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ORIGINAL ARTICLE

DIAGNOSTIC ACCURACY OF IMMATURE PLATELET FRACTION PARAMETERS IN DISTINGUISHING IMMUNE THROMBOCYTOPENIC PURPURA FROM HYPOPRODUCTIVE THROMBOCYTOPENIA IN PEDIATRIC PATIENTS: A CROSS-SECTIONAL STUDY

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Immune thrombocytopenic purpura (ITP) is a common cause of thrombocytopenia in pediatric patients, often requiring differentiation from hypoproductive thrombocytopenia. This study assesses the diagnostic accuracy of immature platelet fraction (IPF) parameters in distinguishing ITP from hypoproductive thrombocytopenia.

A cross-sectional study was conducted at Hazrat Ali Asghar Hospital, Tehran, enrolling 165 children under 18 years with confirmed thrombocytopenia (platelet count <150 × 10^9/L). Participants were selected based on specific inclusion and exclusion criteria. Data were collected using a pre-designed checklist, and complete blood counts with a particular focus on IPF measurements were performed using the BC-6800 automated hematology analyzer. Clinical diagnoses of ITP and hypoproductive thrombocytopenia were confirmed via bone marrow examination and immunophenotyping. Statistical analyses included receiver operating characteristic (ROC) curve analysis to evaluate the diagnostic performance of IPF.

The mean IPF for patients with ITP was significantly higher than for those without (30.5 ± 12.9 vs. 7.4 ± 3.4, $P < 0.001$). The ROC curve analysis yielded an area under the curve (AUC) of 0.96, indicating excellent discriminative ability of IPF. The optimal cutoff value for IPF was determined to be 11.20%, with a sensitivity of 0.97 and specificity of 0.94. Multivariate analysis confirmed an independent association between higher IPF levels and ITP diagnosis (adjusted odds ratio = 1.25, 95% CI: 1.10 - 1.43, $P < 0.001$).

The IPF parameter is a reliable and sensitive diagnostic tool for differentiating ITP from hypoproductive thrombocytopenia in pediatric patients. This study supports the integration of IPF measurement into clinical practice to enhance diagnostic accuracy in children with thrombocytopenia.

Keywords: thrombocytopenia, immature platelet fraction, immune thrombocytopenic purpura, pediatrics

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INTRODUCTION

Pediatric hematology addresses a range of blood disorders, with thrombocytopenia being one of the most prevalent conditions encountered in clinical practice. Among the various etiologies, immune thrombocytopenic purpura (ITP) and hypoproductive thrombocytopenia stand out due to their distinct pathophysiological mechanisms and implications for management (1). ITP is characterized by an autoimmune process leading to increased platelet destruction, while hypoproductive thrombocytopenia results from insufficient platelet production, often linked to bone marrow disorders or systemic diseases (2). The differentiation between these two forms of thrombocytopenia is crucial as it directly impacts treatment strategies and clinical outcomes (3, 4). While bone marrow examination remains the gold standard for distinguishing between these two causes, recent literature indicates that immature platelet fraction (IPF) parameters could be valuable biomarkers in this context (5). IPF is a parameter that reflects the proportion of young, newly released platelets in circulation, measured using fluorescence flow cytometry. This parameter quantifies the percentage of immature platelets out of the total platelet population, which can provide insight into the bone marrow's response to thrombocytopenia. Elevated IPF levels have been associated with increased platelet production, indicating a compensatory response in conditions like ITP, while lower levels may suggest inadequate production in hypoproductive thrombocytopenia (6, 7).

Despite these advances, the majority of existing research has focused on adult populations, leaving a significant gap in our understanding of IPF dynamics in children. Pediatric studies are limited, and the applicability of adult findings to the pediatric population remains uncertain (6, 8). This underrepresentation necessitates a focused investigation into IPF parameters in children, particularly to understand their role in distinguishing between ITP and hypoproductive thrombocytopenia (7, 9). The present study aims to address this gap by comparing IPF parameters in children diagnosed with ITP to those with hypoproductive thrombocytopenia. We hypothesize that distinct differences in IPF profiles will emerge between these groups, reflecting their underlying pathophysiologies. By elucidating these differences, our research seeks to enhance diagnostic accuracy and inform clinical decision-making in pediatric hematology. This study not only aims to validate the utility of IPF as a diagnostic tool but also aspires to contribute novel insights that may lead to improved management strategies for children suffering from thrombocytopenia.

METHODS

Study design and subjects

This diagnostic accuracy cross-sectional study was conducted at Hazrat Ali Asghar Hospital in Tehran, Iran, involving children under 18 years of age, with thrombocytopenia (defined as a platelet count of less than 150 × 10^9/L). The inclusion criteria were being under 18 years of age and having thrombocytopenia confirmed by two independent samples. Children who had received platelet transfusions in the previous five days, as well as those with conditions that could affect IPF values—such as sepsis, other inflammatory diseases, or the use of antiplatelet medications—were excluded from the study.

