Value of Platelet Indices in Diagnosing Etiology of Thrombocytopenia

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Abstract

Background: Platelet parameters are significant, especially in diagnosis of causes of thrombocytopenia. The platelet parameters are widely available as part of full blood count with no extra cost. Thrombocytopenia is of varying etiology, it is broadly divided into three major categories (1) as increased destruction (ITP), (2) decreased production and (3) splenic sequestration/abnormal pooling.

Aims of the study: To investigate the indices of the platelets which include (MPV,PDW,PCT) and to signify its role in the diagnosing the etiology of thrombocytopenia,, if there is any correlation between platelet count and platelets indices and to determine cut off point of MPV for the diagnosis of ITP.

Materials and Methods: 104 cases of Thrombocytopenia (TCP) and 50 control cases having normal platelet count were selected. TCP was defined as platelet count <150 x 10^9/L. Analysis was done by Diagon cell counter and every case was reassessed by Peripheral Smear (P.S.) examination and if necessary also by manual method. Only those cases that had sufficient clinico-hematological work -up and the causes of low platelet count had been reliably established were included in the study.

Results: The study was conducted on 104cases they were broadly categorized into three groups Group A with reduced production, Group B with increased destruction and Group C with abnormal pooling(splenomegaly). In group A, mean platelets count 64.98 x 10^9/l ± 36.5, mean MPV 9.3 Fl ± 1.1 , mean PDW 16.33 Fl±0.73, mean PCT 0.094% ± 0.157, M:F ratio1:1, there were a significant statistical difference in platelets count with control group (P value 0.000) and with group B (p value 0.0420), mean MPV shows significant difference with all control, B and C groups (P value 0.000, 0.000, 0.01 respectively), PDW also shows significant difference with control and C groups (p value 0.000, 0.001 respectively), PCT shows significant statistical difference with control and B groups (p value 0.000, 0.04) respectively.

There was a negative correlation platelets count and PDW.

In group B, mean platelets count 44.51 x 10^9/l ± 33.9, mean MPV 10.3 Fl ± 1.5, mean PDW 16.22 Fl ±0.86, mean PCT 0.049% ± 0.042, M:F ratio 1:4.5, there were a significant statistical difference in platelets count with control group (P value 0.000), with group A (p value 0.0420) and with group C (p value 0.006), MPV shows significant statistical difference with all groups (P value 0.000 for all), PDW shows significant difference with control and C groups (p value 0.000, 0.008 respectively) , PCT with control and group A (p value 0.000, 0.04) respectively. There was a negative correlation platelet count and MPV and PCT.

A cut off point for the diagnosis of ITP is 9.9 with 100% sensitivity and 100 % specificity.

Regarding group C, mean platelets count 80.0 x 10^9/l ± 27.1, mean MPV 8.5 Fl ± 0.84 , mean PDW 15.67 Fl ± 0.84, mean PCT 0.1007% ± 0.139, M:F ratio 1:1.1, there were a significant statistical difference in platelets count with control group (P value 0.000) and group B (p value 0.006), mean MPV shows significant difference with group A and B groups (P value 0.01, 0.000 respectively), PDW shows significant difference with group A and B groups (p value 0.001, 0.008 respectively), while PCT shows significant statistical difference with control and B groups only (p value0.000,0.08) respectively. There was no correlation between platelet count and its parameters.

Conclusion: Platelet indices are useful method to distinguish immune thrombocytopenia from hypoproductive thrombocytopenia and can provide significant data about the underlying causes of thrombocytopenia. MPV can discriminate ITP from hypoproductive thrombocytopenia and cut off point is 9.9 FL and they may postpone ITP patients from doing bone marrow aspiration and to ovoid platelet transfusion, there is negative correlation between MPV and platelets count in ITP patients.

Keywords: Thrombocytopenia (TCP), Idiopathic Immune Thrombocytopenia (ITP), Hypoproductive TCP, Increased Pooling TCP, Mean Platelet Volume(MPV), Platelet Distribution Width (PDW), Plateletscrit (PCT).

