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Original Article

Pathology Section

Platelet Indices in Differentiating Hyperdestructive and Hypoproductive Thrombocytopenia: A Hospital-based Cross-sectional Study

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ABSTRACT

Introduction: Thrombocytopenia may result from impaired platelet production or increased peripheral destruction or consumption. Distinguishing these mechanisms is clinically important, and platelet indices can provide supportive information during the initial evaluation.

Aim: To compare platelet indices between patients classified as having hyperdestructive and hypoproductive thrombocytopenia and to evaluate the distribution of platelet indices across thrombocytopenia severity categories.

Material and Methods: This hospital-based cross-sectional observational study was conducted at RL Jalappa Hospital attached to Sri Devaraj Urs Medical College, Kolar, Karnataka, from December 2014 to July 2016. A total of 190 adults with platelet counts <150×10^9/L were included. Platelet count, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Plateletcrit (PCT), and Platelet Large Cell Ratio (P-LCR) were measured using an ALERE H 560 automated haematology analyser. Patients were classified clinically as hyperdestructive or hypoproductive thrombocytopenia. The data were analysed using distribution testing and non parametric methods.

Results: Of 190 patients, 182 (95.8%) were classified as hyperdestructive and 8 (4.2%) as hypoproductive thrombocytopenia. The extreme imbalance between groups limits the precision of the mechanism-based comparison. Mean MPV was higher in the hypoproductive group than in the hyperdestructive group (8.45±0.77 vs. 6.60±1.74 fL; mean difference, 1.85 fL; 95% CI, 1.18-2.52; p=0.003). In the severity analysis, 26 patients had severe, 82 moderate, and 82 mild thrombocytopenia. MPV, PDW, P-LCR, and PCT differed significantly across severity categories by the Kruskal-Wallis test (p<0.001 for each).

Conclusion: Platelet indices showed significant variation according to thrombocytopenia severity in this cohort. Although MPV was significantly higher in the hypoproductive group than in the hyperdestructive group, this finding was opposite to the predominant pattern reported in the literature and should be interpreted cautiously because the hypoproductive subgroup comprised only eight patients. Platelet indices should therefore be regarded as supportive laboratory parameters rather than standalone diagnostic tests.

Keywords: Mean platelet volume, Plateletcrit, Platelet large cell ratio, Platelet distribution width

INTRODUCTION

Thrombocytopenia, conventionally defined as a platelet count below 150×10^9/L, is a common haematological abnormality with diverse underlying mechanisms. The major pathological mechanisms include impaired platelet production by the bone marrow and increased peripheral destruction or consumption. Distinguishing these mechanisms is clinically relevant because the subsequent diagnostic evaluation and management differ substantially. Automated haematology analysers provide several platelet parameters in addition to platelet count, including MPV, PDW, PCT, and P-LCR. These indices reflect platelet size, variation in platelet size, and circulating platelet mass and may provide indirect information regarding thrombopoietic activity and peripheral platelet turnover [1-5].

The biological rationale for using platelet indices in aetiological assessment is that increased peripheral platelet destruction may stimulate compensatory thrombopoiesis, resulting in the release of larger and younger platelets into the circulation, whereas impaired marrow production may result in normal or smaller circulating platelets. Kaito K et al., demonstrated significantly higher MPV, PDW, and P-LCR in patients with immune thrombocytopenia than in patients with aplastic anaemia and reported useful discriminatory performance for these indices [1]. Bowles KM et al., similarly observed a higher MPV in patients without marrow disease than in those with marrow disease, suggesting that platelet size may provide supportive information regarding the mechanism of thrombocytopenia [4]. Babu E and Basu D reported that P-LCR was useful in the differential diagnosis of abnormal platelet counts and was related to MPV and PDW [3].

However, platelet indices are not universal biological constants. Giacomini A et al., demonstrated variation in platelet parameters according to age, sex, and clinical status using the ADVIA 120 analyser [2]. Latger-Cannard V et al., subsequently demonstrated important inter-analyser differences in MPV, emphasising that values obtained from different automated platforms should not necessarily be compared directly [6]. These findings indicate that both patient characteristics and analytical methodology should be considered when interpreting platelet indices.

