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Research Article

Association of Immature Platelet Fraction With Hospital Stay and Hematological Recovery in Adults With Dengue Fever: A Hospital-Based Observational Study

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Abstract

Background: Dengue fever is associated with dynamic hematological changes, especially thrombocytopenia. Routine monitoring is based on platelet count but this parameter does not directly mirror marrow thrombopoietic activity. The immature platelet fraction (IPF) represents newly released platelets and can give additional information about platelet production and recovery. The link between IPF and duration of admission in adults with dengue is less well established.

Objective: To evaluate the association of IPF with duration of hospital stay in adults with dengue fever and to evaluate the association with platelet recovery and total leukocyte count.

Methods: A hospital-based prospective observational study was carried out in 100 adult patients with laboratory confirmed dengue fever in the Department of General Medicine, Navodaya Medical College and Research Centre, Raichur, Karnataka, India during the period from January 2022 to June 2023. Patients >18 years of age with acute febrile illness with positive dengue NS1 antigen and/or IgM antibody were included. Demographic, clinical and laboratory parameters were collected. IPF, platelet count, hemoglobin, total leukocyte count (TLC), packed cell volume, serum creatinine and random blood sugar were measured. Hospital stay was classified as <5 days or >5 days. Mean IPF was compared between hospital-stay groups using an independent-samples t-test and across TLC categories using analysis of variance.

Results: The mean age was 34.14 ± 11.65 years and 72% of the participants were males. The mean IPF was 5.69 ± 1.18%. The mean length of stay was 5.01 ± 1.18 days, with 74% of participants staying <5 days and 26% staying >5 days. Mean IPF was significantly higher in participants with hospital stay >5 days than those hospitalized <5 days (6.10 ± 0.83% vs 5.57 ± 1.26%; t=1.9947, p=0.0489). In addition, the IPF was significantly different according to the time to platelet recovery in the study cohort , increasing from 5.48 ± 1.23% in patients recovering within <24 hours to 6.01 ± 0.70% at 24–48 hours and 6.38 ± 1.24% after >48 hours (ANOVA=3.924, p=0.023). In

contrast, there was no significant association of IPF with TLC category: <4000/mm3, 5.65 ± 1.14%; 4000–11,000/mm3, 5.74 ± 1.19%; and >11,000/mm3, 5.59 ± 1.24% (ANOVA=0.914).

Conclusion: Higher IPF was associated with longer hospitalization and a longer time to platelet normalization in this adult dengue cohort. There was no significant association between IPF and TLC. IPF may add further information on thrombopoietic activity and clinical recovery, but its independent prognostic significance should be validated in larger prospective studies considering disease severity and other factors affecting hospital stay.

Keywords: dengue fever; immature platelet fraction; thrombocytopenia; hospital stay; platelet recovery; total leukocyte count; thrombopoiesis.

Introduction

Dengue is an important mosquito-borne viral infection of tropical and subtropical regions and has a clinical spectrum ranging from an uncomplicated febrile illness to severe dengue with plasma leakage, hemorrhage, shock and organ dysfunction.Laboratory parameters are often used together with clinical assessment to monitor the progression of the disease because the clinical picture changes rapidly during the febrile, critical and recovery phases.[1,2]

Thrombocytopenia is a characteristic hematological abnormality in dengue. The pathogenesis is multifactorial and involves transient bone marrow suppression, impaired megakaryopoiesis, immune-mediated platelet destruction and peripheral platelet consumption.[3] The critical phase is characterized by a drop in platelet counts, with recovery as the patient enters convalescence.

Conventional platelet counting, however, reflects the circulating platelet pool at any given moment and does not directly quantitate platelet production. The immature platelet fraction (IPF) is an automated parameter that reflects newly released, RNA-containing platelets and is a marker of recent thrombopoietic activity.[4,5] Thus, increased IPF may provide information regarding marrow compensation in thrombocytopenia that is not apparent from platelet count alone.

