Original Article

A study to determine utility of platelet indices in differentiating hyperdestructive and hypoproductive thrombocytopenia

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ABSTRACT

Background: Thrombocytopenia by definition signifies a platelet count below 1,50,000/mm3 but this does not reflect the underlying pathology. Management of these patients significantly depends on identifying the primary cause of thrombocytopenia. With advances in automation, analyzers can now measure platelet parameters like mean platelet volume, Platelet distribution width, and Platelet large cell ratio which are potential biomarkers of platelet morphology. Presently, these non-invasive and cost-efficient diagnostic markers are quite underused. The study aimed to understand the relationship of instrument-derived platelet parameters with respect to the categorizing of thrombocytopenia based on underlying pathophysiology.

Materials and methods: A prospective study was conducted from September 2018 to October 2020consisting of 315 cases of hyperdestructive thrombocytopenia and 54 cases of hypoproductive thrombocytopenia. After collecting the important clinical details, platelet count along with instrument-derived platelet indices was noted. A comparison of platelet indices was done between the two groups.

Results: In the hyper-destructive group, the mean platelet indices were found to be significantly higher in comparison to the hypo-productive group. No significant correlation was obtained between the platelet count severity and various platelet indices. Mean platelet volume had the highest sensitivity and specificity in differentiating hyper-destructive thrombocytopenia from the hypo-productive group.

Conclusions: Platelet indices aid in distinguishing hyper-destructive from hypo-productive causes of thrombocytopenia. Of the three indices analyzed, Mean platelet volume was shown to be a better parameter in differentiating the two groups.

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INTRODUCTION

Platelets are derived from the cytoplasmic fragments of megakaryocytes. They measure 3 -5 μmin diameter and have a volume of 4.5–11 fl. Each megakaryocyte undergoes fragmentation to form approximately 1000 to 3000 platelets with a lifespan ranging from 7-10 days. Along with coagulation factors, they play a major role in hemostasis and in the prevention of bleeding. Platelets also contribute to a large extent in many inflammatoryprocesses, microbial defense mechanisms, healing of wounds,angiogenesis,andremodeling. A platelet

count below 150 x 10⁹/L in the peripheral blood is defined as thrombocytopenia.[1]

The pathomechanism that causes thrombocytopenia can be categorized as impaired platelet production, accelerated platelet destruction, and splenic pooling or sequestration. It is essential to evaluate the underlying cause of thrombocytopenia as it has an impact on the management of these patients.[2]

Bone marrow aspiration has continued to exist as the gold standard for diagnosing and evaluating the cause of thrombocytopenia.This invasive technique is time-consuming and poses the risk of bleeding especially in patients with severe thrombocytopenia. For a better assessment of these patients, innovative, non-invasive, and cost-efficient diagnostic techniques for the diagnosis of thrombocytopenia are required.[3]

Presently, automated hematology analyzers are being used mainly for complete blood counts and red cell indices but, additionally, these analyzers also provide many other parameters which can give much more information for clinical use. However, due to a lack of knowledge, they are not being utilized optimally to their best potential. Platelet indices (MPV, PDW, and P-LCR) are one such underutilized parameter that can help clinicians in screening and diagnosing the disease states.They give important information about the platelet activityand kinetics.[2]Understanding the changes in the platelet indices may help us better understand the probable cause of thrombocytopenia.[4]

Considering a need to identify a simple yet reliable test to categorize thrombocytopenia that could help in patient management, this study was done to understand the relationship of instrument-derived platelet parameters withrespect to the underlying pathophysiology of thrombocytopenia.

MATERIALS AND METHODS:

This study was conducted in the pathology department from September 2018 to October 2020 on thrombocytopenic patientsbeing treated at MVJ Medical College & Research Hospital, a tertiary care center, situated in rural Bangalore. 369 cases of thrombocytopenia were studied during this period.

Inclusion criteria: All cases having platelet count less than 1,50,000/mm³ were included in the study. Artefactual thrombocytopenia caused due to platelet clumping was confirmed by peripheral smear examination.

Exclusion criteria: Caseswhere the hematology analyser did not display results of platelet indices were excluded from the study.