Several subsequent studies have supported the potential role of platelet indices in differentiating thrombocytopenia mechanisms. Parveen S and Vimal M, reported higher MPV in hyperdestructive than hypoproductive thrombocytopenia, while Pujari L et al., reported higher MPV, PDW, and P-LCR in hyperdestructive thrombocytopenia with bone marrow findings supporting the mechanism-based classification [7,8]. Saxena PPB et al., also reported significant variation in MPV, PDW, and P-LCR across thrombocytopenic conditions [9]. Borkataky S et al., reported that platelet volume indices may assist in the differential diagnosis of

thrombocytopenia, supporting their use as adjunctive laboratory parameters [10]. Saran et al., also observed higher platelet indices in hyperdestructive thrombocytopenia, providing further support for the biological association between peripheral platelet destruction and increased platelet production. [11]

The interpretation of MPV is additionally influenced by analytical and preanalytical factors. Bessman JD and Gardner FH described changes in MPV in sepsis-associated thrombocytopenia, while Dumoulin-Lagrange M et al., demonstrated that platelet-volume indices could contribute to the aetiological assessment of thrombocytopenia [12,13]. Thompson et al., provided biological evidence that platelets in immune thrombocytopenia are larger than normal, supporting the relationship between platelet size and altered platelet turnover[14]. Bancroft AJ et al., emphasised the importance of reproducible MPV measurement, while Diaz-Ricart M et al., demonstrated that preanalytical handling of Ethylenediaminetetraacetic Acid (EDTA)-anticoagulated blood can influence platelet-volume measurements [15,16]. Ali U et al., further showed that reference intervals for MPV and related platelet parameters may vary according to sex and analytical system [17]. These observations are particularly relevant when unexpectedly low or high MPV values are observed.

More recently, attention has shifted toward immature platelet parameters as more direct indicators of thrombopoiesis. Li J et al., reported that immature platelet fraction-related parameters could differentiate peripheral platelet destruction from decreased platelet production [18]. Khan MI and Ullah I also demonstrated the potential diagnostic value of MPV, PDW, and P-LCR in immune thrombocytopenia [19]. Benlachgar N et al., reviewed the biological and clinical significance of immature platelets and highlighted their potential role in assessing platelet production [20]. Van De Wyngaert Z et al., reported that immature platelet fraction could help identify peripheral thrombocytopenia [21]. A systematic review and meta-analysis by Walle M et al., found that MPV was generally higher in immune thrombocytopenia than in hypoproductive thrombocytopenia, although diagnostic performance varied among studies [22]. Asghar MB et al., similarly reported high diagnostic accuracy of immature platelet fraction for distinguishing peripheral platelet destruction from bone marrow failure [23].

Despite these observations, the direction and magnitude of differences in platelet indices are not consistent across all populations and analytical platforms. The present study was therefore undertaken to compare MPV, PDW, PCT, and P-LCR between clinically classified hyperdestructive and hypoproductive thrombocytopenia and to examine their variation across predefined severity categories. Particular attention was given to the unexpected mechanism-based MPV finding in the present cohort and to whether platelet indices demonstrate consistent changes with increasing thrombocytopenia severity. Because Receiver Operating Characteristic (ROC) analysis was not performed in the original study, the present work does not make claims regarding sensitivity, specificity, predictive values, Area Under the Curve (AUC), or diagnostic cut-off values.

MATERIALS AND METHODS

The present hospital-based cross-sectional observational study was conducted at RL Jalappa Hospital attached to Sri Devaraj Urs Medical College, Kolar, Karnataka, from December 2014 to July 2016. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1975, revised 2013) and approved by the Institutional Ethics Committee for Human Research, Sri Devaraj Urs Medical College, Kolar, Karnataka (Ethics Committee Approval No. DMC/ KLR/IEC- CER/286/ 2016-17 before commencement of the study. Following approval from the Institutional Ethics Committee, written informed consent was obtained from all eligible participants before their inclusion in the study and collection of blood samples. All eligible patients presenting during the study period were consecutively enrolled resulting in a total sample of 190 participants.

Inclusion criteria: Adults aged >18 years with a platelet count <150×109/L were eligible for inclusion in the study.

Exclusion criteria: Patients with platelet clumping suggestive of pseudothrombocytopenia, patients who had received platelet transfusion within 48 hours before blood sample collection, and those with incomplete clinical information were excluded from the study.

Study Procedure

Following informed consent, 2 mL of venous blood was collected aseptically into an EDTA-containing tube for Complete Blood Count (CBC) analysis. CBC was performed using an ALERE H 560 automated haematology analyser, according to the manufacturer's instructions, using impedance and photometric measurement principles. Peripheral blood smears were prepared and appropriately stained for microscopic examination.

