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Platelet Indices to Identify Hypo Productive and Hyper Destructive Thrombocytopenia

Md. Atiqul Islam[1*], Md. Ashikul Islam[2], Aleya Ferdush Monni[3], Md. Shaidur Rahman[4], Habiba Khatun[5], Md. Ariful Hasan[6]

[1]Junior Consultant, Department of Paediatrics, Upazila Health Complex, Gurudashpur, Natote, Bangladesh
[2]Junior Consultant, Department of Physical Medicine & Rehabilitation, Colonel Maleque Medical College Hospital, Manikganj, Bangladesh
[3]Medical Officer, Upazila Health Complex, Saturia, Manikganj, Bangladesh
[4]Resident Physician, Department of Paediatrics, Dhaka Medical College Hospital, Dhaka, Bangladesh
[5]Medical officer (OPD), Department of Paediatrics, Dhaka Medical College Hospital, Dhaka, Bangladesh
[6]Junior Consultant, Department of Medicine, Upazila Health Complex, Gurudashpur, Natote, Bangladesh

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***Corresponding author:** Dr. Md. Atiqul Islam
Junior Consultant, Department of Paediatrics, Upazila Health Complex, Gurudashpur, Natote, Bangladesh

Abstract **Original Research Article**

***Background*:** Thrombocytopenia is the most common cause of mucocutaneous bleeding in children due to various aetiologies. Hypo production or hyper destruction is the main aetiopathology of thrombocytopenia. Platelet indices might help to identify the underlying aetiopathology of thrombocytopenia. ***Objectives*:** To evaluate platelet indices to identify hypo productive and hyper destructive thrombocytopenia. ***Methods*:** This cross-sectional analytical study was conducted at Dhaka Shishu Hospital from July 2018 to June 2020. Cases were included in the study based on inclusion and exclusion criteria. A complete blood count was performed with a haematology analyzer, and other clinically indicated investigations were conducted to find the etiology of thrombocytopenia. A peripheral blood smear was also examined to estimate platelet count and to rule out pseudo thrombocytopenia and fragmented cells. 138 thrombocytopenic cases were studied divided into hypo-productive (n=60) and hyper-destructive (n=78) groups. Then, the values of the platelet indices of each group were compared with those of the comparison group. Data was analyzed by SPSS version 22. ***Results*:** In hypo productive thrombocytopenia, MPV was 7.68±0.67 fl, and PDW was 10.52±2.25 fl. In hyperdestructive thrombocytopenia, MPV was 10.09±0.85 fl, and PDW was 17.86±6.55 fl. There was a statistically significant (P <0.05) difference of platelet indices compared to normal values in the hypo productive and hyper destructive group. In hypo productive thrombocytopenia, MPV at 7.75 fl showed 76.1% sensitivity and 46.7% specificity, and PDW at 11.55 fl showed 78.3% sensitivity and 65.0% specificity. In hyper-destructive thrombocytopenia, MPV at 9.05 fl showed 89.7% sensitivity and 80.4% specificity, and PDW at 14.3 fl showed 74.4% sensitivity and 71.7% specificity. ***Conclusion*:** In hypo productive thrombocytopenia, platelet indices were significantly lower than normal values, and MPV at 7.75 (fl) showed 76.1% sensitivity and 46.7% specificity, PDW at 11.55 (fl) showed 78.3% sensitivity and 65.0% specificity. In hyper-destructive thrombocytopenia, platelet indices were significantly higher than normal values; MPV (fl) at 9.05 showed 89.7% sensitivity and 80.4% specificity, and PDW at 14.3 (fl) showed 74.4% sensitivity and 71.7% specificity.

Keywords: thrombocytopenia, mean platelet volume, platelet distribution width, hypo productive, hyper destructive.