الخلاصة

معلمات الصفائح الدموية لها أهمية في تشخيص أسباب نقص الصفائح الدموية · هذه المعلمات لها انتشار واسع كجزء من جهاز فحص الدم الاوتوماتيكي وبدون تكلفة إضافية · يقسم نقص الصفائح الدموية إلى ثلاثة مجاميع رئيسية وهي ١. قلـــة إنتـــاج

الصفائح الدموية من نخاع العظم ٢. تكسر الصفائح الدموية في الدم نتيجة وجود أجسام مضادة لها ٣. زيادة تجميع الصفيحات الدموية في الطحال المتضخم. الهدف من هذه الدراسة هو لدراسة معلمات الصفائح الدموية وأهميتها في تشخيص أسباب نقص الصفائح الدموية وإذا كان هناك أي علاقة بين عدد الصفائح الدموية مع هذه المعلمات وكذلك لتحديد الحد الفاصل لحجم الصفائح الدموية لتشخيص نقص الصفائح الدموية نتيجة وجود أجسام مضادة لها في الدم وتفريقها عن قلة إنتاجها من نخاع العظم. تم جمع ١٠٤ مريض لديه نقص في الصفائح الدموية قسمت إلى ثلاثة مجاميع استنادا إلى أسباب نقص الصفيحات الدموية كما ذكر أعلاه وهي مجموعة ا و مجموعة ب ومجموعة ج مع ٥٠ شخص كمجموعة مقارنة لديهم عدد الصفيحات الدموية طبيعي. تم تحليل الدم بجهاز فحص الدم الاوتوماتيكي ومقارنة النتائج بفحص الصفيحات الدموية بالطريقة اليدوية مع وجود صورة الدم أيضا. اوجدت هذه الدراسة ان هناك فرق معنوي في معدل عدد الأقراص الدموية بين مجموعة ا و مجموعة المقارنة ومع مجموعة ب أيضا. معدل حجم الصفيحات الدموية في مجموعة ا لها فرق معنوي مع جميع المجامبع الاخرى(مجموعة المقارنة و ب و ج) . معدل التوزيع للصفائح له فرق معنوي مع مجموعة المقارنة و مجموعة ج. معدل مكداس الصفيحات الدموية له فرق معنوي مع مجموعة المقارنة ومجموعة ب وهناك تناسب عكسي بين عدد الصفائح الدموية ومعدل التوزيع لها. في ما بخص مجموعة ب وجد إن هناك فرق معنوي في معدل عدد الاقراص الدموية مع كل المجاميع الأخرى. معدل حجم الصفائح الدموية له أيضا فرق معنوي مع كل المجاميع الأخرى. معدل التوزيع في مجموعة ب له فرق معنوي مع مجموعة المقارنة ومجموعة ج فقط. معل مكداس الصفيحات الدموية له فرق معنوي مع مجموعة المقارنة ومجموعة ا فقط. هناك تناسب عكسي بين معدل عدد الصفيحات الدموية و معدل حجمها. وجد ان الحد الفاصل لحجم الصفائح الدموية لتشخيص النقص الحاصل نتيجة وجود أجسام مضادة في الدم وتفريقها عن قلة انتاجها من نخاع العظم هو ٩.٩ بنسبة حساسية ١٠٠%. أما مجموعة ج وجد ان هناك فرق معنوي في معدل عدد الصفائح الدموية مع مجموعة المقارنة ومجموعة ب. معدل حجم الصفائح الدموية له فرق معنوي مع مجموعة ا و ب. معدل التوزيع للصفائح مع مجموعة ا و ب و معدل مكداس الصفائح مع مجموعة المقارنة و مجموعة ب. الاستنتاج : إن معلمات الصفائح الدموية لها اهمية في تحديد سبب نقص الصفائح . حجم الصفائح الدموية يلعب دورا مهما في تحديد سبب نقص الصفائح فيما اذا كان بسبب وجود الأجسام المضادة في الدم أو نقص الإنتاج من نخاع العظم حيث وجد إن الحد الفاصل هو ٩.٩ فمتوليتر بنسبة حساسية ١٠٠% وهذا يساعد في تجنب المريض لإجراء فحوصات أكثر تعقيد كفحص نخاع العظم وكذلك يجنبه عملية نقل الصفائح الدموية له كذلك وجد إن هناك تناسب عكسي بين عدد الصفائح الدموية في هذه المجوعة (ب) مع حجم الصفائح أي انه كلما كان عدد الصفائح اقل كلما كان هناك زيادة بنسبة حجم الصفائح الدموية.

الكلمات المفتاحية: نقص الصفائح الدموية، نقص الصفائح الدموية المناعي، نقص انتاج الصفائح الدموية، زيادة تجميع الصفائح في الطحال، معدل حجم الصفائح الدموية، مكداس الصفائح و معدل توزيع الصفائح الدموية.

