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Interest of Immature Platelet Fraction (IPF) in the Etiological Diagnosis of Thrombocytopenia.

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Abstract

Background: Thrombocytopenia is a common hematological abnormality with diverse etiologies, including peripheral platelet destruction and central production failure. The Immature Platelet Fraction (IPF) is a new parameter that quantifies reticulated platelets and provides an indication of the quality of thrombopoiesis.

Objective: This study aimed to evaluate the diagnostic utility of IPF in distinguishing thrombocytopenia etiologies.

Methods: A prospective cross-sectional study was conducted on 120 thrombocytopenic patients for over two months at the Hematology Laboratory of Arrazi Hospital, Marrakesh. IPF was measured using a Sysmex XE-5000 analyzer. Statistical analyses included the Mann-Whitney U test, Kolmogorov-Smirnov test, and Receiver Operating Characteristic (ROC) curves to determine the IPF cutoff values and diagnostic accuracy.

Results: The cohort included 46,7% males and 53,3% females, with a median age of 44 years. The median IPF was 8,0% [1.5–40,6%], with significantly higher values for peripheral thrombocytopenia (9,5%) than for central thrombocytopenia (6,0%; p = 0.019). ROC analysis yielded an Area Under the Curve (AUC) of 0,65, with a cutoff value of 8,1% (sensitivity, 65,9%; specificity, 78,6%). The Kolmogorov-Smirnov test confirmed significant differences in distribution between the groups (p = 0,003).

Conclusion: IPF provides significant insights into thrombocytopenia etiologies, with higher levels observed in peripheral cases. While its moderate discriminatory capacity suggests the need for complementary diagnostic tools such as bone marrow aspiration in central thrombocytopenia. IPF remains a promising marker for improving the diagnostic accuracy in thrombocytopenia management. Standardization of cutoff values and larger studies are needed to refine its clinical application.

Keywords: Immature Platelet Fraction; Peripheral thrombocytopenia; Central thrombocytopenia; Peripheral destruction; Bone marrow failure

1. Introduction

Thrombocytopenia is a frequent hematological abnormality characterized by a decrease in platelet count, often leading to symptoms ranging from mild bruising to severe hemorrhagic complications. Its etiologies are diverse, encompassing mechanisms such as increased peripheral destruction, reduced bone marrow production, or abnormal platelet distribution. An accurate distinction between these causes is critical for guiding therapeutic decisions and optimizing patient outcomes [1, 2].

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Advances in hematology have introduced the Immature Platelet Fraction (IPF) as a novel parameter that reflects thrombopoietic activity. Analogous to reticulocytes in anemia, immature platelets are newly released thrombocytes containing residual RNA, and their quantification provides insights into bone marrow activity and platelet turnover [2, 3].

This study aims to evaluate the diagnostic utility of IPF in differentiating thrombocytopenia etiologies. By comparing IPF values in patients with peripheral and central thrombocytopenia. This provides a basis for integrating this parameter into routine clinical practice.

2. Material and methods

This was a prospective, descriptive, cross-sectional study conducted over two months, from April 20 to June 20, 2021, at the Hematology Laboratory of Arrazi Hospital, Mohammed VI University Hospital Center in Marrakesh.

The inclusion criteria were all hospitalized patients, regardless of age, gender, or reason for admission, in whom thrombocytopenia was detected on a complete blood count (CBC). Blood samples were collected via venipuncture, using tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant.

Analyses were performed on whole blood using a Sysmex XE-5000 analyzer.

This hematology analyzer provides standard CBC results and advanced parameters, including the Immature

Platelet Fraction (IPF), which is expressed as a percentage.

IPF Determination in this analyser is based on platelet numeration in reticulocyte channel, using fluorescence-based technique that detects ribonucleic acid (RNA). On the scatergramm, IPF corresponds to the cloud of immature larger platelets with highest fluorescence.

In cases of thrombocytopenia, a blood smear (BS) was systematically performed and IPF was included in the CBC analysis.

