Original Article

Predictive ValueOfPlateletIndicesForDifferentiating Hyper DestructiveThrombocytopeniaFromHypo Productive ThrombocytopeniaInPatientsAttendingTeritiary Care Hospital

Deepthi Chandrika Chinthalapudi[1], Balasaheb R Yelikar[1]*, Mallanna.S.Mulimani[2]
Anil Reddy Konduru[1] and Savitri M Nerune[1]

[1]Department of Pathology, Shri B M Patil Medical College Hospital & Research Center BLDE (Deemed to be University), Vijayapura, Karnataka INDIA
[2]Department of Medicine, Shri B M Patil Medical College Hospital & Research Center. BLDE (Deemed to be University), Vijayapura, Karnataka INDIA

ABSTRACT

Background: Thrombocytopenia is one of the most critical and complicated clinical conditions to manage. Hence the need for a platelet count has increased over the years in the form of manual smear count and bone marrow examination for discriminating hyper destructive and hypo productive thrombocytopenia. The introduction of platelet indices like mean platelet volume (MPV), platelet distribution width (PDW), Platelet large cell ratio (PLCR) inautomated haematology analyzers has provided a window into the cause of thrombocytopenia in the recent years. Hence this study was undertaken to analyze the utility of these platelet indices in hypo productive and hyper destructive thrombocytopenia.

Methods: A prospective cross-sectional study was conducted on 84 thrombocytopenic patients out of which 49 were hyper destructive and 35 were hypo productive group. The blood samples were analyzed for CBC diff using SYSMEX XN 1000.

Statistical analysis was performed to assess the mean SD, Receiver Operating Curve (ROC) to determine the specificity, sensitivity, positive predictive value (PPV) and negative predictive values (NPV) for platelet parameters. Correlation test to determine association between the continuous variables was done.

Result: All platelet indices were significantly higher in hyper destructive than in hypo productive group. The MPV and PLCR showed better sensitivity and specificity, positive and negative predictive values when compared to PDW in both the groups. There was statistically significant correlation and difference of platelet parameters like MPV, PDW and PLCR between the hyper destructive and hypo productive thrombocytopenia.

Conclusion: The platelet indices MPV and PLCR have better ability to discriminate hyper destructive from hypo productive thrombocytopenia. Evaluating these parameters offers an earlier diagnosis in hyper destructive thrombocytopenia patients avoiding, bone marrow aspiration and even prevent undesirable platelet transfusion.

Keywords: Platelet Indices, Thrombocytopenia, Bone Marrow.

Introduction

Platelets are small sub cellular fragments which circulate in blood with characteristic discoid shapes formed from the cytoplasm of megakaryocyte.[1] For a long time platelet count was done by phase contrast microscopy which was the gold standard method. In case of thrombocytopenia (TCP) for the assessment of definitive cause bone marrow examination was done which is painful, invasive and not desired by the patients.[2] However, with the advancing technologies and the complex computer algorithms, evaluation of platelet parameters like MPV PDW and PLCR using automated haematology analyzers are very helpful in refining the cause of thrombocytopenia as they have a significant role in understanding its cause, at a rapid, relatively non invasive and reliable rate which might be either hyper-destructive or hypo-productive thrombocytopenia.[3] The need for this rapid assessment is essential in managing critical conditions where repeated platelet parameters are monitored on regular basis.[4] To evaluate the "diagnostic predictive value of platelet indices in differentiating hypo productive and hyper destructive thrombocytopenia", this prospective study has been done to further add to the data available and assessing the utility of these parameters in Indian population.

Materials and Methods

This prospective study was conducted in patients who presented to the outpatient departments of medicine,

surgery, obstetrics & gynaecology, paediatrics at Shri B M Patil Medical College & hospital, who are evaluated in Department of Pathology, for thrombocytopenia over a period of November 2016 to June 2018. In this study 84 thrombocytopenic patients were enrolled where 49 had hyper destructive thrombocytopenia and 35 were hypo productive thrombocytopenia.

In cases referred for thrombocytopenia evaluation a short history and informed written consent was taken. Peripheral venous blood was obtained from antecubital venepuncture following standard protocols into tripotassium EDTA vacutainer for complete blood count and analysed within 4hrs to prevent clumping. The complete blood count was performed using SYSMEX XN 1000, 6 part haematology analyzer in CBC DIFF mode where platelet parameters like platelet count, mean platelet volume (MPV), platelet distribution width (PDW) and platelet large cell ratio (PLCR) were available.

