A CROSS-SECTIONAL STUDY EVALUATION OF DIAGNOSTIC IMPLICATIONS OF PLATELET INDICES IN THROMBOCYTOPENIA.

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Abstract

Introduction :

Thrombocytopenia (TCP) refers to a reduction of platelet count below 150 x 109/ L; it's not a disease entity by itself, but a finding that may result from a number of disease processes. Automated hematology analyzers that determine the Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Plateletcrit (PCT), and Platelet Large Cell Ratio (P-LCR), could be very helpful to facilitate the differential diagnosis of thrombocytopenia and to monitor thrombocytopenic conditions.

Materials and methods :

A cross-sectional study of platelet indices of 512 thrombocytopenic samples by automated hematology analyzers was done.

Results :

The cases of thrombocytopenia were classified into hypo-productive (362 cases) and hyper-destructive (150) groups. The most common cause of hypo-productive and hyper-destructive thrombocytopenia was Aplastic anemia and ITP, respectively. All the indices were significantly higher (p-value < 0.05) in hyper-destructive TCP compared to hypo-productive TCP, except Plateletcrit.

Conclusion :

The results of the present study show platelet indices to be a useful and reliable test to differentiate between hyper-destructive thrombocytopenia from the hypo-productive type with statistically significant differences.

Keywords: Thrombocytopenia (TCP), Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Plateletcrit (PCT), Platelet large cell ratio (P-LCR), Submitted: 2023-06-22 Accepted: 2023-06-27

1. Introduction:

Platelets are $3 - 5$ μm sized cytoplasmic fragments formed by the pinching off from the cytoplasmic margins of megakaryocytes. [1] They play a pivotal role in the initiation of clot formation by adhering to damaged blood vessel walls as well as donating their membrane phospholipids for the activation of coagulation factors. [2] Thrombocytopenia (TCP) is usually the manifestation of many other disease processes or may be idiopathic. The normal platelet count in humans is 150–400 x 109/L and hence thrombocytopenia refers to a reduction in platelet count below 150 × 109/L. [1]

All the causes of thrombocytopenia can be grouped into two categories: [a] Hyper-destructive type where there is increased destruction [immunological] or peripheral con-

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sumption and [b] decreased production. [3] Hyper-destructive thrombocytopenias indicate that there is extramedullary platelet destruction with an either normal or compensatory increase in their production in the marrow. Some of the important examples are immune thrombocytopenic purpura (ITP), secondary ITP, and disseminated intravascular coagulopathy (DIC). Hypo-productive thrombocytopenias result from decreased bone marrow production because of primary or secondary bone marrow diseases such as aplastic anemia, megaloblastic anemia, myelodysplastic syndrome, acute leukemia, amegakaryocytic thrombocytopenic purpura, and post-chemotherapy. [4]

The mainstay in the evaluation of these patients of thrombocytopenia lies in the identification of the cause, whether hyper-destruction or hypo-production, based on which the management will differ. Bone marrow evaluation [aspiration/biopsy] still remains the primary investigation in such cases. The main limitation of the bone marrow evaluation is its invasive procedures with the risk of bleeding diatheses in cases of severe thrombocytopenia. [5]

There is gradually increasing evidence that platelet indices such as Mean Platelet Volume (MPV), plateletcrit (PCT), Platelet Distribution Width (PDW), and Platelet Large Cell Ratio (P-LCR) that are available as a part of the report in most the automated hematology analyzers, have a significant role in differentiating hypo-productive causes from hyper-destructive causes of thrombocytopenia. [6-11]

1.1. Aims & Objectives:

This study was undertaken in the Department of Pathology, M.K.C.G. Medical College to assess the prevalence of different types of thrombocytopenia and to evaluate the efficiency of platelet indices to differentiate hyper-destructive type from the hypo-productive type of thrombocytopenia.

2. Material & Methods:

A cross-sectional study was conducted over a period of 2 years from October 2017 – September 2019 in the Department of Pathology, M.K.C.G Medical College and Hospital, Berhampur, Odisha, India after obtaining necessary approval from the Institutional Ethical Committee.

2.1. Inclusion criteria:

Valid informed consent
All cases of thrombocytopenia are diagnosed by Complete Blood Count [CBC] and Peripheral smear

2.2. Exclusion criteria:

Lack of consent
Patients receiving anti platelet drugs like aspirine history of transfusion of blood and blood products within the last 15 days of investigation.
Cases where the Automated analyzer failed to provide the Platelet indices.

