

Original Research

Received 30 June 2026

Revised 24 July 2026

Accepted 07 Aug 2026

Natural Resources for Human Health 2026, Vol. 6 (16s): 1454–1463

KEYWORDS:

Platelet indices, thrombocytopenia, MPV, PCT, PDW, PLCR, Health and wellbeing

Clinical Utility of Platelet Indices in Flagged Thrombocytopenia: Diagnostic Insights

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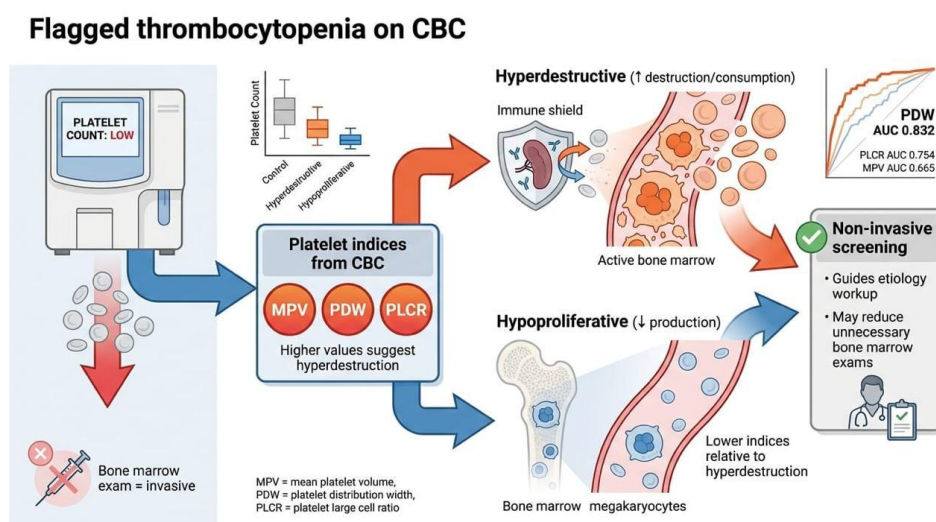
ABSTRACT: Background: Automated blood cell analyzers provide platelet indices that can aid in evaluating thrombocytopenia. These indices include MPV, PDW, PCT, PLCC, and PLCR, routinely reported with complete blood counts. This study investigated their diagnostic value in distinguishing and identifying the underlying cause of thrombocytopenia, potentially improving diagnosis and clinical assessment.

Methods: A comparative observational study involving 100 thrombocytopenic patients and 100 control subjects was conducted. Thrombocytopenia cases were divided into two states based on the outcome of the index values. The platelet indices were also measured.

Results: The indices significantly boosted patients with thrombocytopenia compared to controls ($P < 0.0001$). The platelet indices of hyperdestructive thrombocytopenic patients ($n=79$) were considerably higher than those of hypoproliferative thrombocytopenic patients ($n=21$) ($P < 0.0001$). In particular, MPV, PDW, and PLCR exhibited higher areas under the ROC curve (0.665, 0.823, and 0.754, respectively), suggesting that they were better at predicting, finding, and explaining the difference between the two scenarios of thrombocytopenia.

Conclusion: MPV, PDW, and PLCR are useful for diagnosing thrombocytopenic patients in either hyperdestructive or hypoproliferative scenarios. MPV, PDW, and PLCR provide both sensitivity and specificity, rendering them dependable screening tools for assessing the severity of pathologies that lead to thrombocytopenia.

Graphical Abstract



INTRODUCTION

A lower-than-normal number of platelets in the peripheral blood is known as thrombocytopenia. According to the literature, thrombocytopenia is the leading cause of abnormal bleeding, defined as a platelet count (PLT) of less than $150 \times 10^9/L$. Various anomalies can cause thrombocytopenia, but they usually occur because of four main processes: spurious, hypoproliferative, increased devastation, and aberrant distribution or accumulation of platelets in the tissue [1]. Platelet breakdown typically triggers thrombopoiesis activation. Rapid thrombopoiesis increases the quantity, magnitude, and speed of precursor megakaryocyte development [2].