All data were statistically analyzed using IBM SPSS 22.0 software. For continuous variables, the Mann-Whitney U test and Kolmogorov-Smirnov test were used to compare statistical differences between the two groups.

Receiver Operating Characteristic (ROC) curves were used to determine the optimal IPF cutoff value with the best sensitivity and specificity, and the area under the curve (AUC) was calculated. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Descriptive Analysis

The study included 120 patients, with 46,7% males (n = 56) and 53,3% females (n = 64), with a median age of 44 years [22–56 years].

Patients were admitted to various hospital departments, predominantly the Emergency Department (21,7%, n = 26), followed by the Intensive Care Unit (ICU) and the Hematology Department, each accounting for 16,7% (n = 20). Infectious Diseases and Gastroenterology accounted for 8,3% (n = 10) each, while Pediatric Oncology and Bone Marrow Transplant Units accounted for 1,7% (n = 2) and 3.3% (n = 4), respectively.

The most common clinical pathologies included inflammatory and infectious causes (21,7% each), followed by malignant hematological disorders (13,3%), tumor syndromes (11,7%), and megaloblastic anemia (3,3%). A history of consanguinity has been reported in only 1,7% of the patients.

Biologically, the median platelet count (PC) was 53,0 $\times 10^3/\mu L$ [4–137 $\times 10^3/\mu L$], and the immature platelet fraction (IPF%) had a median of 8,0% [1,5–40,6%].

True thrombocytopenia was identified in 91,7% of cases, while 8,3% had false thrombocytopenia. Peripheral thrombocytopenia was predominant (74,6%, n = 82), with generally higher IPF values, a median of 9,5%, and some

extreme values reaching up to 40%. In contrast, central thrombocytopenia accounted for 25,4% (n = 28) of cases and was characterized by lower IPF levels, a median of 6,0%, and less variability in values (Table 1, Figures 1 and 2).

Table 1 Platelet Count and IPF in cases, with ROC analysis for IPF Cutoff value to differentiate between Group 1 and Group 2

	Platelet count (×103/µL)				**IPF (%)**			
	Mean	**Standard deviation**	**Median**	**Range**	**Mean**	**Standard deviation**	**Median**	**Range**
Cases	55,58	± 33,70	53,0	4 - 137	9,32	± 7,26	8,0	1,5 - 40,6
Cases	IPF (%)							
	Mean		Standard deviation		Median		Range	
Group 1	10,54		± 8,04		9,5		1,5 - 40,6	
Group 2	7,52		± 5,46		6,0		2,2 - 22,0	
p-value1	0,019							
p-value2	0,003							
Area under curve		Standard error		p-value		95% Confidence interval		
0,65		0,05		0,019		0,60 - 0,70		
IPF : Immature Platelet Fraction. 1 : Mann-Whitney U Test. 2 : Kolmogorov-Smirnov test.								