Peripheral blood smear examination was performed for all participants to confirm thrombocytopenia and assess platelet morphology. The presence of giant platelets, when observed, was recorded as supportive evidence of increased peripheral platelet turnover. Schistocytes, blasts, and other abnormal cellular findings were documented when present and were considered during the aetiological assessment.

Aetiological Classification

Patients were classified as having hyperdestructive or hypoproductive thrombocytopenia based on the documented clinical diagnosis, relevant laboratory investigations, peripheral blood smear findings, and other supportive investigations available in the medical records. Hyperdestructive thrombocytopenia included infectious causes, immune-mediated thrombocytopenia, sepsis, drug-related platelet destruction, disseminated intravascular coagulation, and other peripheral consumptive conditions. Hypoproductive thrombocytopenia included bone marrow suppression, leukaemia, aplastic anaemia, megaloblastic anaemia, myelodysplastic syndrome, and infiltrative marrow disorders. Bone marrow examination was performed when clinically indicated, and the findings, when available, were taken into consideration while establishing the underlying mechanism. The final aetiological classification was based on the overall clinical and laboratory assessment and was not determined on the basis of platelet indices alone.

Severity classification: Based on the platelet count, thrombocytopenia was categorised into three severity groups:

Severe: $<20\times10^9$/L

Moderate: 20 to $<50\times10^9$/L

Mild: 50 to $<150\times10^9$/L

This classification included all participants fulfilling the study inclusion criterion of a platelet count $<150\times10^9$/L.

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics version 22.0. The distribution of continuous variables was assessed using the Shapiro-Wilk test and by visual inspection of the data distribution. Normally distributed continuous variables were expressed as mean±Standard Deviation (SD), whereas non-normally distributed variables were expressed as median with Interquartile Range (IQR).

For comparisons between two independent groups, the independent-samples Student's t-test was used for normally distributed variables, while the Mann-Whitney U test was used for non normally distributed variables. For comparisons across the three thrombocytopenia severity categories, One-way Analysis of Variance (ANOVA) was used for normally distributed variables and the Kruskal-Wallis test for non-normally distributed variables. When the Kruskal-Wallis test demonstrated a statistically significant overall difference, pair-wise

Mann-Whitney U tests with Bonferroni adjustment were performed for post-hoc comparisons. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 190 patients with thrombocytopenia were included in the study. Of these, 110 (57.9%) were female and 80 (42.1%) were male. The largest proportion of participants belonged to the 21-30-year age group (63/190, 33.2%), followed by those aged 31-40 years (46/190, 24.2%) [Table/Fig-1].

Age group (years)	Female, n (%)	Male, n (%)	Total, N (%)
<20	10 (9.1)	10 (12.5)	20 (10.5)
21-30	45 (40.9)	18 (22.5)	63 (33.2)
31-40	26 (23.6)	20 (25.0)	46 (24.2)
41-50	19 (17.3)	14 (17.5)	33 (17.4)
51-60	6 (5.5)	9 (11.2)	15 (7.9)
>60	4 (3.6)	9 (11.2)	13 (6.8)
Total	110 (57.9)	80 (42.1)	190 (100.0)

[Table/Fig-1]: Age and gender distribution of patients with thrombocytopenia (N=190).

Based on the clinical and laboratory classification, 182 patients (95.8%) were classified as having hyperdestructive thrombocytopenia, whereas 8 patients (4.2%) had hypoproductive thrombocytopenia. Among patients with hyperdestructive thrombocytopenia, infectious causes were the most frequent 97/182 (53.3%), followed by immune-mediated thrombocytopenia 72/182 (39.5%), obstetric causes 8/182 (4.4%), and other causes 5/182 (2.8%). Among the hypoproductive group, bone marrow suppression accounted for 5/8 cases (62.5%), followed by other marrow disorders 2/8 (25.0%) and leukaemia 1/8 (12.5%) [Table/Fig-2].

Mechanism	Aetiological cause	n (%)
Hyperdestructive (n=182)	Infectious causes	97 (53.3)
	Immune-mediated thrombocytopenia	72 (39.5)
	Obstetric causes	8 (4.4)
	Other causes	5 (2.7)
Hypoproductive (n=8)	Leukaemia	1 (12.5)
	Bone marrow suppression	5 (62.5)
	Other marrow disorders	2 (25.0)
Total	190	100.0

[Table/Fig-2]: Aetiology of thrombocytopenia.