Introduction

Thrombocytopenia (TCP) is not a disease entity by itself, but a finding that may result from a number of disease processes. By definition, there are subnormal numbers of platelets in circulating blood and is one of the most common causes of abnormal bleeding (Lee *et al*.,2009). Low platelet counts can have many causes which can be grouped in to three major categories as increased destruction, decreased production and splenic sequestration/abnormal pooling, based upon the causative process(P Greer *et al*.,2006).In many cases of thrombocytopenia, large platelets are seen in peripheral smear, this size of the platelet was suggested to help in deciding the category of thrombocytopenia long back (Brown *et al*.,1988). Initially the size was noted by microscopic studies only (Latger-Cannard *et al*.,2012). With availability of blood autoanalyzers new platelets indices related to platelet count are being reported. Most important of them are Mean Platelet Volume (MPV), Platelet distribution width (PDW) and Plateletcrit (PCT), (Wiwanitkit,2004; Boos,2007). MPV it is an automatically calculated value that indicates the average size of platelets in the blood, it is an indicator of the bone marrow function, if it is synthesizing platelets normally. A high MPV means over platelets production and a low MPV means decreased production.(Siamak *et al*., 2013; Martin *et al*., 2013) Normal MPV are in a range of 6.5 – 12.0 fL . MPV is easured by dividing plateletcrit by the platelet count multiplied by 10 (MPV: plateletcrit /platelet count ×10) (Laboratory hematology atlas). PDW it

is the measure the degree of anisocytosis of platelets.(Briggs *et al*.,2011) and can demonesrate if platelets are normally distributed or if there is any technical error, standard PDW ranges from 9 to 17 fL (Platelet distribution curves,2011) The plateletcrit: is the result of the MPV and platelet count and similar to the haematocrit of blood, could mean the volume of platelets in the circulation present in a unit volume of blood.(Briggs *et al*., 2011) normal range of PCT is 0.108 - 0.282 % and can be measured by multiplying PDW by platelet count (Plateletcrit (PCT)=PDW x platelet count).The changes in PDW may be the result from recruitment of multiple ploidy classes of megakaryocytes. An increased proportion of higher ploidy classes increase megakaryocyte heterogeneity. The combined interpretation of platelet parameters highly useful in the differential diagnosis of platelet related disorders (Osselaer *et al*., 2007).

Aims of the study: To investigate the indices of the platelets which include (MPV,PDW,PCT) and to signify its role in the diagnosis of the etiology of thrombocytopenia, if there is a correlation between platelet count and its indices and to determine cut off point of MPV for the diagnosis of ITP.

Patients and methods: The present study included 104 thrombocytopenic patients during about 6 months period, peripheral blood sample was obtained and assessed by automated Diagon Coulter D Cell 60, they were divided into three groups, (group A) 46 patients with decreased production, (group B) 39 patients with increased destruction (ITP) and (group C) 19 patients with increased pooling having splenomegaly, 50 age-matched and sex-matched healthy individuals as the control group.

A diagnosis of ITP (group B) was made according to the recommendations of the 'International Consensus Report on the Investigation and Management of ITP' (Provan *et al*.,2010). aking, with special attention to a history of intake of medications known to cause thrombocytopenia or associated viral infections; a bone marrow aspirate showing normal marrow with increased or adequate megakaryocytes showing defective platelet budding and separation; and disease duration less than 3 months. Exclusion criteria were a recent manifestation of active infection, or secondary causes of ITP such as systemic lupus erythematosis. The hypoproductive thrombocytopenia (group A) included patients with acute leukemia, whose diagnosis was based on bone marrow examination, and cytochemical and immunophenotyping criteria, patients with idiopathic aplastic anemia defined by pancytopenia and aplasia on bone marrow examination, patients with myelodysplastic syndrome, in whom the diagnosis was based on bone marrow examination, and patients under chemotherapy.

Group C including patients with large spleen as patients with thalassemia, liver diseases with splenomegaly.

Laboratory assessments of the patient and the control groups included the following:

1. Assessment of complete blood count, MPV, PCT and PDW on Diagon Coulter D Cell 60 Calibration was assessed daily with the commercial calibrant. All whole-blood counts were assayed within 2 h of sample collection.
2. Microscopic examination of a peripheral blood film stained with Leishman stain.

Statistics

Patient data were tabulated and processed using SPSS version 18, variables were expressed as mean, SD, and comparisons between groups using ANOVA test. A *P*-value less than 0.05 was considered statistically significant, cut off point of MPV received from ROC curve estimation.