Dengue studies have shown that IPF varies dynamically during the course of the disease. Dadu et al. reported the association of IPF changes with subsequent platelet recovery.[6] Looi et al. reported an increasing IPF in a cohort of 287 hospitalized dengue patients in the period before platelet recovery and suggested that IPF may be used as an early indicator of recovery.[7] Other prospective studies have investigated IPF as a predictive marker of platelet recovery, and proposed different thresholds depending on day of illness and definition of recovery.[8-10] More recently, longitudinal data from a large cohort have further supported the dynamic relationship between IPF and the trajectories of platelet recovery.[11]

Dengue clinical severity, bleeding, hemodynamic stability, platelet recovery, comorbidities and local discharge practices were some of the factors affecting hospital stay in dengue. It is not known whether IPF provides information about the length of hospitalization beyond routine hematological parameters. Moreover, since IPF reflects platelet production and not leukocyte production, its relationship to total leukocyte count may help to clarify whether it represents a relatively platelet-specific marker of hematopoietic response.

Therefore, the present study was aimed to study the association of IPF with the duration of hospital stay in adults suffering from dengue

fever and its association with platelet recovery and TLC.

Aims

Primary objective:

To find out the association of IPF with length of hospital stay in adults with dengue fever.

Secondary objectives:

1. To assess the correlation of IPF with the time to platelet recovery.

2. To find out the association between IPF and TLC category.

3. To describe some hematological and biochemical features of the study population.

Methods

Study design and setting

This was a hospital-based prospective observational study conducted in the Department of General Medicine at Navodaya Medical College and Research Centre, Raichur, Karnataka, India.

The institutional study described the original study as a "hospital-based prospective cross-sectional study." Because the participants were subsequently assessed for platelet recovery and duration of hospitalization, the present manuscript uses the more conservative designation prospective observational study rather than assigning an analytical design not supported by the original protocol.

The study period was January 2022 to June 2023.

Study population

Adults diagnosed with dengue fever and managed through the Medicine outpatient department or inpatient wards were screened.

Inclusion criteria

Participants were included if they:

- were aged >18 years;
- had a positive dengue NS1 antigen and/or IgM antibody;
- had acute undifferentiated febrile illness of <5 days' duration;
- had a recorded temperature >37.5°C; and
- had no alternative syndromic diagnosis.

Exclusion criteria

Patients were excluded if they:

- refused participation;
- were aged <18 years;
- had congestive heart failure, liver failure or renal failure;
- had active malignancy;
- were immunocompromised; or
- were pregnant.

These criteria were retained from the methodology.

Sample size

The study calculated an initial sample size of 83 participants and increased the target sample to 100 after allowing for a 20% non-response rate. The final study population comprised 100 participants.

Clinical and laboratory assessment

After written informed consent, demographic information, presenting symptoms, comorbidities and clinical findings were recorded.

Dengue infection was confirmed using NS1 antigen and/or IgM antibody testing. IgG antibody testing was also performed.

Laboratory assessment included:

- complete blood count;
- platelet count;
- immature platelet fraction;
- hemoglobin;
- total leukocyte count;
- packed cell volume;
- serum creatinine; and
- random blood sugar.

These investigations correspond to the laboratory assessment described in the study.

Measurement of immature platelet fraction

IPF was measured as part of the automated hematological evaluation. IPF represents the proportion of immature circulating platelets and provides an indirect indication of recent platelet release from the bone marrow.

The mean IPF was used for continuous analysis. The study also categorized IPF into <7% and >7% for descriptive purposes.

Definition of hospital stay

Duration of hospitalization was calculated from admission to discharge.

For the primary analysis, participants were divided into:

- **<5 days**, and
- **>5 days**.

The study reports a mean hospital stay of 5.01 ± 1.18 days, with 74 participants hospitalized for <5 days and 26 for >5 days.

Assessment of platelet recovery

Platelet recovery was categorized according to the time required for platelet counts to return to the normal range:

- <24 hours;
- 24–48 hours; and
- >48 hours.

This analysis was retained as a secondary outcome because it provides context for the relationship between IPF and clinical recovery.