A total of 512 cases of thrombocytopenia by CBC & CPS constituted the study group. A detailed clinical history, examination findings, and other relevant investigation findings were recorded. CBC was performed by Automated Hematology Analyzer (Sysmex XT 2000i). The Total Platelet Count (TPC) and the platelet indices including Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet Large Cell Ratio (P-LCR) & Plateletcrit (PCT) were noted for each case. Peripheral blood smear examination findings with Leishman-stained blood smears were also recorded for all cases and bone marrow aspiration was done when indicated (498 out of 512 cases).

All the cases of thrombocytopenia were grouped into either of the 2 categories i.e. Hypo-productive and Hyper-destructive categories based on relevant clinical history, laboratory findings, and other investigation findings, and the Platelet parameters of each group were compared to find any significant relationship.

Statistical data analysis was done on Microsoft Excel 2012. Continuous variables were expressed as mean SD. Categorical variables were expressed in frequencies and percentages. Data obtained were tabulated using version 22 of the statistical package for social sciences (SPSS).

3. Observation:

The present study observed a definite male preponderance having a male-to-female ratio of 1.55:1. The age distribution was wide ranging from as low as 2 years to as old as 78 years with a mean age of 36.32 years. Maximum patients were found to be in the age ranges of 41 – 50 years [92 cases, 18.2%] and 31 – 40 years [88 cases, 17.1%]. [TABLE 1]

Among the 512 cases in the present study, 362 cases (70.7%) were of hypo-productive thrombocytopenia and 150 cases (29.3%) were of hyper-destructive thrombocytopenia. [TABLE 2] In the Hypo-productive category the different etiologies encountered in decreasing order of prevalence were Aplastic anemia with 122 (23.8%) cases, Megaloblastic anemia with 116 (22.6%) cases, Acute leukemia with 102 (19.9%) cases, MDS (Myelodysplastic syndrome) 13 (2.5%) cases and Multiple myeloma 9 (1.8%) cases. Similarly in the Hyper-destructive category commonest etiology was ITP with 53 (10.4%) cases, Hypersplenism with 48 (9.4%) cases, Dengue fever with 8 (1.6%) cases, Malaria with 5 (1%) cases, CLL 4 (0.8%) cases and rest 32 were associated with sepsis, infections or drug reaction and were categorized as miscellaneous cases.

Total Platelet count in hypo-production thrombocytopenia was 51.3 +/- 31.5 and was 37.5 +/- 31.7 in hyper-destructive thrombocytopenia (p= 0.35). Mean Platelet Volume (MPV) in hypo-productive thrombocytopenia was 10.06 +/- 1.12 while in hyper-destructive thrombocytopenia it was 12.12 +/- 1.45 (p= 0.002). Mean Platelet Distribution Width (PDW) in hypo-productive and hyper-destructive thrombocytopenia were 13.11 +/- 1.65 and 15.31 +/-0.73 respectively (p= 0.002). Mean Platelet- Large Cell Ratio (P-LCR) in hypo-production thrombocytopenia was 30.15 +/- 3.57 and in hyper-destructive thrombocytopenia, it was 35.15 +/- 3.16 (p= 0.001). Mean Plateletcrit (PCT) was 0.07-0.12 and 0.06 – 0.15 in hypo-productive and hyper-destructive thrombocytopenia respectively (p= 0.98). [TABLE 3]

In the hypo-productive group, all indices were lowest in the aplastic anemia group. Mean MPV and P-LCR were highest in multiple myeloma while PDW and PCT were highest in megaloblastic anemia. [TABLE 4] In the hyper-destructive group, all indices were highest in ITP. The lowest MPV and P-LCR were seen in cases of malaria while the lowest PDW and PCT were seen in cases of CLL and dengue respectively. [TABLE 5]

4. Discussion:

Thrombocytopenia can result from a wide range of etiologies which can be grouped into Hypo-productive and Hyper-destructive groups. [12] This categorization is relevant for instituting proper treatment. Bone marrow sampling is an age-old diagnostic modality for differentiating the two groups of thrombocytopenia but has the limitations of being an invasive procedure requiring an experienced hematologist. [13, 14] This necessitates the requirement of a less invasive, easy-to-perform diagnostic modality to categorize the cases of thrombocytopenia.

With the availability of automated blood analyzers new indices related to platelets can be estimated. The most important of them are Plateletcrit (PCT), Mean Platelet Volume (MPV), Platelet distribution width (PDW), and Platelet- large cell ratio (P-LCR). [15] The platelet indices are derived from the platelet distribution curve obtained from impedance or optical methods. [16] The advantages of Automated analyzers over manual methods are that not only they are simple, and less time-consuming with the elimination of observer bias but also provide the various platelet indices. [17]

Although automated cell counters are fairly accurate in determining platelet count, the possibility of instrumental artifacts at low platelet count could not be ruled out and all samples had to be manually checked in Leishman stain for confirmation of thrombocytopenia. In cases of severe thrombocytopenia and the presence of red cell fragmentation, the Platelet histogram cannot be properly drawn and hence indices are not obtained [18, 19]. The present study avoided this problem by discarding cases without indices and

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histograms.

