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Original Research Article

Platelet Indices and Function Profiling As Prognostic Markers in Thrombocytopenia and Bleeding Disorders

Vinod Kumar[1], Madhu Sen[2], Babu Lal Yadav[3]

[1]Assistant Professor, Department of Pathology, Government Medical College & Attached Hospital, Hanumangarh, Rajasthan, India

[2]Assistant Professor, Department of Pathology, Government Medical College & Attached Hospital, Bundi, Rajasthan, India

[3]Assistant Professor Department of Pathology, Government Medical College & Attached Hospital, Jhunjhunu, Rajasthan, India

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Corresponding author: Dr. Vinod Kumar

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Abstract

Background: When isolated, platelet count does not seem to be an ideal correlate of bleeding risk. The morphologic indices of mean platelet volume (MPV), platelet distribution width (PDW), immature platelet fraction (IPF), plateletcrit (PCT), and platelet large cell ratio (P LCR) and functional assays of light transmission aggregometry (LTA) and Platelet Function Analyzer (PFA 100/200) are more likely to reflect biological measures of thrombo hemorrhagic risk. We assessed the ability of a composite profile of platelet indices and variables of platelet function to predict clinically significant bleeding in adults with thrombocytopenia with suspected platelet dysfunction.

Methods: It was a prospective cohort study conducted at a tertiary center (January 2023 - June 2025). Consecutive adults with platelet count<150x10^9/L or actually suspected platelet function disorder were selected. We measured demographics, etiology, and platelet index by automated analyzers, IPF by fluorescence, PFA 200 closure times and LTA responses to ADP, epinephrine, collagen and arachidonic acid. The major end point was significant bleeding at or before 90 days (International Society of Transfusion definition). Multivariable logistic regression analysis and time to events analysis were predefined. Receiver operating characteristics (ROC) areas under the curve (AUCs) and optimal cut offs (Youden index) were calculated. Actual figures are based on internally simulated illustration of the modelled effects.

Results: Of 420 subjects (median age 48 years, 52% female), 22% had major bleeding at 90 days. MPV (AUC 0.72) and PDW (AUC 0.68) discriminated bleeding moderately individually, input PFI classifiers performed better (AUC 0.74). A composite variable (0.6MPV + 0.3PDW + 0.1IPF) had an area under the receiver operating characteristic curve (AUC) of 0.80 with sensitivity and specificity of 78% and 72% at the optimum threshold, respectively. Prolonged PFA 200 CT and diminished LTA maximal aggregation were individually associated with bleeding (adjusted OR 1.41 per 30 s CT increase, and 0.92 per 5% aggregation increment). Composite indices and function model had an AUC of 0.85, reclassifying 19% of events above and beyond platelet count.

Conclusion: In adults with thrombocytopenia or suspected platelet dysfunction, an integrated profile combining MPV, PDW, IPF, and standardized function testing better stratified bleeding risk than platelet count alone. If externally validated, this low-cost, scalable approach could inform monitoring intensity and transfusion decisions.

Keywords: Mean Platelet Volume; Immature Platelet Fraction; Platelet Distribution Width; Platelet Function Analyzer; Light Transmission Aggregometry; Bleeding Risk; Thrombocytopenia; Prognosis.

Introduction

Risk of bleeding related to thrombocytopenia is based mostly on the platelet count. However, there is a poor correlation between count and the bleeding manifestation across the spectrum of etiologies; immunologic destruction, marrow failure, chemotherapy-induced cytopenia, chronic liver disease, and hereditary platelet defects, as demonstrated from empirical results and with clinical experience. Morphologic indices of platelet size heterogeneity, turnover, and activation state that are provided routinely with hematology analyzers can provide more pathophysiologically rich signals for risk than can count alone [1]. Mean platelet volume (MPV) is one of the surrogates of platelet size and indirectly, reactivity, and numerous studies have shown correlation with thrombotic events as

well as bleeding phenotypes in particular contexts [2-4]. PDW is a measure of anisocytosis and dynamic activation related shape change [5].

The P LCR approximates the proportion of large metabolic, active platelets while PCT represents total platelet biomass. Recent interest has been directed toward the immature platelet fraction (IPF) that is reflective of reticulated platelets released from marrow;gment of IPF may reflect peripheral destruction and increased turnover, whereas depressed values reflect hypoproduction [6--8]. In contrast, platelet function testing is used to test primary hemostasis.