INTRODUCTION

Blood is a liquid form of connective tissue. The cellular component of blood contains erythrocytes, leucocytes, and platelets. The number of each cell in the blood is maintained within well-defined limits unless the balance of production or elimination is disturbed by pathological processes [1]. Thrombocytopenia is the most common cause of bleeding manifestation in children due to various etiologies. Platelets are essential to maintain the integrity of the endothelium and control hemorrhage [2]. Qualitative or quantitative deficiency of platelets causes bleeding manifestations [3]. Normal platelet count is 150,000/mm^3 to 4,50,000/mm^3 of blood. Thrombocytopenia is defined as a platelet count below 150,000/mm^3 of blood [4]. The severity of bleeding manifestation varies with the severity of thrombocytopenia. A platelet level below $10x10^9$/L is the

risk of spontaneous life-threatening intracranial or gastrointestinal hemorrhage [5].

Thrombocytopenia is not a disease entity by itself but a finding that may result from a number of disease processes. There are two main mechanisms involved in the etiopathogenesis of thrombocytopenia: one is decreased production by the bone marrow (hypo-productive), and another is increased peripheral destruction (hyper-destructive) [6]. In hypo, a productive state decreases platelet production either due to a decrease in the number of megakaryocytes or failure of the megakaryocyte to deliver an appropriate number of viable cells [7]. Hyper-destructive thrombocytopenias are mainly caused by extramedullary destruction of platelets with normal or increased bone marrow (BM) activities [4].

Identifying the underlying aetiopathology of thrombocytopenia is necessary for further investigations and management plans. The gold standard for discriminating between these two mechanisms is bone marrow examination, but it is an invasive procedure and requires an expert [8]. Platelet-derived indices could be useful in the initial approach for the differential diagnosis of thrombocytopenia and can avoid invasive investigations [9]. Platelet indices are platelet morphology obtained from an automatic complete blood count. Platelet indices are underutilized in clinical practice [10]. The most common platelet indices are mean platelet volume (MPV) and platelet distribution width (PDW). Platelet indices provide information about the patho-mechanism of thrombocytopenia [11]. These are sensitive, non-invasive, inexpensive biomarkers [12].

Invasive procedures like bone marrow aspiration needed some time to identify the causative relationship of thrombocytopenia. An automated complete blood count analyzer provides platelet indices, which might give clues to types of thrombocytopenia. Such a type of study is not done in our setting. So, this study might provide information regarding types of thrombocytopenia to avoid bone marrow aspiration. The study aimed to evaluate platelet indices to identify hypo productive and hyper destructive thrombocytopenia. A secondary aim of the study was to evaluate the sensitivity & specificity of platelet indices to identify hypo-productive thrombocytopenia and hyperdestructive thrombocytopenia.

MATERIALS AND METHODS

This study was designed as a cross-sectional analytical study and conducted at Dhaka Shishu Hospital from July 2018 to June 2020. Children aged one month to 15 years who presented with thrombocytopenia in the inpatient department of Dhaka Shishu (children) Hospital were included in this study. The study excluded the history of platelet transfusion 15 days before sample collection. A total of 138 thrombocytopenic cases were selected by purposive sampling. The independent variables were age and sex, and the dependent variables were platelet count, mean platelet volume (MPV), and platelet distribution width (PDW). The study's purpose, procedure, importance, and benefit were explained to the parents/guardian and informed written consent was obtained.