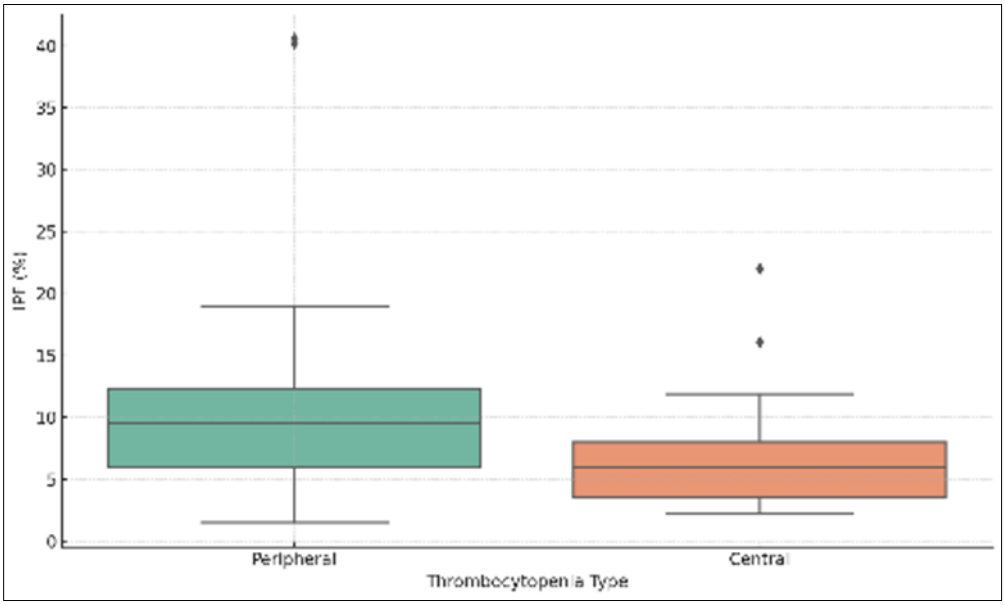

Figure 1 IPF levels between peripheral and central thrombocytopenia groups

Bone marrow aspiration was performed in 24 of the 28 patients with central thrombocytopenia. Among these cases, 58,0% exhibited normal cellularity, 25,0% had hypocellular marrow, 8,0% presented with acellular (aplastic) marrow lacking megakaryocytes, and 8,0% were diagnosed with acute leukemia. Notably, the diagnosis of aplasia was not confirmed via biopsy.

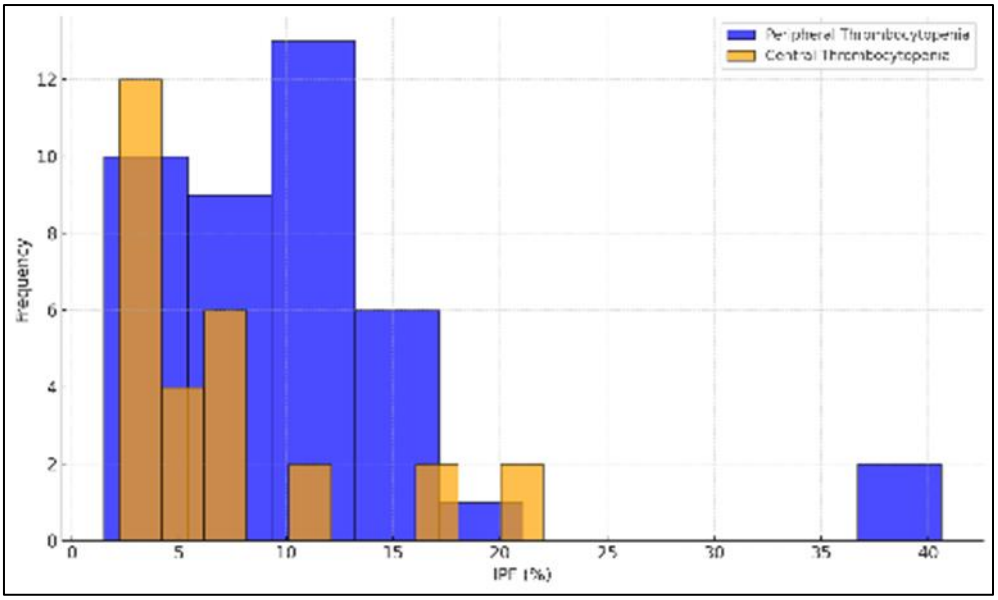

Figure 2 IPF distribution for both groups

3.2. Statistical Analysis

The Mann-Whitney U test was used to compare IPF levels between peripheral and central thrombocytopenia, yielding a U-statistic of 1490,0 and a *p-value* of 0,019 ($p < 0,05$).

This indicated a significant difference between the two groups, with peripheral thrombocytopenia showing significantly higher IPF levels than central thrombocytopenia (Table 1, Figures 1 and 2).