In the original mechanism-based analysis, the mean platelet count was 61,698±93,265/µL in the hyperdestructive group and 65,750±49,236/µL in the hypoproductive group, with no statistically significant difference (p=0.903). In contrast, mean MPV was significantly higher in the hypoproductive group (8.45±0.77 fL) than in the hyperdestructive group (6.60±1.74 fL; p=0.003). No statistically significant differences were observed for PDW, P-LCR, or PCT in the original analysis. Because of the substantial difference in group size, particularly the small number of hypoproductive cases, these mechanism-based findings should be interpreted cautiously [Table/Fig-3].

Severity-based analysis showed 26 patients (13.2%) had severe thrombocytopenia, 82 (43.4%) had moderate thrombocytopenia and 82 (43.4%) had mild thrombocytopenia [Table/Fig-4].

The median MPV increased progressively across the severity categories, from 5.45 fL (IQR: 4.68-7.23) in severe thrombocytopenia to 6.00 fL (IQR: 5.10-6.70) in moderate and 7.30 fL (IQR: 6.30-8.10) in mild thrombocytopenia. Similarly, the median PDW was 0.00 (IQR: 0.00-12.30), 18.95 (IQR: 15.90-22.05), and 19.05 (IQR: 16.60-21.78) in the severe, moderate, and mild groups, respectively.

The median P-LCR increased from 23.19% (IQR: 18.98-25.70) in severe thrombocytopenia to 25.00% (IQR: 22.08-29.59) in moderate and 28.62% (IQR: 23.24-34.07) in mild thrombocytopenia. Median PCT values were 0.210% (IQR: 0.176-0.248), 0.246% (IQR: 0.214-0.288), and 0.280% (IQR: 0.221-0.336) in the respective severity categories.

The Kruskal-Wallis test demonstrated statistically significant differences across the three severity categories for all four platelet indices: MPV (H=23.16, p<0.001), PDW (H=35.68, p<0.001), P-LCR (H=17.84, p<0.001), and PCT (H=16.55, p<0.001).

Overall, the severity-based analysis demonstrated a significant variation in MPV, PDW, P-LCR, and PCT across increasing platelet-count categories, with the highest median values generally observed among patients with mild thrombocytopenia and the lowest values among those with severe thrombocytopenia.

Post-hoc Pair-wise Comparisons

Post-hoc pair-wise comparisons were performed using the Mann-Whitney U test with Bonferroni adjustment to identify differences between individual thrombocytopenia severity categories. For MPV, significant differences were observed between severe and mild thrombocytopenia (adjusted p=0.0166) and between moderate and mild thrombocytopenia (adjusted p<0.001), whereas the difference between severe and moderate thrombocytopenia was not significant (adjusted p=1.000). For PDW, significant differences were observed between severe and moderate thrombocytopenia (adjusted p<0.001) and between severe and mild thrombocytopenia (adjusted p<0.001), while the difference between moderate and mild thrombocytopenia was not significant (adjusted p=1.000). For P-LCR, significant differences were observed between severe and

Parameters	Hyperdestructive	Hypoproductive	Mean difference (95% CI)	p-value
Platelet count	61,698±93,265	65,750±49,236	4,052 (–45,000 to 53,000)*	0.903
MPV (fL)	6.60±1.74	8.45±0.77	1.85 (1.18 to 2.52)	0.003
PDW (%)	16.21±18.96	24.26±19.77	8.05 (approximately -5.7 to 21.8)*	0.242
P-LCR (%)	25.09±6.01	27.16±6.43	2.07 (approximately -2.5 to 6.6)*	0.343
PCT (%)	0.25±0.06	0.22±0.09	–0.03 (approximately -0.09 to 0.03)*	0.060

[Table/Fig-3]: Platelet indices in hyperdestructive and hypoproductive thrombocytopenia.

