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Research Article

Immature Platelet Fraction and Platelet Recovery in Adults With Dengue Fever: A Prospective Hospital-Based Study

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Abstract

Background: Thrombocytopenia is a common hematologic manifestation of dengue fever and is typically monitored by serial platelet counts. Platelet count alone, however, is not a direct measurement of the rate of marrow thrombopoiesis. The immature platelet fraction (IPF) is a measure of newly released reticulated platelets and may provide information regarding platelet production and recovery.

Objective: To assess the relationship of IPF with the severity of thrombocytopenia at admission and to find out if IPF varies according to the duration of platelet recovery in adult dengue fever patients.

Methods: In this prospective hospital-based study, 100 adults with laboratory-confirmed dengue fever who attended or were admitted to Department of General Medicine, Navodaya Medical College and Research Centre, Raichur, India between January 2022 and June 2023 were included. Participants aged >18 years with acute febrile illness and positive for dengue NS1 antigen and/or IgM antibody were included. Demographic, clinical and laboratory data were obtained. Platelet count and IPF were measured, and platelet recovery was defined as <24 hours, 24–48 hours, or > >48 hours. Mean IPF among the platelet-count and platelet-recovery categories was compared using analysis of variance.

Results: The mean age of the participants was 34.14 ± 11.65 years and 72% of them were males. Fever (81%), headache (78%) and myalgia (75%) were the commonest symptoms. 98% of the patients on admission had platelet count <1.5 lakh/mm³ and mean platelet count was 72,575.76 ± 33,865.91/mm³. The mean IPF was 5.69 ± 1.18% and 85% had IPF <7%. Platelet counts returned to the normal range in <24 hours in 67% of participants, in 23% in 24–48 hours, and in 10% in > >48 hours. Mean IPF was significantly different in various admission platelet count categories 6.11 ± 0.83% for platelet counts <0.5 lakh/mm³, 5.67 ± 1.14% for 0.5–1 lakh/mm³ and 5.02 ± 1.31% for 1–1.5 lakh/mm³ (ANOVA=6.112, p=0.003). Mean IPF was also significantly different by platelet-recovery time (5.48 ± 1.23% for <24 hours, 6.01 ± 0.70% for 24-48 hours, and 6.38 ± 1.24% for >48 hours; ANOVA=3.924, p=0.023).

Conclusion: In adults with dengue fever, higher IPF was associated with greater

thrombocytopenia at admission and a longer time to platelet normalization. IPF, when interpreted with serial platelet counts, may provide complementary information concerning thrombopoietic activity. Additional prospective studies with serial IPF are needed to determine the predictive value of IPF for platelet recovery, independent of other factors.

Keywords: dengue fever; immature platelet fraction; thrombocytopenia; platelet recovery; thrombopoiesis; platelet count.

Introduction

Dengue is a viral infection spread by mosquitoes and has a broad spectrum of clinical manifestations from an uncomplicated febrile illness to a severe disease with plasma leakage, hemorrhage, shock and organ dysfunction. The clinical course is dynamic and hematologic changes, in particular thrombocytopenia, play a central role in patient monitoring.[1,2]

Thrombocytopenia is one of the most characteristic laboratory abnormalities in dengue and may be due to several interacting mechanisms including transient bone-marrow suppression, impaired megakaryopoiesis, peripheral platelet destruction and consumption.[3] Platelet counts generally fall during the critical phase and then rise during recovery. A routine platelet count, however, reflects the circulating pool of platelets at a point in time and does not measure ongoing platelet production directly.

The immature platelet fraction is an automated measure of newly released platelets containing RNA. The rapid entry of immature platelets into circulation after release from megakaryocytes means that IPF is a useful surrogate marker of thrombopoietic activity.[4,5] Its potential value in dengue is particularly relevant because platelet production can increase before a measurable recovery of the circulating platelet count.

IPF has been studied in dengue in several studies. Frequent platelet recovery within 24–48 hours after an increase in IPF was reported by Dadu et al.[6] Looi et al.[7] observed a gradual increase in IPF before platelet recovery and proposed that IPF may be an early marker of recovery. Since then, prospective studies have been performed to determine specific IPF thresholds to predict platelet recovery, but the thresholds reported have varied by day of illness, patient population, and definition of recovery.[8-10] A recent longitudinal study in 667 dengue patients also reported an association between baseline IPF and subsequent platelet-recovery trajectories, supporting the notion that IPF is a dynamic rather than static biomarker .[11]

But, despite growing evidence, clinical interpretation of IPF remains challenging. Specifically, a high IPF does not necessarily reflect impending normalization of platelet counts, but may reflect active marrow compensation for substantial peripheral platelet loss. Therefore it is important to understand the relationship between the IPF, the degree of thrombocytopenia and the subsequent time to platelet recovery.