Numerous immune-related and non-immunological factors can quickly deplete platelets. Immunological reasons include abnormalities of the collagen vascular structure and autoimmune, idiopathic, and secondary infections. Hemolytic uremic syndrome, DIC, thrombotic thrombocytopenic purpura, and thrombotic microangiopathies involve non-immunologic events [1]. Hypoplasia of megakaryocytes, ineffective thrombopoiesis, and stem cell disorders such as myelofibrosis, myelodysplastic syndrome, metastasis, leukemia, lymphoma, multiple myeloma, alcoholic liver disease, and infection can all contribute to diminished platelet production [3]. Although bone marrow inspection is crucial in establishing the etiology of thrombocytopenia, it is an intrusive, costly, time-consuming, and hazardous procedure that increases the risk of bleeding in cases of profound thrombocytopenia [4].

Utilizing sophisticated technology, hematology analyzers provide specific characteristics that offer platelet insights. These parameters, commonly known as platelet indices, have been discussed in medical literature [5]. Platelet indices serve as characteristics of platelet activation, providing diagnostic and prognostic insights into various clinical contexts. MPV refers to the platelet volume used to evaluate the presence of progenitor cells (megakaryocytes) in the bone marrow. When platelet production is reduced, there is an increase in the size and activity of young platelets, leading to excess MPV. The elevation of MPV indicates platelet size and activation, and serves as a useful marker for platelet turnover. MPV is a parameter used to quantify average platelet size [6]. Platelet Distribution Width (PDW) is a direct measurement of variation in platelet size. This indicates the diversity in platelet shape and has proven beneficial in distinguishing between thrombocytopenia caused by reduced platelet production and platelet destruction [6].

Plateletcrit (PCT) is a numerical indicator of the total mass of platelets in the blood. It is a useful screening technique for identifying abnormalities in platelet counts. The Platelet Large Cell Ratio [PLCR] is a measure of the proportion of larger

platelets in the bloodstream and is used to assess platelet function. PLCR measures the ratio between larger platelets and the overall platelet count. It has an inverse relationship with platelet count and a direct relationship with MPV and PDW [7]. Platelet indices can discriminate between hypoproliferative and hyperdestructive thrombocytopenia. Research suggests a favorable diagnostic correlation between MPV, PDW, and PLCR [8,9]. This study sought to determine the clinical utility of platelet indices (MPV, PDW, PCT, PLCC, and PLCR) in detecting hyperdestructive or hypoproliferative episodes of thrombocytopenia, assessing condition severity, and evaluating their sensitivity and specificity.

MATERIAL AND METHODS:

This observational, analytical, and comparative study assessed patients with thrombocytopenia and matched controls at the Hematology Department of Port Sudan Ahlia University, Sudan. The study was performed from January to June 2024, in which 100 thrombocytopenia cases were evaluated. The study included 100 healthy controls who did not exhibit the traits of interest, acting as a baseline for comparison. This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Port Sudan Ahlia University Research Ethics Committee (PAU-REC) under approval no. PAU-REC/2/1 (date of approval: December 15, 2023). All the study participants provided written informed consent. Based on the outcome of the platelet indices, the study population was divided into two states: hyperdestructive and hypoproliferative.

Inclusion and Exclusion criteria

Enrollment in the trial was restricted to confirmed hematological patients whose platelet count was $<150 \times 10^9/L$, with or without bone marrow studies, as verified by a hematology analyzer. To preclude pseudothrombocytopenia, peripheral blood smears were reviewed and stained with May-Grünwald-Giemsa (MGG) stain. Patients with a history of blood transfusion, antiplatelet drugs, pregnancy, chemotherapy, radiotherapy, or other treatments that can cause thrombocytopenia were excluded.

Study data

Data, including age, sex, and preliminary clinical diagnosis, were gathered from patients' medical reports. Based on clinico-hematological evidence, the patients were categorized into a state characterized by hyperdestruction of platelets (immune thrombocytopenic purpura (ITP), sepsis, malaria, dengue, *H. pylori*, and hypersplenism) and a state characterized by hypoproliferation of platelets (myelodysplastic syndrome (MDS), megaloblastic anemia, aplastic anemia, and leukemia).

Laboratory analysis

K3EDTA anti-coagulant vacutainers were used to collect blood samples for complete blood count (CBC) analysis. The collected samples were promptly examined using a semi-automated hematology analyzer (Mindray BC30s, TH-25012734, 2022, China). The Mindray Coulter utilizes the impedance principle to measure red blood cells (RBC) and platelets. Next, platelet indices were established and the mean platelet volume (MPV), platelet distribution widths (PDW), plateletcrit (PCT), platelet large cell count (PLCC), and platelet large cell ratio (PLCR) were determined. Three-level quality control checks were performed twice a day. All outcomes were acceptable.

