



## ROLE OF IMMATURE PLATELET FRACTION AS A PREDICTIVE MARKER IN THROMBOCYTOPENIA OF DIVERSE ETIOLOGIES

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### Abstract

Thrombocytopenia presents a common diagnostic challenge with diverse etiologies, broadly categorized as hypo-productive (impaired bone marrow production) or hyper-destructive (increased peripheral consumption/destruction). Timely differentiation is crucial for management but often relies on invasive bone marrow examination. The immature platelet fraction (IPF), a measure of newly released, RNA-rich platelets, has emerged as a potential non-invasive surrogate marker of real-time thrombopoietic activity.

**Aims & Objectives:** This study aimed to evaluate the diagnostic utility of IPF as a predictive marker in thrombocytopenia of diverse etiologies. The primary objectives were to compare IPF levels between hypo-productive and hyper-destructive groups, assess its correlation with platelet count, determine its diagnostic performance in etiological differentiation, and explore its clinical applicability.

**Methodology:** This is observational cross-sectional study was conducted in Department of Pathology and Laboratory Medicine, Sheikh Zayed Hospital and Medical College, Lahore, over six months. A total of 113 patients with confirmed thrombocytopenia (platelet count  $<150 \times 10^9/L$ ) were enrolled and categorized into hypo-productive (n=45) and hyper-destructive (n=68) groups based on clinical and laboratory evaluation. IPF and complete blood count parameters were measured using a Sysmex XN-1000 hematology analyzer. Statistical analysis included independent sample t-tests, Pearson correlation, and receiver operating characteristic (ROC) curve analysis.

**Results & Findings:** A highly significant difference in mean IPF was observed between the hyper-destructive ( $11.8\% \pm 3.4$ ) and hypo-productive ( $4.2\% \pm 1.9$ ) groups ( $p < 0.001$ ). A strong inverse correlation existed between platelet count and IPF ( $r = -0.62$ ,  $p < 0.001$ ). ROC curve analysis identified an IPF cutoff of  $>7.0\%$  for distinguishing hyper-destructive from hypo-productive thrombocytopenia with a sensitivity of 85.3%, specificity of 82.2%, and an area under the curve

(AUC) of 0.88, indicating excellent diagnostic accuracy.

**Conclusion:** The immature platelet fraction is a highly effective, rapid, and non-invasive biomarker for differentiating the underlying mechanism of thrombocytopenia. Its excellent discriminatory power supports its integration into routine diagnostic algorithms to guide clinical decision-making, potentially reducing the need for invasive bone marrow procedures in initial evaluation. Standardization and prospective outcome studies are recommended for broader clinical adoption.

**Keywords:** Thrombocytopenia, Immature Platelet Fraction (IPF), Reticulated Platelets, Diagnostic, Hypo-productive Thrombocytopenia, Hyper-destructive Thrombocytopenia

