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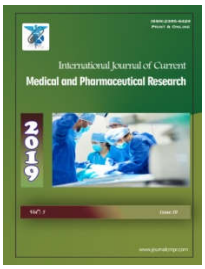

Research Article

THE ROLE OF PLATELET INDICES AS PREDICTIVE MARKERS OF IMMUNE THROMBOCYTOPENIC PURPURA (ITP) IN BONE MARROW ASPIRATE: A STUDY IN A TERTIARY CARE CENTRE

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ABSTRACT

Introduction: Thrombocytopenia is considered to be one of the most important causes of abnormal bleedings. It is necessary to ascertain whether the thrombocytopenia is due to hyperdestruction or hypoproduction. Hyperdestructive thrombocytopenias are caused by extramedullary destruction of platelets while hypoproductive thrombocytopenias are caused by a decreased production of platelets by the bone marrow. Platelet indices (PIs) can be used as predictive markers of ITP in thrombocytopenic patients, thus avoiding bone marrow aspirations.

Material and Methods: A total of 365 cases of thrombocytopenia (on automated analyser and peripheral blood film examination) with platelet counts <150 x 10^9/l in whom bone marrow aspiration was indicated were retrieved from the records over a period of one year and divided into two broad groups: cases of thrombocytopenia due to hyperdestruction (i.e. ITP, 68 patients) and cases of thrombocytopenia due to hypoproduction (i.e. Non-ITP , 297 patients). Platelet indices of these two groups were compared.

Results: Comparison between the two groups showed that platelet count (10^9/L) and PCT (%) were higher in patients in the hypoproductive group and this difference was found to be statistically significant. Comparison of the MPV (fl) and PDW between the two groups showed that both were higher in patients in the hyper destructive group (not statistically significant). P-LCC (10^9/L) was found to be higher in hypoproductive group and was statistically significant.

Conclusion: Patients with ITP had significantly lower platelet counts, PCT (%) and P-LCC and higher MPV than patients of non-ITP causes.

INTRODUCTION

The primary role of platelets is in maintaining hemostasis. Normal platelet count is between 150.0 and 410.0 x 10^9/l. [1]In the clinical practice, thrombocytopenia is considered to be one of the most important causes of abnormal bleedings. [2]Evaluating a cause of thrombocytopenia requires a careful clinical history along with thorough examination and investigations. It is necessary to ascertain whether the thrombocytopenia is due to hyperdestruction or hypoproduction.[2,3] Hyperdestructive thrombocytopenias are caused by extramedullary destruction of platelets. These are usually associated with a normal or an increased production of platelets by the marrow and include conditions like immune thrombocytopenic purpura (ITP), secondary ITP and disseminated intravascular coagulation (DIC). On the other hand, hypoproductive thrombocytopenias are caused by a decreased production of platelets by the bone marrow which can be due to primary or secondary bone marrow diseases eg. aplasticanemia, megaloblasticanemia, acute leukemia, myelodysplastic syndrome or postchemotherapy. For such a differentiation, bone marrow examination is required (aspiration and/or biopsy) wherein the megakaryocyte count is taken as the gold standard for the diagnosis. This, however, is an invasive procedure and a careful examination by the hematopathologist is required.[2]

Platelet indices (PIs) are a group of parameters which are derived from routine blood counts and are inexpensive to measure. These are measured by an automated cell counter, which is available in majority of healthcare centres. Of these, mean platelet volume (MPV) and platelet distribution width (PDW) are the best validated. MPV has also been shown to be a sensitive and specific parameter to differentiate between thrombocytopenia caused by ITP and that caused by aplastic anemia.[4] According to a few recent studies, hyperdestructive thrombocytopenias are usually associated with a higher MPV than normal reference values. This occurs due to an increased platelet production by hyperactive bone marrow. Hypoproductive thrombocytopenias on the other hand, have lower values of MPV because of an inadequate platelet production in the bone marrow. [5]A comparatively fewer studies have demonstrated the role of other platelet indices in determining the same.

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Therefore, the aim of our study was to retrospectively investigate the cause of thrombocytopenia as diagnosed on bone marrow aspiration and to correlate with the values of PIs in peripheral blood. We also aimed to establish PIs as predictive markers of ITP in thrombocytopenic patients and also to critically evaluate if these indices could be helpful enough to avoid an invasive procedure, as a bone marrow aspiration, in discriminating thrombocytopenia due to hypoproductive or hyperdestructive causes.