Blood samples were collected in EDTA tubes and processed using Sysmex KX 21 hematology analyzer. To prevent platelet swelling by the anticoagulant, the samples were analyzed within three hours of venipuncture.Platelet parameters that were recorded for all cases included platelet count, MPV, PDW, and PLC-R.The findingsof additional tests done in the evaluation of thrombocytopenia, such as quantitative Buffy Coat (QBC), sepsis profile, dengue serology, and bone marrow examination along with other relevant clinical informationwere recorded from the hospital case files.Based on these details, thrombocytopenia cases were grouped into 2 categories:1) Hyper-destructive thrombocytopenia2) Hypo-productive thrombocytopenia

Data collected was entered into Microsoft Excel and was analyzed using SPSS 22 software. Qualitative data was represented in the form of frequencies and proportions. The chi-square test was used as a test of significance. Quantitative data was represented as mean and standard deviation. ANOVA (Analysis of Variance) and Paired t-test were used as the test of significance to identify the mean difference between the two study groups.The correlation between the platelet indices and platelet count was studied using the Pearson Correlation coefficient and ROCcurve to obtain a reliable cut-off value of the indices.p-value<0.05 was considered as statistically significant.

RESULTS:

The study included 369 cases of thrombocytopenia of which 315 cases belonged to hyperdestructive group and 54 cases to hypoproductive group.The majority of patients in hyperdestructive group, were in the age group of less than ten years 87 (27.6%) while 11 (20.4%) cases inhypoproductive groupwere in the age group ofsecond, fourth, and fifth decades of life. (Table 1)A male predominance (58.4%) was observed in hyperdestructive group while a slight female preponderance (51.9%) was noted in hypoproductive group. Dengue accounted for the maximum number of hyperdestructive thrombocytopenic cases (48.6%) followed by sepsis (15.5%) (Fig 1) and immune thrombocytopenic purpura (8.3%) (Fig 2). Common causes for hypoproductivethrombocytopenia includedmegaloblastic anemia (70.4%) (Fig 3) followed by acute leukemia (18.5%). (Table 2).

Table 1: Age distribution among the cases in hyperdestructive and hypoproductive group

Age	Hyperdestructive		Group Hypoproductive	
	Count	%	Count	%
<10 years	87	27.6%	8	14.8%
11 to 20 years	52	16.5%	11	20.4%
21 to 30 years	60	19.0%	4	7.4%
31 to 40 years	31	9.8%	11	20.4%
41 to 50 years	37	11.7%	11	20.4%
51 to 60 years	24	7.6%	2	3.7%
61 to 70 years	15	4.8%	5	9.3%
71 to 80 years	9	2.9%	2	3.7%
Total	315	100.0%	54	100.0%

Table 2: Distribution of hyperdestructive and hypoproductive groups according to etiology

Clinical Diagnosis	HYPERDESTRUCTIVE		Total	
	Count	%	Count	%
Acute Gastroenteritis	11	3.5%	11	3.0%
Acute Pancreatitis	5	1.6%	5	1.4%
Birth Asphyxia	1	0.3%	1	0.3%
CKD	8	2.5%	8	2.2%
CLD	5	1.6%	5	1.4%
CVD	7	2.2%	7	1.9%
Dengue	153	48.6%	153	41.5%
Diabetes	7	2.2%	7	1.9%
Febrile Seizures	3	1.0%	3	0.8%
Filariasis	2	0.6%	2	0.5%
ITP	26	8.3%	26	7.0%
Malaria	5	1.6%	5	1.4%
Meningoencephalitis	10	3.2%	10	2.7%
Pregnancy Induced Hypertension	7	2.2%	7	1.9%
Scrub Typhus	2	0.6%	2	0.5%
Sepsis	50	15.9%	50	13.6%
Snake Bite	3	1.0%	3	0.8%
Viral Fever	10	3.2%	10	2.7%
	315	100.0%		
HYPOPRODUCTIVE				
Acute Leukemia	10	18.5%	10	2.7%
Aplastic Anemia	4	7.4%	4	1.1%
Storage Disorders	2	3.7%	2	0.5%
Megaloblastic Anemia	38	70.4%	38	10.3%
Total	54	100.0%	369	100.0%

Most of the cases in the study had platelet count in the range of 51,000 to 1 lakh/cumm.(Table 3). There was a significant difference in the mean values of platelet count, MPV, PDW, and P-LCR between hyperdestructive and hypoproductive groups. (Table 4) However, no significant correlation between platelet count and platelet indices i.e. MPV, PDW, and P-LCR) was noted inhyperdestructive (p-value: 0.767, 0.350, and 0.957 respectively), and hypoproductivegroups (p-value: 0.743, 0.300, and 0.763 respectively).