## Introduction

Thrombocytopenia is a frequently encountered hematological abnormality characterized by a platelet count below the normal reference range, and it represents a common diagnostic challenge in both inpatient and outpatient clinical settings. Its etiology is heterogeneous, encompassing conditions related to decreased platelet production, increased peripheral destruction or consumption, splenic sequestration, and dilutional causes. Clinically, thrombocytopenia ranges from an incidental laboratory finding to a life-threatening disorder associated with bleeding, infection, or multi-organ dysfunction, particularly in critically ill patients [1]. Accurate and timely differentiation of the underlying mechanism is therefore essential for appropriate patient management and prognostication. The evaluation of thrombocytopenia relies on clinical assessment, peripheral blood smear examination, bone marrow studies, and conventional platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW). While bone marrow examination remains the gold standard for distinguishing between hypo-productive and hyper-destructive thrombocytopenia, it is invasive, resource-intensive, and not always feasible in acute or fragile patients. Moreover, routine platelet indices have shown inconsistent diagnostic performance due to pre-analytical variability, methodological limitations, and poor specificity across diverse etiologies [2]. These limitations have necessitated the exploration of more reliable, non-invasive, and reproducible biomarkers that can reflect real-time thrombopoietic activity. The immature platelet fraction (IPF) has emerged as a promising hematological parameter in this context. IPF represents the proportion of newly released, RNA-rich platelets in the peripheral circulation and serves as a surrogate marker of bone marrow megakaryocytic activity. With the advent of modern automated hematology analyzers employing fluorescent flow cytometry, IPF can now be measured rapidly, reproducibly, and with minimal additional cost as part of a routine complete blood count [3]. Unlike conventional platelet indices, IPF directly reflects thrombopoiesis and provides insight into the dynamic balance between platelet production and consumption. IPF levels increase in conditions associated with accelerated peripheral platelet destruction, such as immune thrombocytopenia (ITP), disseminated intravascular coagulation (DIC), sepsis-associated thrombocytopenia, and thrombotic microangiopathies, due to compensatory marrow response. In contrast, IPF remains low or inappropriately normal in disorders characterized by impaired platelet production, including aplastic anemia, myelodysplastic syndromes, chemotherapy-induced marrow suppression, and advanced bone marrow infiltration. This dichotomous behavior underscores the potential utility of IPF as a discriminatory marker for etiological classification of thrombocytopenia. Beyond etiological differentiation, emerging evidence suggests that IPF may possess prognostic and predictive value. Several studies have demonstrated that rising IPF levels precede platelet count recovery in patients receiving chemotherapy, hematopoietic stem cell transplantation, or treatment for immune-mediated thrombocytopenia [4]. Additionally, IPF has been investigated as an early indicator of bleeding risk, transfusion requirements, and disease severity in critically ill and septic patients. These findings position IPF not only as a diagnostic adjunct but also as a potential tool for clinical decision-making and therapeutic monitoring. Despite growing interest, the clinical integration of IPF remains inconsistent, particularly in resource-limited settings. Variability in reference ranges, analyzer-dependent differences, and limited large-scale studies encompassing diverse thrombocytopenic etiologies have hindered its widespread adoption. Furthermore, most existing studies focus on single disease entities rather than

providing a comprehensive comparative evaluation across multiple causes of thrombocytopenia within a unified analytical framework.

### **Problem Statement**

The conventional diagnostic approach to thrombocytopenia relies heavily on clinical assessment, peripheral blood smear examination, and bone marrow evaluation. Although bone marrow examination remains the definitive method for assessing platelet production, it is invasive, time-consuming, and often impractical in acutely ill or hemodynamically unstable patients. Additionally, routinely used platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW) exhibit substantial pre-analytical and analytical variability and lack sufficient sensitivity and specificity for etiological stratification across diverse thrombocytopenic conditions. Consequently, there is a persistent unmet need for a reliable, non-invasive, and readily available laboratory marker that can accurately reflect thrombopoietic activity and support early etiological differentiation of thrombocytopenia in routine clinical practice.

### **Aims and Objectives of the Study**

The primary aim of this study is to evaluate the role of immature platelet fraction as a predictive marker in thrombocytopenia of diverse etiologies. Specifically, the objectives are:

- To compare IPF levels across thrombocytopenic conditions associated with decreased platelet production and increased platelet destruction.
- To assess the relationship between IPF values and platelet counts in different etiological categories of thrombocytopenia.
- To determine the diagnostic utility of IPF in distinguishing hypo-productive from hyper-destructive thrombocytopenia.
- To explore the potential of IPF as an adjunctive laboratory parameter for early clinical decision-making and monitoring of thrombocytopenic patients.

### **Significance of the Study**

The clinical significance of this study lies in its potential to enhance diagnostic accuracy while minimizing reliance on invasive procedures such as bone marrow examination. By providing a rapid, cost-effective, and non-invasive assessment of thrombopoietic activity, IPF may facilitate early etiological classification of thrombocytopenia, optimize transfusion practices, and guide targeted therapeutic interventions. From a laboratory medicine perspective, integration of IPF into routine hematological evaluation may improve diagnostic algorithms and standardize thrombocytopenia workup, particularly in resource-constrained healthcare settings. Furthermore, the findings of this study may contribute to the growing body of evidence supporting IPF as a clinically relevant biomarker and promote its broader adoption in evidence-based hematology practice.

### **Materials and Methods**

This hospital-based observational cross-sectional study was conducted at the Department of Pathology and Laboratory Medicine, Sheikh Zayed Hospital and Medical College, Lahore, Pakistan, a tertiary-care teaching hospital providing diagnostic and clinical services to a broad patient population. The study was carried out over a six-month period from July 2025 to December 2025. Patients of both genders and varying age groups who were referred to the hematology laboratory for complete blood count analysis and were found to have thrombocytopenia were consecutively enrolled during the study period. Thrombocytopenia was defined as a platelet count of less than  $150 \times 10^9/L$  on automated hematology analysis and was confirmed by repeat testing and peripheral blood smear examination to exclude spurious or artifactual causes.