The present study was done to assess the association of IPF and severity of admission platelet count and to find out the relation of IPF and time taken for platelet counts to return to normal range in adults with dengue fever.

Objectives

Primary objective:

To assess the correlation of immature platelet fraction with severity of platelet count on admission in adults with dengue fever.

Secondary objective:

Comparison of IPF for different categories of platelet recovery time.

Methods

Study design and setting

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

The institutional study describes the study as "hospital-based prospective cross sectional study". Participants were followed thereafter for platelet recovery, and the current manuscript is conservatively described as a prospective hospital-based observational study without assigning an analytical design not explicitly supported by the original protocol. The study was carried out between January 2022 and June 2023.

Participants

Patients with dengue fever attending the Medicine outpatient department or admitted in the General Medicine wards were screened for eligibility.

Inclusion criteria

Participants were eligible if they:

1. Age >18 years;

2. positive dengue NS1 antigen and/or IgM antibody test

3. acute undifferentiated febrile illness of <5 days' duration;

4. had a documented temperature >37.5°C; and 5. had no other syndromic diagnosis.

Exclusion criteria

Patients were excluded if they were:

1. declined to participate;

2. were <18 years of age;

3. Congestive heart failure, liver failure, renal failure, active malignancy, or immunocompromised status; or

4. were pregnant.

These criteria were retained from the original study methodology.

Study sample size

The study calculated an initial sample size of 83 participants and increased the target sample to 100 after allowing for an anticipated 20% non-response rate. Ultimately, 100 participants were recruited.

Clinical and laboratory examination

Demographic data and clinical history were collected after written informed consent was obtained. All the subjects were subjected to general and systemic examination.

Dengue testing was done for NS1 antigen, IgM antibody and IgG antibody. For the study, participants with positive NS1 antigen and/or IgM antibody test were defined as laboratory-confirmed dengue cases.

Laboratory investigations done were CBC, platelet count, IPF, dengue serology, PCV, serum creatinine and random blood sugar.

IPF measurement

IPF was determined by the automated hematological evaluation. IPF is the proportion of immature/reticulated platelets in circulating platelets and provides an indirect measurement of recent platelet production.

For descriptive analysis, IPF was categorized as <7% and >7% based on the categorization in the study.

Evaluation of platelet recovery

Platelet counts were followed during the hospitalization. For the primary recovery analysis, participants were classified based on the time to recovery of platelet counts to the normal range:

• <24 hours;

• 24–48 hours;

• >48 hours.

The study presents these categories for all 100 participants.

Outcomes

The main analytical results were:

1. Difference in mean IPF by admission platelet count categories; and

2. difference in mean IPF by platelet recovery time categories.

This study was not designed to establish a validated IPF diagnostic or prognostic cut-off, and ROC analysis, sensitivity, specificity and predictive values were not performed.

Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were presented as mean ± standard deviation.

The mean IPF was compared among the three admission platelet-count groups and three platelet-recovery groups by one-way analysis of variance. Two-sided p value <0.05 was considered as statistical significance.

The original study reports t-test, chi-square testing and ANOVA with a significance threshold of $p < 0.05$.

Ethical Approvals

Ethical approval: The study was approved by the Institutional Ethics Committee of Navodaya Medical College Hospital and Research Centre, Raichur on 08 July 2022. All the participants provided written informed consent.

Results

Participant 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 31–40 years, 13% were 41–50 years and 10% were >51 years. Males constituted 72% of the cohort.

Table 1. Demographic characteristics of the study population

Variable	n (%)
Age	
<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 characteristics

Fever was the commonest presenting 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 frequently documented abnormal clinical sign (20%), while 70% had no abnormal sign recorded.Most participants (93%) had no recorded comorbidity. Diabetes mellitus was reported in 4% and hypertension in 5%.

Platelet-count profile:-The mean platelet count at admission was 72,575.76 ± 33,865.91/mm³. This increased to 141,383.84 ± 44,692.76/mm³ at 24 hours, 150,727.27 ± 34,613.29/mm³ at 48 hours and 170,555.56 ± 14,151.95/mm³ at discharge.