Baseline characteristics were recorded, history was taken, and a thorough physical examination was done. Ten cases of platelet transfusion within 15 days were excluded from the study. A complete blood count was done for the cases with incomplete information about platelet indices or time duration (n=25), and peripheral blood film was performed for all cases. With all aseptic precautions, 2ml venous blood was collected with anticoagulant (EDTA) for haemogram and peripheral blood film. Each sample was analyzed within 30 minutes of collection to avoid false high MPV values due to EDTA-induced platelet swelling. A complete blood count was done using Mythic 22 automated haematology analyzer of five parameters manufactured by Intertek, Switzerland. Seven cases with irreproducible reports of platelet indices were excluded from the study. A peripheral blood smear was examined to estimate platelet count and to rule out pseudo thrombocytopenia and fragmented cells. Peripheral blood film was examined by an expert pathologist, and bone marrow was examined by an expert Paediatric hematologist. Ten cases with pseudo thrombocytopenia were also excluded from the study. According to the clinical indication, necessary investigations were conducted to establish the diagnosis. After the diagnosis was established, patients (n=138) were divided into two groups, according to diagnosis. Group-1 was hypo-productive thrombocytopenia, and Group-2 was hyper-destructive thrombocytopenia. In group-1 there were acute lymphoblastic leukaemia (n=41), acute myeloid leukaemia (n=3), aplastic anaemia (n=15), and fanconi anaemia (n=1). In group-2 there was septicemia (n=38), immune thrombocytopenic purpura (n=18), dengue fever (n=14), disseminated intravascular coagulation (n=2), hemolytic uremic syndrome (n=3) and systemic lupus erythometosus (n=3). For comparison group 138, age and sex-matched children of 1 month to 15 years old who were admitted at Dhaka Shishu Hospital for other ailments were taken for those who had normal platelet count, RBC, and WBC count. Their platelet indices were recorded.

Statistical analyses were conducted using the software package for Social Science (SPSS), version 22. Data were expressed as numbers, percentages, and mean±SD. An independent sample t-test was done to compare quantitative variables. An ROC curve was used to observe the sensitivity and specificity. P-value <0.05 was considered statistically significant in all the analyses. Ethical clearance was taken from the ethical

committee of the Bangladesh Institute of Child Health (BICH).

RESULT

The mean (±SD) age (in years) of the study group was 5.197± 3.59; in comparison, the group was 4.30±3.79. Age differences among the groups were not significant (p≥0.05). Both in the study group and in comparison, the male group was 82 (59%), and the female was 56 (41%). In hypo-productive (38, 63.34%) and hyper destructive (69, 88.5%) groups, most patients were 0-5 years old.

Table 1: Demographic characteristics of the study group and comparison group

Characteristics	Study group (n=138)	Comparison group (n=138)	P value
Age (in years) ±SD	5.197± 3.59	4.30±3.79	0.154^{ns}
Sex			
Male	82 (59%)	82 (59%)	
Female	56 (41%)	56 (41%)	

Quantitative data were expressed as mean±SD and qualitative data as frequency and percentage. Statistical analysis was done by independent sample t-test to compare two groups and considered significant p<0.05.
ns = non-significant;

Table 2: Comparison of platelet indices between hypo productive and comparison group

Platelet indices	Hypoproductive (n=60)	Comparison group (n=138)	P value
Platelet count/mm^3 (M±SD)	54,130.00 ± 35,334.10	3,06,956.52 ± 70,945.97	0.000^{***}
MPV (fl)	7.68±0.67	8.27±1.03	0.001^{**}
PDW (fl)	10.52±2.25	14.75±5.89	0.000^{***}

Quantitative data were expressed as mean±SD. Statistical analysis was done by independent sample t-test to compare two groups and considered significant p<0.05.
*** = P <0.001
** = P <0.01

Table 2 showed mean platelet count of the hypo-productive group was 54,130.00±35,334.10/mm3 of blood; in comparison, group was 3,06,956.52±70,945.97/mm3. MPV in the productive group was 7.68±0.67 (fl); in comparison, the group was 8.27±1.03 (fl). PDW in the hypo productive group was 10.52±2.25 (fl), and in comparison, the group was 14.75±5.89 (fl). Statistically, highly significant differences were found in mean platelet count (p<0.001), MPV (p<0.01), and PDW (p<0.001) between hypo productive and comparison groups.