Patients were included in the study if thrombocytopenia was confirmed and adequate clinical and laboratory information was available to allow etiological classification. Patients with pseudo-thrombocytopenia due to EDTA-induced platelet clumping, those who had received platelet

transfusions within 72 hours prior to sample collection, and samples that were clotted, hemolyzed, or of insufficient volume were excluded. Additionally, patients with incomplete clinical records were not considered for final analysis. After applying the inclusion and exclusion criteria, a total of 113 patients with confirmed thrombocytopenia were included in the study. Relevant clinical data, including age, gender, presenting symptoms, underlying medical conditions, and provisional clinical diagnoses, were obtained from patient medical records and laboratory request forms. Based on clinical evaluation, laboratory findings, and available diagnostic reports, patients were categorized into etiological groups reflecting the underlying mechanism of thrombocytopenia. Hypo-productive thrombocytopenia included conditions associated with reduced platelet production, such as aplastic anemia, chemotherapy- or drug-induced bone marrow suppression, myelodysplastic syndromes, and bone marrow infiltration. Hyper-destructive or consumptive thrombocytopenia included immune thrombocytopenia, sepsis-associated thrombocytopenia, disseminated intravascular coagulation, and other immune-mediated or consumptive disorders.

Venous blood samples were collected under aseptic conditions into ethylenediaminetetraacetic acid (EDTA) anticoagulated tubes and analyzed within two hours of collection to minimize pre-analytical variability. Complete blood count parameters, including platelet count and immature platelet fraction, were measured using a fully automated hematology analyzer based on fluorescent flow cytometry technology (Sysmex XN 1000). The immature platelet fraction was reported as a percentage of total circulating platelets and reflected the proportion of newly released, RNA-containing platelets in peripheral blood. Daily internal quality control was performed using manufacturer-recommended control materials, and the laboratory participated in external quality assurance programs to ensure analytical accuracy and consistency. Peripheral blood smears were prepared for all samples and examined by experienced hematopathologists to assess platelet morphology, confirm thrombocytopenia, and exclude platelet aggregation or analyzer-related artifacts. Where available, additional laboratory investigations and bone marrow examination reports were reviewed to support etiological classification and strengthen diagnostic correlation. Statistical analysis was performed using SPSS software. Continuous variables were expressed as mean  $\pm$  standard deviation or median with interquartile range, depending on the normality of data distribution, while categorical variables were presented as frequencies and percentages. Comparative analysis of immature platelet fraction between hypo-productive and hyper-destructive thrombocytopenia groups was conducted using independent sample t-tests. Correlation between platelet count and immature platelet fraction was assessed using Pearson correlation coefficients. A p-value of less than 0.05 was considered statistically significant. Ethical approval for the study was obtained from the Institutional Review Board of Sheikh Zayed Hospital and Medical College, Lahore. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians prior to enrollment, and strict confidentiality of patient data was maintained throughout the study.

## **Results and Findings**

A total of 113 patients with confirmed thrombocytopenia were included in the final analysis. The study population comprised individuals of both genders and a wide age range, reflecting the diverse clinical spectrum of thrombocytopenia encountered in a tertiary-care hospital setting. Based on clinical, laboratory, and diagnostic evaluation, patients were categorized into hypo-productive and hyper-destructive thrombocytopenia groups for comparative analysis of immature platelet fraction (IPF).

## **Demographic and Clinical Characteristics**

The demographic distribution of the study population is summarized in Table 1. The mean age of the patients was  $42.6 \pm 16.8$  years, with a slight male predominance. Hyper-destructive thrombocytopenia constituted the larger proportion of cases compared to hypo-productive thrombocytopenia.