Platelet count, MPV, PDW and PLCR were documented for each case as well as the platelet count was verified using Manual smear review. Cases falling into the category of hypo productive group were further evaluated by bone marrow study following institutional protocol. Patients who, after detailed clinical assessment and laboratory tests were diagnosed to have an immunological basis for thrombocytopenia and recent manifestation of blood transfusions.

Statistical Analysis: Data was analyzed using SPSS software v.23.0. and Microsoft office.

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean, standard deviation (SD) were used. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. Bivariate correlation analysis using Pearson's correlation coefficient (r) was used to test the strength and direction of relationships between the interval levels of variables. Receiver operating curve (ROC) analysis for Sensitivity- specificity was done to check relative efficiency. The p-value of < 0.05 was considered to be statistically significant.

Results
A total of 84thrombocytopenic patients were enrolled in the present study. Among these patients, 49 had hyper destructive thrombocytopenia (without bone marrow disease) and 35 had hypo productive thrombocytopenia (with bone marrow disease).

Males were predominantly affected in hypo productive and hyper destructive thrombocytopenia with 41.4% and 58.6%. Dengue (19) and malaria (11) i.e; 38.8% and 22.5%

were the more prevalent aetiologies in hyper destructive thrombocytopenia category. While Erythroid hyperplasia (15) and acute myeloid leukemia (11) i.e; 42.8% and 31.4% were the most common causes for hypo productive thrombocytopenia (Table 1.).

The mean SD value for MPV in hypo productive & hyper destructive TCP was 10.40±2.05 and 11.52±1.20 with a p value of 0.002 which was statistically significant. The mean SD value for PLCR in hypo productive & hyper destructive TCP was 30.17±10.02 and 37.44±8.31 with a p value of 0.001 which was statistically significant. The mean SD value for PDW in hypo productive & hyper destructive TCP was 14.15±4.26 and 14.41±4.00 with a p value 0.772 which was not statistically significant. (Table 2)

Pearson correlation studies between the platelet count and platelet indices in hypo productive TCP are showing weak negative correlation for MPV -0.108. PDW and PLCR are showing significant positive correlation 0.274 and 0.004 with a p value of 0.112 and 0.981 which is not statistically significant. The reason for the lower values of correlation may be due to non linear relation between MPV, PDW, PLCR with platelet count and smaller sample size.

Pearson correlation between the platelet count and platelet indices in hyper destructive TCP cases shows positive correlation for MPV 0.067 with a p value of 0.64 which is statistically not significant. There is a negative correlation between the platelet count and platelet indices PDW -0.001 and PLCR -0.113 with a p value of 0.99 and 0.44 which is statistically not significant (Fig.1). The reason may be due to non linear relationship between the platelet count and platelet indices and a smaller sample size.

ROC curve analysis
The area under the curve (AUC) gives the probability that a patient with bone marrow disease has lower values of the measurement (MPV, PDW, PLCR). The AUC shows lines shifting towards the left upper corner particularly for the MPV and PLCR giving an area of 0.673 (67.3%) and 0.711 (71.1%) respectively and PDW giving an area of 0.548 (54.8%) (Fig.2).

MPV of <11.05 fl can identify thrombocytopenic patients as hypo productive with 66.7% sensitivity and 59.2 % specificity. Likewise, PDW of <12.80 fl have 51.4% of sensitivity and 63.3% of specificity. PLCR with <33.90% have 68.6% of sensitivity and 67.3% of specificity. The platelet indices MPV and PLCR in particular have better sensitivity and specificity to diagnose hypo productive TCP. MPV of > 11.05 fl can identify thrombocytopenic patients as hyper destructive TCP with 67.3 % sensitivity and 65.7% specificity. PDW of >12.80 fl show 63.3%

sensitivity and 51.4% specificity and PLCR of > 32.55 % show 73.5% sensitivity and 65.7% specificity. The platelet indices MPV and PLCR in particular have better sensitivity and specificity to diagnose hyper destructive TCP (Table.3).

The NPV & PPV for the hypo productive and hyper destructive TCP at different MPV, PDW and PLCR

threshold levels show MPV of > 11 fl has a NPV of 70.21% and MPV of <8 fl has a PPV of 100%. It was observed that the positive predictive value was variable when compared with different MPV thresholds for hyper destructive thrombocytopenia. Likewise PDW of > 14 fl has a NPV of 65% and < 12 fl has a PPV of 51.85%. PLCR of > 35% has a NPV of 73.17% in hyper destructive TCP and < 25% has a PPV of 88.24% in hypo productive TCP.(Table.4)

Table 1: Etiological distribution of hyper destructive and hypo productive thrombocytopenia cases.