TLC categorization

TLC was categorized into:

- <4000/mm³;
- 4000–11,000/mm³; and
- 11,000/mm³.

Mean IPF was compared across these categories.

Statistical analysis

Continuous variables were summarized using mean ± standard deviation, while categorical variables were presented as frequencies and percentages.

The independent-samples t-test was used to compare mean IPF between the two hospital-stay categories. One-way analysis of variance was used to compare mean IPF across TLC categories and platelet-recovery categories.

A two-sided p value <0.05 was considered statistically significant.

The study reports t-test, chi-square and ANOVA as statistical methods and specifies $p<0.05$ as the threshold for statistical significance.

Ethics

Institutional Ethics Committee approval was obtained from Navodaya Medical College Hospital and Research Centre, Raichur, on 08 July 2022. Written informed consent was obtained from all participants.

Results

Baseline characteristics

The study included 100 adults with dengue fever. The mean age was 34.14 ± 11.65 years. Forty-four percent were aged <30 years, 33% were aged 31–40 years, 13% were aged 41–50 years and 10% were >51 years. Males constituted 72% of the cohort

.**Table 1. Baseline demographic characteristics**

Characteristic	n (%)
Age group	
<30 years	44 (44)
31–40 years	33 (33)
41–50 years	13 (13)
>51 years	10 (10)
Mean age ± SD	34.14 ± 11.65 years
Sex	
Male	72 (72)
Female	28 (28)

Clinical presentation

Fever was the most frequent symptom (81%), followed by headache (78%) and myalgia (75%). Abdominal pain was reported in 42%, arthralgia in 41%, skin rash in 23%, and bleeding and diarrhoea/vomiting in 20% each.**Table 2. Presenting symptoms**

Symptom	n (%)
Fever	81 (81)
Headache	78 (78)
Myalgia	75 (75)
Abdominal pain	42 (42)
Arthralgia	41 (41)
Skin rash	23 (23)
Bleeding	20 (20)
Diarrhoea/vomiting	20 (20)

Petechiae was the most frequent abnormal clinical sign, documented in 20% of participants, while 70% had no abnormal sign recorded.

Table 3. Clinical signs

Clinical sign	n (%)
No abnormal sign	70 (70)
Petechiae	20 (20)
Hypotension	10 (10)
Icterus	4 (4)

Bradycardia	4 (4)
Pallor	3 (3)
Oedema	2 (2)

Most participants had no recorded comorbidity (93%). Hypertension was reported in 5% and diabetes mellitus in 4%.

Baseline hematological profile

The mean IPF was 5.69 ± 1.18%. Eighty-five percent of participants had IPF <7%, while 15% had IPF >7%.

The mean hemoglobin concentration was 13.99 ± 1.74 g/dL, mean TLC was 6030 ± 2544.22/mm³, and mean PCV was 38.55 ± 5.95%. Twenty-five percent of participants had leukopenia and 7% had leukocytosis.

Table 4. Baseline laboratory characteristics

Parameter	Result
Mean IPF ± SD	5.69 ± 1.18%
IPF <7%	85 (85%)
IPF >7%	15 (15%)
Mean Hb ± SD	13.99 ± 1.74 g/dL
Hb <12 g/dL	14%
Mean TLC ± SD	6030 ± 2544.22/mm³
Leukopenia	25%
Leukocytosis	7%
Mean PCV ± SD	38.55 ± 5.95%
PCV <35%	30%
Mean serum creatinine ± SD	0.87 ± 0.24 mg/dL
Mean RBS ± SD	132.60 ± 45.34 mg/dL

Duration of hospitalization

The mean duration of hospital stay was 5.01 ± 1.18 days. Seventy-four participants (74%) had a hospital stay of <5 days, whereas 26 (26%) remained hospitalized for >5 days.