In regard to the prevalence rate of the two subcategories of thrombocytopenia, the present study observed a higher rate for the hypo-productive category (71% of cases). The prevalence rate was variable among different studies. [4, 17 & 20]

The platelets in the peripheral blood are a mixture of variable-sized ones ranging in volume from 7.2 − 11.7 fL. The automated analyzers use the electrical impedance to draw the platelet distribution curve and determine the MPV by the logarithmic transformation of the curve to get a geometric mean. Increased MPV suggests increased platelet diameter and this can be used as a marker of platelet production and its activation as young platelets are larger in size and during activation, the platelets acquire a spherical shape with lots of pseudopods that contributes to an increase in the diameter. [21]

In reference to the MPV, the present study observed a statistically significant variation between the two subcategories of thrombocytopenia; the mean MPV was significantly higher for hyper-destructive thrombocytopenia (12.5 fL) compared to hypo-productive thrombocytopenia (10.5fL) with a P value of 0.002. The high value of MPV in the hyper-destructive category could be explained by the fact that there is a compensatory increase in the bone marrow production of platelets and the newly produced platelets are larger in size. [18, 20]

PDW is a parameter that indicates the size variability between the circulating platelets and thus is affected by variations in the size and shape of platelets. The automated analyzers measure the PDW at the level of 20% relative height of the platelet distribution curve. The variation in MPV and PDW is usually in the same direction in different conditions. [4, 21]

In the present study mean PDW in hyper-destructive thrombocytopenia was 15.5 fL and was significantly higher than the hypo-productive type which was 13.5 fL [p = 0.002] The high PDW could possibly be caused by the release of young platelets due to compensatory increase in bone marrow activity. [4]

Platelet large cell ratio (P-LCR), which is presented as a percentage, is an indicator of circulating larger platelets (> 12 fL), with the normal range being 15 − 35%. [22] In the present study, the mean P-LCR value in cases of hyper-destructive thrombocytopenia was 35% and in the hypo-productive type, it was 30%. The difference was found to be statistically significant with P value of 0.001.

The Plateletcrit [PCT] indicates the volume occupied by the platelets in the blood and is expressed as a percentage; normal range being 0.22 − 0.24% [23, 24]. No significant correlation was obtained between the mean PCT values in hyper-destructive and hypo-productive thrombocytopenia cases, P-value 0.98.

The significant difference in the values of the various Platelet indices between the hyper-destructive and hypo-proliferative categories of thrombocytopenia in the present study is concordant with most of the studies as evident from Table 6.

5. Conclusion:

All cases of thrombocytopenia must be properly categorized for administering appropriate treatment as hypo-proliferative cases need platelet transfusion whereas hyper-destructive cases need proper management of the primary cause rather than platelet transfusion which can have a more detrimental effect by initiating more immunological destruction [antibody to heterologous antigens]. Though bone marrow study can help in differentiating the two types of thrombocytopenia, it is not to be preferred as it is an invasive procedure that requires expertise for performing as well as interpretation.

Platelet indices obtained from Automated hematology analyzers are found in the present study as a reliable diagnostic modality for categorizing the cases of thrombocytopenia into the two subtypes.

6. Limitations:

The main limitation of the present study is the cases of thrombocytopenia where the instrument

fails to provide the various platelet indices due to fragmented RBCs or contaminants.

7. Recommendations:

We recommend categorizing hypo-productive thrombocytopenia into megaloblastic and non-megaloblastic subtypes.

8. Acknowledgment:

None

9. List of abbreviations:

TCP- Thrombocytopenia
MPV- Mean Platelet Volume
PDW- Platelet Distribution Width
PCT- Plateletcrit
P-LCR- Platelet Large Cell Ratio
ITP- Immune thrombocytopenic purpura
DIC- Disseminated intravascular coagulopathy
CBC- Complete blood count
CPS- Chronic pain syndrome
CLL- Chronic lymphocytic leukemia

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Nil.

11. Conflict of interest:

None.