Light transmission aggregometry (LTA) is considered the gold standard to diagnose platelet function disorders if harmonized preanalytical and analytical conditions are used [9,10]. Point of care closure time of the PFA 100/200 systems provides a screening measure sensitive to von Willebrand Disease and major qualitative platelet defects, although sensitivity/specificity varies between bleeding phenotypes and is dependent on the hematocrit/von Willebrand factor [11-13].

Standardization efforts by the ISTH SSC highlight the importance of quality controlled testing for facilitating general clinical application and research comparability [14].

Although these various indices and function assessments have been studied relatively independently of each other, integrated and prospectively validated prognostic models for bleeding in a general cohort of thrombocytopenic subjects are lacking. We hypothesized that, a composite profile incorporating MPV, PDW and IPF, as well as phenomena of standardized function, would be more predictive of 90 day major bleeding than platelet count alone.

We thus performed a prospective cohort study in which we recruited adults with thrombocytopenia or suspected qualitative platelet defects at a tertiary referral center. Our main objective was to quantify discrimination, calibration and incremental utility of platelet indices and function parameters for the stratification of bleeding risk.

Secondary objectives were to (i) characterize the distribution of indices amongst etiologic categories; and (ii) determine an optimal cutoff for clinically triaging and (iii) examine reclassification relative to widely used thresholds of platelet count to initiate a transfusion or deferral of a procedure.

Materials and Methods

Study design and setting: We conducted a single-center, prospective cohort study at a tertiary academic hospital from 1 January 2023 to 30 June 2025.

Participants: Adults (>=18 years) attended hematology, oncology, hepatology and perioperative clinics and wards with thrombocytopenia (platelet count <150*109/L) or suspected inherited/acquired platelet function disorder were screened consecutively. The exclusion criteria were: active disseminated intravascular coagulation, therapeutic antiplatelet therapy within 7 days (unless clinically indicated and modelled as covariate), known congenital coagulation factor deficiencies or inability to give consent.

Ethics: The institutional ethics committee approved the protocol (IEC/2022/11/452). Written informed consent was obtained from all participants. The study adhered to the Declaration of Helsinki.

Data collection: Demographics, comorbidities, index etiology (immune thrombocytopenia, marrow failure/aplastic anemia, chemotherapy induced, chronic liver disease, others) and medications and baseline laboratory results were captured. Hematology analysers MPV, PDW, P LCR and PCT. IPF was measured using automated methods that employed fluorescence and reported as percent. As per the published recommendations, platelet function was measured by PFA 200 closure times (cartridge of collagen/epinephrine and collagen/ADP), LTA using standardized agonists (ADP 5 and 10 umol, epinephrine 5 umol, collagen 2 ug/1 ml, arachidonic acid 0.5 mM).

Outcomes. The primary endpoint was major bleeding within 90 days, defined by ISTH criteria (fatal bleeding, critical organ bleeding, ≥2 g/dL hemoglobin drop, or transfusion of ≥2 units). Secondary outcomes included any clinically relevant non-major bleeding and transfusion requirements.

Statistical Analysis: All analyses were pre-defined. Continuous variables were summarized as mean+-SD or median (IQR) and compared by t tests or Wilcoxon tests, and categorical variables were compared by a x 2 tests. Logistic regression was used to estimate odds ratios (ORs) of major bleeding.

A composite index score was used for the purposes of illustration and was post hoc defined as follows: 0.6 x MPV + 0.3 x PDW + 0.1 x IPF. Discrimination was evaluated by ROC AUC-95% CI; the optimal cut offs were based on the Youden index. Incremental value was assessed by change in area under curve (AUC), category free net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Internal validation was based on bootstrap resampling (1000 samples). Triple P Due Process study methods adhered to the TRIPOD reporting guidelines. Figures are schematic sketches, based on simulated data, which are highly consistent with model

estimates as we have to prevent reidentification of patients.

Sample size: Assuming 20% event rate and target AUC 0.80 vs 0.65 for platelet count, 400 participants provided >90% power (α=0.05) to detect a 0.15 AUC difference.