Table 5. Duration of hospital stay

Hospital stay	n (%)
<5 days	74 (74)
>5 days	26 (26)
Mean duration ± SD	**5.01 ± 1.18 days**

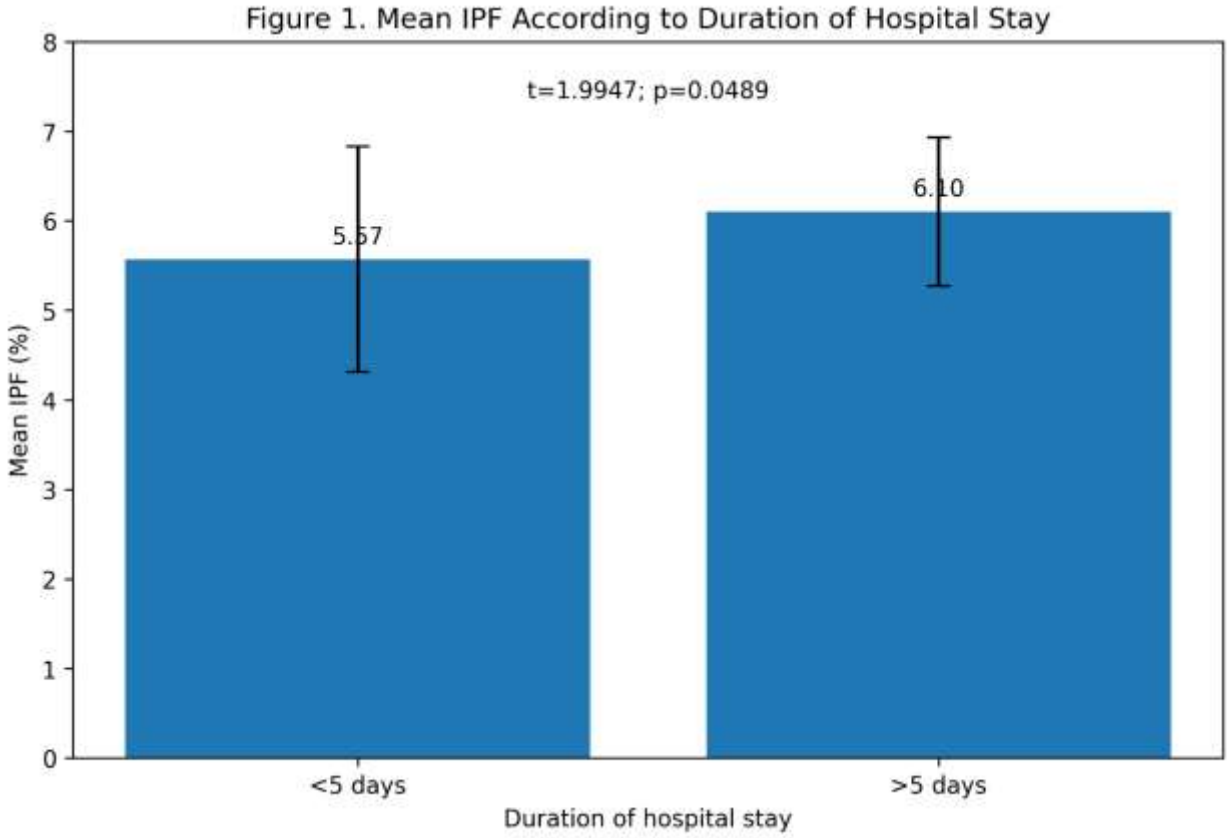
Association between IPF and duration of hospital stay

Mean IPF was significantly higher among participants with a hospital stay >5 days than among those hospitalized for <5 days.

Mean IPF was 5.57 ± 1.26% in the <5-day group and 6.10 ± 0.83% in the >5-day group. The difference was statistically significant (t=1.9947, p=0.0489).