12. Publisher details

13. References:

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Table 1: **AGE & SEX DISTRIBUTION OF CASES**

AGE	NO.OF CASES	MALE	FEMALE	%
1-10 YEAR	51	36	15	9.96
11-20 YEAR	61	45	16	12.1
21-30 YEAR	73	40	33	14.1
31-40 YEAR	88	49	39	17.1
41-50 YEAR	92	61	31	18.2
51-60 YEAR	81	41	40	15.7
61-70 YEAR	60	35	25	11.6
71-80 YEAR	6	4	2	1.2
TOTAL	512	311(60.7%)	201(39.3%)	100

Table 2: **ETIOLOGICAL CLASSIFICATION OF CASES**

HYPO-PRODUCTION	NO.OF CASES	%	HYPER-DESTRUCTION	NO. OF CASES	%
1.APLASTIC ANEMIA	122	24	**1.IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)**	53	10
2.MEGALOBLASTIC ANEMIA	116	22	**2.HYPERSPLENISM**	48	9
3.ACUTE LEUKEMIA	102	10	**3.MALARIA**	05	1
4.MYELO DYSPLASTIC SYNDROME (MDS)	13	02	**4.DENGUE**	08	1.6
5.MULTIPLE MYELOMA (MM)	09	01	**5.CHRONIC LYMPHOID LEUKEMIA (CLL)**	04	0.8
			6.MISCELLANEOUS	32	6.3
TOTAL NO. CASES	362	71		150	29
TOTAL CASES = 512					

Table 3: **PLATELET INDICES**

PLATELET INDICES (MEAN+/-SD)	HYPOPRODUC-TION	HYPERDESTRUC-TION	P-VALUE
1.PLATELET COUNT (X10^3 /MM)	51.3+/-31.5	37.5+/-31.7	0.35
2.MPV (FL)	10.06+/-1.12	12.12+/-1.45	0.002
3.PDW (FL)	13.11+/-1.65	15.31+/-0.73	0.002
4.P-LCR (%)	30.15+/-3.57	35.15+/-3.16	0.001
5.PCT (%)	0.07-0.120	0.06-0.15	0.98

Table 4: **PLATELET INDICES IN HYPO-PRODUCTION THROMBOCYTOPENIA**

CASE	NO.OF CASES (%)	MPV (MEAN+/-SD) FL	PDW(MEAN+/-SD) FL	P-LCR (MEAN+/-SD) %	PCT (MEAN+/-SD) %
APLASTIC ANEMIA	122 (24%)	9.06+/-1.12	12.11+/-1.65	28.15+/-3.57	0.03-0.12
MEGA-LOBLASTIC ANEMIA	166 (22%)	10.7+/-1.13	13.15+/-1.75	30.15+/-2.57	0.06-0.15
ACUTE LEUKEMIA	102 (10%)	10.5+/-1.15	13.11+/-1.65	30.16+/-1.57	0.05-0.13
MDS	13 (2%)	10.7+/-1.12	12.18+/-1.55	31.17+/-2.37	0.03-015
MULTIPLE MYELOMA	09 (1%)	11.2+/-1.13	13.12+/-1.75	31.19+/-2.58	0.05-0.12

Table 5: **PLATELET INDICES IN HYPER-DESTRUCTION THROMBOCYTOPENIA**

CASE	NO.OF CASES (%)	MPV (MEAN+/-SD) FL	PDW (MEAN+/-SD) FL	P-LCR (MEAN+/-SD) %	PCT (MEAN+/-SD) %
ITP	53(10%)	13.5 +/- 2.5	16.30+/-0.72	36.14+/-3.15	0.07-0.12
HYPER-SPLENISM	48(09%)	12.5+/- 1.3	15.30+/-0.65	35.15+/-3.16	0.06-0.15
MALARIA	05(01%)	12.1+/- 1.2	14.30+/-0.66	34.15+/-3.17	0.05-0.13
DENGUE	08(1.6%)	12.6+/- 1.5	15.31+/-0.75	34.16+/-2.76	0.03-0.14
CLL	04(0.8%)	12.5 +/- 2.6	14.30+/-0.61	35.13+/-2.15	0.04-0.15
MISCEL-LA-NEOUS	32(06%)	12.15 +/- 1.6	15.32+/-0.55	35.16+/-2.17	0.05-0.15

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Table 6: **COMPARISON OF PLATELET INDICES AMONG VARIOUS STUDIES**

Platelet indices	Baig et al [7]	Elsywefy et al [6]	Kuna et al [24]	Khaleel et al [10]	Present study
Hypo-production					
Platelet count	51.8	45.3	67.4	64.23	51.3
MPV	8.5	9.08	8.14	10.08	10.06
PDW	14.1	16.9	18.6	13.83	13.11
PLCR	31.9	27.57	14.4	-	30.15
PCT	0.08-0.12	-	0.06	0.06	0.07-0.12
Hyper-destruction					
Plt count	39.6	35.8	69.5	39.30	37.5
MPV	11.6	9.97	12.4	12.33	12.12
PDW	15.16	17.11	20.4	15.61	15.31
PLCR	34.3	41.67	45.6	-	35.15
PCT	0.09-0.14	-	0.08	0.06	0.06-0.15