Ninety-eight percent of participants had platelet counts <1.5 lakh/mm³ at admission. This proportion declined to 35% at 24 hours, 26% among those assessed at 48 hours and 0% among those assessed at discharge.

Table 3. Platelet counts during hospitalization

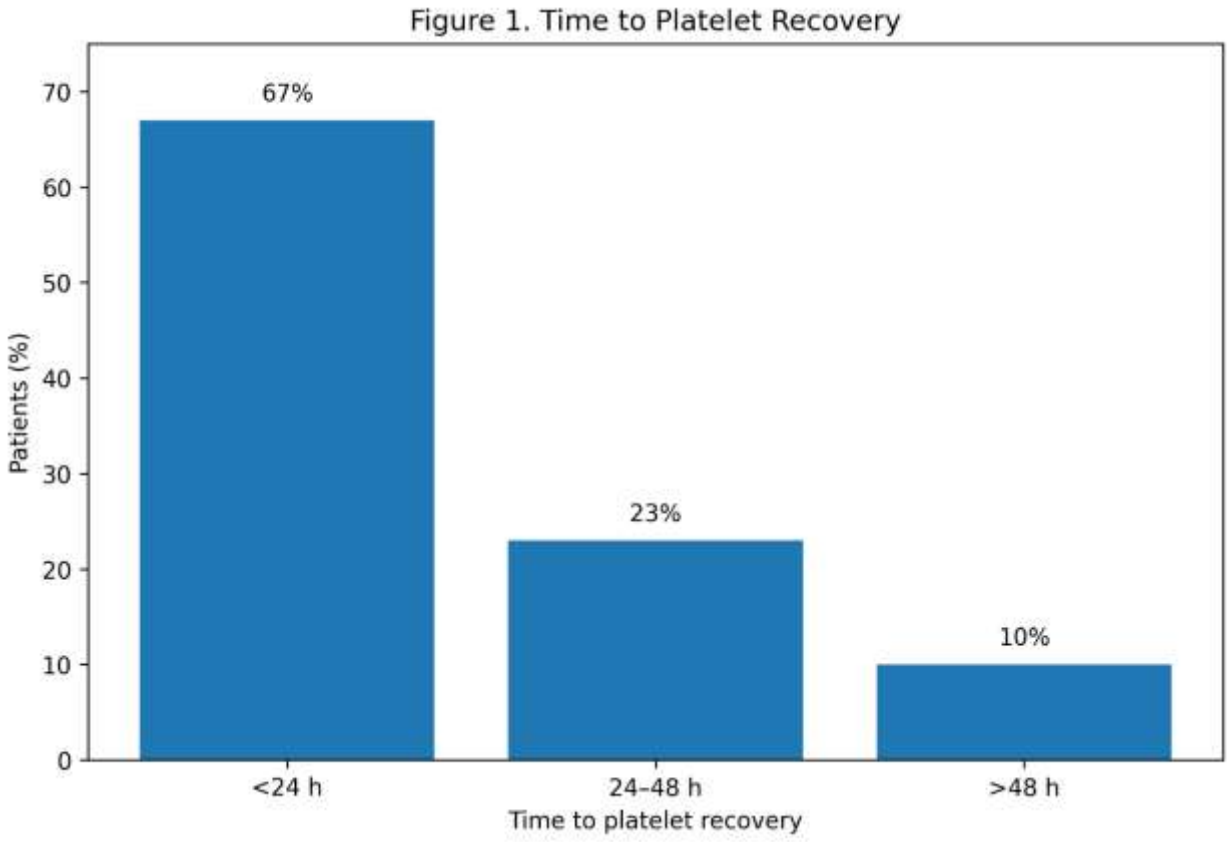
Assessment	n	Mean platelet count ± SD (/mm³)	<1.5 lakh/mm³
Admission	100	72,575.76 ± 33,865.91	98 (98%)
24 hours	100	141,383.84 ± 44,692.76	35 (35%)
48 hours	35	150,727.27 ± 34,613.29	9 (26%)
Discharge	12	170,555.56 ± 14,151.95	0 (0%)

Time to platelet recovery

Platelet counts returned to the normal range within <24 hours in 67 participants (67%), within 24–48 hours in 23 (23%), and after >48 hours in 10 (10%).