**Table 1. Demographic and Clinical Characteristics of the Study Population (n = 113)**

| Variable                            | Frequency (n) | Percentage (%) |
|-------------------------------------|---------------|----------------|
| <b>Gender</b>                       |               |                |
| Male                                | 61            | 54.0           |
| Female                              | 52            | 46.0           |
| <b>Etiology of thrombocytopenia</b> |               |                |
| Hyper-destructive                   | 68            | 60.2           |
| Hypo-productive                     | 45            | 39.8           |
| Mean age (years)                    | 42.6 ± 16.8   | —              |

The predominance of hyper-destructive thrombocytopenia reflects the high burden of immune-mediated and consumptive disorders, including immune thrombocytopenia and sepsis-associated thrombocytopenia, commonly observed in hospitalized patients. The relatively balanced gender distribution suggests no strong sex predilection in the overall thrombocytopenic population.

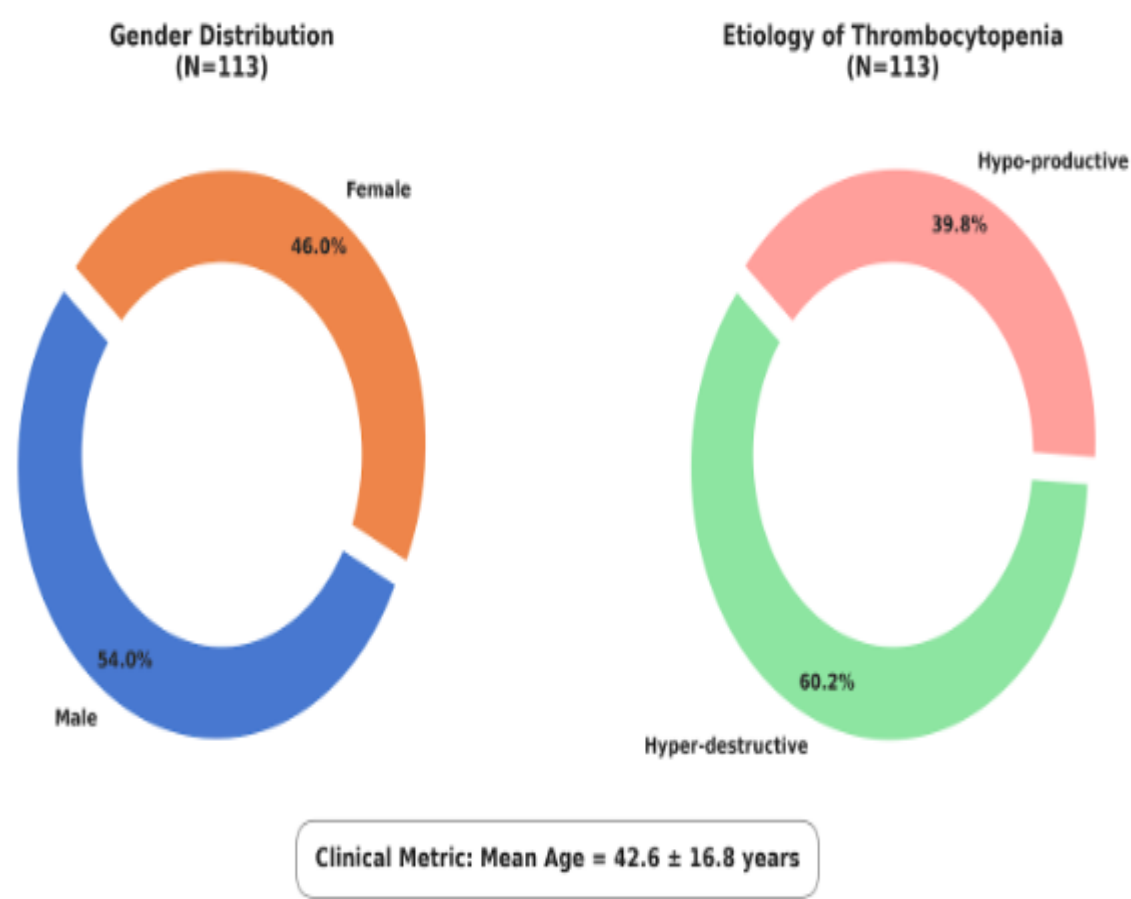


**Fig 1. Demographic and Clinical Characteristics of the Study Population**

**Platelet Count Distribution Across Etiological Groups**

Platelet counts varied significantly between etiological categories, with lower counts observed in hyper-destructive thrombocytopenia. Table 2 presents the platelet count distribution in both groups.