Data collection and measurements

Data were collected using census sampling from October 2020 to August 2022 via a pre-designed checklist that included demographic and clinical information, such as age, sex, and the underlying cause of thrombocytopenia.

Blood samples were collected to perform complete blood counts (CBC) for all patients. A volume of 3 cc of venous blood was drawn from each patient into CBC tubes containing EDTA as an anticoagulant. The samples were gently inverted five times to ensure proper mixing. All samples were stored at room temperature and analyzed within eight hours of collection. The CBC was analyzed using the BC-6800 auto hematology analyzer, employing fluorescence flow cytometry with the So Cube technology. In this process, the reticulocyte mode of the device was activated, allowing for the staining of mRNA within the cytoplasm of platelets. Fluorescence intensity was assessed using a laser, with higher fluorescence indicating a greater presence of immature platelets. Approximately 1 ml of peripheral blood was specifically allocated for measuring the IPF. The IPF was calculated based on the proportion of immature platelets and expressed as a percentage of the total platelets (10). Additionally, CBC indices such as WBC, Hb, platelet count, and RDW were measured for all patients.

The clinical diagnoses of ITP and hypo-productive thrombocytopenia were confirmed based on bone marrow examination and immunophenotyping, in accordance with the standard criteria outlined by international guidelines (11-13).

Sample size estimation

Sample size estimation was based on a presumed effect size of 0.3, a power of 95%, and a type I error of 5% using G*Power software version 3.1.3 with the sample size calculation formula for correlational studies. The total adequate sample size was determined to be 166 participants.

Ethical considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board at Iran University of Medical Sciences (code: IR.IUMS.FMD.REC.1400.543). After providing a detailed explanation of the study's objectives and procedures, informed consent was obtained from the parents or guardians of all participating children, with assent sought from children when appropriate, in accordance with age and cognitive ability. Confidentiality of participants' data was strictly maintained throughout the study. All collected data were anonymized, and identifying information was securely stored and accessible only to authorized personnel. In this study, participants were not subjected to any additional risks beyond those associated with standard clinical practice.

Statistical analysis

Statistical analysis was performed using the SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated for all relevant variables, including demographic data and laboratory results. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. To assess the diagnostic accuracy of IPF parameters in distinguishing between ITP and hypoproductive thrombocytopenia, receiver operating characteristic (ROC) curve analysis was conducted. The area under the ROC curve (AUC) was calculated to evaluate the discriminative ability of IPF values between the two groups (with and without ITP). Optimal cut-off values for IPF parameters were established using Youden's index, which maximizes the sum of sensitivity and specificity. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for these cut-off values. To further validate these findings, a multivariate analysis using logistic regression was conducted to assess the impact of age, gender, and disease type on IPF. Additionally, Pearson correlation coefficients were computed to explore the relationship between IPF and other continuous variables. To assess differences in IPF means across groups (e.g., ITP, ALL, Aplastic Anemia), one-way ANOVA was utilized, followed by post-hoc Tukey's HSD test for pairwise comparisons. Statistical significance was set at a p value of < 0.05 for all tests.

RESULTS

Participants

A total of 165 children under 18 years of age diagnosed with thrombocytopenia participated in this study. Among the participants, 93.94% were aged 1 to 10 years, and 51.52% were male. The majority of participants (52.73%) presented to the hospital due to bruising, and 46.06% were diagnosed with ITP. Individual and disease characteristics of the participants are summarized in Table 1.

Table 1. *Demographic and clinical characteristics of participants (N=165)*

Characteristic		Frequency (n)	Percentage (%)
Age	<1	3	1.82
	1-10	156	94.55
	>10	6	3.64
Gender	Male	85	51.52
	Female	80	48.48
Reason for hospital visit	Bruise	87	52.73
	Common cold	1	0.61
	Epistaxis	23	13.94
	Fever	34	20.61
	Pain	4	2.42
	Weakness and lethargy	18	10.91
Type of disease	ITP	76	46.06
	ALL	66	40.00
	Aplastic anemia	23	13.94

IPF in the diagnosis of ITP

As indicated in Table 2, the mean IPF for patients with ITP was significantly higher than that for patients without ITP (30.5 ± 12.9 vs. 7.4 ± 3.4, $P < 0.001$). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of IPF in distinguishing between ITP and hypoproductive thrombocytopenia. The area under the ROC curve (AUC) was calculated to be 0.96, indicating excellent discriminative ability. The optimal cutoff value for IPF, determined using the Youden's index, was 11.20%, with a sensitivity of 0.97 and specificity of 0.94 (Table 3, Figure 1).