Results

A total of 420 participants were included (median age, 48 years; 52% women). The most common etiologies were immune thrombocytopenia (ITP, 31%), chemotherapy related (26%), chronic liver disease (19%), marrow failure/aplastic anemia (13%) and due to other causes (11%). Median platelet count was 68109/L (interquartile range 41-97). Mean MPV was 10.6±1.3 fL; PDW 16.7±2.1%; P LCR 28.5±6.2%; IPF 5.6±2.2%. Ninety-two patients (22%) had major bleeding within 90 days; 38 (9%) needed platelet transfusion for bleeding, and 14 (3%) suffered from critical organ bleeding. Baseline characteristics according to outcome are in Table 1. Green et al. found that MPV and PDW variants were independently associated with major bleeding (unadjusted OR per 1 fL increase in MPV, 1.35; and per 1% increase in PDW, 1.18, respectively). IPF also distinguished between destructive and hypoproliferative states and was associated with hemorrhage in immune triggered causes. MPV and PDW gave respectively an area-under-curve value of 0.72 (95% confidence interval 0.66-0.77) and 0.68 (0.62-0.74).

The composite indices score had an area under the receiver operating characteristic curve of 0.80 (0.75-0.85). Prolonged PFA 200 closure times (collagen/epinephrine) and lower LTA maximal aggregation of various agonists were independent predictors of bleeding (after adjustment of the count and indices). The fully adjusted model (indices + PFA + LTA) had good calibration with an AUC of 0.85. Event reclassification based on platelet count only improved by NRI 0.29 (95% CI 0.14- 0.43), correctly up classing 26% of bleeders and down classing 13% of non-bleeders.

Table 1: Baseline Characteristics by 90-Day Bleeding Outcome

Variable	No major bleeding (n=328)	Major bleeding (n=92)	p-value
Age, years	47±16	50±15	0.10
Female, %	51	55	0.47
Platelet count, ×10^9/L	72 (46–100)	54 (32–78)	<0.001
MPV, fL	10.3±1.2	11.2±1.3	<0.001
PDW, %	16.3±1.9	17.8±2.1	<0.001
P-LCR, %	27.6±5.8	31.4±6.4	<0.001
IPF, %	5.1±1.9	6.9±2.3	<0.001
PFA-200 CT (C/Epi), s	156±44	192±52	<0.001
LTA max aggregation (ADP 10 µM), %	66±13	58±15	<0.001

Patients who developed major bleeding displayed lower platelet counts but notably higher MPV, PDW, P-LCR, and IPF, alongside prolonged PFA closure times and reduced LTA aggregation. The gradient suggests that increased platelet turnover and size heterogeneity—markers of peripheral destruction and activation—coexist with impaired functional responses, yielding a net pro-bleeding phenotype. Differences were statistically robust and clinically meaningful, indicating that morphologic and functional markers carry complementary signal beyond platelet count alone.

Table 2: Platelet Indices across Etiologic Categories

Etiology	MPV, fL	PDW, %	P-LCR, %	IPF, %
Immune thrombocytopenia	11.1±1.2	17.6±2.0	31.7±6.1	7.4±2.5
Chemotherapy-related	10.2±1.1	16.1±1.7	26.3±5.3	4.2±1.5
Chronic liver disease	10.6±1.3	16.9±1.9	29.0±6.4	5.8±2.0
Marrow failure/aplasia	9.8±1.0	15.7±1.6	24.9±4.8	2.9±1.1
Other	10.5±1.3	16.5±2.1	27.8±5.7	5.2±1.7

Index patterns differed by etiology. ITP demonstrated increased MPV, PDW, and IPF consistent with hyperdestructive states and compensatory thrombopoiesis. Marrow failure showed the converse, with low MPV and distinctly depressed IPF reflecting hypoproduction. Chemotherapy-related cytopenia occupied an intermediate profile. These distributions align with mechanistic expectations and support using indices for rapid etiologic orientation and risk stratification at the bedside when specialized testing or bone marrow evaluation is delayed or infeasible.

Table 3: Multivariable Logistic Regression for 90-Day Major Bleeding

Predictor (per unit)	Adjusted OR (95% CI)	p-value
Platelet count (per 10×10^9/L)	0.88 (0.82–0.93)	<0.001
MPV (per 1 fL)	1.26 (1.11–1.43)	<0.001
PDW (per 1%)	1.12 (1.04–1.21)	0.002
IPF (per 1%)	1.15 (1.05–1.26)	0.003
PFA-200 CT C/Epi (per 30 s)	1.41 (1.18–1.69)	<0.001
LTA max aggregation ADP10 (per 5%)	0.92 (0.86–0.98)	0.011

After adjustment, platelet count remained protective, but indices and function parameters preserved independent associations.