Results

Descriptive analyses

This study included 104 patients with thrombocytopenia, who were classified as follows: Group A included 46 patients with hypoproductive thrombocytopenia., these included 23 male and 23 female patients, with a male: female ratio of:1. Their ages ranged from 3 to 80 years, with a mean age of 40.2 ± 19.5 years.

Group B included 39 patients with newly diagnosed idiopathic ITP. There were 7 male and 32 female patients, with a male: female ratio of 1:4.5. Their ages ranged from 1 to 70 years, with a mean age of 19.38 ± 20.6 years.

Group C included 19 patients with splenomegaly, there were 9 male and 10 female patients, with a male: female ratio of 1:1.1. Their ages ranged from 3 to 65 years, with a mean age of 38.8 ± 10.03 years.

Fifty healthy age-matched and sex-matched individuals were selected for comparison as the control group.

Comparative analyses

Platelet counts and platelets indices were compared between groups A and B (Table 1), A and C (Table 2), B and C (Table 3) as well as between each of

the patient groups and the control group (Table 4), (Table 5) and (Table 6).

Platelet counts show significant statistical differences between the patients groups and the control group (p value 0.000) and between group A and B (p value 0.042), between B and C (P Value 0.006), but no significant difference between group A and C (P Value 0.232).

MPV value shows a significant difference between the patient groups and the control groups (p value 0.000) except between group C and control group , there is not significant statistical difference (p value 0.100).

In all groups of thrombocytopenic patients (group A,B and C), there are significant differences of MPV value between them (P value less than 0.05).

Regarding PDW, there is also a significant s difference between the control group and group A and B(P value 0.000) except for group C and the control group where there is no statistical difference (P Value 0.255).

There is a significant statistical difference between group A and C (P Value 0.001) and A and between group B and C (P Value 0.008), while there is no significant statistical difference between group A and B (P Value 0.48).

PCT shows significant statistical difference between the control group and the three patients groups (P Value 0.000), and there is a statistical difference between group A and B (P Value 0.049), and there is no statistical significance between group A and C, B and C (P value 0.83 , 0.08 respectively).

Table (1) Comparison of mean Platelet count and indices between A and B groups

Platelets count and indices	Group A	Group B	P- Value
Platelets (mean ±SD) (x 10^9/L)	64.98±36.5	44.51±33.91	0.042*
MPV (mean ± SD) (FL)	9.358±1.192	10.397±1.592	0.000*
PDW (mean ± SD) (FL)	16.334±0.733	16.223±0.863	0.480
PCT (mean ± SD) (%)	0.0946±0.157	0.0491±0.042	0.049*

MPV: Mean Platelet Volume, **PDW:** Platelet distribution Width , **PCT** : Plateletcrit

* mean significant

Table (2) Comparison of mean Platelet count and indices between A and C groups

Platelets count and indices	Group A	Group C	P- Value
Platelets (Mean ±SD) (x 10^9/L)	64.98±36.5	80±27.19	0.232
MPV (Mean ± SD) (FL)	9.358±1.192	8.594±0.846	0.018*
PDW (Mean ± SD) (FL)	16.334±0.733	15.678±0.843	0.001*
PCT (Mean ± SD) (%)	0.0946±0.157	0.1007±0.139	0.833

MPV: Mean Platelet Volume, **PDW:** Platelet distribution Width , **PCT** : Plateletcrit
* mean significant

Table (3) Comparison of mean Platelet count and indices between B and C groups

Platelets count and indices	Group B	Group C	P- Value
Platelets (Mean ±SD) (x 10^9/L)	44.51±33.91	80±27.19	0.006*
MPV (Mean ± SD) (FL)	10.397±1.592	8.594±0.846	0.000*
PDW (Mean ± SD) (FL)	16.223±0.863	15.678±0.843	0.008*
PCT (Mean ± SD) (%)	0.0491±0.042	0.1007±0.139	0.082

MPV: Mean Platelet Volume, **PDW:** Platelet distribution Width , **PCT** : Plateletcrit
* mean significant

Table (4) Comparison of mean Platelet count and indices between Control and A groups

Platelets count and indices	Group A	Control group	P- Value
Platelets (Mean ±SD) (x 10^9/L)	64.98±36.5	264.34±36.81	0.000
MPV (Mean ± SD) (FL)	9.358±1.192	8.07±0.833	0.000
PDW (Mean ± SD) (FL)	16.334±0.733	15.456±0.520	0.000
PCT (Mean ± SD) (%)	0.0946±0.157	0.2128±0.0503	0.000