Table 2. *IPF Mean values in patients with and without ITP*

Group	Mean IPF (SD)	P-value
Without ITP	7.4 (3.4)	<0.001
With ITP	30.5 (12.9)	

Table 3. *Diagnostic accuracy of IPF for ITP diagnosis*

Parameter	Value
Optimal cut-off value	11.20%
Sensitivity	0.97
Specificity	0.94
Positive predictive value	0.85
Negative predictive value	0.98
Area under ROC curve (AUC)	0.96

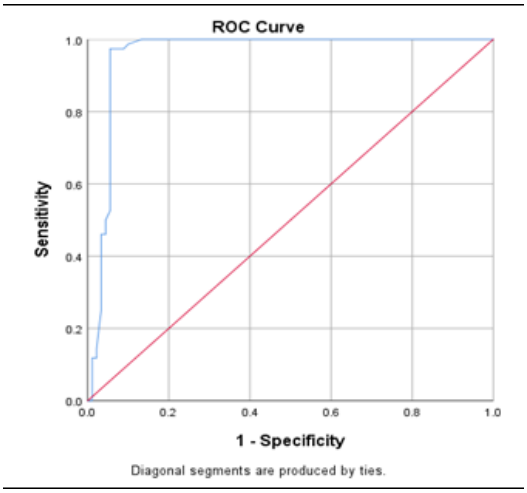

Figure 1. *Receiver operating characteristic (ROC) curve for distinguishing ITP from other causes of hypoproductive thrombocytopenia*

Patient characteristics and their relationship with IPF

Table 4 summarizes the relationship between patient characteristics and mean IPF values. A significant difference in mean IPF was observed across different disease types ($P < 0.001$). Additionally, significant correlations were identified between IPF and key laboratory parameters, including WBC, Hb, and platelet count. A negative correlation was observed between IPF and WBC ($R = -0.239$, $P = 0.002$), with patients exhibiting low WBC levels (<4 x 10^9/L) showing a higher mean IPF (25.00 ± 10.00) compared to those with high WBC levels (>11 x 10^9/L) (12.00 ± 8.00). Similarly, a negative correlation was found between IPF and platelet count ($R = -0.290$, $P < 0.001$). Patients with low platelet counts (<50 x 10^9/L) demonstrated a significantly higher mean IPF (27.00 ± 12.00) than those with high platelet counts (>100 x 10^9/L) (8.5 ± 5.00). In contrast, a positive correlation was identified between Hb and IPF ($R = 0.288$, $P < 0.001$). Patients with low Hb levels (<8 g/dL) had a lower mean IPF (10.50 ± 7.50), while those with high Hb levels (>12 g/dL) exhibited a higher mean IPF (28.00 ± 11.50). These findings highlight that IPF levels increase with rising Hb levels, suggesting a distinct relationship between bone marrow activity and hemoglobin concentration.

To further validate these findings, a multivariate analysis using logistic regression was conducted to assess the impact of age, gender, and disease type on IPF. After adjusting for these variables, the association between IPF and ITP remained significant (adjusted odds ratio = 1.25, 95% CI: 1.10 - 1.43, $P < 0.001$), confirming that higher IPF levels are independently associated with the diagnosis of ITP.

Table 4. *IPF by individual and disease characteristics*

Characteristic		Frequency (n)	IPF Mean (SD)	P-value
Age	<1	3	16.00 (20.00)	0.380
	1-10	156	18.20 (16.20)	
	>10	6	9.50 (13.40)	
Sex	Male	85	19.20 (15.60)	0.274
	Female	80	16.40 (16.60)	
Type of Disease	ITP	76	30.50 (12.90)	<0.001
	ALL	66	5.60 (3.30)	

IPF: Immature platelet fraction; ITP: Immune thrombocytopenia; ALL: Acute lymphoblastic leukemia.

DISCUSSION

Differentiating ITP from hypoproductive thrombocytopenia in pediatric patients is crucial for effective management and treatment outcomes. Our study adds to this important area by demonstrating the diagnostic accuracy of IPF as a reliable biomarker. Our findings indicate that the mean IPF for patients with ITP was significantly higher than for those without ITP. This result aligns with recent findings by Asghar et al. (14), who reported that IPF was significantly elevated in hyperdestructive thrombocytopenia compared to hypoproductive conditions, with a median IPF of 21% in