Table 4. Time required for platelet recovery

Recovery time	n (%)
<24 hours	67 (67)
24–48 hours	23 (23)
>48 hours	10 (10)
Total	**100 (100)**

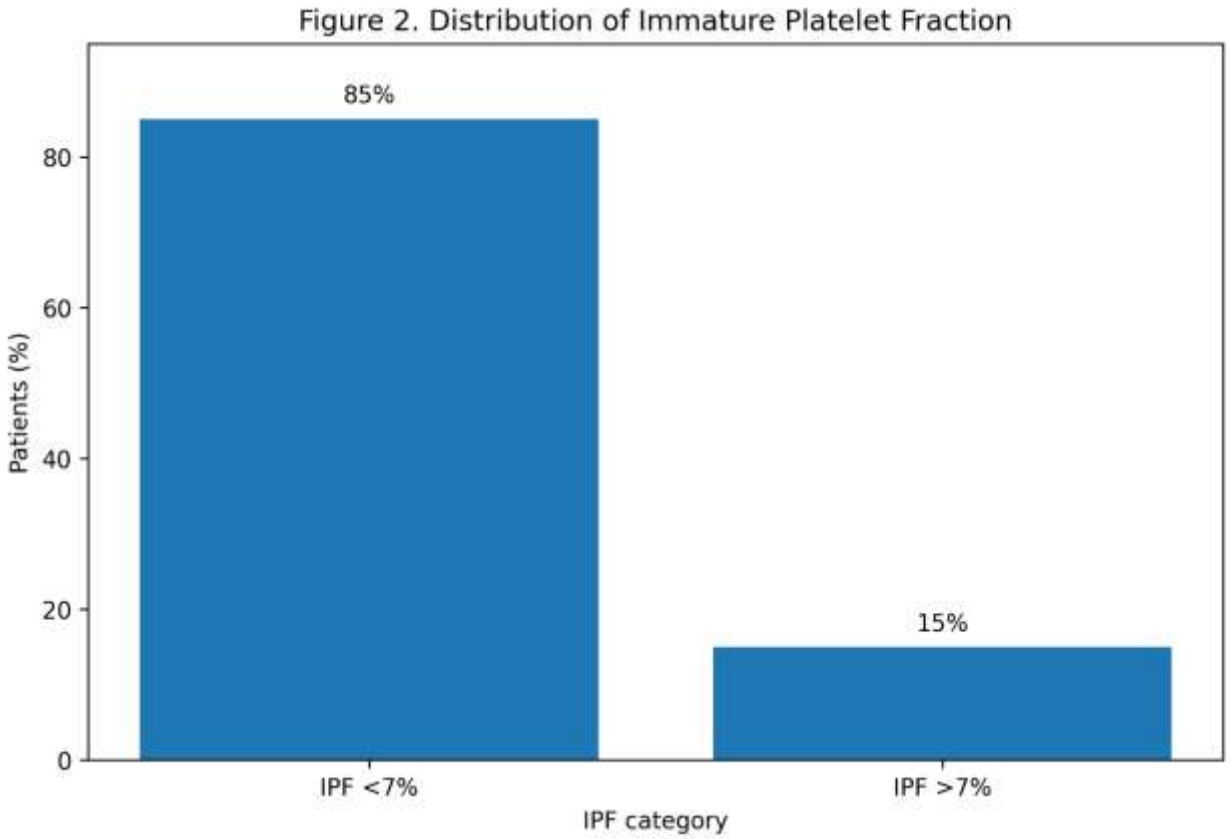


Immature platelet fraction

The mean IPF was 5.69 ± 1.18%. Eighty-five participants (85%) had IPF <7%, whereas 15 (15%) had IPF >7%.