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminatory capacity of IPF. The optimal cutoff value was 8,1%, with an Area Under the Curve (AUC) of 0,65, indicating moderate discriminatory capacity. At this threshold: Sensitivity was 65,9%, and Specificity was 78,6% (Figures 3 and 4).

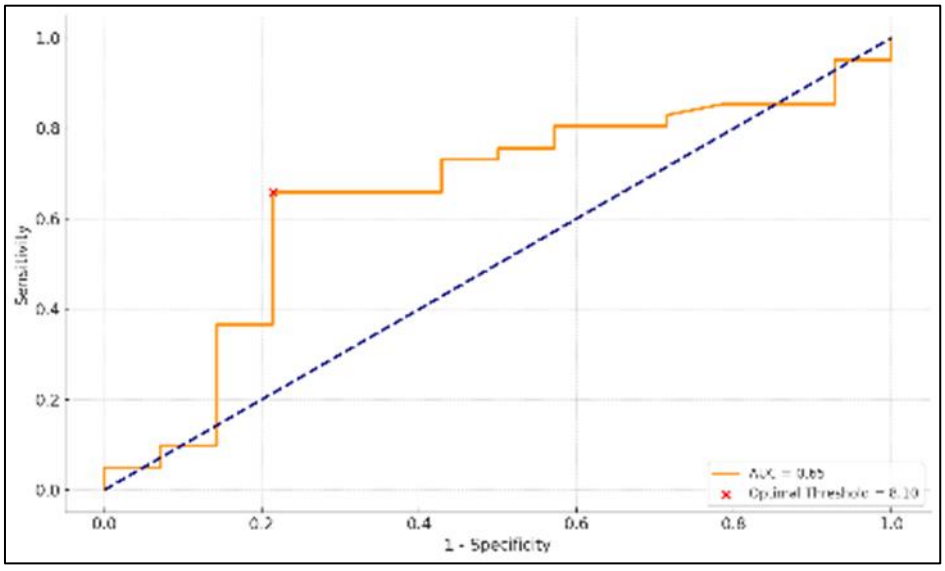

Figure 3 ROC curve to determine the sensitivity and specificity of the IPF to discriminate between the two groups

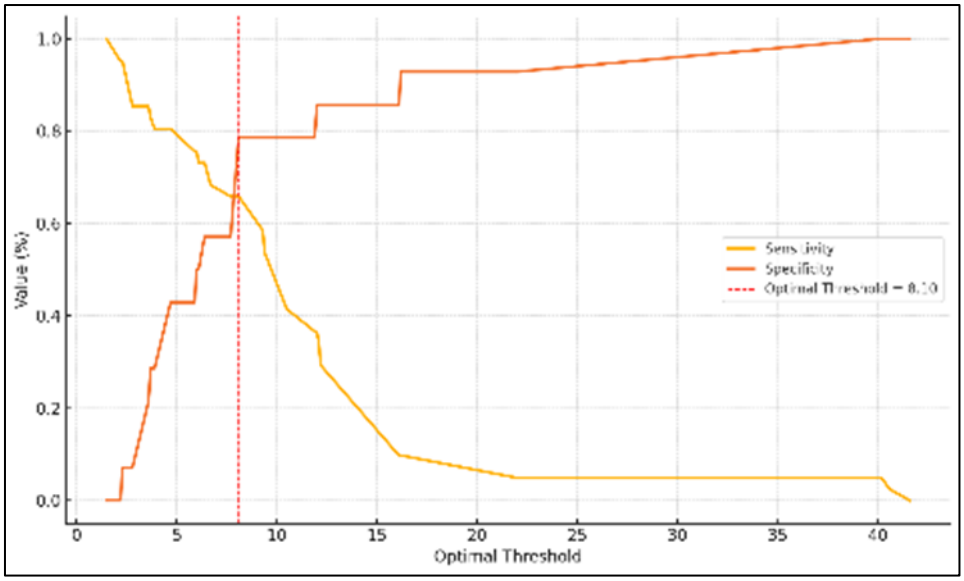

Figure 4 Evolution of sensitivity and specificity as a function of IPF thresholds

The Kolmogorov-Smirnov test was used to compare the cumulative distribution functions of the two groups. The results showed a KS statistic of 0,444 with a *p-value* of 0,003 ($p < 0,05$), confirming a significant difference between the distributions of the two types of thrombocytopenia (Figure 5).