HYPER DESTRUCTIVE THROMBOCYTOPENIA		
Diagnosis	**N %**	
Alcoholic liver disease (ALD)	10	20.4
Dengue fever	19	38.8
Idiopathic thrombocytopenia (ITP)	1	2.0
Malaria	11	22.5
HIV	2	4.1
Sepsis	6	12.2
Total	**49**	**100.0**
HYPO PRODUCTIVE THROMBOCYTOPENIA		
Diagnosis N %		
Acute Lymphoblastic Leukaemia (ALL)	8	22.9
Acute Myeloid Leukaemia (AML)	11	31.4
Aplastic Anemia	1	2.9
Erythroid Hyperplasia	15	42.8
Total	**35**	**100.0**

Table 2: Mean SD values in hyper destructive and hypo productive thrombocytopenia.

Parameters	HYPO PRODUCTIVE THROMBOCYTOPENIA	HYPER DESTRUCTIVE THROMBOCYTOPENIA	p value
	Mean±SD	**Mean±SD**	
Platelet count (lakhs/cumm)	0.53±0.29	0.69±0.32	0.016
MPV(fl)	10.40±2.05	11.52±1.20	0.002*
PDW(fl)	14.15±4.26	14.41±4.00	0.772
PLCR(%)	30.17±10.02	37.44±8.31	<0.001*

*Note: * significant at 5% level of significance (p<0.05)*

Table 3: Sensitivity and Specificity of platelet indices at different cut off points in hypo productive and hyper destructive thrombocytopenia.

HYPO PRODUCTIVE GROUP			HYPER DESTRUCTIVE GROUP		
Cut-off value	**Sensitivity(%)**	**Specificity(%)**	**Cut-off value**	**Sensitivity(%)**	**Specificity(%)**
MPV					
<6.60	0.0	100.0	>9.25	98.0	28.6
<8.95	20.0	98.0	>10.25	85.7	40.0
<10.15	40.0	91.8	>10.65	75.5	48.6
<10.75	51.4	73.5	>11.05	67.3	65.7

HYPO PRODUCTIVE GROUP			HYPER DESTRUCTIVE GROUP		
Cut-off value	Sensitivity(%)	Specificity(%)	Cut-off value	Sensitivity(%)	Specificity(%)
<11.05	66.7	59.2	>11.30	55.1	68.6
PDW					
<7.10	0.0	100.0	>10.55	87.8	22.9
<10.45	20.0	87.8	>11.90	73.5	40.0
<12.80	51.4	63.3	>12.80	63.3	51.4
<13.75	57.1	55.1	>13.55	55.1	54.3
<14.35	60.0	49.0	>14.15	51.0	60.0
PLCR					
<16.60	0.0	100.0	>22.25	95.9	25.7
<25.50	48.6	95.9	>28.10	85.7	51.4
<33.65	65.7	67.3	>32.55	73.5	65.7
<33.90	68.6	67.3	>34.25	63.3	68.6
<40.65	80.0	36.7	>36.45	55.1	68.6

Table 4: The NPV & PPV for the hypo productive and hyper destructive TCP at different MPV, PDW and PLCR threshold levels.

