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ORIGINAL ARTICLE

A PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE THE ROLE OF THE IMMATURE PLATELET FRACTION IN PREDICTING SEVERITY OF THROMBOCYTOPENIA AND OCCURRENCE OF BLEEDING MANIFESTATION IN PATIENTS OF DENGUE INFECTION

Sumeet Pitkar[1], Keyur Mahajan[2], Shailesh Kanvinde[3], Tarun Kumar[1].

[1]Department of Pediatrics, Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, India,
[2]Pediatric Infectious Diseases, Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, India,
[3]Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, India.

ABSTRACT

Background: Dengue is a mosquito-borne viral infection frequently associated with thrombocytopenia. The Immature Platelet Fraction (IPF) measures young, reticulated platelets and serves as a biomarker for thrombopoiesis. While it is a potential predictor of platelet recovery, its clinical utility in managing pediatric dengue remains under investigation.

Aims and Objectives: To assess the role of baseline IPF in predicting the severity of thrombocytopenia (platelet nadir), time to platelet recovery and the occurrence of bleeding manifestations in pediatric dengue patients.

Materials and Methods: This prospective observational study was conducted at Deenanath Mangeshkar Hospital from July 2018 to April 2020. A total of 105 patients under 18 years with confirmed dengue and thrombocytopenia (platelet count <1,00,000/mm³) were enrolled. Baseline and serial IPF levels and platelet counts were monitored and compared with clinical bleeding scores.

Results: The median age was 8 years. Baseline IPF (normal 0.2–6.6% vs. high >6.6%) showed no statistically significant correlation (p>0.05) with platelet nadir, time to reach nadir, or time to recovery. Bleeding occurred in 24% of patients and was strongly associated with low absolute platelet counts rather than baseline IPF levels.

Conclusion: Baseline IPF is not a reliable predictor of platelet dynamics or bleeding risk in pediatric dengue. Absolute platelet counts remain a more accurate indicator of bleeding risk. While IPF is a rapid, economical tool, serial monitoring rather than a single baseline measurement is recommended to capture the dynamic nature of bone marrow recovery.

ARTICLE HISTORY

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KEYWORDS

Dengue, Immature Platelet Fraction, Thrombocytopenia, Pediatric Dengue.

Introduction

Dengue is a mosquito-borne viral infection that can lead to potentially fatal complications and is frequently associated with thrombocytopenia. It is caused by any of the four dengue virus serotypes (DENV 1–4), which belong to the genus Flavivirus and are transmitted primarily by the Aedes aegypti mosquito. Prevalent in tropical and subtropical regions, these viruses cause a range of outcomes, from asymptomatic seroconversion to severe symptomatic disease. Symptomatic dengue is a dynamic, systemic illness with a broad clinical spectrum ranging from non-severe to severe manifestations.

Following the incubation period, the illness begins abruptly. In moderate to severe cases, it progresses through three distinct phases: febrile, critical and recovery. Due to its dynamic nature, disease severity often becomes apparent only around defervescence—the transition from the febrile to the afebrile phase—which frequently coincides with the onset of the critical phase. Although the disease's manifestations are complex, management is relatively simple, inexpensive and highly effective if correct interventions are instituted early. A successful clinical outcome depends on remaining alert to the specific problems that arise during each phase, allowing for a rational approach to case management.[1]

The primary haematological abnormalities in dengue are thrombocytopenia and leucopenia. To better understand the changing cellular dynamics in moderate to severe cases, the Immature Platelet Fraction (IPF) has emerged as a novel biomarker. The IPF measures young, reticulated platelets—larger cells recently released from the bone marrow that possess a higher RNA content. These are quantified by automated haematology analysers using a reticulocyte detection

Address for Correspondance: Sumeet Pitkar, Department of Pediatrics, Deenanath Mangeshkar Hospital and Research Centre, Pune - 411004, Maharashtra, India.
Email: sumeetpitkar@gmail.com

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channel and are reported as a percentage of the total platelet count (%-IPF).[2]

Because IPF levels rise as bone marrow platelet production increases, measuring IPF in a peripheral blood sample provides an assessment of thrombopoiesis, much like a reticulocyte count measures red cell production. Serial monitoring of IPF in dengue patients with thrombocytopenia can be highly beneficial; a rising trend indicates active bone marrow recovery, suggesting that the platelet count will soon rise. This allows clinicians to avoid unnecessary platelet transfusions and their associated complications, such as alloimmunization, immunosuppression, graft-versus-host disease and the transmission of infections.