MATERIAL AND METHODS

Patients: Based on clinical and laboratory information, patients attending the Department of Clinical Hematology of a tertiary care hospital in Haryana, with a platelet count of <150.0 x 10^9/l were chosen retrospectively and divided into two broad groups: cases of thrombocytopenia due to hyperdestruction (i.e. ITP, 68 patients) and cases of thrombocytopenia due to hypoproduction(i.e. Non-ITP , 297 patients). Written informed consent was obtained from all participants.

Blood and Bone marrow collections: The present study was conducted with approval from the ethics committee of the institution. EDTA anti-coagulated venous blood samples were collected from patients. A peripheral smear examination was also performed to exclude pseudothrombocytopenia. Examination of bone marrow aspirate was carried out for all of the above patients and reported individually by two pathologists.

Instruments and Quality Control: The complete blood count was carried out and platelet indices measured using Mindray BC5800 five part automated analyser within two hours of sample collection. Caliberation was assessed daily with the commercial calibrant and monitored twice daily.

Statistical Analysis: The data were analysed using SPSS version 17.0 program for Windows. Data were presented as numbers and percentage or median and range, when appropriate. The independent student's t-test and Pearson's correlation test were used for analysis. A p-value of <0.05 was considered statistically significant. Receiver Operating Characteristic curves were created using GraphPad Prism software. Based on ROC curves, the cut-off range for the indices, wherever possible, were determined to simultaneously maximize both sensitivity and specificity.

RESULTS

A total of 365 cases of thrombocytopeniawith platelet counts<150 x 10^9/l in whom bone marrow aspiration was indicated were retrieved from the records over a period of one year dating from between1st January 2018 to 31st December 2018. A total of 193 females and 172 males comprised the study group. According to the diagnoses, these cases were divided into 2 groups: Hyperdestructive[ITP] (n= 68) and hypoproductive thrombocytopenia (n=297).

Table 1 shows the final diagnoses for patients who had platelet counts <150 x 10^9/l.

Table I Underlying diseases of the thrombocytopenic patients for whom BMA was carried out

Diagnosed cause of thrombocytopenia	Number of Patients (%)
Hyperdestructive [ITP cases]	68(18.63)
Hypoproductive[Non-ITP cases]	297(81.36)
Mixed Nutritional Deficiency	05(1.36)
MegaloblasticAnemia	19(5.2)
Non Specific Myeloid Reaction	15(4.1)
Eosinophilic Myeloid Reaction	01(0.27)
Erythroid Hyperplasia	54(14.8)
Acute Lymphocytic Leukemia	44(12.05)
Acute MyelogenousLeukemia	42(11.5)
Myelodysplastic Syndrome	12(3.28)
Hypoplastic Marrow	32(8.76)
Aplastic Anemia	26(7.120
Chronic Lymphoproliferative Disorder	21(5.75)
Metastatic Malignancy	01(0.27)
Chronic MyelogenousLeukemia- Blast Crisis	07(1.91)
Plasma Cell Dyscrasia	09(2.46)
Marrow Suppression secondary to Viral infection	08(2.19)
Marrow Suppression secondary to tuberculosis	01(0.27)
TOTAL	**365**

The laboratory characteristics of the patients in the respective groups are demonstrated in Table 2. Statistically significant differences were observed in platelet count, plateletcrit (PCT), and platelet- large cell count (P-LCC) between the two groups of patients.

Table II Laboratory characteristics in the groups of patients with thrombocytopenia

Characteristic	ITP	Non-ITP	P-value
Platelet Count (x10^9/l)	39.2±37.8	53.9±39.7	**0.006**
MPV(fl)	8.5±2.2	8.3±1.8	0.631
PDW	17.4±1.8	17.4±1.2	0.919
PCT(%)	0.035±0.037	0.048±0.038	**0.007**
P-LCC (10^9/L)	12.8±16.1	17.1±15.3	**0.04**

Comparison between the two groups shows that platelet count (10^9/L) and PCT (%) are higher in patients in the non-ITP group and this difference was found to be statistically significant with a p-value of 0.006 and 0.007 respectively. Comparison of the MPV (fl) and PDW between the two groups shows that both are higher in patients in the ITP group. However, this difference was found to be statistically non-significant (p-value 0.631 and 0.919 respectively). On the other hand, P-LCC (10^9/L) was found to be higher in non-ITP group and was statistically significant with a p value of 0.04. (Figure 1)