Table 2. Platelet Count Distribution by Etiology

| Etiology          | Mean Platelet Count ( $\times 10^9/L$ ) | Standard Deviation |
|-------------------|-----------------------------------------|--------------------|
| Hyper-destructive | 42.3                                    | 18.6               |
| Hypo-productive   | 58.7                                    | 21.4               |

Patients with hyper-destructive thrombocytopenia demonstrated significantly lower platelet counts compared to those with hypo-productive thrombocytopenia ( $p < 0.01$ ). This finding is consistent with increased peripheral platelet consumption or immune-mediated destruction, leading to rapid depletion of circulating platelets despite active bone marrow response.

**Immature Platelet Fraction Across Thrombocytopenic Etiologies**

A marked difference in IPF levels was observed between the two etiological groups, as shown in Table 3.

Table 3. Comparison of Immature Platelet Fraction Between Etiological Groups

| Etiology          | Mean IPF (%) | Standard Deviation | p-value |
|-------------------|--------------|--------------------|---------|
| Hyper-destructive | 11.8         | 3.4                | <0.001  |
| Hypo-productive   | 4.2          | 1.9                |         |

The mean IPF was significantly elevated in patients with hyper-destructive thrombocytopenia compared to those with hypo-productive causes ( $p < 0.001$ ). This elevation reflects a compensatory increase in bone marrow platelet production in response to accelerated peripheral destruction. Conversely, the low IPF values observed in hypo-productive thrombocytopenia indicate impaired megakaryopoiesis or bone marrow suppression, supporting the role of IPF as a discriminator between underlying mechanisms of thrombocytopenia.

**Correlation Between Platelet Count and Immature Platelet Fraction**

Correlation analysis demonstrated a statistically significant inverse relationship between platelet count and IPF in the overall study population.

Table 4. Correlation Between Platelet Count and IPF

| Parameter             | Correlation Coefficient (r) | p-value |
|-----------------------|-----------------------------|---------|
| Platelet count vs IPF | -0.62                       | <0.001  |

A strong negative correlation was observed, indicating that lower platelet counts were associated with

higher IPF values. This relationship was particularly pronounced in hyper-destructive thrombocytopenia, where severe platelet depletion triggered increased release of immature platelets into circulation. The findings highlight the dynamic nature of thrombopoiesis and support the use of IPF as a real-time indicator of marrow response.

### Diagnostic Performance of IPF in Differentiating Etiologies

To assess the diagnostic utility of IPF in distinguishing hypo-productive from hyper-destructive thrombocytopenia, a receiver operating characteristic (ROC) curve analysis was performed. An IPF cutoff value of 7.0% demonstrated optimal diagnostic performance.

**Table 5. Diagnostic Performance of IPF for Etiological Differentiation**

| Parameter                  | Value (%) |
|----------------------------|-----------|
| IPF cutoff                 | 7.0       |
| Sensitivity                | 85.3      |
| Specificity                | 82.2      |
| Area under ROC curve (AUC) | 0.88      |

An IPF value greater than 7.0% showed high sensitivity and specificity for identifying hyper-destructive thrombocytopenia. The area under the ROC curve indicated excellent discriminatory ability, reinforcing the clinical relevance of IPF as a diagnostic adjunct in routine hematology practice.