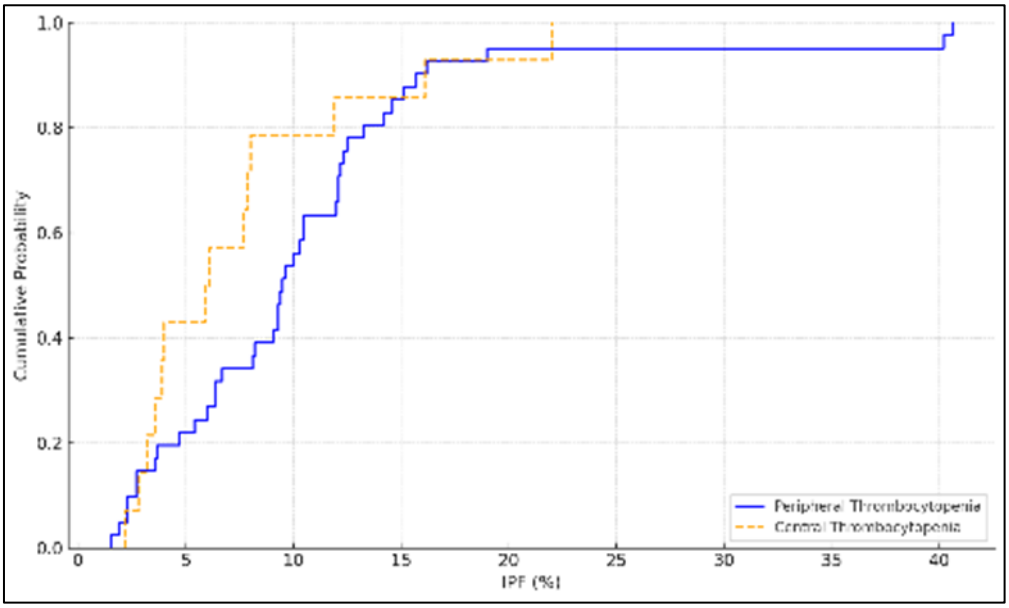

Figure 5 Cumulative IPF distribution functions (Kolmogorov-Smirnov test)

These results highlight the statistically significant differences in IPF levels between peripheral and central thrombocytopenia. The moderate discriminatory capacity of IPF, along with the identified optimal thresholds, provide valuable insights for clinicians in the differential diagnosis of thrombocytopenia.

4. Discussion

The Immature Platelet Fraction (IPF) has proven to be a valuable tool in the differential diagnosis of thrombocytopenia, providing critical insights into the underlying etiologies and bone marrow thrombopoietic activity. Diagnosing thrombocytopenia can be particularly challenging because of the complex mechanisms involved, making it difficult to distinguish between central and peripheral origins. This underscores the importance of reliable markers like IPF. To evaluate its diagnostic relevance, we compared the findings of our study with those in the existing literature, focusing

on parameters such as age, sex, associated pathologies, platelet count, overall IPF values, and differentiation of IPF between peripheral and central thrombocytopenia [1, 2, 3].

In our study, the median age of the patients was 44 years, which is consistent with reports by *Ali et al.* (median: 42 years) and *Javed Butt et al.* (median: 33 years) [4, 5]. This age range reflects the broad applicability of IPF analysis across adult populations. Conversely, *Cannavo et al.* primarily studied a younger cohort of patients presenting immune thrombocytopenic purpura (ITP) and disseminated intravascular coagulation (DIC) [1]. The sex distribution in our cohort was nearly balanced (46,7% male, 53,3% female), consistent with the findings of *Ferreira et al.*, who reported no significant sex differences in IPF-related studies, emphasizing that thrombocytopenia is not sex-specific [2].