Given that no universal criteria currently exist for managing thrombocytopenia in dengue, %-IPF serves as a reliable predictor of platelet recovery, aiding physicians in making informed treatment decisions.[3] The IPF is typically identified using the Sysmex XE-2100 haematology analyser via the reticulocyte channel, employing a fluorescent dye, a precise gating system and specialized "IPF Master" software. For this study, the normal reference range for IPF was established as 0.2% to 6.6%.

Role of immature platelet fraction

The Immature Platelet Fraction (IPF) and Reticulated Platelets (RP) are essential markers for evaluating thrombopoiesis. RP are the youngest platelets in circulation, containing residual mRNA that can be identified via methylene blue staining or flow cytometry using fluorescent dyes like thiazole orange.[4]

Research highlights their clinical utility in the following ways:

- Diagnostic Correlation: A strong correlation exists between RP and IPF, particularly in patients with thrombocytopenia caused by peripheral platelet destruction.[5]
- Differential Diagnosis: Measuring these parameters helps distinguish between central marrow failure (low activity) and peripheral destruction (high activity). An RP percentage above 11% serves as a highly sensitive indicator of increased thrombopoietic activity.[6]
- Automated Quantification: Modern automated methods quantify these young platelets as the IPF. This process uses proprietary dyes (polymethine and oxazine) that stain intracellular RNA, allowing flow cytometers to distinguish mature platelets from immature ones.

Ultimately, these measurements are vital for elucidating the pathophysiology of various thrombocytopenic disorders.

Aims And Objectives

AIM:

To assess the role of the immature platelet fraction in predicting severity of thrombocytopenia and occurrence of bleeding manifestation in dengue patients.

OBJECTIVES:

1. **Primary objectives:**
   - Correlation of IPF at baseline
   - With subsequent platelet count nadir.
   - Occurrence of bleeding manifestation.
2. **Secondary objectives:**
   - Predict time of platelet recovery to more than 1 lakh.
   - Correlation of IPF at baseline with Increase of platelet count by >20,000 per cc mm.
   - Define the range of baseline IPF value in Dengue patient with thrombocytopenia.
   - Correlate change in IPF value in 48hr/72hr with baseline (if platelet count <50,000/cc mm)

Material And Methods

Study Site: Deenanath Mangeshkar Hospital

Study Design: Prospective, Observational study.

Study Population: All the patients <18 years admitted/ treated in OPD in Deenanath Mangeshkar Hospital with Dengue(Dengue NS1/Dengue IgM positive).

Sample Size with Justification: Based on literature,[2] assuming that platelet recovery occurs within 24 hours after attaining the peak IPF, among 84% dengue patients, with the maximum error in the estimate we are willing to tolerate say ± 10%, at confidence level 95% and 80% power, required sample size would be 105 dengue patients.

Formula used to estimate sample size with substitution of values:

To estimate proportion p in the study population (% patients with platelet recovery within 24h after attaining the peak IPF), sample size required is

$n = p(1-p)[(z\alpha + z1-\beta)/(p-p0)]2$

where,

- n is sample size
- **p =0.84 (84%** patients with platelet recovery within 24h after attaining the peak IPF)
- α is Type I error **=5%; zα=1.96 two sided,** zα =1.64 one sided
- β is Type II error, 1−β is power; **z1−β=0.84 for 1−β=80%**
- Effect size= **(p-p0) = ±0.10 (10%)**

Time Frame to Address the Study: July 2018 to April 2020.

Inclusion Criteria: All of below

1. Dengue NS1 and /or IgM positive.
2. Age <18 years.
3. Thrombocytopenia (platelet count<100000 per cc mm)

Exclusion Criteria: any one of below

1. Patients with other platelet disorders.
2. Patients on any chemotherapy or any drug known to cause thrombocytopenia.
3. Marrow failure syndromes.
4. Liver diseases /Hypersplenism.
5. Any patient who received platelet transfusion.

In these cases, thrombocytopenia has different causes. So, it will confound the assessment findings.

Methodology:

- Patient registered in OPD/admitted in Deenanath Mangeshkar Hospital and Research Centre.
- Fulfilling inclusion criteria.
- Baseline assessment including clinical examination and lab investigation.

Clinical examination

- Patient will be assessed at baseline for bleeding.
- Other manifestation of dengue.
  - Hypotension
  - Oedema
  - Ascites
  - Pleural effusion
  - Bleeding scores
- Lab investigation will include.
  - Haemogram
  - IPF

Follow-up assessment including clinical examination and lab investigation.