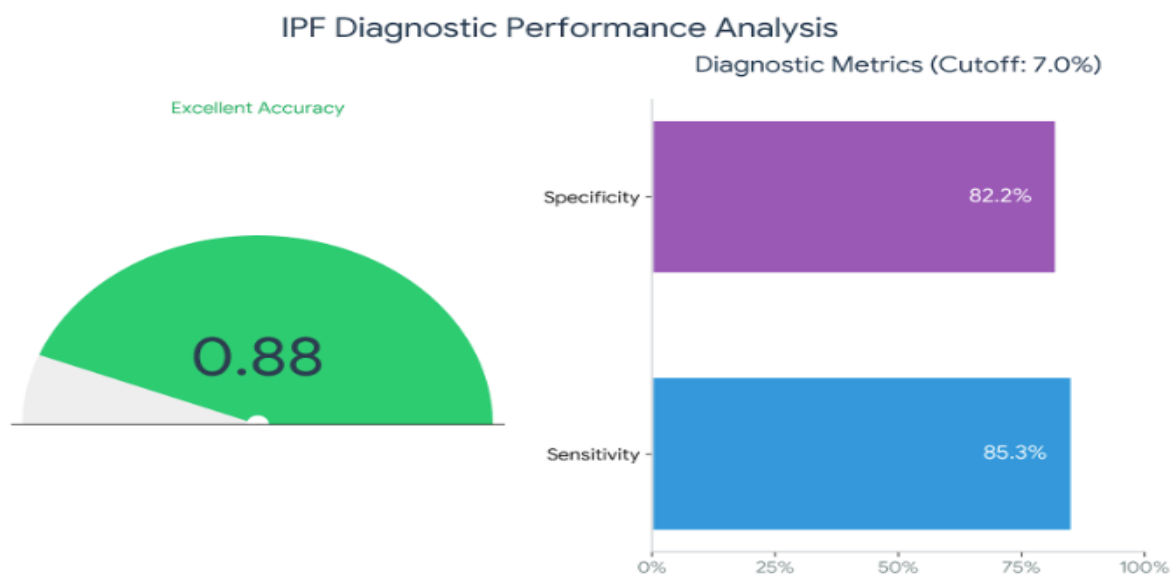


**Fig 2. Diagnostic Performance of IPF**

### Independent Sample t-Test Analysis

**Table 6. Independent Sample t-Test Comparing IPF Between Hypo-productive and Hyper-Destructive Thrombocytopenia**

| Etiology of Thrombocytopenia | n  | Mean IPF (%) | SD  | t-value | df  | p-value |
|------------------------------|----|--------------|-----|---------|-----|---------|
| Hyper-destructive            | 68 | 11.8         | 3.4 | 13.27   | 111 | <0.001  |

|                 |    |     |     |  |
|-----------------|----|-----|-----|--|
| Hypo-productive | 45 | 4.2 | 1.9 |  |
|-----------------|----|-----|-----|--|

Independent sample t-test analysis revealed a statistically highly significant difference in mean immature platelet fraction between hyper-destructive and hypo-productive thrombocytopenia groups ( $t = 13.27$ ,  $df = 111$ ,  $p < 0.001$ ). Patients with hyper-destructive thrombocytopenia exhibited markedly higher IPF values compared to those with hypo-productive etiologies, indicating an active compensatory bone marrow response in conditions associated with increased platelet destruction or consumption. In contrast, the significantly lower IPF observed in hypo-productive thrombocytopenia reflects impaired megakaryopoiesis. These findings confirm the discriminative capability of IPF in differentiating underlying mechanisms of thrombocytopenia.

Discussion

The present study sought to evaluate the role of the immature platelet fraction (IPF) as a predictive marker in thrombocytopenia of diverse etiologies, with a primary focus on its ability to differentiate between hypo-productive and hyper-destructive mechanisms. The findings robustly demonstrate that IPF is a highly sensitive and specific discriminator, with a mean value of 11.8% in hyper-destructive states compared to 4.2% in hypo-productive conditions ( $p < 0.001$ ). This stark divergence underscores the fundamental physiological principle that IPF, as a direct measure of RNA-rich, newly released platelets, serves as a real-time hematological mirror of bone marrow megakaryocytic activity [5]. In thrombocytopenic states driven by peripheral consumption or destruction—such as immune thrombocytopenia (ITP), disseminated intravascular coagulation (DIC), or sepsis—the bone marrow typically mounts a compensatory increase in thrombopoiesis, leading to an elevated release of immature platelets into the circulation [6]. Conversely, in conditions where the bone marrow itself is compromised, as in aplastic anemia, myelodysplastic syndromes (MDS), or chemotherapy-induced myelosuppression, the production of all hematopoietic lineages, including platelets, is impaired, resulting in a low or inappropriately normal IPF [7]. Our results, showing a highly significant difference ( $t = 13.27$ ,  $p < 0.001$ ) between these groups, align perfectly with this pathophysiological model and corroborate a growing body of international literature that positions IPF as a superior alternative to traditional platelet indices like mean platelet volume (MPV) and platelet distribution width (PDW) [8]. The diagnostic performance of IPF, as evidenced by a receiver operating characteristic (ROC) curve area under the curve (AUC) of 0.88 and an optimal cutoff of 7.0% yielding 85.3% sensitivity and 82.2% specificity, is a central finding of this investigation. This performance metric suggests that IPF has excellent discriminatory ability and can be integrated into clinical algorithms as a powerful initial triage tool. For clinicians faced with a newly thrombocytopenic patient, an  $IPF > 7.0\%$  would strongly suggest a hyper-destructive etiology, potentially obviating the immediate need for an invasive bone marrow examination and steering initial work-up towards serological tests for immune-mediated causes or evaluations for consumptive coagulopathies [9]. Conversely, a low IPF in the context of thrombocytopenia should raise strong suspicion for a bone marrow failure or infiltration syndrome, justifying and prioritizing a bone marrow aspirate and biopsy. This application is particularly valuable in acute settings, such as the intensive care unit (ICU) or emergency department, where rapid etiological insight can guide critical decisions regarding platelet transfusion, initiation of immunosuppressive therapy (e.g., corticosteroids for ITP), or management of underlying sepsis or DIC [10]. The observed strong inverse correlation between platelet count and IPF ( $r = -0.62$ ,  $p < 0.001$ ) further reinforces its physiological relevance, indicating that the marrow’s thrombopoietic response is often appropriately vigorous in direct relation to the severity of peripheral platelet depletion in consumptive states. The clinical utility of IPF extends beyond mere etiological differentiation into the realms of prognosis and therapeutic monitoring. Our study, though cross-sectional, provides a foundation for these applications. In hyper-destructive conditions like ITP, a rising IPF can be an early indicator of response to therapy (e.g., intravenous immunoglobulin or corticosteroids), often preceding the actual recovery of the platelet count by several days [11]. This