MPV: Mean Platelet Volume, **PDW:** Platelet distribution Width , **PCT** : Plateletcrit
* mean significant

Table (5) Comparison of mean Platelet count and indices between control and B groups

Platelets count and indices	Group B	Control group	P- Value
Platelets (Mean ±SD) (x 10^9/L)	44.51±33.91	264.34±36.81	0.000
MPV (Mean ± SD) (FL)	10.397±1.592	8.07±0.833	0.000
PDW (Mean ± SD) (FL)	16.223±0.863	15.456±0.520	0.000
PCT (Mean ± SD) (%)	0.0491±0.042	0.2128±0.0503	0.000

MPV: Mean Platelet Volume, **PDW:** Platelet distribution Width , **PCT** : Plateletcrit
* mean significant

Table (6) Comparison of mean Platelet count and indices between Control and C groups

Platelets count and indices	Group C	Control group	P- Value
Platelets (Mean ±SD) (x 109/L)	80±27.19	264.34±36.81	0.000
MPV (Mean ± SD) (FL)	8.594±0.846	8.07±0.833	0.100
PDW (Mean ± SD) (FL)	15.678±0.843	15.456±0.520	0.255
PCT (Mean ± SD) (%)	0.1007±0.139	0.2128±0.0503	0.000

MPV: Mean Platelet Volume, **PDW:** Platelet distribution Width , **PCT** : Plateletcrit
* mean significant

Correlation studies

In group A patients (hypoproductive thrombocytopenia) , there is significant negative correlations between PDW and platelet count(r=-0.420, P=0.004), other parameters shows no significant correlations.

In patients with ITP(group B), significant negative correlations between MPV, PCT and Platelet count (r = - 0.346, P = 0.031), (r = - 0.621, P = 0.000) respectively ,and there is no significant correlation of other parameters.

Group C patients (Increased pooling), there is no significant correlation between platelet count and its parameters (Table 7).

Table (7) Correlations between platelet count with platelet indices in thrombocytopenic patients

Group	MPV	PDW	PCT
A	- 0.184	- 0.420**	0.232
B	- 0.346*	- 0.271	0.621**
C	0.411	- 0.082	0.199

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Diagnostic performance characteristics of platelet indices

Diagnostic performance characteristics of platelet indices were determined by receiver-operating characteristic curve analysis.

A cutoff value greater than 9.9 fl for MPV with100% sensitivity and 100 % specificity for the diagnosis of ITP [Figure 1])

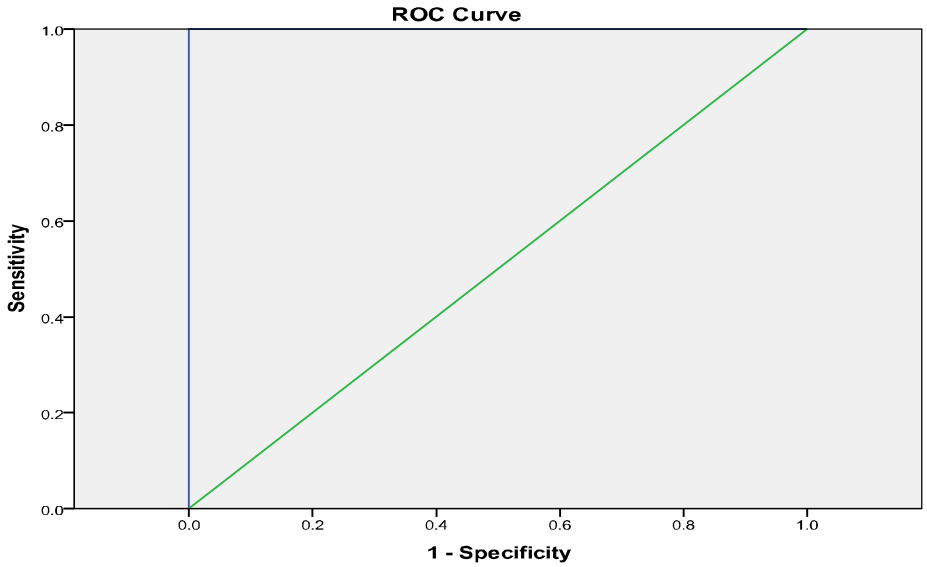

Figure (1) ROC curve comparing area covered by MPV in ITP patients.