Table 5. Distribution of IPF

IPF category	n (%)
<7%	85 (85)
>7%	15 (15)
Mean ± SD	**5.69 ± 1.18%**



Association between IPF and admission platelet count

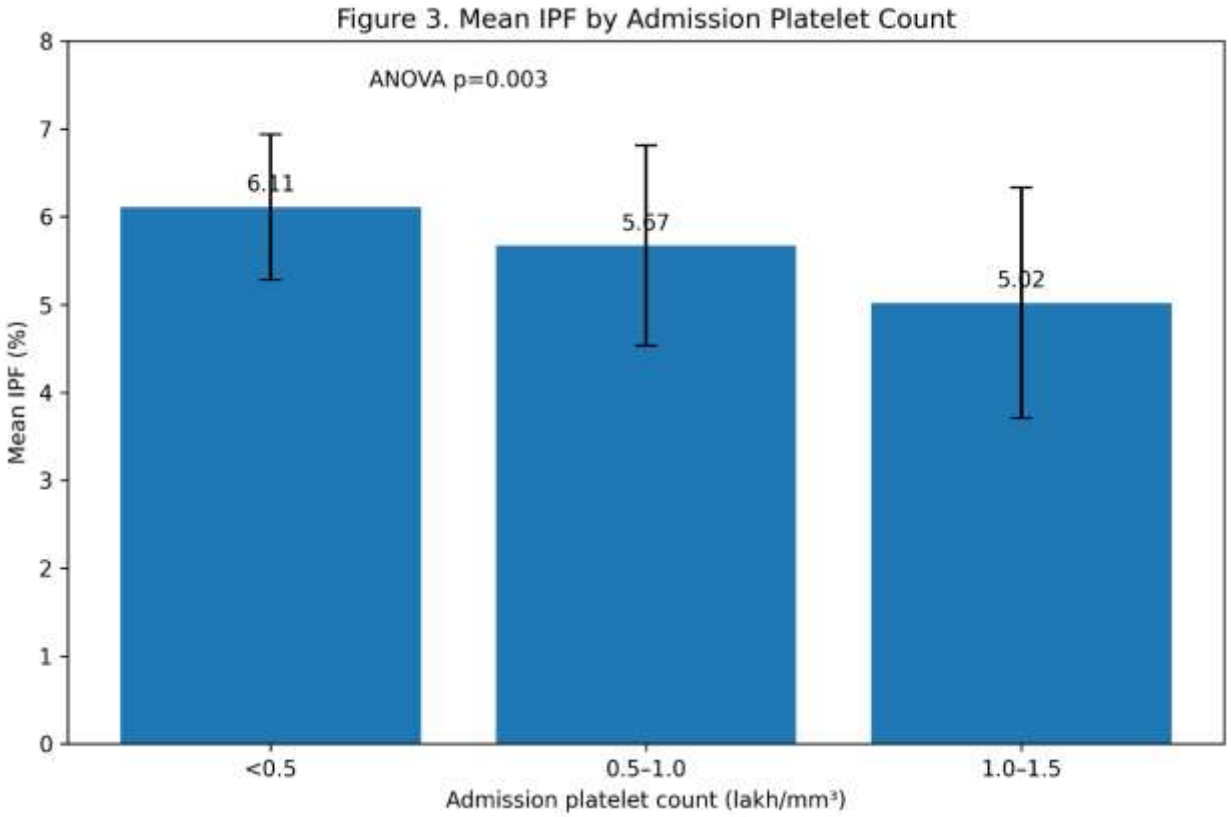
Mean IPF differed significantly according to admission platelet-count category.

Patients with platelet counts <0.5 lakh/mm³ had a mean IPF of 6.11 ± 0.83%. Mean IPF was 5.67 ± 1.14% among those with platelet counts of 0.5–1 lakh/mm³ and 5.02 ± 1.31% among those with platelet counts of 1–1.5 lakh/mm³.

The overall difference was statistically significant (ANOVA=6.112, p=0.003).

Table 6. Association between admission platelet count and IPF

Admission platelet count (lakh/mm³)	n	Mean IPF ± SD (%)
<0.5	30	6.11 ± 0.83
0.5–1.0	47	5.67 ± 1.14
1.0–1.5	21	5.02 ± 1.31
ANOVA		**6.112; p=0.003**