Table 3: Distribution of Hyperdestructive and Hypoproductive groups according to range of platelet count

		Group				Total		P value
		Hyper destructive		Hypoproductive				
		No. of Cases	%	No. of Cases	%	No. of Cases	%	
Platelet count	<20000	31	9.8%	7	13.0%	38	10.3%	
	21000 to 50000	79	25.1%	18	33.3%	97	26.3%	0.457
	51000 to 100000	186	59.0%	26	48.1%	212	57.5%	
	>1 lakh	19	6.0%	3	5.6%	22	6.0%	
	Total	315	100.0%	54	100.0%	369	100.0%	

ROC Curve (Fig 4)was plotted to obtain the cut-off values for all the 3 indices (MPV,PDW & P-LCR) and calculate the sensitivity, specificity, Negative Predictive Value (NPV) and Positive Predictive Value (PPV) in differentiating Hyperdestructive and Hypoproductive thrombocytopenia cases.Sensitivity for mean platelets count, MPV, PDW, L-PCR was 66.67%, 88.57%, 85.40%, 42.54% respectively, specificity was 52.38%, 70.37%, 48.15%, 83.33%respectively, NPV was 90.16%, 51.4%, 36.1%, 19.9% respectively and PPV was 19.35%, 94.6%, 90.6%, 93.7% respectively.On analysis, MPV was found to have the highest area under the curve and thus the highest sensitivity in differentiating the two groups. This was followed in decreasing order by P-LCR, PDW, and Platelet Count.

Table4: Comparison of Mean Platelet count,Mean MPV, Mean PDW & Mean P-LCR between Hyperdestructive and Hypoproductive groups

| Mean		Platelet count					P value
		SD	Minimum	Median	Maximum		
Group	Hyper destructive	62034.92	27750.97	10000.00	63000.00	140000.00	<0.001
	Hypoproductive	53388.89	27829.95	11000.00	57500.00	130000.00	
		MPV					
Group	Hyper destructive	10.71	1.21	7.00	10.70	16.40	<0.001
	Hypoproductive	9.03	1.16	7.10	9.00	11.90	
		PDW					
Group	Hyper destructive	15.18	4.00	8.50	14.60	41.70	<0.001
	Hypoproductive	13.54	3.38	8.00	12.55	20.10	
		P-LCR					
Group	Hyper destructive	31.39	7.23	8.10	31.10	52.00	<0.001
	Hypoproductive	27.02	6.81	14.20	28.20	39.80	

DISCUSSION:

The study included 369 cases of thrombocytopenia. Based on the clinical diagnosis and the ancillary test reports, thrombocytopenia cases were categorized into hyperdestructive thrombocytopenia (315 cases, 85.4%) and hypoproductive thrombocytopenia (54 cases, 14.6%). Similar incidences have been noted by other authors in literature; Vidyadhar et al(81.4%), Gulati et al(79%), and Parveen et al (78.3%). [5,6,7] Of the 315 hyperdestructivecases studied, a majority of cases (72.7%) were due to dengue, ITP and sepsis.Vidyadhar et al also found a higher proportion of dengue and sepsis(47.3%)cases in their study.[5] However, the authors unlike our study did not encounter ITP cases as noted by us. Gulati et alalso found dengue, ITP, and sepsis cases together accounting for 46.8% of total cases. [6]However, they had a lesser number of dengue cases in their study.
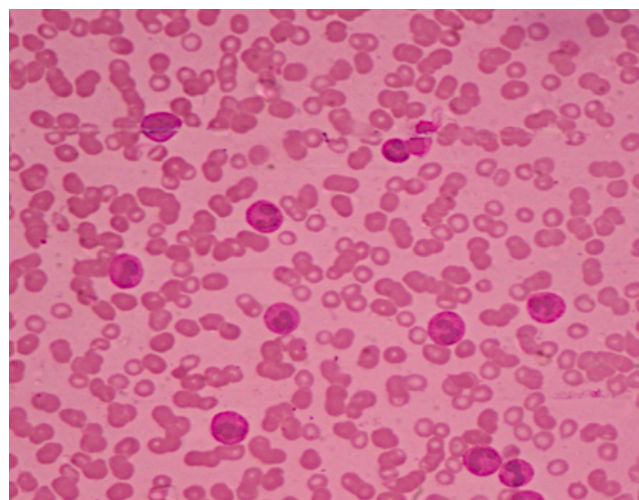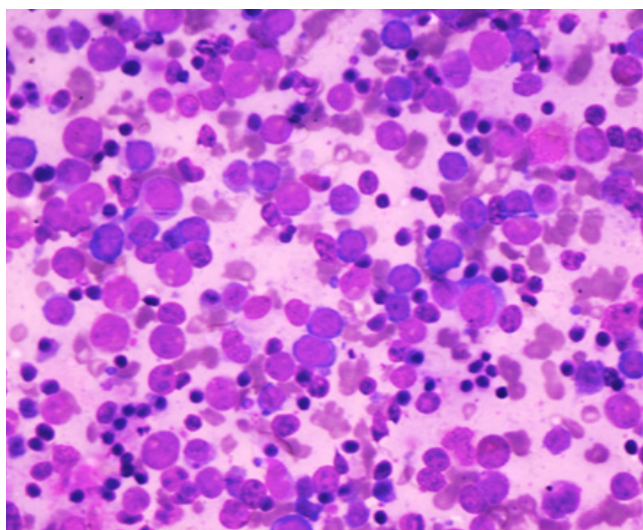

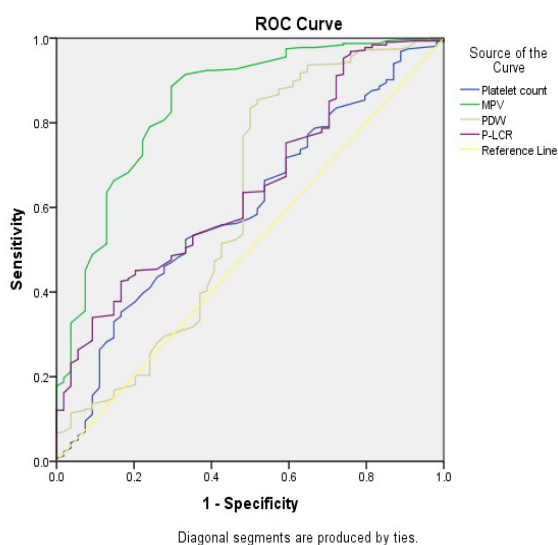*Figure1:* *Case of sepsis with neutrophilic leukocytosis and thrombocytopenia(Leishman stain: 40X)*
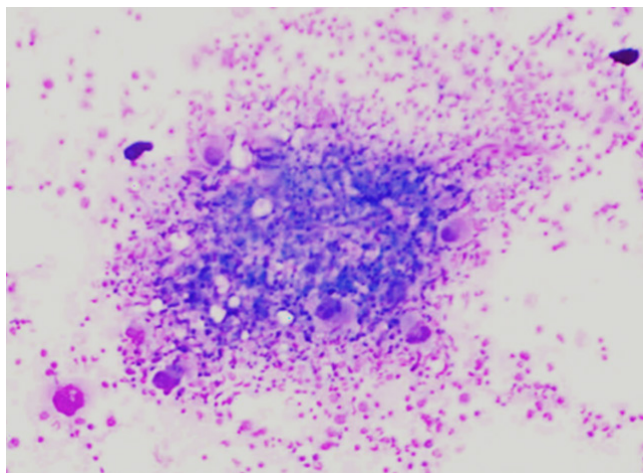
Figure2: *Bone marrow showing increased megakaryocytes in ITP (Giemsa stain: 10X)*