| MPV threshold	No. of Hyper destructive cases	NPV (%)	Threshold	No. of Hypo productive cases	PPV (%)
>13	5	55.56	<13	31	41.33
>12	18	69.23	<12	27	46.55
>11	33	70.21	<11	21	56.76
>10	45	67.16	<10	13	76.47
>9	48	63.16	<9	7	87.50
>8	49	61.25	<8	4	100.00
PDW threshold					
>20	5	62.50	<20	32	42.11
>18	8	53.33	<18	28	40.58
>16	16	57.14	<16	23	41.07
>14	26	65.00	<14	21	47.73
>12	36	63.16	<12	14	51.85
>10	44	57.89	<10	3	37.50
PLCR threshold					
>50	4	80.00	<50	34	43.04
>45	6	54.55	<45	30	41.10
>40	18	69.23	<40	27	46.55
>35	30	73.17	<35	24	55.81
>30	39	72.22	<30	20	66.67
>25	47	70.15	<25	15	88.24
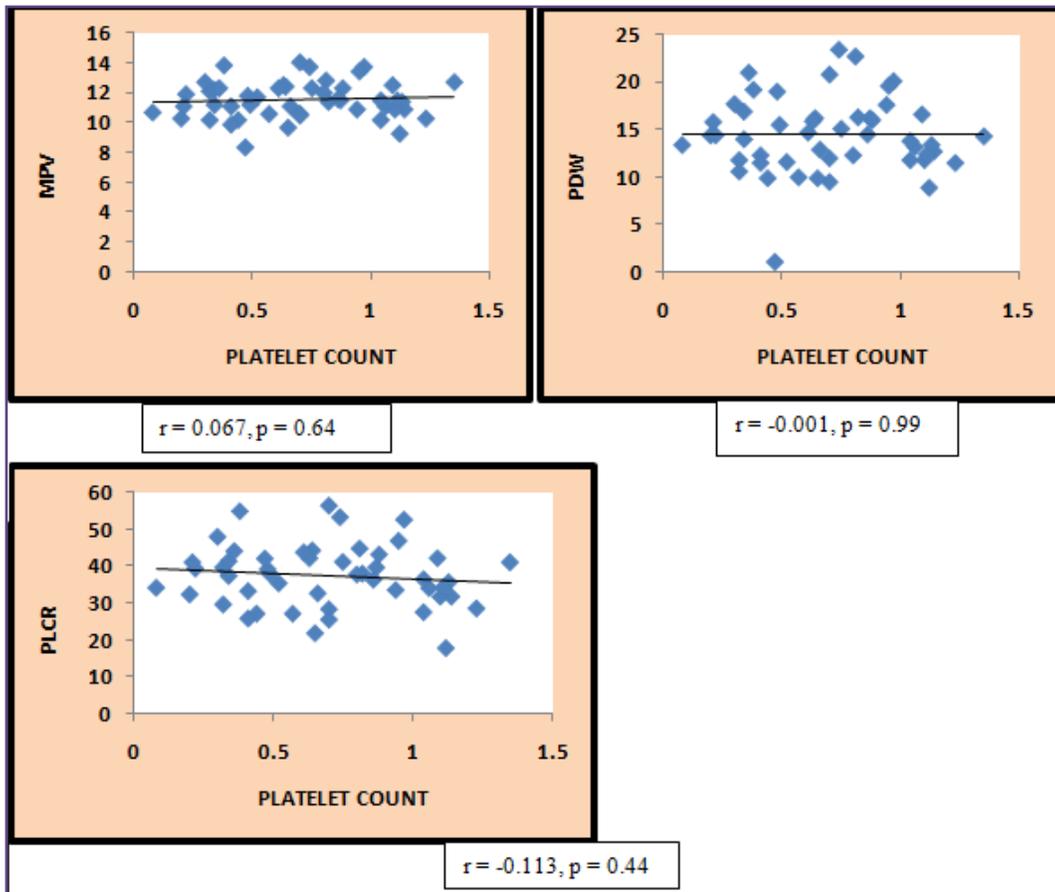
Fig. 1: Correlation between platelet count and MPV, PDW, P-LCR in patients with hyper destructive thrombocytopeniar = correlation coefficient.
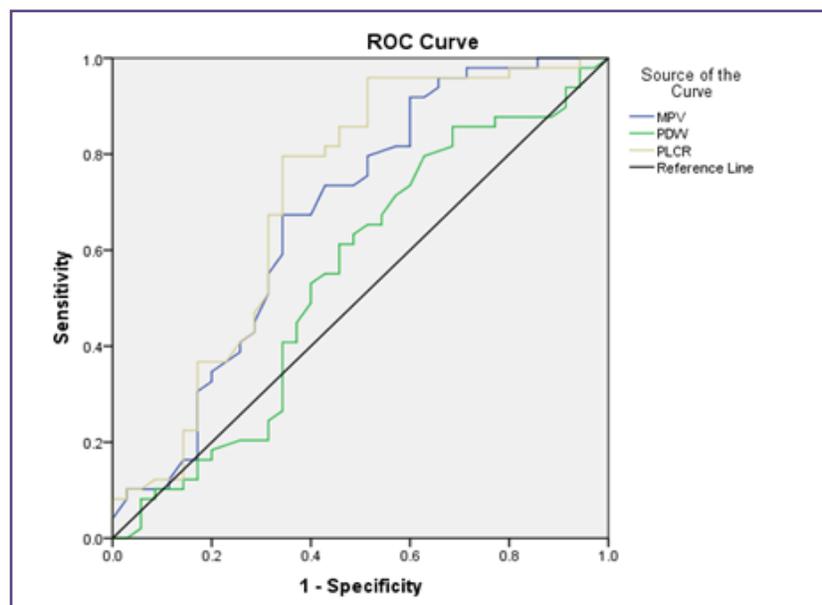

Fig. 2: ROC analysis.