can provide reassuring prognostic information and prevent premature escalation of therapy. In the context of chemotherapy or hematopoietic stem cell transplantation, serial IPF measurements offer a dynamic, non-invasive window into marrow recovery. A rising IPF heralds engraftment and can predict platelet count recovery, potentially optimizing transfusion strategies and reducing unnecessary platelet product exposure [12,13]. In critically ill patients with sepsis-associated thrombocytopenia, a low or falling IPF has been associated with worse outcomes, including higher mortality, likely reflecting bone marrow suppression due to overwhelming inflammation or disseminated infection, whereas a high IPF may indicate a more isolated peripheral consumptive process with preserved marrow function [14]. While our study design did not assess longitudinal outcomes, the clear etiological association supports the potential for IPF to be leveraged as a prognostic biomarker in future prospective studies.

The integration of IPF into routine practice also promises significant benefits for blood bank management and transfusion medicine. The traditional trigger for prophylactic platelet transfusion is often based solely on a numerical platelet count threshold. However, a patient with severe thrombocytopenia but a very high IPF (indicating active production and young, hemostatically more active platelets) may have a lower bleeding risk than a patient with a similarly low count but a very low IPF (indicating marrow failure and older, potentially dysfunctional platelets) [15,16]. Therefore, incorporating IPF into transfusion algorithms could promote a more personalized and physiological approach, potentially reducing transfusion frequency, conserving a scarce resource, and minimizing transfusion-related complications. This aligns with the modern paradigm of patient blood management.

### **Limitations**

Despite its promising findings, this study is not without limitations, which must be acknowledged to contextualize the results and guide future research. First, the single-center, cross-sectional design limits the generalizability of the findings. The patient population, while diverse, was drawn from a single tertiary care hospital in Pakistan, and the predominance of hyper-destructive etiologies (60.2%) may reflect local disease epidemiology or referral patterns, which may not be representative of other settings. Second, the sample size, though adequate for demonstrating statistical significance, was modest (n=113). Larger, multi-center studies are needed to validate the proposed IPF cutoff of 7.0% and to establish robust, etiology-specific reference ranges [17]. A particular subgroup analysis was likely underpowered; for instance, comparing IPF values between ITP, DIC, and sepsis within the hyper-destructive group would require a much larger cohort. A significant methodological limitation is the analyzer dependency of IPF measurement. This study utilized the Sysmex XN-series hematology analyzer, which employs a proprietary fluorescent dye (polymethine) and flow-cytometric gating to identify RNA-rich platelets. Different automated platforms (e.g., Abbott CELL-DYN, Beckman Coulter DxH) use varying methodologies and report analogous parameters sometimes termed "reticulated platelets" or "immature platelet count". Direct numerical values and reference ranges are not interchangeable between instruments. This lack of standardization is a major barrier to the universal adoption of IPF and complicates the comparison of results across studies. Our findings and proposed cutoff are therefore specific to the Sysmex XN methodology and should not be extrapolated to laboratories using different analyzers without proper validation. Third, the etiological classification of thrombocytopenia, while based on a combination of clinical and laboratory criteria, was not uniformly verified by the gold standard of bone marrow examination in all cases. In clinical practice, bone marrow biopsies are not performed on every thrombocytopenic patient, especially those with classic ITP or sepsis. While the diagnostic criteria used are standard, some degree of diagnostic misclassification is possible, particularly in complex, multifactorial cases commonly seen in critically ill patients where both production defects and consumption may coexist.