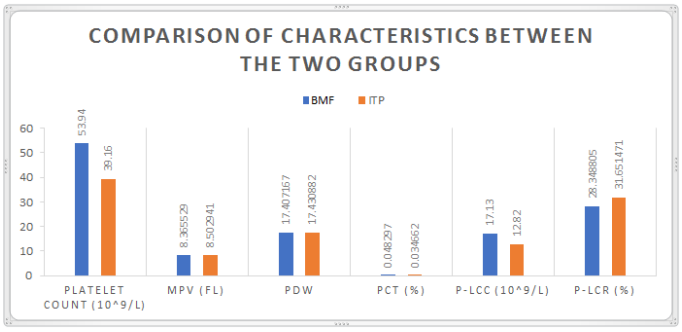

Figure 1

Correlation between platelet volume indices (PVI) and platelet count: Figure 2 shows the scatter plots for correlation between the parameters platelet count (10^9/L) and MPV (fl) in (A) patients with thrombocytopenia due to hyperdestructive causes and (B) patients with hyproproductive thrombocytopenia due to various causes. In cases of ITP, a poor positive correlation was observed and was found to be non-significant. On the other hand, a moderate positive correlation was found between these parameters in cases of non-ITP. Figure 3 reveals correlation between platelet count and PDW, which was found to be non-significant for both the

groups although showing a poor positive correlation in cases of ITP and a poor negative correlation in non-ITP cases. The correlation between the parameters platelet count (10^9/L) and P-LCC (10^9/L) in cases of ITP is depicted in figure 4(A) which showed an excellent positive correlation and was found to be significant with a p-value of <0.001. The correlation between these parameters in non-ITP cases also showed an excellent positive correlation which was also found to be significant with a p value of <0.001. [Figure 4(B)]

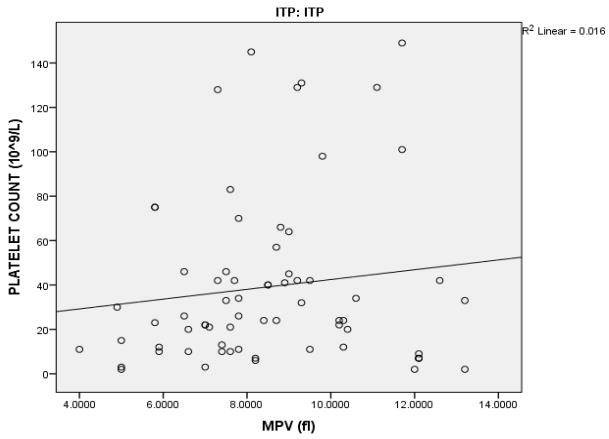

Figure 2(A)

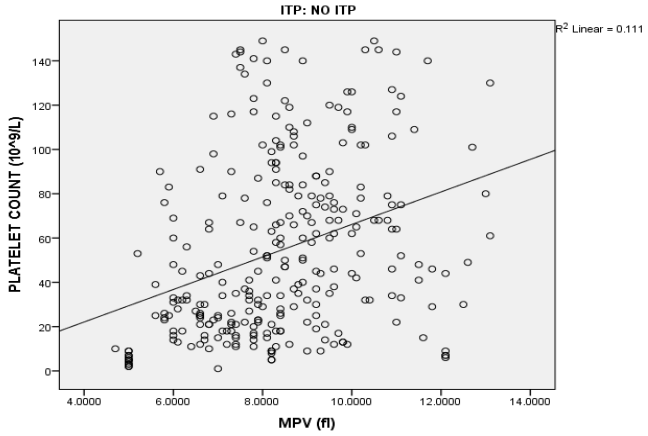

Figure 2 (B)

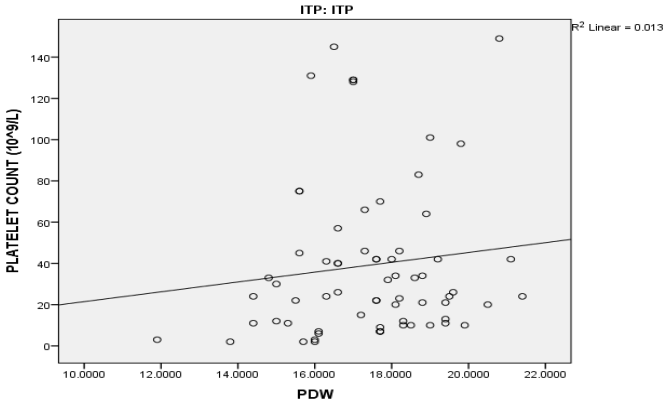

Figure 3 (A)