Platelet-count category	n	MPV, median (IQR), fL	PDW, median (IQR)	P-LCR, median (IQR), %	PCT, median (IQR), %
Severe (<20×10^9/L)	26	5.45 (4.68-7.23)	0.00 (0.00-12.30)	23.19 (18.98-25.70)	0.210 (0.176-0.248)
Moderate (20-<50×10^9/L)	82	6.00 (5.10-6.70)	18.95 (15.90-22.05)	25.00 (22.08-29.59)	0.246 (0.214-0.288)
Mild (50-<150×10^9/L)	82	7.30 (6.30-8.10)	19.05 (16.60-21.78)	28.62 (23.24-34.07)	0.280 (0.221-0.336)
Kruskal-Wallis H	-	23.16	35.68	17.84	16.55
p-value	-	<0.001	<0.001	<0.001	<0.001

[Table/Fig-4]: Distribution of platelet indices according to thrombocytopenia severity.

Platelet index	Comparison	Unadjusted p-value	Bonferroni-adjusted p-value	Interpretation
MPV	Severe vs Moderate	0.6669	1	Not significant
MPV	Severe vs Mild	0.005522	0.01657	Significant
MPV	Moderate vs Mild	3.372e-06	1.012e-05	Significant
PDW	Severe vs Moderate	4.523e-08	1.357e-07	Significant
PDW	Severe vs Mild	9.57e-09	2.871e-08	Significant
PDW	Moderate vs Mild	0.7572	1	Not significant
P-LCR	Severe vs Moderate	0.03071	0.09212	Not significant
P-LCR	Severe vs Mild	0.0001368	0.0004105	Significant
P-LCR	Moderate vs Mild	0.004824	0.01447	Significant
PCT	Severe vs Moderate	0.008489	0.02547	Significant
PCT	Severe vs Mild	0.0002167	0.0006501	Significant
PCT	Moderate vs Mild	0.01764	0.05291	Not significant

[Table/Fig-5]: Post-hoc pair-wise comparisons of platelet indices across thrombocytopenia severity categories.

mild thrombocytopenia (adjusted p<0.001) and between moderate and mild thrombocytopenia (adjusted p=0.014), whereas the severe-versus-moderate comparison was not significant (adjusted p=0.092). For PCT, significant differences were observed between severe and moderate thrombocytopenia (adjusted p=0.025), and between severe and mild thrombocytopenia (adjusted p<0.001); however, the moderate-versus-mild comparison was not statistically significant after Bonferroni adjustment (adjusted p=0.053). These findings indicate that the significant overall differences observed by the Kruskal-Wallis test were mainly attributable to differences involving the severe or mild thrombocytopenia categories [Table/Fig-5].

DISCUSSION

Thrombocytopenia results from heterogeneous pathological processes, and distinguishing increased peripheral destruction from impaired platelet production is an important component of its evaluation. Automated platelet indices have attracted interest because they are generated routinely during CBC analysis and may provide indirect information regarding platelet production and turnover. The present study provides two principal observations: first, hyperdestructive thrombocytopenia predominated markedly in the study population; and second, MPV, PDW, P-LCR, and PCT varied significantly across platelet-count severity categories.

In the present cohort, 182 of 190 patients (95.8%) were classified as having hyperdestructive thrombocytopenia, whereas only 8 (4.2%) were classified as hypoproductive. Infectious causes constituted the largest subgroup within the hyperdestructive category. This predominance probably reflects the hospital-based case mix and the contribution of infectious and immune-mediated conditions during the study period. However, the extreme imbalance between the two mechanism-based groups substantially reduces statistical power and makes the estimates for the hypoproductive group imprecise. Therefore, the mechanism-based comparison should be interpreted as exploratory rather than definitive.

The most notable finding in the original mechanism-based analysis was the significantly higher MPV in the hypoproductive group (8.45±0.77 fL) compared with the hyperdestructive group (6.60±1.74 fL; p=0.003). This finding differs from the predominant pattern reported in previous studies. Kaito K et al., reported higher MPV, PDW, and P-LCR in immune thrombocytopenia than in aplastic anaemia, consistent with increased peripheral platelet turnover in hyperdestructive thrombocytopenia [1]. Bowles KM et al., likewise found that patients without marrow disease had a higher mean MPV than patients with marrow disease (9.8 versus 8.1 fL), supporting the use of platelet size as a marker of the likely mechanism of thrombocytopenia [4]. Parveen S and Vimal M also reported higher MPV in hyperdestructive than hypoproductive thrombocytopenia (12.3±0.9 versus 10.17±1.3 fL) [7]. More recently, Pujari L et al., reported significantly higher MPV, PDW, and P-LCR in hyperdestructive thrombocytopenia than in hypoproductive thrombocytopenia, with bone marrow findings supporting the mechanism-based classification [8]. Thus, the direction of the MPV difference observed in our study is opposite to that reported in these studies.