Figure3: *Bone Marrow in Megaloblastic anemia showing erythroid hyperplasia and megaloblasts. (Giemsa stain: 40X)*

Figure 4: *ROC Curve showing validity of Platelet Indices in differentiating Hyper destructive and hypoproductive thrombocytopenia*

Hypoproductive thrombocytopenia accounted for 54 of the total 369 cases (14.6 %). Of these, a majority of cases (70.37%) were due to megaloblastic anemia followed by acute leukemia (18.5%) and Aplastic anemia (7.4%)**.** Similar observations have been documented byVidyadhar et alwhere only these two conditions accounted for all the 13 cases of hypoproductive thrombocytopenia.[5]Megaloblastic anemia generally presents with vague and nonspecific symptoms and remains unrecognized unless thoroughly evaluated. Gulati et al documented 52.4% cases of megaloblastic anemia cases which is lesser compared to our study.[6]This could be because they had a second group of dimorphic anemia in their study. They found a similar incidence of acute leukemias (14.28%) and aplastic anemia (9.5%) as noted in the present study (18.51% & 7.4%) respectively.

On analyzing the age distribution among hyperdestructiveand hypoproductive groups, it was observed that 63.1% of cases in the hyperdestructive group were found to be in the first three decades of life. Of these cases, a majority were in the first decade (27.6%), followed by a nearly equal distribution of cases (19% and 16.5%) in the second and third decades respectively. This distribution could be explained by the pattern of cases encountered, where most cases belonged to ITP, dengue, and sepsis which are all known to occur more commonly in this age range.[7,8,9] Similarly, 48.2 % of cases in the hypoproductive group were found between the second to fifth decades of life where commonly encountered cases were those of megaloblastic anemia and acute myeloid leukemia which are more common in these age groups.[10,11]

A male predominance was seen in hyperdestructive group (58.4%) while a slight female predominance was noted in hypoproductive group (51.9%). The majority of the cases in hypoproductive group were cases of megaloblastic anemia which is known to have a female preponderance, especially in the reproductive age group.[12] In contrast to our study,Kaito et al found a female preponderance in both the groups studied (51.3% and 67.5%) respectively.[13]The prominent difference in the hypoproductive group noted by Kaito et al[12]could be a result of the smaller sample size and the bulk of cases (49.4%) being ITP which is known to be frequent among females.

Hypoproductive thrombocytopenia group recorded a lower mean platelet count. A similar finding was seen in the study by Vidyadhar et al.[5] Contrary to this, Parveen et aland Elsewefy et al did not find any significant difference between the mean platelet count and the type of thrombocytopenia.[2,14]These discrepancies could be related to the wide range of cases encountered in each study.Elsewefy et al studied only ITP cases in their hyperdestructive group.[14]

MPV isan analyser-calculated measure of thrombocyte volume.In our study, hyperdestructive group showed a higher mean MPV (10.71 ± 1.21) when compared to the hypoproductive group (9.03 ± 1.16). In hyperdestructive cases, there is accelerated platelet destruction in the

periphery leading to increased platelet production in the marrow. This results in the release of many young, large, and immature platelets in the blood which tend to become smaller over 7 – 10 days. These younger platelets are active functionally, metabolically, and enzymatically compared to smaller ones.[15]On activation platelets change shape from biconcavediscs to spherical which ultimately causes MPV to rise.[1]This shows that MPV can be used as an early marker to detect the platelet function, production rate,and activation.[16]Vidyadhar et al[5] and Norasethada et al[17]also established a significant difference in MPV values between the two groups.However, a study done by Khanna et al[18] did not find a significant difference between the mean MPV value among the two groups. Their study proposed that a combined evaluation of all the platelet parameters along with newer entities like reticulated platelet count could give a better idea about the mechanism of thrombocytopenia.[18]