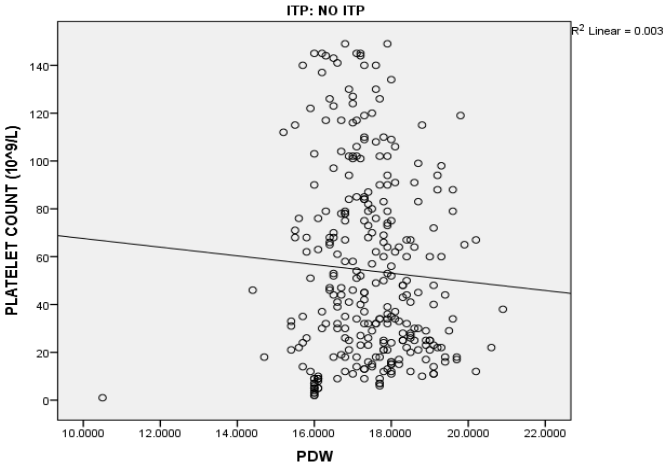

Figure 3 (B)

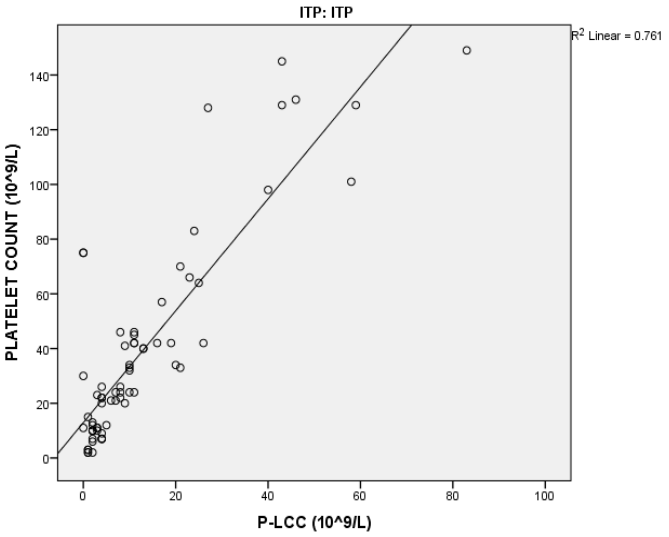

Figure 4 (A)

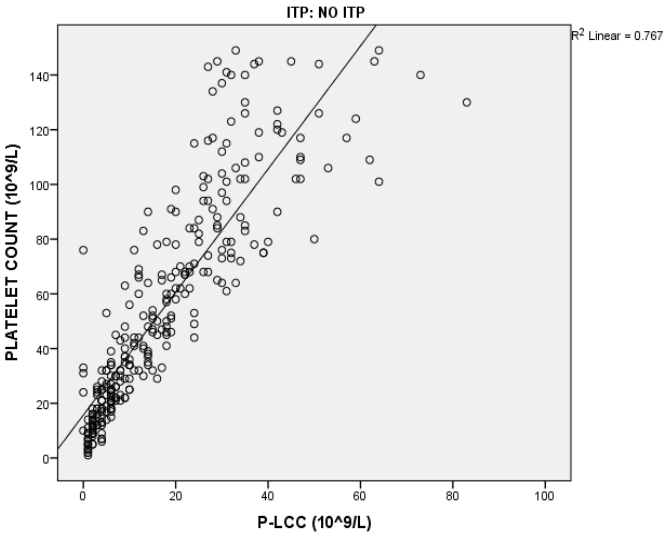

Figure 4 (B)

Role of PVIs in prediction: In the present study, we evaluated whether or not the platelet indices could be used as reliable markers for predicting ITP in cases of thrombocytopenia. It was revealed that only PCT (%) had some significance in predicting ITP while no role of the other indices could be determined. As per our study, an ideal cut-off value of 0.028% for the same was found for the cohort studied. At a value

greater than or equal to 0.028%, the sensitivity and specificity of PCT were found to be maximum i.e. 59.4 and 57.4 respectively. PCT showed a positive predictive value of 23.6% and negative predictive value of 85.2% at the said cut-off. The diagnostic accuracy was found to be 57.06%.

Figure 5 shows the area under the curves (AUCs) of PCT, MPV and PDW in receiver operating characteristic (ROC) analysis. These are 0.372, 0.506 and 0.511 respectively for the diagnosis of ITP in thrombocytopenic patients in the present cohort. MPV and PDW, thus, were found to be not good parameters for prediction of ITP while PCT with an area of 0.372 was shown to be a good parameter, with a p-value of 0.001 (highly significant).