Statistical analysis

The data were analyzed using SPSS (version 25, Chicago, IBN, IL, USA). The descriptive variables were quantified using frequencies and percentages. A correlation test was used to examine the relationship between the continuous variables. The Kolmogorov-Smirnov test results, which assess the normality of data assumed to follow a normal distribution, showed that the variables were not normally distributed in each group. Nonparametric, Mann-Whitney, and Wilcoxon signed-rank tests were used to compare the groups. The ANOVA test was used to compare the groups with the control group. Receiver Operating Characteristic (ROC) curves were used to compare the platelet characteristics of MPV, PDW, and PLCR between patients with hyperdestructive/consumptive thrombocytopenia and those with hypoproliferative thrombocytopenia. The optimal diagnostic threshold for platelet indices that had the highest combined sensitivity and specificity was also established. The area under the curve (AUC) and 95% confidence interval (CI) were computed for each plot. Significance was attributed to P-values <0.05 in all analyses.

RESULTS

The current study involved 200 participants ranging in age from 2 to 88 years. Patients and controls had mean ages of 40.84 ± 18.5 and 31.52 ± 18.6 , respectively. Among the 100 individuals diagnosed with thrombocytopenia, 61 [61%] were males and 39 (39%) were females. Of the 100 controls, 60 (60%) were male and 40 (40%) were female. Of the patients, 51% were males and

28% were females, and they were classified as having hyperdestructive thrombocytopenia. 10% of the patients were male and 11% were female, all of whom were diagnosed with hypoproliferative thrombocytopenia. The predominant age group for thrombocytopenia in patients with a hypoproliferative state was 45 years, whereas that in patients with a hyperdestructive state was 39.7 years. Categorical analysis did not reveal a statistically significant correlation between the research categories and age ($P=0.096$).

Interestingly, our research revealed an association between sex and thrombocytopenia, indicating that males are at a much higher risk of developing thrombocytopenia [odds ratio, 2.0; 95% CI 0.758-5.299]. The hyperdestructive condition had an odds ratio of (1.165 (95% CI 0.929-5.299)). However, the hypoproliferative condition had an Odds Ratio of [0.581 (95% CI 0.273-1.238)]. A hypoproliferative state was observed more often in men than in women (42.9% vs. 33.3%). The three groups showed a modest dominance of males, with an overall male-to-female ratio of 1.53:1 (**Table 1**).

A comparison was made using the platelet indices of the hypoproliferative, hyperdestructive, and healthy control groups were compared. The platelet count, MPV, PDW, PCT, PLCC, and PLCR showed statistically significant differences between the groups (**Table 2**). Platelet indices were greater in cases of hyperdestructive thrombocytopenia than in cases of hypoproliferative thrombocytopenia. Conversely, the PCT level of healthy controls was higher than that of patients with hypoproliferative and hyperdestructive thrombocytopenia (Table 2). MPV, PDW, PCT, PLCC, and PLCR were statistically significant in all three groups ($P=0.000$), as evidenced by the correlation between PLT and platelet indices (**Table 3**).

Platelet indices in a variety of clinical settings

Platelet indices were analyzed under various clinical conditions. The results indicated that the platelet count was significantly higher in leukemia and markedly lower in the hypocellular marrow (aplastic). Other platelet indices such as MPV were higher in patients with ITP, Hypersplenism, and *Helicobacter pylori*. Patients with sepsis and ITP exhibited a significantly higher prevalence of PLCC, whereas those with aplastic anemia exhibited an exceedingly low prevalence. PLCR levels were higher in individuals with *Helicobacter pylori* and ITP and lower in those with leukemia. However, leukemia contained only one sample (**Table 4**).

Platelet indices among cases of ITP and dengue

The mean values of MPV, PDW, PLCC, and PLCR were higher in ITP patients than in dengue patients. PCT levels were similar in both groups, but dengue slightly increased platelet count (**Table 4**). When compared to the ITP and dengue groups, the mean values of PLT, MPV, PCT, PLCC, and PLCR in both groups were not statistically significant ($P=0.117$, $P=0.091$, $P=0.308$, $P=0.599$, $P=0.126$, respectively). At the same time, PDW was significantly associated with the etiology of thrombocytopenia ($P=0.000$).