In our cohort, inflammatory and infectious causes were predominant (21,7% each), followed by malignant hematological disorders (13,3%), and tumor syndromes (11,7%). These findings align with those of *Cannavo et al.*, who observed elevated IPF values in inflammatory conditions, such as ITP (median: 11,8%, range: 5,3–54,3%) and sepsis-associated thrombocytopenia [1]. Similarly, *Jeon et al.* reported higher IPF values in ITP (median: 8,7%) than in other thrombocytopenic disorders, highlighting IPF's utility of IPF in distinguishing immune-mediated thrombocytopenia from other causes [3]. However, the overlap in IPF values between conditions, as noted by *Cybulska et al.*, suggests that additional diagnostic parameters may be required for ambiguous cases [6].

The median platelet count in our study was 53,0 $\times 10^3/\mu L$ [4–137 $\times 10^3/\mu L$], which is comparable to that reported by *Ferreira et al.*, who reported similar platelet counts in chemotherapy-induced thrombocytopenia and bone marrow failure [2]. Notably, *Cannavo et al.* observed significantly lower platelet counts in patients with central thrombocytopenia, consistent with our finding of a lower median platelet count in patients with central thrombocytopenia [1]. This reinforces the importance of integrating the platelet count with IPF to differentiate between peripheral and central etiologies.

Several studies have established reference ranges for IPF in healthy individuals, providing a baseline for interpreting the pathological values. *Briggs et al*. reported an IPF range of 1,1–6,7% with a median of 3,4% [7]. Similarly, *Goel et al.* documented a slightly narrower range of 0,7–5,7% with a median of 2,4% [8]. Other authors such as *Dadu et al.* (0,7–4,3%) and *Cho et al.* (0,4–5,4%) observed consistent intervals [9,10], while *Abe et al.* described a broader range of 1–10,3% [11]. Collectively, these studies suggest that normal IPF values generally fall between 0,4% and 6,7%, with a median clustering of approximately 2–3,5%.

Table 2 Analyzers, measurement methods and cutoff value of IPF reported by authors [1-12]

Author	**Analyzer**	**Method**	**Cutoff value of IPF (%)**
Butt et al.	Sysmex XN-1000	Specific Platelet fluorescence (PLT-F) : Flow cytometry-based, which relies on fluorescent dyes that stain RNA within immature platelets.	–
Sobia et al.	Sysmex XN-550		–
Ali et al.	Sysmex XN-10		–
Goel et al.	Mindary BC-6800		5,95
Cannavo et al	Sysmex XE-2100	Reticulocyte channel with fluorescence-based RNA staining for immature platelet analysis.	–
Jeon et al.			7,0
Briggs et al.			–
Dadu et al.			–
Abe et al.			7,7
Cho et al.			6,1
Cybulska et al.	Sysmex XE-5000		–
Ferreira et al.			–
Our study			8,1

In our study, IPF was measured using a Sysmex XE-5000 analyzer via the Reticulocyte Channel, employing fluorescence-based RNA detection. This method aligns with those used by *Cannavo et al.* and *Ferreira et al.,* who also used Sysmex analyzers with reticulocyte channels. However, *Jeon et al.* and *Sobia et al.* employed XN-series analyzers with a dedicated PLT-F channel, which offers enhanced sensitivity for platelet-specific measurement. Similarly, *Goel et al.* used Mindray BC-6800, which employs a flow cytometry-based approach but lacks channel specificity for platelets. Although reticulocyte-based methods are robust, PLT-F channels in newer analyzers show promise for greater diagnostic precision [1-12] (Table 2).

Our median global IPF was 8,0% [1,5–40,6%]. This value aligns with the findings from other studies investigating global IPF levels in patients with thrombocytopenia. *Jeon et al.* reported a median IPF of 8,7% in thrombocytopenic populations [3]. These elevated global IPF values underscore the relevance of this parameter as an indicator of abnormal platelet turnover in thrombocytopenic states. This comparison confirmed that the median IPF value of 8,0% observed in our cohort was consistent with the global trends reported in the literature, further supporting its diagnostic utility.