- After explaining the patient about the study and obtaining consent to participate, their blood sample will be collected in a K2EDTA bulb. Haemogram with IPF was done at first visit, 2nd IPF was done in patients whose platelet count remains below 50,000 and /or does not increase by more than 20,000/cc mm from baseline.
- If platelet <50,000/cc mm Haemogram was done on daily basis in IPD patients till platelet increase to >50,000/cc mm and if platelet >50,000/cc mm haemogram was done on alternate day till platelet count> 1 lakhcc mm. For OPD patients irrespective of platelet count, haemogram was done on alternate day basis.
- Normal Reference range of IPF was considered from 0.2 to 6.6 %, which was the reference range of pathology laboratory of Deenanath Mangeshkar Hospital.
- Bleeding manifestation assessed in all patients as per given score:

Buchanan bleeding scores:

Overall bleeding severity:

0 – **None** – definitely no new haemorrhage of any kind

1 – **Minor** – few petechiae (•100 total) and/or •5 small bruises (•3 cm diameter); no mucosal bleeding

2 – **Mild** – many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter); no mucosal bleeding

3 – **Moderate** – overt mucosal bleeding (epistaxis, gum bleeding, oropharyngeal blood blisters, menorrhagia, gastrointestinal bleeding, etc.) that does not require immediate medical attention or intervention

4 – **Severe** – mucosal bleeding or suspected internal haemorrhage (in the brain, lung, muscle, joint, etc.) that requires immediate medical attention or intervention

5 – **Life-threatening or fatal** – documented intracranial haemorrhage or life threatening or fatal haemorrhage in any site.

Statistical Methods for Analysis of Data:

Data was managed in MS-Excel and analyzed using **SPSS version 20.0.** Quantitative variables are presented as mean, median and standard deviation, while categorical data are expressed as frequencies (%).

Statistical significance was set at $\mathbf{p < 0.05}$. Comparative analysis utilized **Student's t-tests** (unpaired) for continuous variables and **Chi-square or Fisher's exact tests** to examine associations between categorical variables.

Results And Observations:

The present prospective observational study was conducted from July 2018 to April 2020. A total number of 105 patients of dengue fever, who presented in Deenanath Mangeshkar Hospital and met the inclusion criteria, were enrolled in the study after obtaining informed consent.

1. Patient Demographics and Clinical Presentation

The study included 105 patients with a median age of 8 years. Most patients **(82%)** presented for study enrolment on **Day 2** of fever. All patients were NS1 positive, with a significant portion showing concurrent IgM positivity.

Table 1: Demographics and Serology.

Parameter	Data
Gender	Male: 51 (49%) | Female: 54 (51%)
Median Age	Male: 9 years | Female: 7 years
Serology	NS1 Only: 45% | IgM Only: 15% | Both: 39%

2. Correlation of Baseline IPF with Platelet Dynamics

Patients were divided into Group I (<30,000/mm³) and Group II (>30,000/mm³) to analyze the impact of baseline Immature Platelet Fraction (IPF) on platelet nadir and recovery.

Table 2: IPF Correlation with Platelet Nadir & Recovery (Median Values).

Group	Base-line IPF	Platelet Nadir (/mm³)	Time to Nadir (Days)	Time to Recovery (>1Lakh)
Group I	Normal	23,000	1	>5 Days
	High	22,000	1	>5 Days
Group II	Normal	77,000	1	2 Days
	High	71,000	1	4.5 Days

Remarks: Baseline IPF (Normal 0.2–6.6% vs. High >6.6%) showed **no statistically significant correlation** ($p > 0.05$) with platelet nadir, time to reach nadir, or the time required for platelet recovery in either group.

3. Bleeding Manifestations

Incidence of bleeding was recorded in 24% (n=25) of patients, predominantly those with lower absolute platelet counts.

Table 3: Bleeding Incidence by Group and Baseline IPF.

Group	Baseline IPF	Patients with Bleeding
Group I (<30k)	Normal	10 (90%)
	High	6 (85%)
Group II (>30k)	Normal	8 (9.5%)
	High	1 (9%)

Remarks: Bleeding risk was strongly associated with **low absolute platelet counts** rather than baseline IPF levels. Patients in Group I had significantly higher bleeding rates regardless of whether their IPF was normal or high.

4. Longitudinal IPF Trends

For patients requiring repeat testing (n=19) due to stagnant platelet counts after 48–72 hours, results were highly variable.

Table 4: Change in IPF from Baseline (at 48–72 hours).