Degree of thrombocytopenia with clinical categories

At a mean age of 42.53 ± 18.42 years, 56 patients with clinical categories 45/56 [80.4%] hyperdestructive state and 11/56 (19.6%) hypoproliferative condition exhibited mild thrombocytopenia. Males represented 34/56 (60.7%) and females 22/56 (39.3%). On a mean age of 38.55 ± 15.31 years, 29 patients with clinical categories 24/29 (82.8%) hyperdestructive condition and 5/29 (17.2%) hypoproliferative were distinguished by moderate degree thrombocytopenia. In total, 17/29 individuals (58.6%) were identified as males, while 12/29 (41.4%) were identified as females. Of these, Similarly, an extreme degree of thrombocytopenia was observed in 15 participants with clinical categories of hyperdestructive (10/15 (66.7 %)) and hypoproliferative (5/15 (33.3%)) conditions, with a mean age of 38.93 ± 24.11 years. 10/15 (66.7%) were male and 5/15 (33.3%) were female. Despite this, an insignificant correlation was found between the patients' current categories and the degree of thrombocytopenia ($P=0.431$). ROC curve analysis revealed that platelet indices (MPV, PDW, and PLCR) were valuable tools for predicting the severity of troubles that cause thrombocytopenia. MPV (AUC = 0.665, 95%CI 0.591-0.740, sensitivity = 62.0%, specificity = 55.0%, and cut-off = 9.3 fL ($P=0.000$)). PDW (AUC = 0.832, 95% CI = 0.773–0.891, sensitivity = 79.0%, specificity = 70.0%, and cut-off = 16.0 fL ($P=0.000$)). The performance of the PLCR model was evaluated using (AUC = 0.754, 95% CI 0.688-0.820, sensitivity = 95%, specificity = 52%, and the cut-off was determined to be = 22.0% ($P=0.000$)). Previous results are represented in **Figure 1**.

DISCUSSION

Megakaryocytes generate platelets, which are essential for blood coagulation. Thrombocytopenia is the medical term used to

describe a low platelet count of less than $150 \times 10^9/L$ in the blood. Thrombocytopenia is mostly caused by either increased destruction or decreased generation of platelets, and these reasons are classified in the study [10]. Extracorporeal platelet consumption and destruction, along with an increase in megakaryocyte production in the bone marrow, are the two main causes of accelerated platelet destruction.

The decrease in production is caused by numerous bone marrow illnesses, both primary and secondary, such as megaloblastic anemia, aplastic anemia, and leukemia [4,11,12]. Assessing the mechanism of thrombocytopenia using clinical approaches is challenging. Therefore, platelet indicators significantly impact identifying this mechanism, aiding future therapy [4,11]. In thrombocytopenia, it is unnecessary to employ bone marrow examination as the initial diagnostic procedure, as it is invasive. The comprehensive blood counts that the automated analyzer produces include platelet indices and platelet counts give shreds of evidence in this way [13]. This study was designed to evaluate the diagnostic reliable capacity of five platelet indices, including MPV, PCT, PLCC, PLCR, and PDW, in patients with thrombocytopenia. The primary purpose of the clinical test conducted in our study was to determine whether a low platelet count in patients was due to reduced platelet generation or enhanced platelet devastation and to uncover the underlying causes of thrombocytopenia.

The mean age of the current study patients with hyperdestructive and hypoproliferative thrombocytopenia was comparable to that of a previous investigation [14]. The prevalence of males in our research was consistent with that found in earlier investigations [15]. The hyperdestructive state accounted for 79% of the cases, while the hypoproliferative state accounted for 21%. This finding is consistent with the studies conducted by Parveen and Vimal [4], Reddy et al. [14], and Katti et al. [8], but it contrasts with the studies undertaken by Chaitra et al. [12] and Al-Sharifi [16]. During the hyperdestructive condition, most patients exhibited a non-ITP etiology, primarily due to dengue infections. The dengue virus directly damages platelets and, in certain instances, hinders the development of megakaryocytes, resulting in thrombocytopenia. Disseminated intravascular coagulation (DIC) causes splenic sequestration of platelets, along with platelet consumption and coagulation abnormalities [1]. The finding above was remarkably similar to the study scenario.