the hyperdestructive group versus 6.5% in the hypoproductive group, emphasizing IPF's role in reflecting the underlying pathophysiology associated with increased platelet destruction. Moreover, our ROC curve analysis revealed an AUC of 0.96, indicating excellent discriminative ability for IPF in differentiating ITP from hypoproductive thrombocytopenia. This finding is consistent with Adly et al. (15), who suggested that IPF could serve as a rapid and inexpensive automated marker for distinguishing thrombocytopenia due to destruction versus production issues. They identified an optimal cut-off value for IPF at 9.4%, achieving a sensitivity of 88% and specificity of 85.7%, which supports our findings that higher IPF values correlate with ITP. Supporting our results, Goel et al. (5) found that the mean IPF was significantly higher in patients with increased peripheral destruction of platelets (13.4%) compared to those with decreased production (4.6%). Their study established an optimal cutoff of 5.95% for differentiating the two conditions, with a sensitivity of 88% and specificity of 75.9%. This further underscores the utility of IPF as a diagnostic tool in clinical settings. Additionally, our study aligns with findings from a recent study conducted by Shetageri et al. (16), which evaluated the utility of platelet indices in differentiating hyperdestructive from hypoproductive thrombocytopenia. Their prospective analysis involving 315 cases of hyperdestructive thrombocytopenia and 54 cases of hypoproductive thrombocytopenia revealed that mean platelet indices were significantly higher in the hyperdestructive group, reinforcing the importance of distinguishing these conditions.

Another significant contribution to this discussion is the work by McDonnell et al. (9), which highlighted the utility of IPF in differentiating ITP from bone marrow failure (BMF) and predicting bleeding risk. Their retrospective study involving 272 patients found that an IPF greater than 5.2% effectively distinguished ITP from BMF with 93% sensitivity and 91% specificity. They also noted that lower absolute immature platelet numbers correlated with severe bleeding, indicating that IPF measurement not only aids in diagnosis but also in identifying patients at increased risk of hemorrhage. This finding emphasizes the potential clinical utility of IPF in managing pediatric ITP patients. Negash et al. (17) corroborate our findings by showing that platelet indices, including IPF, were significantly higher in ITP patients compared to those with hypoproductive thrombocytopenia. Their study demonstrated that IPF exhibited strong predictive capacities, suggesting that this parameter may enhance diagnostic accuracy and reduce the need for invasive procedures like bone marrow aspiration.

In our study, we observed significant negative correlations between IPF and laboratory parameters such as WBC, Hb, and platelet count. This relationship suggests that IPF may reflect the overall hematologic status of the patient, which is consistent with the observations by Strauss et al. (10), who noted elevated IPF in acute ITP cases, indicating accelerated platelet turnover. Furthermore, Ali et al. (18) demonstrated that the IPF% was significantly higher in cases of increased platelet consumption, reinforcing the diagnostic value of IPF in diverse clinical scenarios. The multivariate analysis in our study confirmed that higher IPF levels were independently associated with the diagnosis of ITP, highlighting its practical utility in clinical settings. Jeon et al. (7) also found that IPF could effectively distinguish ITP from other causes of thrombocytopenia, reporting a median IPF of 8.7% in the ITP group versus 5.1% in non-ITP cases. They proposed a diagnostic predictive scoring model that considers IPF as a critical parameter, further emphasizing the importance of IPF in clinical practice. A recent systematic review and meta-analysis by Walle et al. (19) further supports our findings, revealing that the pooled mean value of IPF significantly increased in ITP patients compared to those with hypoproductive thrombocytopenia. The pooled sensitivity and specificity of IPF in differentiating the conditions were notable, reinforcing its role as a reliable, non-invasive diagnostic tool that can enhance clinical decision-making.

Despite the promising findings of our diagnostic accuracy cross-sectional study, several limitations should be acknowledged. First, the cross-sectional design limits the ability to establish causality, as it captures data at a single point in time. Second, while our sample size was adequate for the analysis, the distribution of cases between hyperdestructive and hypoproductive thrombocytopenia was unequal, which may affect the robustness of comparisons. Additionally, variations in laboratory techniques and equipment across different institutions may impact the consistency of IPF measurements. Lastly, the study focused primarily on IPF; thus, other relevant clinical factors and platelet parameters that may influence the diagnosis were not extensively analyzed.

In conclusion, our findings validate the utility of IPF as a non-invasive diagnostic tool in pediatric patients with thrombocytopenia. By elucidating distinct differences in IPF profiles between ITP and hypoproductive thrombocytopenia, we aim to enhance diagnostic

accuracy and inform clinical decision-making. Future research should focus on larger, multicenter studies to further confirm these findings and explore the implications of IPF in guiding treatment strategies for children with thrombocytopenia. This approach will not only improve patient outcomes but also pave the way for standardized diagnostic protocols in thrombocytopenia management.

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board at Iran University of Medical Sciences, approval number IR.IUMS.FMD.REC.1400.543, issued on December 14, 2021.

Competing Interest

The authors declare no relevant conflicts of interest.

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