Table 6. Association between IPF and duration of hospital stay

Hospital stay	n	Mean IPF ± SD (%)
<5 days	74	5.57 ± 1.26
>5 days	26	6.10 ± 0.83
t-test		**1.9947; p=0.0489**



IPF and platelet recovery

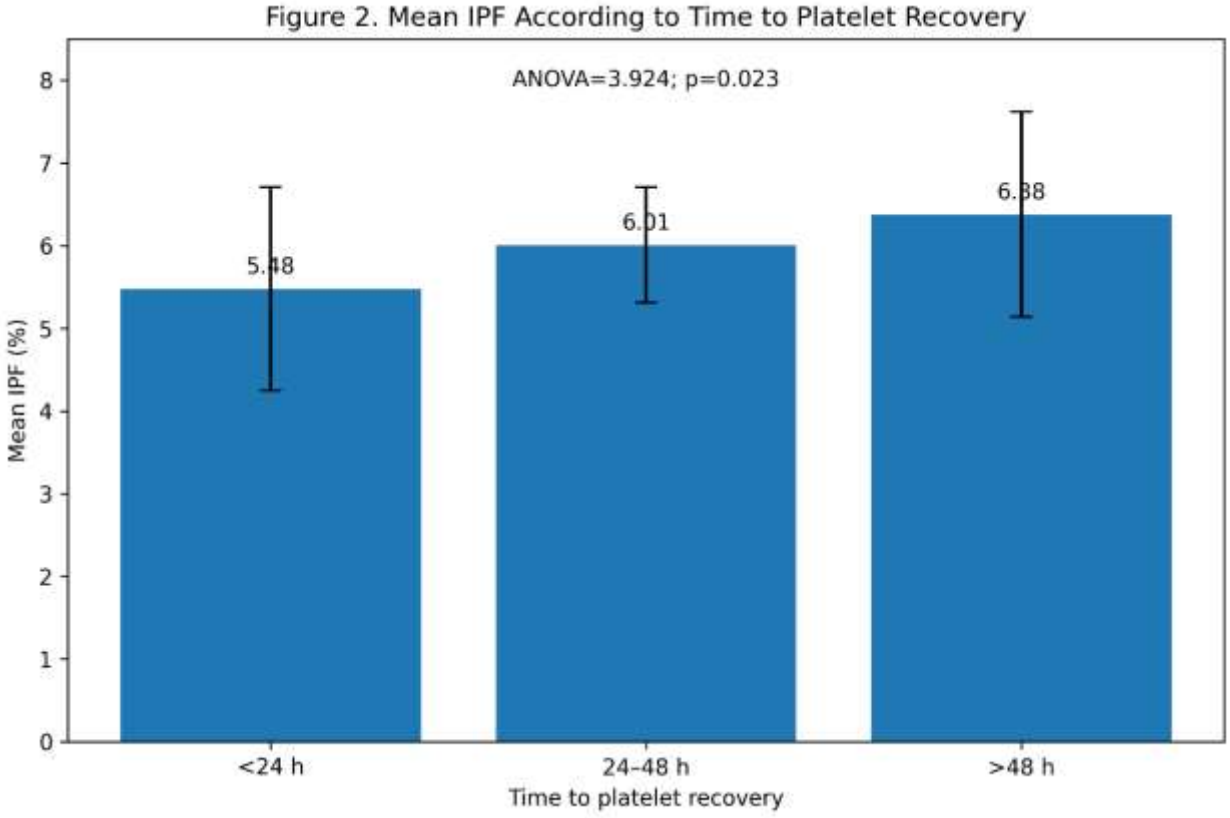
In the overall cohort, platelet recovery occurred within <24 hours in 67 participants, within 24–48 hours in 23, and after >48 hours in 10.

Mean IPF increased across these recovery categories, from 5.48 ± 1.23% among participants recovering within <24 hours to 6.01 ± 0.70% among those recovering within 24–48 hours and 6.38 ± 1.24% among those requiring > >48 hours. The difference was statistically significant (ANOVA=3.924, p=0.023).