Patients with peripheral thrombocytopenia in our study showed significantly higher IPF levels (median: 9,5%) than those with central thrombocytopenia (median: 6,0%). These findings are consistent with those of *Cybulska et al.*, who reported median IPF values of 16,2% for peripheral thrombocytopenia and 10,2% in bone marrow failure, respectively [6]. *Sobia et al.* further demonstrated a statistically significant difference ($p < 0.001$) between peripheral (25,5%) and central (8,2%) thrombocytopenia, supporting the diagnostic potential of IPF in distinguishing between these etiologies [12]. Similarly, *Jeon et al.* identified an optimal cutoff value of 7,0% for differentiating ITP from other thrombocytopenias, which is comparable to our cutoff value of 8,1% (AUC: 0,65) [3].

The Mann-Whitney U test in our study revealed a statistically significant difference in IPF levels between peripheral and central thrombocytopenia, with a *p-value* of 0,019 ($p < 0,05$). This finding aligns with the results reported by *Cybulska et al.*, who observed a highly significant difference with a *p-value* < 0,001, and *Jeon et al.*, who also documented significant differences with a *p-value* < 0,01 [6, 3]. These consistent findings highlight the sensitivity of IPF in distinguishing between thrombocytopenia subtypes, particularly in settings in which peripheral destruction and central hypoproduction are the main etiologies.

Additionally, the Kolmogorov-Smirnov test in our study revealed a KS statistic of 0,444 with a *p-value* of 0,003 ($p < 0,05$), confirming a statistically significant difference in the cumulative distribution functions of IPF values between peripheral and central thrombocytopenia. This supports the notion that the IPF distributions for these two groups differ meaningfully, further emphasizing their utility in differentiating the underlying mechanisms of thrombocytopenia. Similar findings were reported by *Cybulska et al.*, who used distribution-based analyses to validate IPF differences across thrombocytopenia subtypes [6].

ROC curve analysis demonstrated moderate discriminatory capacity for IPF, with an Area Under the Curve of 0,65. This AUC value, although moderate, is consistent with the results reported by *Cannavo et al.*, who observed IPF variability in diagnostic accuracy across different conditions [1]. *Ferreira et al.*, however, reported a higher diagnostic accuracy with an AUC of 0,80 ($p < 0,0001$), indicating that IPF's discriminatory potential may vary based on population characteristics and underlying pathologies [2].

These combined statistical analyses, Mann–Whitney U, Kolmogorov-Smirnov, and ROC, highlight the significant role of IPF as a diagnostic marker. While the Mann-Whitney U test establishes significant group differences, the Kolmogorov-Smirnov test confirms meaningful distributional differences. The moderate discriminatory capacity observed in our ROC analysis underscores the need for further studies to refine IPF cutoff values and improve diagnostic performance across diverse thrombocytopenic states.

5. Conclusion

In conclusion, these findings confirm the utility of IPF as a valuable parameter for differentiating thrombocytopenia etiology. Elevated IPF values are strongly associated with peripheral platelet destruction, whereas lower values suggest bone marrow failure. However, moderate discriminatory power and occasional overlaps underscore the importance of combining IPF with other diagnostic tools, such as bone marrow aspiration and platelet indices, to improve the diagnostic accuracy.

Comparisons across studies highlight the robustness of IPF in distinguishing peripheral thrombocytopenia from central thrombocytopenia. Nevertheless, the lack of standardized IPF cutoff values across analyzers and populations remains a challenge.

Future research should aim to address this by expanding cohort sizes and refining diagnostic algorithms, thereby enhancing IPF's role of IPF as a reliable, noninvasive, and cost-effective marker in the management of thrombocytopenia.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

Disclosure of conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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