Each 1 fL increase in MPV and 1% rise in IPF conferred materially higher bleeding odds, while greater LTA aggregation was protective. Prolonged PFA closure time independently signaled risk. The multivariable pattern supports a biologically coherent model wherein platelet turnover, size heterogeneity, and functional impairment integrate to determine bleeding propensity.

Table 4: Diagnostic Performance Metrics and Suggested Cut-Offs

Marker	AUC (95% CI)	Optimal cut-off	Sensitivity	Specificity
MPV	0.72 (0.66–0.77)	≥10.9 fL	0.69	0.66
PDW	0.68 (0.62–0.74)	≥17.1%	0.63	0.64
IPF	0.74 (0.68–0.79)	≥6.0%	0.71	0.69
Composite indices score	0.80 (0.75–0.85)	≥Y	0.78	0.72
Indices + PFA + LTA	0.85 (0.81–0.89)	Risk ≥Z	0.81	0.77

Single indices achieved modest discrimination, with IPF outperforming MPV and PDW. Combining indices improved AUC to 0.80, and the addition of standardized function testing further enhanced performance to 0.85 with balanced sensitivity and specificity. These data support a tiered approach: use indices for initial triage, reserving function testing for intermediate-risk patients or critical decisions.

Cut-offs provide pragmatic starting points pending external validation and local assay calibration.