Prior research has revealed that platelet counts were higher in the hyperdestructive group versus the hypoproliferative group, consistent with our study findings [2,4,15]. Nevertheless, certain investigations have shown that the average platelet count in the hypoproliferative group was greater than that in the hyperdestructive group [5,17]. Platelet indices exhibited a notable disparity between hypoproliferative and hyperdestructive states of thrombocytopenia [3,17]. Nevertheless, MPV, PDW, PLCC, PCT, and PLCR displayed notable distinctions, demonstrating superior discriminatory capabilities between the two groups. The present study found that the MPV threshold was 9.57 fl in the hypoproliferative group and 9.92 fl in the hyperdestructive group. These values were lower than those reported in earlier studies [5, 15]. These investigations found a substantial difference in the value of MPV between the hypoproliferative and hyperdestructive groups. The possible reason for this could be the limitations of automated hematology analyzers in distinguishing platelets from other blood cells of comparable size, such as schistocytes or white blood cells, immune complexes, or cell debris. Another factor that may contribute to this discrepancy is the difference in frequency between the two groups being studied. MPV serves as a clue to bone marrow function and platelet dynamics. Additionally, it's applicable as a proxy marker for bleeding. An elevated MPV level denotes an increase in the shedding of platelets by megakaryocytes. However, MPV is also enhanced in cases with consumptive or destructive thrombocytopenia. A decreased MPV is linked to bone marrow repression and an elevated susceptibility to bleeding [6].

Based on our study, we realized a substantial and meaningful distinction between the hypoproliferative and hyperdestructive groups, as well as among both groups and the control group, concerning PDW. However, a previous study indicated that PDW levels were augmented in patients with hyperdestructive states compared to hypoproliferative patients [18]. This finding was also consistent with our results. In our investigation, we noticed that the levels of PCT were relatively higher in the hyperdestructive group versus the hypoproliferative group. The hypoproliferative group had a lower PCT versus the hyperdestructive group in a study that closely resembled our findings [4]. Nevertheless, Khaleel KJ et al. [17] found that the levels of PCT matched in both the hyperdestructive and hypoproliferative groups.

People with ITP and dengue had different MPV, PCT, PDW, PLCC, and PLCR values. The average values of MPV, PLCC, PLCR, and PDW were marginally higher in the ITP cases versus the dengue cases. Comparing the mean values of MPV, PCT, PLCC, PLCR, and PDW among the ITP and dengue groups revealed they were statistically insignificant. However, PCT was raised in dengue cases, which could be attributed to hemoconcentration since PCT represents the volume percentage of platelets. The P-LCR and PLCC were considerably elevated in patients with thrombocytopenia and reduced in those with thrombocytosis. The variable showed an inverse correlation with platelet count [7]. Additionally, PLCR and PLCC were

employed to monitor platelet activation [19]. Our investigation found that hyperdestructive patients had greater levels of PLCR and P-LCC as opposed to hypoproliferative individuals. These results are in line with prior research [3].

In the present study, the hyperdestructive thrombocytopenic group had the most cases of dengue ($n = 51$), ITP ($n = 10$), and malaria ($n = 9$). This pattern resembles that found by Katti et al. [8] and Parveen S et al. [4], where malaria was the second most common disease after dengue. The anti-dengue virus antibody attaches to the dengue antigen and is then adsorbed to platelets, causing their death through immune-mediated mechanisms [6]. In our situation, malaria is also a frequent cause of thrombocytopenia. In contrast to megaloblastic anemia, the present study demonstrates that the average values of MPV and PDW were greater in ITP. Even so, PCT was consistent in both groups. The average level of MPV in the ITP group was statistically insignificant; however, it was higher than that in megaloblastic marrow. In their study, Rajashekar RB et al. [2] found that the average platelet indices were significantly greater in the hyperdestructive group than in the hypoproliferative group. However, they also found no statistically significant difference between the etiologies of thrombocytopenia and platelet indices. These outcomes are the same as our findings.

Our investigation revealed that MPV, PDW, and PLCR as platelet indices are sensitive and specific when screening for thrombocytopenic patients. A study published by Chandra et al. found that the sensitivity and specificity of MPV, using a cut-off mark of 8.15 fL, were 67.7% and 65%, respectively [20]. Chandra recommended prioritizing a bone marrow biopsy over depending on MPV as a screening test [20]. In a separate study performed by Tang et al., it was proposed that MPV had a sensitivity of 70.3% and a specificity of 74.8%. These figures indicate that MPV is not a suitable screening method for immune thrombocytopenia [21]. Nevertheless, a study designed by Aponte-Barrios et al., found that MPV, PDW, and PLCR have elevated sensitivity and specificity in diagnosing immunological thrombocytopenia. The result emphasizes using these indices as a screening tool [22]. Al-Sharifi suggested a threshold of 9.9 fL for MPV, which achieved a sensitivity and specificity of 100% [16]. Our study is distinct because we can diagnose troubles that cause thrombocytopenia with the platelet indices' sensitivity and specificity. Understanding the matter of thrombocytopenia is pivotal for proper patient care and avoiding unnecessary procedures, transfusions, and potentially dangerous drugs. Therefore, there is a requirement for novel non-invasive diagnostic methods to detect thrombocytopenia [23].