PDW is an indicator of variability in platelets size and ranges from 8.0–14.0 fL.[13]Present study had a mean PDW of 15.18 ± 4.0 in hyperdestructive group while 13.54 ± 3.38 in hypoproductive group which was statistically significant with a p-value of <0.001. This high PDW in hyperdestructive thrombocytopenia is largely due to the release of a heterogeneous population of platelets having variable sizes attributable to the pseudopodia formation during platelet activation.These findings were similar to the study done by Khairkar et al and Singh et al.[19,20]Contrary to this, Parveen et al and Chinthalapudi et aldid not find any significant difference in PDW values among the two groups.[2,21] In the study done by Chinthalapudi et aleven though the mean PDW values (14.41 ± 4.00) were similar to our study(13.54 ± 3.38)in hypoproductive group, they did not find a significant difference from the hyperdestructive group.They suggested that the variations could be attributable to the varied types of hematology analyzers utilized in different trials.[21]Babu et al also noticed increased platelet heterogeneity in both hyperdestructive and hypoproductive thrombocytopenia.[22]

The normal reference range for P-LCR is 10–30%.[18]Our study had a mean P-LCR of 31.39 ± 7.23 in hyperdestructive group and 27.02 ± 6.81 in hypoproductive group which was statistically significant. P-LCR represents the percentage of all platelets having a volume of more than 12 fl; thus, the values are higher in hyperdestructive cases compared to its hypoproductive counterpart. Kaito et al, Elsewefy et al and Islam et alalso got similar results of higher P-LCR values in ITP patients compared to hypoproductive thrombocytopenic patients.[13,14,23]

ROC curve is a graphical representation of sensitivity on the y-axis and specificity on the x-axis for varying cut-off points of test values. Thus, the area under the ROC curve is a useful metric for calculatingthe validity of a diagnostic test. A shift of the ROC curve to the upper left always indicates a better test.[24]

In the study, ROC curvesplotted for platelet indices showed a left shift with the highest Area Under the Curve (AUC) for MPV (0.846), followed by P-LCR (0.649), and lastly PDW (0.611).As a result, MPV may be considered the most effective metric for distinguishing hyperdestructive from hypoproductive groups.Negash et al also recorded a higher AUC for MPV (0.876) and P-LCR (0.816.) in comparison to PDW (0.708) in identifying ITP cases.[25]Similar findings were observed by Vidyadhar et al where he found AUC for MPV (0.99) to be the highest followed by Plateletcrit (0.85) and PDW(0.54) at MPV cut off of >10 fl, PDW cut off > 18and Plateletcrit > 0.75%.[5]Contrary to this finding, Kaito et al who evaluated only ITP and aplastic anemia cases observed the highest AUC for PDW (9343.4) followed by P-LCR (9305.0) and MPV (9104.8).[13]

Disparities between various studies evaluating platelet indices in thrombocytopenia could stem from pre-analytical and analytical variables. Common preanalytical variables include; the method of venipuncture, anticoagulant used, interval time between the blood collection and analysis& time between the symptom onset and blood tests done. For analytical variables, a lack of harmonization among different analyzers may play an important role. The measurement techniques (impedance or optical) used along with instrument calibration can all lead to variations in platelet indices. Literature suggests that there is minimal variationin platelet count when different technologies are used, however,there is significant variance observed inplatelet indices. Variationsin hematology analyzers across different centers should be viewed as a constraint in comparing the platelet indicesdocumented in various studies.[1]

Limitations of the study: One of the drawbacks of our study wasthe lesser number of cases in hypoproductive group.A higher number of cases would help in yielding better reproducible results. Since ours was a single-center study in a limited population, research of greater scale and a meta-analysis of numerous studies would be more helpful to demonstrate the therapeutic importance of these parameters.

Conclusion: Knowledge about the variation of platelet indices in thrombocytopenia cases will help in avoiding invasive bone marrow examination and unnecessary interventions. Changes in platelet volume indices can provide the clinician with an initial clue about the possible mechanism of thrombocytopenia.In our study, out of the three platelet indices, MPV with the highest area under the curve had the maximum sensitivity and specificity in differentiating hyperdestructive from hypoproductive cases. In the future,the diagnostic accuracy of platelet indices in the differential diagnosis of thrombocytopenia can be substantially increased by higher quality research designs and standardized measurements for platelet indices.

Conflict of Interest: NIL

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