Table 3: Comparison of platelet indices between hyper destructive and comparison group

Platelet indices	Hyper destructive (n=78)	Comparison group (n=138)	P value
Platelet count/mm^3 (M±SD)	71,592.30 ± 42,693.03	3,06,956.52 ± 70,945.97	0.000^{***}
MPV (fl)	10.09±0.85	8.27±1.03	0.000^{***}
PDW (fl)	17.86±6.55	14.75±5.89	0.009^{**}

Data were expressed as mean±SD. Statistical analysis was done by independent sample t-test to compare two groups and considered significant p<0.05.
*** = P <0.001
** = P <0.01

Table 3 showed that the mean platelet count of the hyper destructive group was 71,592.30±42,693.03/mm3 of blood; in comparison, the group was 3,06,956.52±70,945.97/mm3 of blood. MPV in the hyper destructive group was 10.09±0.85 (fl); in comparison, the group was 8.27±1.03 (fl). PDW in the hyper destructive group was 17.86±6.55 (fl), and in comparison, the group was 14.75±5.89 (fl). Statistically highly significant differences were found in mean platelet count (P<0.001), MPV (P<0.001), and PDW (P<0.01) between hyper destructive and comparison groups.

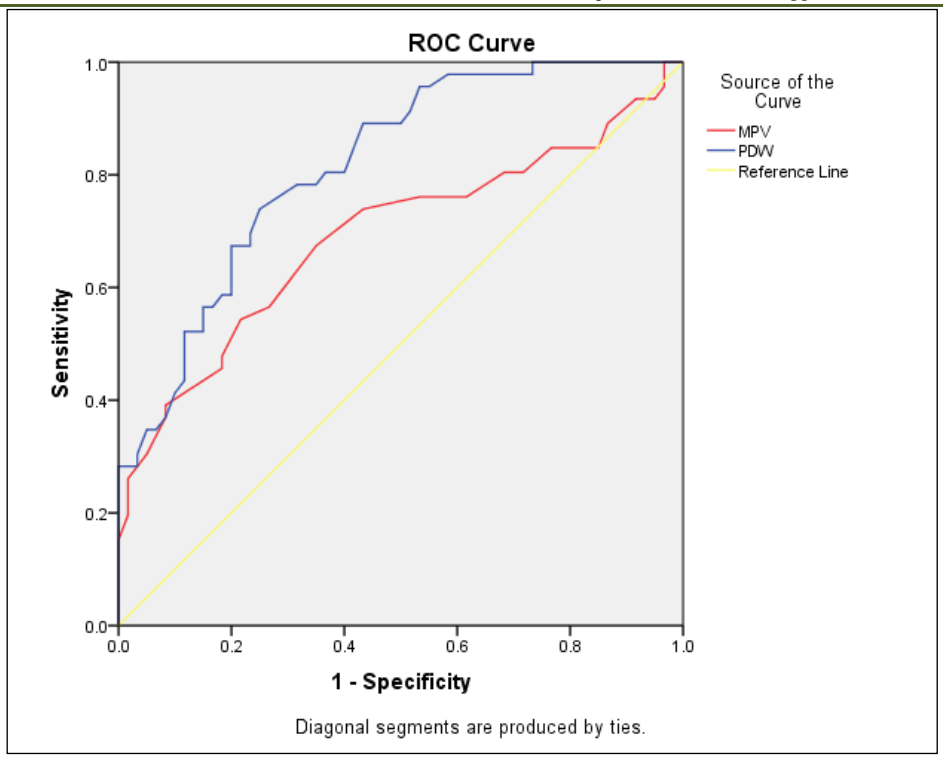

Figure 1: ROC curve of MPV and PDW of hypo productive group (n=60)