This study is limited by its single-site design, conducted exclusively in a tertiary care medical center. Therefore, the data collected may not accurately represent the broader community. Furthermore, the limited sample size of the hypoproliferative thrombocytopenic group categories may restrict the findings of this study. Platelet function tests should be included in the future.

Table 1. Characteristics of patient categories and controls

Variable	Number of cases	Age (mean $\pm$ SD)	Sex	
			Male	
Female				
Hyperdestructive	79	39.67 $\pm$ 17.2	51(64.6%)	28 (35.4%)
Hypoproliferative	21	45.24 $\pm$ 22.4	10 (47.6%)	11 (52.4%)
Controls	100	31.52 $\pm$ 18.6	60 (60.0%)	40 (40.0%)
Total	200		121	79

Table 2. Comparative analysis of average platelet indices across patient categories and healthy controls.

Variables	Hyperdestructive state (n=79)	Hypoproliferative state (n=21)	Controls (n=100)	P. value
PLT μ L	101.5 $\pm$ 35.4	87.0 $\pm$ 42.4	256.7 $\pm$ 66.6	< 0.001
MPV fL	9.9 $\pm$ 1.3	9.5 $\pm$ 1.5	9.1 $\pm$ 0.96	< 0.001

PDW Fl	16.6±1.7	16.4±1.7	15.5±14.6	< 0.001
PCT %	0.10±0.03	0.08±0.04	0.23±0.05	< 0.001
PLCC µL	28.0±11.1	23.5±12.0	52.5±18.9	< 0.001
PLCR %	28.7±8.8	28.2±8.7	21.0±6.8	< 0.001

Table 3. Correlation between platelet count and platelet indices across all study groups

Variables	Number of cases	Platelet count ($10^3/\mu\text{L}$)	
		r-value	P-value
MPV	200	-0.320**	< 0.001
PDW	200	-0.573**	< 0.001
PCT	200	0.976**	< 0.001
PLCC	200	0.766**	< 0.001
PLCR	200	-0.514**	< 0.001

Table 4. Platelet indices under diverse clinical scenarios

Disease Categories	No. of Cases	PLT (mean±SD)	MPV (mean±SD)	PDW (mean±SD)	PCT (mean±SD)	PLCC (mean±SD)	PLCR (mean±SD)
Hyperdestructive diseases							
Sepsis	7	101.4±36.2	9.9±0.62	15.2±1.9	0.10±0.03	29.3±9.6	29.6±3.7
ITP	10	93.5±48.3	10.4±1.8	16.5±0.74	0.09±0.05	28.8±16.0	34.1±11.6
Malaria	9	108.7±21.7	9.8±1.1	16.7±0.61	0.11±0.02	28.0±7.8	26.1±6.7
Dengue	51	103.9±34.0	9.8±1.3	16.1±1.8	0.10±0.04	28.2±10.9	27.9±8.9
H. pylori	2	63.0±36.0	11.5±1.9	18.2±1.1	0.08±0.05	27.4±21.7	39.9±11.5
Hypersplenism	2	86.0±42.4	10.6±0.28	15.2±2.0	0.09±0.05	28.5±16.8	32.2±1.67
Hypoproliferative diseases							
MDS	5	74.6±45.0	9.2±0.97	16.4±1.7	0.06±0.04	18.2±11.1	25.4±5.2
Megaloblastic anemia	11	98.6±36.5	9.2±0.4	16.4±0.72	0.09±0.04	25.2±10.4	24.9±4.6
Aplastic anemia	2	17.5±2.1	10.6±4.5	17.3±3.7	0.02±0.01	7.8±1.9	44.1±5.3
Leukemia	1	130±0.0	9.4±0.0	11.7±0.0	0.12±0.0	27.6±0.0	21.2±0.0