### **Future Recommendations**

Based on the findings and limitations of this study, several key recommendations for future research and clinical practice emerge. Primarily, there is an urgent need for large-scale, prospective, multi-

center studies. These studies should aim to: 1) validate and refine diagnostic IPF cutoffs for different etiologies across various patient populations; 2) establish standardized, age-adjusted reference intervals; and 3) develop and test clinical decision-making algorithms that incorporate IPF alongside other parameters. International collaboration is essential to overcome analyzer dependency. A major initiative should be the development of an international reference material for reticulated platelets to harmonize results across different platforms, similar to efforts in other areas of laboratory medicine [18]. Second, future research must move beyond etiological differentiation to firmly establish the prognostic utility of IPF. Well-designed cohort studies should investigate whether IPF at presentation independently predicts clinical outcomes such as bleeding risk, requirement for therapeutic interventions, length of hospital stay, and mortality in specific conditions like sepsis, ITP, and post-chemotherapy aplasia. Randomized controlled trials could assess whether IPF-guided transfusion strategies are non-inferior or superior to standard count-based protocols in terms of bleeding outcomes and platelet product utilization. Third, the role of IPF in specific and complex clinical niches deserves focused exploration [19]. These include: differentiating pre-eclampsia/HELLP syndrome from other thrombotic microangiopathies; assessing marrow reserve in patients with chronic liver disease being evaluated for procedures; monitoring patients on myelosuppressive drugs; and early detection of transplant engraftment or rejection. The integration of IPF with other emerging biomarkers, such as thrombopoietin levels or platelet RNA sequencing profiles, could further enhance diagnostic and prognostic precision [20]. From a clinical and laboratory practice perspective, professional societies in hematology and laboratory medicine should work towards developing consensus guidelines on the clinical indications for IPF testing and its interpretation. Educational initiatives are needed to increase awareness among clinicians about the availability and utility of this parameter, which is often underutilized despite being automatically generated by modern analyzers. Laboratories should establish and validate their own reference ranges and clinically report IPF with interpretative comments to guide clinicians, especially in the context of thrombocytopenia.

### **Conclusion**

This study adds to the compelling evidence that the immature platelet fraction is a highly valuable, rapid, and non-invasive biomarker for the etiological classification of thrombocytopenia. The significant elevation of IPF in hyper-destructive conditions compared to hypo-productive states, coupled with its strong diagnostic performance (AUC 0.88), affirms its role as a reliable discriminator that can streamline the diagnostic pathway. By providing a real-time assessment of bone marrow thrombopoietic activity, IPF has the potential to reduce reliance on invasive bone marrow examinations in appropriate clinical contexts, guide initial therapeutic decisions, optimize transfusion practices, and offer prognostic insights. While limitations related to study design, analyzer standardization, and the need for longitudinal validation persist, the clinical utility of IPF is undeniable. As automated hematology analyzers capable of measuring IPF become ubiquitous, it is incumbent upon both laboratory professionals and clinicians to integrate this powerful parameter into routine diagnostic algorithms. Future research focused on standardization and outcome-based studies will be crucial to fully realize the promise of IPF in moving towards a more personalized, physiologic, and efficient approach to the management of the thrombocytopenic patient. The immature platelet fraction, therefore, stands not merely as a novel laboratory value, but as a transformative tool in modern hematological practice.

### **Conflict of Interest**

The authors declare no conflict of interest related to this study.

### **Authors Contribution**

- Concept & Design of the study: *Hussain Farooq*
- Drafting: *Saima Iram & Nabila Akram*
- Data analysis: *Rabia Ameer & Hussain Farooq*
- Critical Review & Final approval: *Ujala Aymun & Uzma Chohan*

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