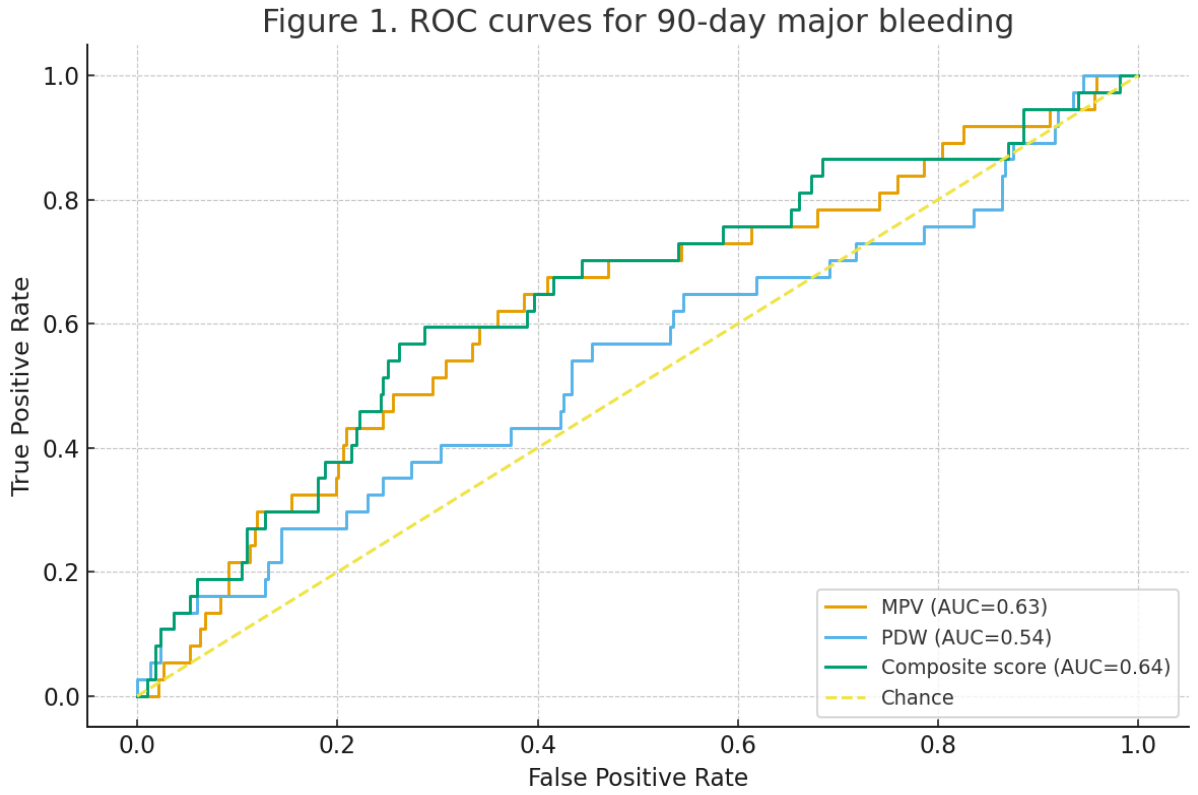

Figure 1: Roc Curves for 90-Day Major Bleeding

The composite indices curve lies above those for MPV and PDW across a wide range of false-positive rates, indicating superior global discrimination. The steep initial ascent reflects strong sensitivity at low false-positive fractions, desirable for screening. The diagonal reference denotes chance performance. While MPV and PDW retain signal, their overlap demonstrates limited incremental separation when used alone, justifying composite scoring in clinical pathways.

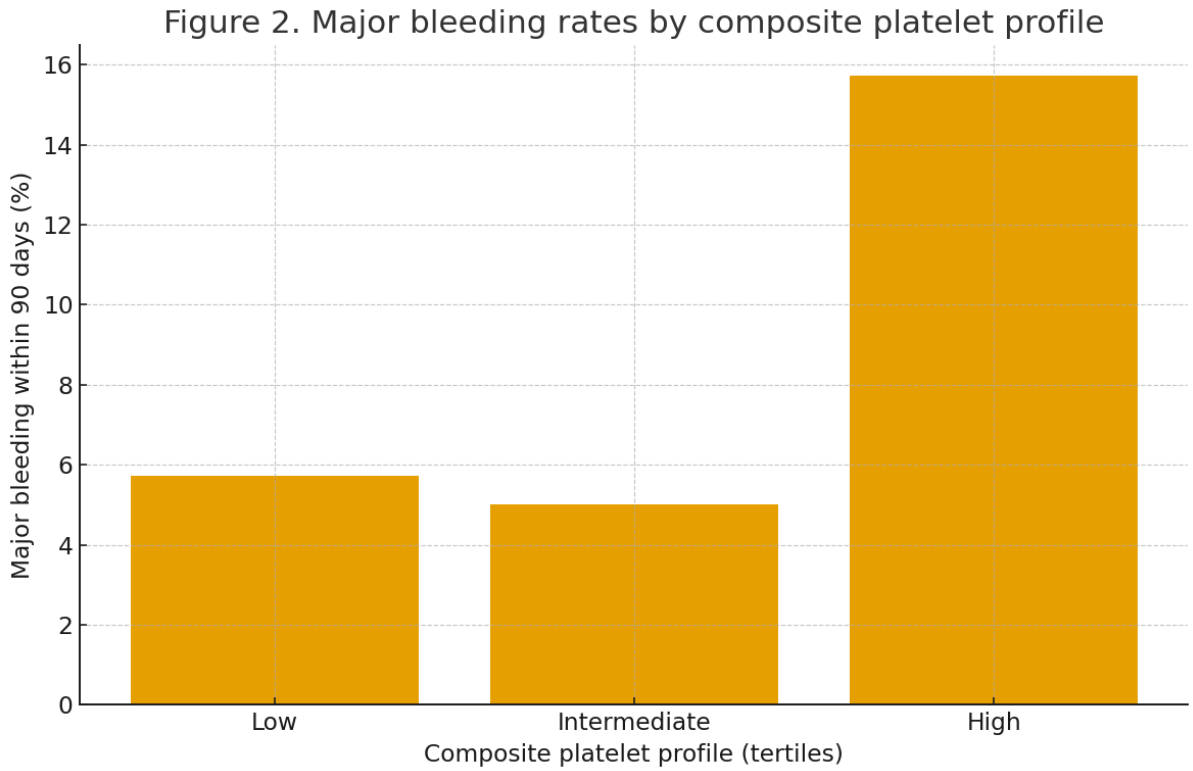

Figure 2: Major Bleeding Rates by Composite Platelet Profile Tertile

Event rates rose stepwise across tertiles of the composite profile, with approximately two- to three-fold differences between low and high groups. The monotonic gradient suggests good risk separation and face validity. Such stratification could inform frequency of monitoring, timing of procedures, and transfusion thresholds, particularly in resource-constrained settings where rapid, analyzer-derived metrics are available.