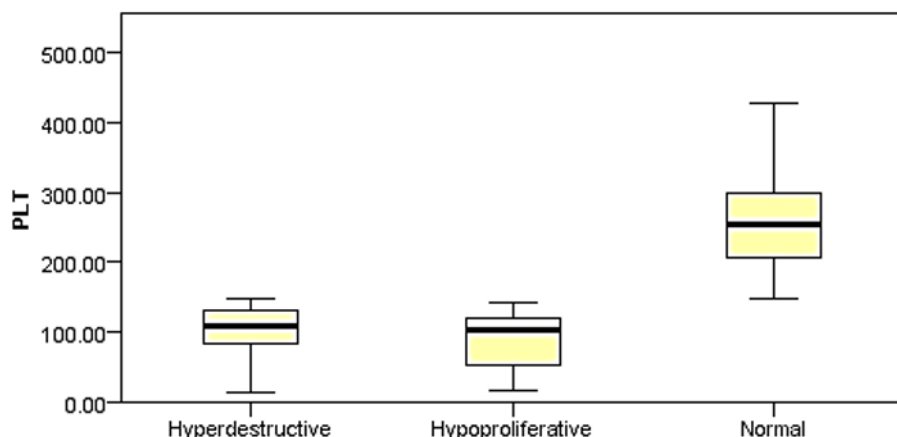


Figure 1. Platelet counts across the categories of the study

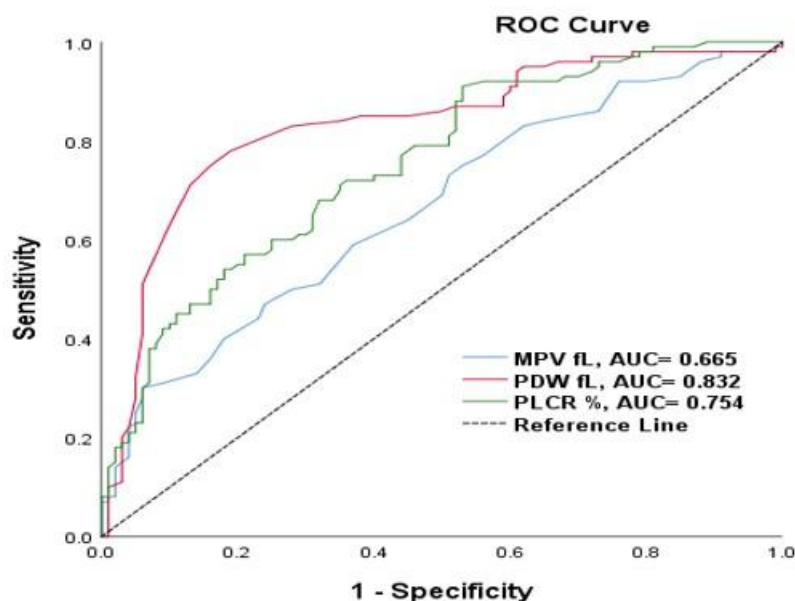


Figure 2. ROC curve contrasting the area covered by MPV, PDW, and PLCR in the categories of thrombocytopenic cases

CONCLUSION

Platelet indices assist in distinguishing between hypoproliferative (decreased platelet generation) and hyperdestructive (increased platelet destruction) forms of thrombocytopenia. Moreover, MPV is a reliable marker differentiating between hyperdestructive and hypoproliferative thrombocytopenia scenarios. PDW serves as conclusive proof that demonstrates the heightened reactivity in people with thrombocytopenia. This study also revealed that MPV, PDW, PLCC, and PLCR are laboratory evidence for anticipating disease severity. Ultimately, platelet indices offer useful insights for detecting thrombocytopenia. Therefore, in all instances of thrombocytopenia, clinicians must examine platelet indices, since they assist in determining the likely etiology of thrombocytopenia.

Ethical Considerations

This study conformed to the Declaration of Helsinki and was approved on December 15, 2023, by the PAU-REC, Port Sudan Ahlia University, Port Sudan, Sudan (code PAU-REC/2/1).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Declaration of Conflicting Interests

The authors declare no conflict of interest.

Data Availability Statement

Most relevant data are available in the main text; further data are available from the corresponding author upon reasonable request.

Acknowledgment

The authors extend their appreciation to Prince Sattam bin Abdulaziz University for funding this research work through the project number (PSAU/2026/03/44722).

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