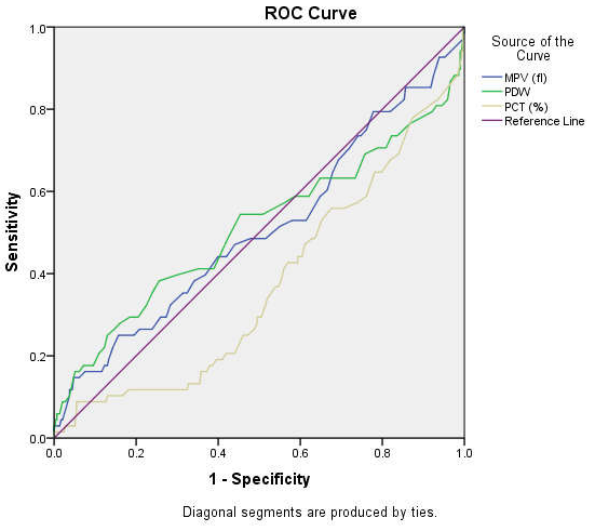

Figure 5

DISCUSSION

The modern hematology laboratories utilize automated cell counters to increase the accuracy and speed of analysis and to decrease chances of human error. [6] Different analyzers use different principles for cell counting- electrical impedance, optical light scatter and immunofluorescentflowcytometry. Platelet indices are also calculated in these machines with the same sample and in the same run without bringing extra costs. [7,8]Platelet indices are biomarkers of platelet activation and are related to the morphology and proliferation kinetics of the platelets. Among these, PCT, MPV, PDW, P-LCC and platelet-large cell ratio (P-LCR) are the platelet parameters determined together in automatic complete blood counts. [9]Some of these indices such as MPV have recently been studied as predictive marker for different diseases including myocardial infarction, haemorrhagic diathesis or hypothyroidism.[10,11,12]Few studies have also been carried out to establish the role of platelet indices in differentiating patients of thrombocytopenia due to ITP or due to BMF.[2,4]This study was also conducted to assess and analyse the role of platelet indices as a discriminating guide for hyperdestructive(ITP) or hypoproductive (Non-ITP) causes in thrombocytopenic patients.

All patients in our study underwent a bone marrow examination, the gold standard investigation in discriminating between thrombocytopenia due to ITP and BMF and was used to validate the utility of platelet indices for the same. The present study revealed higher values of MPV and PDW in patients with ITP as compared to non-ITP patients. However, such a difference was not found to be statistically significant. This was in concordance with study conducted by Numbenjapon*et al*.[2]In studies by Diquattro *et al* [13] and Xu *et al* [4], however, such a difference was found to be statistically significant.

In concordance with the study by Xu *et al* [4], our study showed platelet count significantly lower in ITP patients than in non-ITP patients. However, such was not the case in the study by Numbenjapon *et al* [2].

Similar to the observations in study by Tang YT *et al* [14], in our study too PCT was found to be significantly lower in ITP than in cases of non-ITP.

Another finding that our study revealed was a significantly lower P-LCC in ITP cases than in non-ITP cases(p=0.04). We performed a correlation of platelet count with various platelet indices. Out of these, only P-LCC showed a positive correlation in both ITP and non-ITP cases and was found to be significant. To our knowledge, this result has not been previously reported.

Both MPV and PDW showed a poor positive correlation with platelet count in ITP patients. Such a correlation was not significant in our study. However, in the study by Xu*et al*[4], a notable positive correlation between platelet count and PDW was demonstrated in the ITP group.

Following the results of our study, as measured by ROC curve analysis, only PCT was found to be a predictor of ITP, with a cut-off value of 0.028 that maximized both sensitivity and specificity i.e. 57.4% and 57%, a positive predictive value of 23.6% and negative predictive value of 85.2% respectively (when compared with the gold standard, i.e. bone marrow examination). The diagnostic accuracy of PCT was found to be 57.06%.In the study by Tang YT *et al*[14], receiver-operating characteristic analysis was done.PCT gave a sensitivity of 89.8% and specificity of 84.7% at a cutoff of 0.085 in diagnosis of ITP.

Although a BM study is not recommended as the first line diagnostic investigation for cases of suspected ITP, there is a lack of reliable yet not invasive diagnostic tests and hence BM examination is rather an overused diagnostic approach.[2]Our results suggest that PCT represent megakaryopoietic activity in bone marrow and may be reliable markers in ITP diagnosis.

CONCLUSION

The results of present study revealed that patients with hyperdestructive thrombocytopenia had significantly lower platelet counts, PCT (%) and P-LCC than patients of thrombocytopenia due to hypoproduction. MPV, on the other hand, was found to be higher in ITP than in non-ITP patients, although this was not found to be significant.Based on a clinical examination alone, an accurate diagnosis of the underlying cause of thrombocytopenia is sometimes not possible. In this regard, the use of PCT, along with other clinical findings should be further evaluated as to whether it can be a useful tool to the clinician for predicting ITP and hence avoiding BM aspiration.

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