Sensitivity and specificity were calculated from different coordinate points of the ROC curve. MPV had better sensitivity and specificity in discriminating the hyperdestructive thrombocytopenia (**Tables 8**). An MPV of > 9.9 fl

can identify patients as having ITP with 100 % sensitivity, 100 % specificity.

Table (8) Sensitivity and specificity of the platelet indices for ITP at different cut off points from ROC curve coordinates

Cut off points	Sensitivity	Specificity
9.6 FL	100 %	20 %
9.8 FL	100 %	13 %
9.9 FL	100 %	100 %
10.0 FL	87 %	100 %
10.1 FL	83 %	100 %

Discussion

The diagnosis and treatment of thrombocytopenia is a growing component in the practice of hematology. Although platelet indices, such as MPV, PDW, and PCT, have been available in routine automated platelet determinations and their clinical usefulness has been made (Xu *et al.*, 2013).

Thrombocytopenia is a commonly associated with many diseases and has many causes, one of the important causes of platelet destruction is the immune thrombocytopenia, in which autoantibodies causing their premature destruction by the reticular endothelial system, particularly in the spleen (Woods *et al.*,1984). Decreased bone marrow production due to malignancy, leukemias, aplastic anemia, invasive tumors and chemotherapy, and its diagnosis requires hematological morphological

examination, bone marrow examination ,immunophenotyping, and karyotyping, which are familiar only to hematologists (Xu *et al.,* 2013).

The present study was conducted on 104 thrombocytopenic patients: 39 patients had ITP, designated as the hyperdestructive thrombocytopenia group, and 46 patients had hypoproductive thrombocytopenia, 19 patients had splenomegaly and 50 apparently normal individuals matched for age and sex constituted the control group.

This study showed that MPV shows a significant statistical difference between the ITP patients and the control group , between the hypoproductive group and the control group and between the increased pooling(splenomegaly) and the control group . While (Borkataky *et al.,* 2009) found no significant statistical difference in the MPV between the destructive thrombocytopenia groups and the control group or between hypoproductive and the control groups.

Meanwhile, ITP (group B) patients showed significantly higher MPV results than hypoproductive thrombocytopenic patients (group A), also patients with splenomegaly (group C) had a significant statistical difference over group A and B .

A cut off value of MPV which is more than 9.9 fl was helpful to differentiate between idiopathic ITP and hypoproductive thrombocytopenic patients with 100%. Sensitivity and 100 % specificity. Similarly, other researchers such as (Kaito *et al.* 2005; Ntaios *et al.* 2008; Xu *et al.* 2013; and Shah *et al.,* 2013) reported that MPV was greater in ITP in comparison with hypoproductive thrombocytopenia , which is meant an increase in the synthesis of platelets, and they estimate a cut off values more than 9 fl to even more than 11 fl.

With regard to PDW, there was no significant statistical difference between the two patient groups A and B, while there is a significant statistical difference between group C and A, group C and B and there is a significant statistical difference between the control group and group A and C. Similarly (DA Elsewefy *et al.*) found that there was no significant difference between the hypoproductive and destructive groups. In contrast, (Shah *et al.*2013; Borkataky *et al.,* 2009)found that the PDW was higher in ITP patients

compared with acute myeloid leukemia patients and nonmegaloblastic hypo proliferative patients, respectively.

PCT in this study had a significant statistical difference between the control group and the other three groups (A, B, and C), also there is a significant statistical difference between group A(hypoproductive) and group B (Increased destruction) while there is no significant statistical difference between group A, B compared with group C. PCT mean a volume percent of thrombocytes and it is a result of PDW multiplied by platelet count so it greatly affected by the degree of severity of thrombocytopenia of any cause. (Martin *et al*.,2013)

There were a negative correlation between platelet count and both MPV and PCT in hyperdestructive group (ITP) patients , but there are no significant correlation between platelet count and MPV in group A and C . PDW also shows a negative correlation with platelet count in group A. Similarly in Baynes. *et al* study

there were an inverse relation between MPV and platelet count in patients with ITP and preserved MPV- platelets count relationship in non ITP patients. (Baynes *et al*., 1988).

Conclusion: Platelet indices is very useful values in distinguishing ITP (destructive thrombocytopenia) from hypoproductive thrombocytopenia and can provide significant data about the underlying etiology of thrombocytopenia. MPV can discriminate ITP from hypoproductive thrombocytopenia and cut off point is 9.9 FL and they may postpone ITP patients from doing bone marrow aspiration and to

ovoid platelet transfusion, there is negative correlation between MPV and platelets count in ITP patients.

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