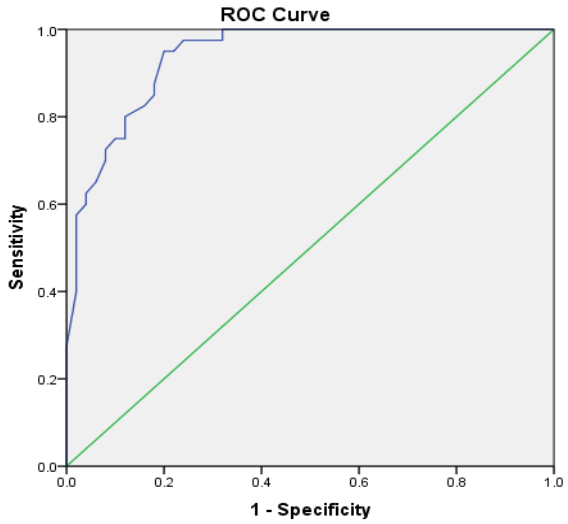


Figure 2: ROC for PDW



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)].

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.

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