Several factors may account for this discrepancy. The most important is the very small hypoproductive subgroup (n = 8). A single or small number of atypical observations can have a substantial effect on the estimated mean in such a small group, and the possibility of a type I statistical error cannot be excluded. In addition, the aetiological composition of the two groups in the present study differed from the more tightly defined comparison groups used by Kaito K et al., who specifically compared immune thrombocytopenia with aplastic anaemia [1]. The hyperdestructive group comprised several clinical conditions, including infectious, immune-mediated, obstetric, and other consumptive causes, while the hypoproductive group also included heterogeneous marrow disorders. Such clinical heterogeneity may influence platelet production and platelet size differently and may partly explain the divergence from previous reports.

Analytical and preanalytical factors should also be considered. The present study used an ALERE H 560 automated haematology analyser, whereas previous studies used different analytical platforms. Latger-Cannard V et al., demonstrated a 20-25% variation in MPV measurements between three haematology analysers and emphasised the lack of universal external calibration for MPV [6]. Therefore, absolute MPV values should be interpreted in the context of the analyser used. The relatively low MPV values observed in the present hyper destructive group are also noteworthy because the original manuscript reported an analyser reference interval of 8-12 fL. This discrepancy warrants verification of the analyser-specific reference interval, raw data, sample-processing interval, and data-entry procedures. EDTA-related changes in platelet volume and delays between blood collection and analysis may further influence MPV and should be considered when interpreting historical laboratory data.

The severity-based reanalysis produced a more consistent pattern. Median MPV increased progressively from 5.45 fL in severe thrombocytopenia to 6.00 fL in moderate and 7.30 fL in mild thrombocytopenia, with a significant overall Kruskal-Wallis result (H=23.16, p<0.001). PDW, P-LCR, and PCT also differed significantly across the three severity categories. Post-hoc analysis showed that MPV differed significantly between severe and mild and between moderate and mild thrombocytopenia, whereas the severe-versus-moderate comparison was not significant. For PDW, significant differences were observed between severe and moderate and between severe and mild categories, but not between moderate and mild categories. P-LCR differed significantly between

severe and mild and between moderate and mild groups, while PCT differed significantly between severe and moderate and between severe and mild groups, with the moderate-versus-mild comparison not reaching the Bonferroni-adjusted significance threshold.

The progressive increase in MPV with increasing platelet count is biologically plausible, as patients with less severe thrombocytopenia may retain a greater proportion of circulating larger platelets, whereas severe thrombocytopenia may be associated with more pronounced platelet depletion. The significant variation in PDW and P-LCR is also consistent with changes in platelet-size distribution and the proportion of larger platelets as platelet counts change. Saxena PPB et al., similarly reported significant changes in MPV, PDW, and P-LCR across thrombocytopenia-related clinical categories, supporting the observation that platelet indices may vary with disease severity [9]. However, comparisons with that study should be made cautiously because the patient categories and analytical methods were not identical.

The present study findings also partially agree with Babu E and Basu D, who observed that P-LCR was related to MPV and PDW and tended to be higher in destructive thrombocytopenia than in hypoproliferative thrombocytopenia [3]. In contrast, the mechanism-based analysis in our cohort did not demonstrate significant differences in PDW, P-LCR, or PCT. The difference may be related to the markedly unequal group sizes, clinical heterogeneity, and analyser-specific measurement characteristics. Similarly, Giacomini A et al., demonstrated that platelet parameters vary with age and sex and that platelet indices differ between thrombocytopenic patients and reference subjects, emphasising that platelet parameters should be interpreted within the context of the population and analytical system [2].

The findings of the present study therefore provide supportive, rather than definitive, evidence of the clinical usefulness of platelet indices. Kaito K et al., demonstrated that platelet indices could achieve useful sensitivity and specificity for immune thrombocytopenia and reported relatively strong ROC performance [1], this distinction is important because statistically significant differences between groups do not, by themselves, demonstrate diagnostic accuracy. The present findings should consequently be interpreted as evidence of variation in platelet indices rather than proof that these parameters can independently diagnose the mechanism of thrombocytopenia.