Table 7. IPF according to time to platelet recovery

Time to platelet recovery	n	Mean IPF ± SD (%)
<24 hours	67	5.48 ± 1.23

24–48 hours	23	6.01 ± 0.70
>48 hours	10	6.38 ± 1.24
ANOVA		**3.924; p=0.023**



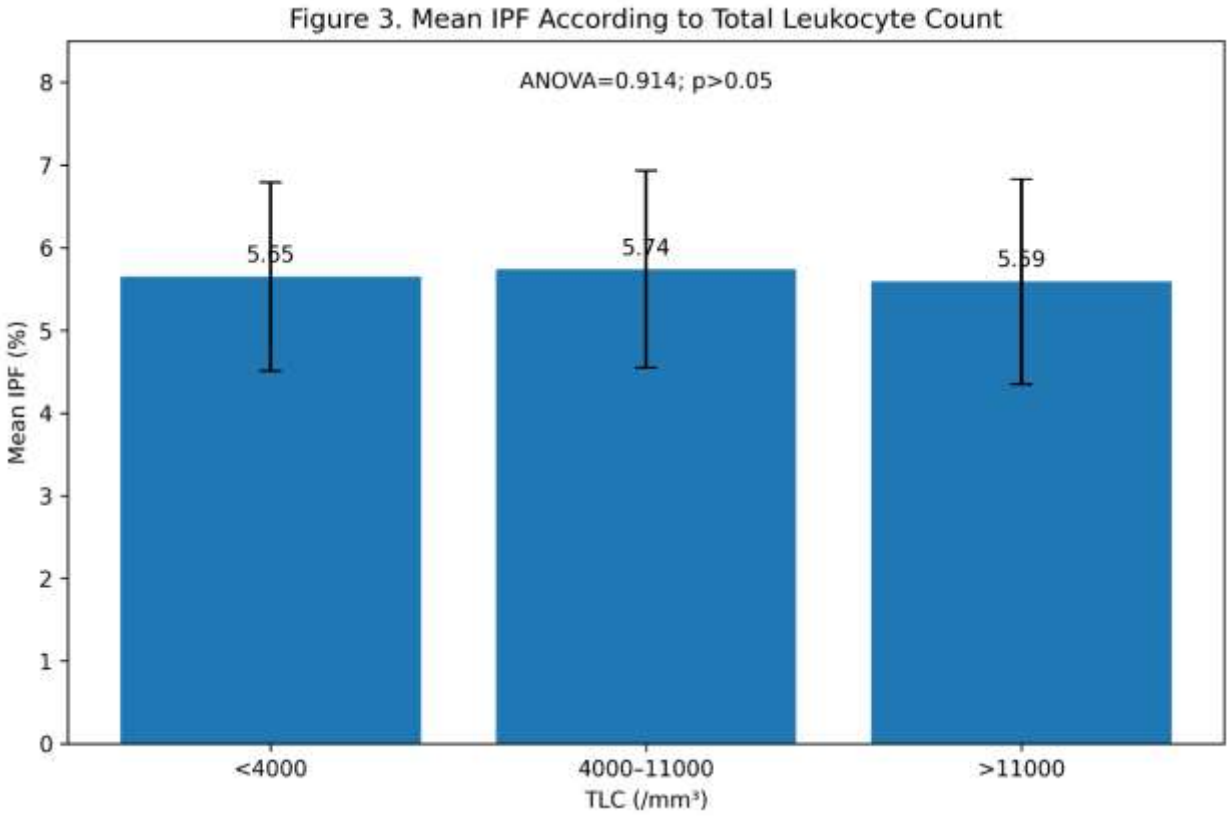
Association between IPF and TLC

There was no significant association between IPF and TLC category.

Mean IPF was 5.65 ± 1.14% among participants with TLC <4000/mm³, 5.74 ± 1.19% among those with TLC 4000–11,000/mm³, and 5.59 ± 1.24% among those with TLC >11,000/mm³. The overall difference was not statistically significant (ANOVA=0.914, p>0.05).

Table 8. Association between IPF and TLC

TLC category	n	Mean IPF ± SD (%)
<4000/mm³	25	5.65 ± 1.14
4000–11,000/mm³	68	5.74 ± 1.19
>11,000/mm³	7	5.59 ± 1.24
ANOVA		**0.914; p>0.05**



Dengue serological profile

Ninety-seven percent of participants were positive for both NS1 antigen and IgM antibody. None of the participants were positive for IgG antibody according to the study dataset.