Discussion

Platelets are gaining importance in the present day with the list of diseases getting updated from time to time where platelet count is needed for better management as well as monitoring. So there is an active need for having a precise and accurate platelet count. The method for obtaining the count should be relatively non invasive, cost effective and rapid. Automated analyzers have covered a lot of ground over the last few decades and are on par with the manual smear count today. Platelet count when interpreted with parameters like MPV PDW and PLCR forms a valuable diagnostic modality in assessing thrombocytopenia. To evaluate the utility of these platelet indices a total of 84 cases were analyzed and stratified as hyper destructive (49) and hypo productive (35) group in this study. In hypo productive group, males were 24 and females were 11, in hyper destructive group, males were 34 and female were 15. In hypo productive and hyper destructive group mean platelet count was statistically significant showing 0.53 (±0.29) x10^9/L and 0.69 (±0.32)x10^9/L.

In the present study the Mean SD of MPV are higher in hyper destructive and hypo productive groups. The MPV of > 11(fl) shows 67.3% sensitivity, 65.7% specificity and 70.2% NPV in hyper destructive TCP and MPV of <11 (fl) shows 65.7% sensitivity and 59.2% specificity in hypo productive TCP and MPV of < 8 (fl) has a PPV of 100% in hypo productive TCP at different MPV threshold levels.

Table.7 shows study done by Negash M *et al.* which reported that MPV are significantly higher in hyper destructive cases with 67% sensitivity and 95% specificity than hypo productive cases with 74% sensitivity and 70% specificity and also with 88% PPV and 81% NPV

respectively.[5] Kaito K *et al.* and Islam S *et al.* reported that MPV >11 (fl) has sensitivity (87%, 73.33%) and specificity (80%,80%) respectively to make a diagnosis of hyper destructive thrombocytopenia .[6,7]

Platelet indices MPV, PDW and PLCR are showing high mean values in hyper destructive group than in hypo productive group. Among these platelet indices, MPV and PLCR are statistically significant and PDW is not statistically significant in hyper destructive and hypo productive thrombocytopenia in the present study when compared to other studies.

Study done by Kaito K *et al.* Khaleel K *et al.* and Numbenjapon *et al.* and Farweez B *et al.* found that MPV and PDW was significantly higher in hyperdestruction group compared to hypo productive thrombocytopenia. In hyper destructive thrombocytopenia, bone marrow compensates actively for the platelet loss and start releasing young larger platelets ("left shift") which tend to decrease in size during its 7-10 days life span. The high PDW in hyperdestruction could be explained because of the newly formed platelets that are larger than circulating platelets, which tend to decrease in size with age in the circulation similar to reticulocytes with increased mean volume. As a result, in patients with thrombocytopenia secondary to hyperdestruction the PDW is increased, reflecting active compensatory mechanism in bone marrow with release of young platelets.[6,8,9,10] In our study also we found a significant low (10.40 ± 2.05) mean MPV in the hypoproduction group than in the hyperdestruction group (11.52 ± 1.20).

In the present study MPV, PDW and PLCR was significantly higher and these indices were effective in distinguishing

Table 5: Comparision and distribution of thrombocytopenia cases with similar studies.

Platelet indices	Present study (84)		Negash et al. (83)		Kaito et al. (79)		Islam et al. (60)	
hyper destructive thrombocytopenia								
Cut off ranges	sensitivity	specificity	sensitivity	Specificity	Sensitivity	specificity	sensitivity	Specificity
MPV >11 (fl)	67.3%	65.7%	67 %	95%	87.2 %	80%	73.3 %	80 %
PDW >14 (fl)	51 %	60 %	61 %	62%	76.9 %	90%	86.6 %	93.3%
PLCR > 33 (%)	73.5 %	65.7 %	67 %	88 %	91.4 %	73%	73.3 %	90 %
Hypo productive thrombocytopenia								
Cut off ranges	sensitivity	specificity	sensitivity	specificity	Sensitivity	specificity	sensitivity	Specificity
MPV< 10 (fl)	40 %	91%	74 %	70 %	-	-	-	-
PDW< 15 (fl)	60 %	49 %	76 %	55 %	-	-	-	-
PLCR <31 (%)	68.6 %	67.3 %	76 %	67 %	-	-	-	-

these two types of thrombocytopenia. Among all the platelet indices, MPV and PLCR are more reliable and have better discriminating potential to differentiate between the hypo productive and hyper destructive thrombocytopenia which are statistically significant.