Change Type	Patients (n)	Percentage
Decrease	8	32%
Increase	5	20%
Static	6	24%

Remarks: Due to the small sample size in this subset, no definitive clinical conclusion could be drawn regarding serial IPF changes and immediate recovery.

Discussion

Dengue fever remains a critical health burden in tropical regions like India, with annual global estimates reaching 100 million cases, including 500,000 instances of severe manifestations such as Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).[7] To mitigate the risks of unnecessary platelet transfusions and their associated side effects, researchers have investigated various novel markers to predict recovery. Our 1.5-year prospective study at Deenanath Mangeshkar Hospital evaluated 105 pediatric patients to determine if the Immature Platelet Fraction (IPF) could reliably predict clinical outcomes.

Our primary analysis focused on whether baseline IPF could predict the platelet nadir or the time taken to reach it. By stratifying patients into two groups (<30,000/mm³ and >30,000/mm³), we found that baseline IPF levels—whether normal or high—did not significantly influence the depth of the nadir or the duration of the decline. These results indicate that a single baseline IPF measurement is not a reliable predictor of the clinical course regarding platelet drop.

Regarding bleeding manifestations, our findings showed no significant association with baseline IPF. Instead, bleeding risk was clearly driven by absolute platelet counts; 94% of patients in Group I (<30,000/mm³) experienced bleeding compared to only 10% in Group II, regardless of their IPF levels. While McDonnell et al. identified an IPF <10.4% as an independent predictor of bleeding in ITP (8), our findings suggest this does not translate directly to dengue-induced thrombocytopenia. Therefore, a high baseline IPF should not be considered "bleeding-protective" in these patients.

Correlation with platelet recovery also revealed discrepancies with existing literature. Unlike studies by Renuka & Swasthik, which associated high IPF (>4.3%) with recovery within 24–48 hours,[9] our data showed no such correlation. Although Larke et al. suggests IPF typically rises 24–48 hours before recovery,[10] we observed that recovery depends heavily on the day of illness and initial counts; in some cases, recovery exceeded five days even with a high baseline IPF.[11] This underscores the limitation of a single baseline measurement and highlights the necessity of serial monitoring.

Finally, our cohort exhibited a typical IPF range of 0.2%–6.6%, with only 10 patients presenting with high levels. This distribution differs from Ahmad et al, who reported high admission IPF in over 80% of patients (12). These variations likely stem from different cut-off values or the timing of hospital presentation. Our longitudinal data showed significant volatility, with IPF decreasing in 32% and increasing in 20% of re-tested patients. This supports the conclusion that the bone marrow's regenerative response is dynamic and cannot be accurately captured by an initial baseline test alone.

Conclusion

- **Diagnostic Value:** IPF remains an economical and rapid tool for assessing thrombocytopenia due to its ease of repeatability and quick turnaround time.
- **Prediction of Platelet Dynamics:** Baseline IPF was not a reliable predictor of the platelet nadir or the time to reach nadir in this study population.
- **Bleeding Risk Assessment:** Initial IPF levels did not correlate with bleeding symptoms over the subsequent five days. Instead, the absolute baseline platelet count proved to be a more accurate predictor of bleeding risk.
- **Platelet Recovery:** Contrary to some existing literature suggesting recovery within 24–48 hours for patients with high IPF, this study found that baseline IPF cannot definitively predict the timing of platelet recovery.

Study Limitations

- **Scope and Generalizability:** As an urban, single-center study, these findings may not represent broader populations. Future multicentric research with a more diverse patient base is needed to validate these results.
- **Subgroup Analysis:** The small sample size of patients with severe thrombocytopenia limited our ability to establish a statistically significant link between IPF and clinical outcomes in the highest-risk group.
- **Baseline vs. Trend:** Relying on baseline measurements may have missed the dynamic nature of IPF. Longer follow-up and serial monitoring are necessary to accurately map how IPF fluctuations relate to recovery or bleeding.

Clinical Recommendations

- **Prioritize Serial Monitoring:** A single baseline IPF is insufficient for predicting clinical progression. Frequent, serial monitoring is recommended,

- particularly for high-risk patients with low initial platelet counts.
- **Optimize Transfusion Timing:** An increasing IPF trend serves as an early sign of bone marrow recovery. Recognizing this "rebound" can help clinicians avoid unnecessary prophylactic platelet transfusions.
- **Integrated Clinical Assessment:** While IPF is a fast, cost-effective tool, it should not be used in isolation. Clinical decisions regarding bleeding risk must integrate absolute platelet counts with the broader clinical picture.

Compliance with Ethical Standards

Funding: None

Conflict of Interest: None

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