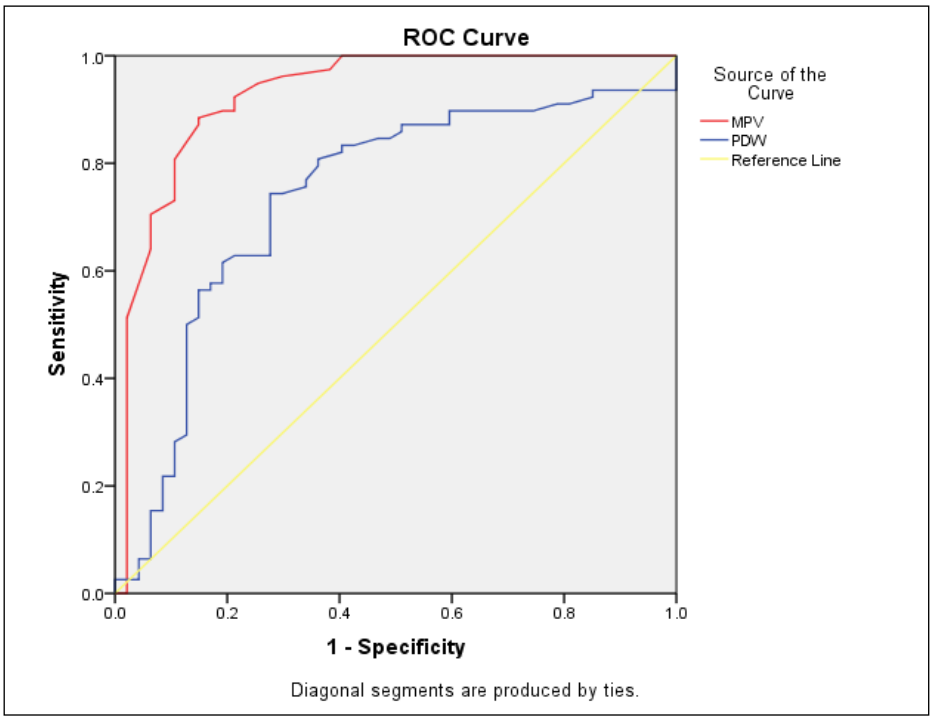

Figure 2: ROC curve of MPV and PDW of a hyper destructive group (n=78)

Receiver operating characteristic (ROC) curves of MPV and PDW of the hypo-productive group showed that the area under the MPV curve was 0.691 and the area under the PDW curve was 0.818. ROC curves of MPV and PDW of the destructive group showed that the area under the MPV curve was 0.927, and the area under the PDW curve was 0.735. In hypo productive thrombocytopenia, MPV at 7.75 (fl) showed 76.1% sensitivity and 46.7% specificity, PDW at 11.55 (fl) showed 78.3% sensitivity and 65.0% specificity. In hyper destructive thrombocytopenia, MPV at 9.05 (fl) showed 89.7% sensitivity and 80.4% specificity, and PDW at 14.3 (fl) showed 74.4% sensitivity and 71.7% specificity.

Table 4: Sensitivity and specificity of the platelet indices for diagnosis of hypo productive thrombocytopenia at different cut-off points from ROC curve coordinate

Platelet indices	Value of indices	Sensitivity (%)	Specificity (%)
MPV (fl)	6.10	100	3.30
	7.05	84.8	15.0
	7.75	76.1	46.7
	8.05	56.5	73.3
	9.20	15.2	100
PDW (fl)	9.30	100	26.7
	10.05	97.8	36.7
	11.55	78.3	65.0
	11.95	69.6	76.7
	15.00	28.3	100

Values of indices are presented as femtoliter. Sensitivity and specificity are expressed as percentages.

Table 4 shows the sensitivity and specificity of MPV (fl) and PDW (fl) of hypo productive thrombocytopenia at different cut of value for MPV and PDW. MPV at 7.75 (fl) showed 76.1% sensitivity and 46.7% specificity, and PDW at 11.55 (fl) showed 78.3% sensitivity and 65.0% specificity.

Table 5: Sensitivity and specificity of the platelet indices for diagnosis of hyper destructive thrombocytopenia at different cut-off points from ROC curve coordinate

Platelet indices	Value of indices	Sensitivity (%)	Specificity (%)
MPV (fl)	8.05	100	43.5
	8.45	100	60.9
	9.05	89.7	80.4
	9.55	73.1	89.1
	10.05	47.4	97.8
PDW (fl)	9.80	93.6	2.20
	13.15	84.6	50.0
	14.3	74.4	71.7
	15.5	57.7	80.4
	39.55	2.6	100

Values of indices are presented as femtoliter. Sensitivity and specificity are expressed as percentages.