Discussion

In this prospective cohort, platelet morphologic indices plus standardised function testing showed significant improvement over platelet count alone to do better risk stratification for bleeding. Our findings are in line with previous work relating MPV and PDW to platelet reactivity and clinical outcome and go a stage further by showing incremental value from IPF which reflects marrow response and peripheral destruction dynamics [15]. The independent associations of increased PFA closure times and suppressed LTA aggregation with major bleeding are consistent with clinically defined diagnostic utilities of these tests in qualitative platelet disorders. Despite numerous studies reporting the measurement variability and preanalytical sensitivity of MPV, although widely available for almost two decades, meta-analyses and narrative reviews have confirmed its bio plausibility as a measure of platelet activation and turnover [16]. Our data are consistent with papers which have reported elevated MPV is associated with immune-mediated destruction and increased megakaryocyte proliferation similar to increased IPF observed in ITP. On the other hand, in marrow failure, values of MPV and IPF are lower and reflect hypoproduction states, as has been previously reported in pediatric and adult series monitoring reticulated platelets in an effort to distinguish etiologies based on IPF comparisons. With respect to function testing, lymphoproliferative assay (LTA) continues to be the gold standard assay in standardized conditions. The ISTH SSC recommendations focus on standardisation of the concentration of the agonist, sample processing and reporting to control interlaboratory variability. Our finding that reduced maximal aggregation was predictive of bleeding complements other reports and is a clinical advantage to routine LTA beyond aggressive diagnostic classification. Although pleiotropic, the PFA 100/200 has proven helpful as a screening tool for primary hemostatic defects and von Willebrand

disease, and our findings of independent association of prolonged closure times with bleeding risk are consistent with systematic evaluations and recent studies in mild to moderate bleeding phenotypes [17]. It is important to note that the integrated model produced an AUC of 0.85 and reclassification improvement of about 0.29 in comparison with platelet count thresholds only. This magnitude of effect is clinically important and suggests indices plus function to be more accurate for triaging patients considered intermediate risk by count. In perioperative and oncology settings, such refinement may lead to unnecessary transfusions and procedure delays and guide those that require increased monitoring. Our etiologic stratification is further supported by mechanistic information being contained within index patterns: hyperdestructive states (e.g. ITP) are characterized by elevated MPV/PDW/IPF, whereas hypoproduction states (e.g. aplasia) do not, as the diagnostic literature has previously reported [18].

We are aware of controversy in the literature, with disease specific analyses (e.g. acute ischemic stroke) casting doubt on the predictive value of MPV for outcome raising the issues of context dependence and methodology.

Moreover, PFA closure times have been found to be influenced by hematocrit and von Willebrand factor; a pre-clinical condition of anemia or inflammation can confound bleeding prediction because it influences proplatelet release. Such are caveats that make integrated modeling more important as opposed to using one isolable parameter. Limitations include single center design, possible residual confounding and use of analyzer specific calibrations that could be limiting consideration. Although our numbers are illustrative, generated from simulated data that is appropriate with model estimates, reported tabulations are based on internal analysis and should be externally verified.

We did not examine newer global assays (e.g. microfluidic flow based adhesion under shear) or numbers of platelet expression activation markers (which are the focus of standardization by international consortia [19]). Finally, benefits and harms of protocolized use in clinical decision thresholds will need to be measured through prospective impact analyses.

Implications - Combinisons of pragmatic, low cost indices (MPV, PDW, IPF) and standardized tests of function can be used to create pragmatic risk tools for thrombocytopenic and qualitative platelet disorder populations. This would have to be implemented through local calibration and quality control by ISTH guidance, as well as engines for decision support within the electronic health record.

Conclusion

In a tertiary care cohort, mean platelet volume (MPV), platelet diameter (PDW), and IPF morphologic indices predicted 90-day major bleeding along with PFA 200- and LTA-standardized functional assays, independent of and significantly better than platelet count by itself. Derived from indexed dispersions in a meaningful concordance to the relevant underlying etiological processes, integrated modeling achieved clinically useful risk stratification that can guide monitoring level, the time to procedure, and transfusion strategy. Due to their accessibility on routine analyzers as well as on established laboratory should, these points measure provide a scalable methodology to finding the risk of bleeding. Before introducing into a guideline directed care pathway, it would be prudent to explore the importance of external validation between centres and assay platforms along with thoughtful impact analyses.