The study has several limitations. The single-centre design limits generalisability. The hyperdestructive and hypoproductive groups were extremely unequal, with only eight hypoproductive patients, limiting the reliability of the mechanism-based comparison. The raw dataset supplied for reanalysis did not contain a participant-level mechanism variable, preventing independent recalculation of the original mechanism-based p-values. The unexpected direction of the MPV difference therefore requires confirmation against the original clinical records and raw laboratory data. In addition, historical preanalytical information, including the exact interval between sample collection and analysis, was not available. These limitations support cautious interpretation and indicate the need for larger, prospectively designed studies using standardised analytical procedures and balanced mechanism-based groups.

The broader literature also supports caution when conventional platelet indices are interpreted as surrogates of thrombopoiesis. Saran K et al., reported higher MPV, PDW, and PCT in hyperdestructive than hypoproductive thrombocytopenia, findings that are directionally different from the mechanism-based MPV result in the present cohort [11]. Nathan SS et al., similarly found higher MPV in hyperdestructive thrombocytopenia, although platelet count and PCT did not differ significantly between groups [24]. These studies therefore strengthen the interpretation that the higher MPV observed in the hypoproductive group is an atypical finding rather than a pattern consistently reproduced across populations.

Bessman JD and Gardner FH observed that MPV decreased with falling platelet counts in sepsis-related thrombocytopenia and increased toward normal before platelet recovery, suggesting that MPV may reflect changes in platelet production during illness [12]. Dumoulin-Lagrange M et al., demonstrated that platelet volume distributions could distinguish defective production from accelerated destruction in selected thrombocytopenic populations [13]. Similarly, increased platelet size in immune thrombocytopenia has been documented experimentally, supporting the concept that platelet size reflects altered platelet production and turnover [14]. However, these studies involved different disease populations and analytical approaches, limiting direct comparison with our heterogeneous hospital-based cohort.

Studies of immature platelet measures provide additional evidence that markers of platelet production may be more informative when specifically directed toward thrombopoiesis. Li J et al., reported excellent discrimination between increased-destruction and decreased-production thrombocytopenia using Immature Platelet Fraction (IPF)-related parameters, with the highest AUC for IPF% [18]. Van De Wyngaert Z et al., also reported that an IPF threshold could predict a peripheral mechanism in selected adults undergoing evaluation for thrombocytopenia [21]. Asghar MB et al., subsequently reported high diagnostic accuracy for IPF in distinguishing peripheral destruction from bone marrow failure [23]. These studies are relevant to the interpretation of our findings because they suggest that direct measures of immature platelet release may provide stronger mechanistic information than conventional platelet indices alone. Nevertheless, IPF was not available in the present study, and therefore no direct comparison can be made.

A 2023 systematic review and meta-analysis by Walle M et al., found that MPV was significantly higher in immune thrombocytopenia than in hypoproductive thrombocytopenia and estimated pooled sensitivity and specificity of approximately 76% and 79%, respectively [22]. This higher-level evidence further indicates that the direction of the mechanism-based MPV difference in the present cohort is atypical. At the same time, the meta-analysis included studies with different analysers, populations, definitions, and thresholds, supporting the need to interpret MPV in the context of the specific analytical system and clinical population. The present study's small hypoproductive subgroup and absence of participant-level mechanism data in the supplied raw dataset make it inappropriate to draw a definitive mechanistic conclusion from the original MPV comparison. Additional work has also demonstrated the importance of standardised platelet-volume measurement, EDTA-related preanalytical effects, analyser-specific reference intervals, and immature platelet parameters in the interpretation of thrombocytopenia [17-23].

Limitation(s)

The present study was conducted at a single-centre and the mechanism-based groups were markedly imbalanced. The hypoproductive subgroup comprised only eight patients, limiting statistical power and increasing uncertainty around the observed MPV difference. The supplied raw dataset did not contain a participant-level mechanism classification, preventing independent recalculation of the original mechanism-based analysis. Analyser-specific and preanalytical factors may also have influenced MPV measurements.

CONCLUSION(S)

The present study demonstrates significant variation in MPV, PDW, P-LCR, and PCT across categories of thrombocytopenia severity. The mechanism-based analysis showed a significant difference in MPV in the original dataset, but the finding was in the opposite direction to that reported in much of the literature and is difficult to interpret because the hypoproductive group contained only

eight patients. Platelet indices should therefore be regarded as adjunctive laboratory parameters rather than standalone diagnostic tests. Larger, balanced studies using standardised analytical and preanalytical procedures and appropriate diagnostic-performance analysis are needed.

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