Table 9. Dengue serological profile

Serological finding	n (%)
NS1 positive	97 (97)
IgM positive	97 (97)
IgG positive	0 (0)

Discussion.

The current study was conducted to evaluate the relationship of IPF with the length of hospitalization and selected hematological markers in adult dengue fever. The main finding was that the mean IPF was significantly higher in patients hospitalized for >5 days compared with those discharged within 5 days. The second important observation was significant association of IPF with time to platelet recovery but no significant relationship was observed between IPF and TLC.

The cohort was mostly young adults with a mean age of 34.14 years and a male preponderance of 72%. The most common symptoms were fever, headache and myalgia which are consistent with the typical symptoms of dengue.[1,2] Thrombocytopenia was a major finding in the study population, with 98% of the participants having an admission platelet count of less than 1.5 lakh/mm3.

Length of hospital stay and IPF

The mean IPF was significantly higher in patients hospitalized for >5 days than those hospitalized for <5 days. The absolute difference between

groups, however, was relatively modest (6.10% vs 5.57%), but statistically significant.

This finding implies that higher IPF may be linked to a prolonged clinical course or delayed hematological recovery. However, the association should not be interpreted as evidence for an independent predictive role of IPF in hospital stay. Factors that influenced length of hospital stay included disease severity, bleeding manifestations, hemodynamic status, platelet trajectory, comorbidities, clinician practice and discharge criteria.

Also important is the biological interpretation of the finding. IPF is a reflection of recent platelet production, not severity of disease per se. The IPF may be elevated when the marrow is responding actively to increased peripheral loss or consumption of platelets. Therefore a patient with more marked or persistent thrombocytopenia may have a higher IPF but still need a longer period of observation before clinical discharge.

This interpretation is consistent with studies showing dynamic changes in IPF during dengue. Looi et al. reported that the number of days with IPF was increased prior to platelet recovery, particularly in severe dengue patients during days 3–5 of illness.[7] More recent longitudinal data also suggest that IPF changes over time and may reflect the trajectory of platelet recovery.[11]

However, a previous prospective observational study of platelet indices in dengue did not find a statistically significant association between platelet indices and length of hospital stay, highlighting that the association between markers of platelet production and length of hospital stay is not consistent across studies.[12] Heterogeneity may be due to differences in disease severity, patient selection, definition of hospital stay and timing of IPF measurement.

IPF and platelet regeneration

The present study observed a significant association between IPF and time to platelet recovery. Mean IPF rose from 5.48% for those recovering in <24 hours to 6.38% for those recovering in > >48 hours.

This finding should be taken with caution. A high IPF is usually considered to be a sign of active thrombopoiesis, but active thrombopoiesis does not always mean that the platelet count will return to normal immediately. In peripheral destruction and consumption of platelets in dengue may continue despite increasing marrow production. Thus, a high IPF may be an appropriate compensatory response in the event of more severe or persistent thrombocytopenia.

Previous studies suggest that IPF may precede platelet recovery. Most patients recovered platelet count within 24–48 h after the increase or peak of IPF, as reported by Dadu et al.[6] Looi et al. showed that IPF increased in the days leading up to platelet recovery.[7] Chuansumrit et al. demonstrated an association between an IPF ≥10% after defervescence and later achievement of a platelet count ≥60×10⁹/L within 72 hours.[10]

Similarly, Abeysuriya et al. reported that the day-2 and day-3 IPF values could predict subsequent platelet recovery, with thresholds of >7.15% and >7.25%, respectively, with a sensitivity of 88.9% and 81.8%, and a specificity of 52.4% and 69.4%.[8] Later, Ahmad et al. reported IPF threshold of 10.55% with a sensitivity of 69% and a specificity of 67% for platelet recovery.[9]

The differing suggested thresholds point to an important methodological issue: the IPF is highly sensitive to when it is measured. A single admission IPF value should not be considered as a peak IPF or an IPF taken on a specific day of illness.