Table 5 shows the sensitivity and specificity of MPV (fl) and PDW (fl) of hyper destructive thrombocytopenia at different cut of value for MPV and PDW. MPV at 9.05 (fl) showed 89.7% sensitivity and 80.4% specificity, and PDW at 14.3 (fl) showed 74.4% sensitivity and 71.7% specificity.

DISCUSSION

This study showed 60 cases in the hypo-productive group, 78 were in the hyper destructive group, and males were predominant in both groups. A study on febrile thrombocytopenia in children showed male predominance [13]. A similar type of finding was observed on platelet indices in children with sepsis [14] and in febrile children with thrombocytopenia [15], but some authors found females to be predominant in their study [9]. This study result showed there was a significantly low mean platelet count ($p<0.001$), MPV ($p<0.01$), and PDW ($p<0.001$) in hypo productive group in comparison to the comparison group. Similar types of findings were observed in platelet indices and their diagnostic role in pediatric thrombocytopenias [16] and platelet indices to differentiate between hypo productive and hyper productive thrombocytopenia in children [17]. However, Kamal *et al*., showed there was no statistically significant difference in MPV between the comparison group and the productive group [18]. In another study, Reddy *et al.*, found there was no statistically significant difference in PDW in hypo productive and comparison groups [19]. This study also showed there was a significantly low mean platelet count ($p<0.001$) but high MPV ($p<0.001$) and PDW ($p<0.01$) in hyper destructive group compared to the comparison group. Similar types of findings were observed by different authors in their study [16-19].

In a study in Receiver operating characteristic (ROC) curves of hypo productive thrombocytopenia, Kaito *et al*., observed more area under the MPV (0.910) and PDW (0.934) curve compared to this study [20]. ROC curves in hyper destructive group Negash and Tsegaye found less area under MPV (0.876) and PDW (0.708) curves compared to this study [21,22]. However,

some authors observed less area under MPV (0.900) but more area under the PDW (0.938) curve than this study. Al-Musawi, Al-Kabi in hypo productive thrombocytopenia in children MPV at 10.6 (fl) showed 86% sensitivity and 90% specificity. PDW at 16 (fl) showed 80% sensitivity and 95% specificity [17]. In another study, MPV at 10.75 (fl) showed 74% sensitivity and 70% specificity, and PDW at 15.5 (fl) showed 76% sensitivity and 55% specificity [21]. In another study, MPV 10.8 (fl) showed 86% sensitivity and 90% specificity, while PDW 18 (fl) showed 80% sensitivity and 95% specificity [2].

The utility of platelet indices in hyperproductive thrombocytopenia MPV at 12.6 (fl) showed 50% sensitivity and 64% specificity. PDW at 20 (fl) showed 40% sensitivity and 98% specificity [17]. In another study, MPV at 11.05 (fl) showed 67% sensitivity and 95% specificity, while PDW at 14.25 (fl) showed 61% sensitivity and 62% specificity [21]. In another study, MPV at 12.8 (fl) showed 50% sensitivity and 94% specificity, and PDW at 22 (fl) showed 40% sensitivity and 98% specificity [2]. This difference may be due to the hematology analyzer and study design variations.

CONCLUSION

In hypo productive thrombocytopenia, platelet indices were significantly lower than normal values, MPV at 7.75 (fl) showed 76.1% sensitivity and 46.7% specificity, PDW at 11.55 (fl) showed 78.3% sensitivity and 65.0% specificity. In hyper destructive thrombocytopenia, platelet indices were significantly higher than normal values; MPV (fl) at 9.05 showed 89.7% sensitivity and 80.4% specificity, PDW at 14.3 (fl) showed 74.4% sensitivity and 71.7% specificity.

Limitations

- The study population was selected from one selected Hospital in Dhaka city, so the study result may not reflect the exact picture of the country.
- There is a wide variation of platelet indices, and this difference may be due to variations in the analyzer.

Recommendation

- Further study with a wide variety of samples is necessary to determine the test's accuracy.
- Each sample should be analyzed with an individual analyzer to overcome the variation of the analyzer.

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Conflicts of interest: There is no conflict of interest

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