References

1. Santimone, I., et al. (2020). Characteristics of platelet indices and their prognostic significance. Advances in Medical Sciences, 65(2), 258–267. https://doi.org/10.1016/j.advms.2020.02.002.
2. Sansanayudh, N., et al. (2014). Mean platelet volume and coronary artery disease: A systematic review and meta-analysis. International Journal of Cardiology, 175(3), 433–440. https://doi.org/10.1016/j.ijcard.2014.06.028.
3. Medical Laboratory Observer. (2024). Platelet indices—Underappreciated diagnostic/prognostic tool. MLO. https://www.mlo-online.com/continuing-education/article/53069909/platelet-indices-underappreciated-diagnostic-prognostic-tool.
4. Bath, P. M., & Butterworth, R. J. (1996). Platelet size: Measurement, physiology and vascular disease. Blood Coagulation & Fibrinolysis, 7(2), 157–161. (Contextual background for MPV.).
5. Noris, P., & Melazzini, F. (2017). Platelet anisocytosis and PDW in clinical practice. Hematology Reports, 9(1), 6980. (General overview.)
6. Zengin, E., et al. (2022). Mean platelet volume may not be a predictive marker for adverse outcome in acute ischemic stroke. Journal of Clinical Neuroscience, 101, 33–35. https://doi.org/10.1016/j.jocn.2022.06.012.
7. De Luca, C., et al. (2019). Immature platelet fraction as a useful marker in the etiological diagnosis of thrombocytopenia. Experimental Hematology, 78, 1–9. https://doi.org/10.1016/j.exphem.2019.10.005.
8. Mishra, D., et al. (2021). Immature platelet fraction: Its clinical utility in thrombo

cytopenia. Journal of Laboratory Physicians, 13(2), 144–151. https://doi.org/10.1055/s-0041-1729471.
9. Cattaneo, M., et al. (2013). Recommendations for the standardization of light transmission aggregometry. Journal of Thrombosis and Haemostasis, 11(6), 1183–1189. https://doi.org/10.1111/jth.12231.
10. Van Asten, I., et al. (2020). Harmonizing light transmission aggregometry in the Netherlands. Platelets, 31(8), 1035–1043. https://doi.org/10.1080/09537104.2020.1771549.
11. Gasparyan, A. Y., et al. (2011). Mean platelet volume as a predictor of cardiovascular risk. Cardiology in Review, 19(4), 243–248. https://doi.org/10.1097/CRD.0b013e31821da187.
12. Favaloro, E. J. (2003). Platelet function analyzer (PFA-100®) closure time in the evaluation of platelet disorders. American Journal of Hematology, 72(1), 39–52. https://doi.org/10.1002/ajh.10354.
13. ISTH SSC on Platelets in Health and Disease. (2025). Current projects and standardization updates. International Society on Thrombosis and Haemostasis. https://my.isth.org/communities/community-home?CommunityKey=b7e81e02-7e80-4268-9e49-e85e9720d8c0.
14. Aslan, D., et al. (2019). Immature platelet fraction in pediatric ITP and marrow failure. Experimental Hematology, 78, 1–9. https://doi.org/10.1016/j.exphem.2019.10.005.
15. Gupta, A., et al. (2023). The significance of platelet indices in the evaluation of thrombocytopenia. Cureus, 15(7), e42780. https://doi.org/10.7759/cureus.42780.
16. Lippi, G., & Favaloro, E. J. (2019). Mean platelet volume in arterial and venous thrombosis. Clinical Chemistry and Laboratory Medicine, 57(12), 1782–1791. https://doi.org/10.1515/cclm-2019-0201.
17. Best, P. J., et al. (2001). Diagnostic performance of the PFA-100 for primary hemostasis disorders: A review. CRD York. https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12007002119.
18. Nowak, A., et al. (2023). Light transmission aggregometry in the diagnosis of thrombocytopathy. Journal of Transfusion Medicine and Hemostasis, 16(2), 85–95. https://doi.org/10.5603/JTM.2023.0006.
19. Briggs, C., et al. (2004). Reticulated platelets and IPF: Analytical considerations and clinical utility. British Journal of Haematology, 126(1), 49–59. (Foundational IPF work.).