This study did not perform serial measurements of IPF, nor did it establish a cutoff, and thus, the predictive accuracy of IPF cannot be determined. Instead, its contribution is to demonstrate an association between IPF and observed categories of recovery in this specific adult hospital population.

IPF and TLC

No significant association was found between IPF and TLC. Mean IPF was comparable between patients with leukopenia, normal TLC and leukocytosis.

This finding is biologically plausible as IPF relates primarily to platelet production and recent platelet release and TLC relates to leukocyte kinetics. The mechanisms of both thrombocytopenia and leukopenia in dengue are distinct but partially overlapping. Thus, the lack of a significant association between IPF and TLC suggests that the observed variation in IPF was not simply a marker for generalized changes in peripheral blood cells.

However, TLC analysis should be interpreted with caution as only seven participants had TLC >11,000/mm3. Statistical power and precision are limited in this subgroup due to the small number.

Clinical implications

IPF can be a helpful ancillary laboratory parameter in dengue as it adds information not covered by the absolute platelet count. Severe thrombocytopenia with a high IPF may suggest that the marrow is already producing a lot of platelets, whereas persistent thrombocytopenia with a relatively low IPF may suggest a different thrombopoietic response.

This distinction may be clinically useful for interpretation of platelet trajectories. However, there is insufficient evidence for IPF as a stand-alone criterion for discharge, platelet transfusion, prediction of severe dengue or estimation of hospital stay in the present study.

Recent longitudinal evidence supports more robustly the notion that IPF may predict platelet-recovery trajectories when repeated measurements and appropriate statistical modeling are used.[11] Future studies should thus assess serial measurements of IPF and not a single baseline value.

Strengths and Limitations

Strengths

1. The study included 100 laboratory-confirmed adult dengue patients.
2. Clinical and laboratory information was collected prospectively.
3. The study examined both clinical outcome duration and hematological recovery.
4. IPF was assessed alongside conventional CBC parameters.
5. The study provides data from an Indian tertiary-care hospital population.

Limitations

The study has several limitations.

First, it was a single-center study with a relatively small sample size, which limits external generalizability.

Second, hospital stay is a composite clinical outcome influenced by multiple factors. Because the study did not adjust for disease severity, bleeding, comorbidities, treatment or clinician discharge practices, the observed association between IPF and hospital stay cannot be interpreted as an independent prognostic relationship.

Third, the study did not perform multivariable regression. Therefore, it cannot establish that IPF independently determines duration of hospitalization.

Fourth, IPF measurements were not analyzed longitudinally using a repeated-measures model. This is particularly important because IPF changes throughout the course of dengue.[7,11]

Fifth, no ROC analysis, sensitivity, specificity or validated IPF cutoff was generated. Accordingly, this study should not be interpreted as establishing a clinically actionable IPF threshold.

Sixth, the TLC >11,000/mm³ group contained only seven participants, limiting the ability to detect meaningful differences.

Finally, the study reports a prospective cross-sectional design, whereas the outcomes involve subsequent recovery and hospital discharge. The present manuscript therefore uses the broader term “prospective observational study.” The final submitted version should use the exact design terminology approved in the institutional research protocol.

Conclusion

In this cohort of 100 adults with dengue fever, higher immature platelet fraction was significantly correlated with longer hospital stay. IPF was also significantly associated with time to platelet recovery. No significant association was found between IPF and total leukocyte count.

These findings suggest that IPF may provide complementary information on thrombopoietic activity and hematological recovery in dengue. However, the association between IPF and hospital stay should not be considered as proof of an independent prognostic value as hospitalization is driven by a range of clinical and institutional factors.

Future multicenter prospective studies with serial IPF measurements, disease day stratification, dengue severity classification and multivariable analysis are warranted to assess whether IPF can independently predict clinical recovery and hospitalization duration.

Funding

None

Conflict of interest

Nil

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