"The first possible explanation for such differences between the present study and the above studies could be the kind of automated hematology analyzers that is used for enumerating the platelet count and platelet parameters. A study conducted by Kaito K *et al*. in Japan using Sysmex-XE2100 analyzer (Kobe, Japan) reported a mean MPV of 10.2 fl in hypo productive and 12.2 fl in hyper destructive patients, whose values are closer to the present study".[6]

"The second possible reason could be the actual difference in the population and platelet indices from age and sex wise distribution, number of study participants and country to country. A study done by Negash et al mentioned that Hong *et al*. in healthy Chinese adults using Sysmex XT 2100 indeed confirmed variations of platelet indices between regions.[5] Studies done by kharikar *et al* mentioned that Babu E and Basu D suggested that it is not always possible to record platelet indices in the presence of red cell fragmentation, in severe thrombocytopenia.[11] We also avoided this problem by discarding cases without indices and selected only those cases which had platelet indices and provided a histogram. In the present study we are used Sysmex XN1000 hematology fully automated analyzer which works on the principal of hydrodynamic focusing and flow cytometry.

Kaito K *et al*. reported that correlation studies between the platelet count and platelet indices showed an inverse correlation between platelet count, PDW and PLCR. However, no significant correlation between platelet indices and platelet count was found in immune thrombocytopenia. Negash M *et al*. observed that there was statistically significant negative correlation between platelet count and the platelet indices in hyper destructive patients. However, the platelet count and platelet indices did not show significant correlation in Hypo productive patients.[5,6]

In the present study there was a statistically significant negative correlation between the platelet count, PDW and PLCR in hyper destructive thrombocytopenia. MPV is showing significant positive correlation. There was a negative correlation between the MPV in hypo productive thrombocytopenia. There is a positive correlation between the platelet count and PDW and PLCR. However, there is no significant correlation between platelet count and platelet indices in hyper destructive & hypo productive thrombocytopenia.

Study done by Kaito K *et al*. reported ROC curves with large AUC and among the three parameters, PDW and PLCR were more reliable markers for distinguishing hyper destructive from hypo productive thrombocytopenia. Negash M *et al*. concluded that MPV and PLCR are more reliable markers, giving an area of 87.6% and 81.6% respectively to distinguish hyper destructive from hypo productive Thrombocytopenia.[5,6]

In the present study the ROC analysis showed the Area under curve (AUC) showed lines shifting towards the left upper corner particularly for MPV and PLCR giving an area of 67.3% and 71.1% respectively where PDW is decline in the AUC graph with area of 54.8% respectively. MPV of > 11 (fl) has a NPV of 70.2% in hyper destructive thrombocytopenia and < 8 (fl) has PPV of 100% in hypo productive thrombocytopenia at different MPV threshold levels. PLCR of > 35% has a NPV of 73% in hyper destructive TCP and PLCR of < 20% has a PPV of 83% in hypo productive TCP at different PLCR threshold levels, Whereas PDW of >14 (fl) has a NPV of 65% in hyper destructive TCP and PDW of <12 (fl) has a PPV of 51.85% in hypo productive TCP at different PDW threshold levels.

Therefore the platelet indices MPV and PLCR could be helpful to have a better prediction capacity for differentiating hyper destructive and hypo productive thrombocytopenia during the early diagnosis of the thrombocytopenia patients.

Conclusion

Automated hematology analyzers have incremental improvement in accuracy and reliability, which were comparable with manual smear count, over the years. Along with the platelet count the additional parameters like MPV PDW and PLCR were able to classify the thrombocytopenia based on etiology into hypo productive and hyper destructive thrombocytopenia with a significant sensitivity and specificity. Based on these observations, analyzers stratification of these cases provides a reliable modality for the management of thrombocytopenia where in invasive procedures like bone marrow study is not feasible. Further studies with large number of cases in each sub groups are needed to explore the role of the platelet indices and the role of other new parameters like immature platelet fraction (IPF) in thrombocytopenia used and also to find the diagnostic role of platelet indices in various other diseases.

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*Corresponding author:
Dr. Balasaheb R Yelikar, Professor & HOD, Department of Pathology, Shri B M Patil Medical College Hospital & Research Center, BLDE (Deemed to be University), Vijayapura, Karnataka 586103 INDIA
Phone: +91 9448139588
Email: yelikar61@gmail.com