Association between IPF and time to platelet recovery

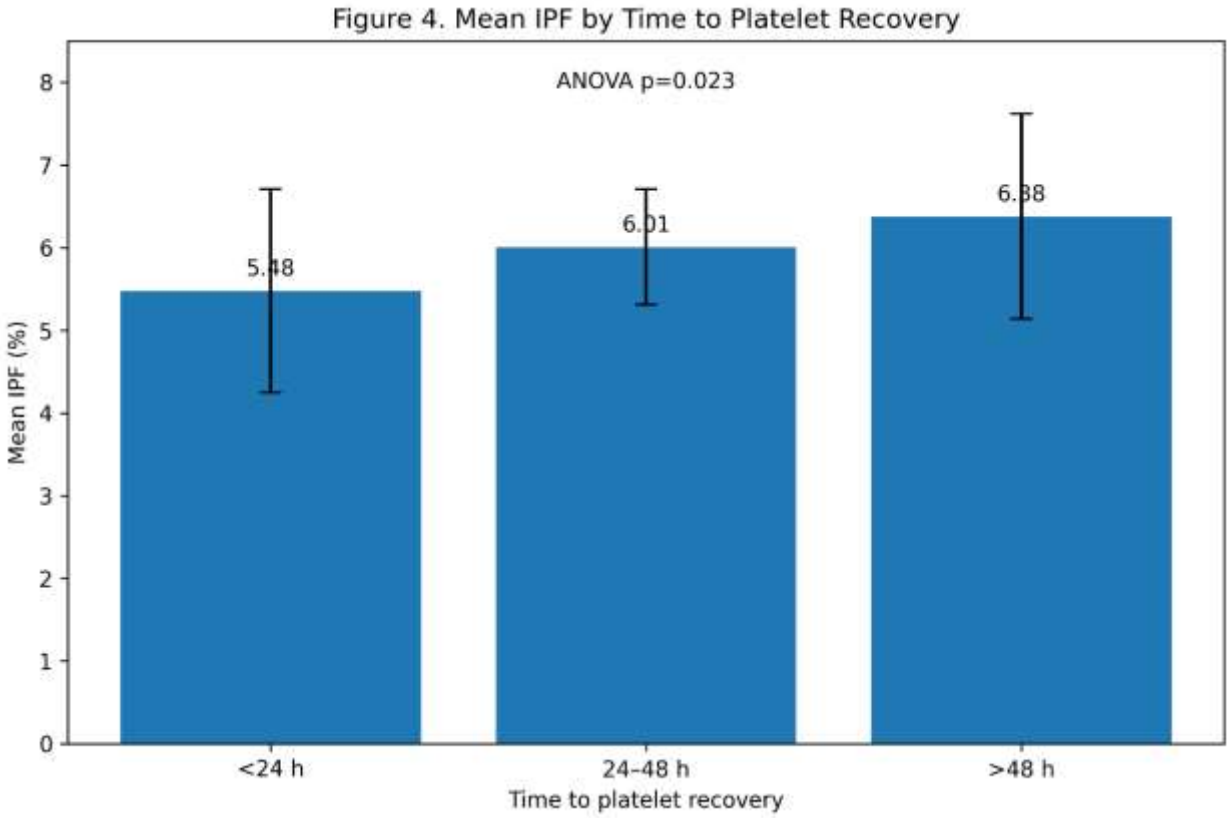
Mean IPF increased across categories of increasing time to platelet recovery.

The mean IPF was 5.48 ± 1.23% among participants whose platelet counts recovered within <24 hours, 6.01 ± 0.70% among those requiring 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. Association between IPF and 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**



Discussion

This study assessed IPF in association with thrombocytopenia and after platelet recovery in 100 adults with dengue fever. There were two important observations. Participants with lower admission platelet counts had significantly higher mean IPF. Second, mean IPF differed significantly by time to platelet recovery, with higher IPF values observed in participants requiring longer for platelet normalization.

The mean age of the cohort was 34.14 years and 72% of the participants were males. The commonest clinical manifestations were fever, headache and myalgia. These results are in line with the broad clinical phenotype of dengue reported in previous studies, although demographic distributions differ considerably depending on geographical and hospital populations.[1,7]

Hematological findings revealed significant thrombocytopenia at presentation. Ninety-eight percent of the participants had platelet counts below 1.5 lakh/mm³. The mean admission platelet count was approximately 72,600/mm³. The later increase in platelet count during hospitalization was in keeping with the recovery phase expected in dengue.[1,2] Association of IPF with admission platelet count

The strongest finding of this study was a significant difference in IPF among admission platelet-count categories. The highest mean IPF was observed in the participants having platelet count <0.5 lakh/mm³ and the lowest in the patients having platelet count between 1 and 1.5 lakh/mm³.

The finding is biologically plausible. Low circulating platelet count may be associated with increased marrow production, leading to increased release of immature platelets. Thus, IPF can provide information about the direction and intensity of thrombopoietic activity which cannot be obtained from platelet count alone.[4,5]

Our findings are consistent with previous work showing increased IPF during dengue associated

thrombocytopenia. IPF increased up to several days prior to platelet recovery and was therefore observed to be an early marker of evolving platelet kinetics by Looi et al.[7] A prospective study by Abeysuriya et al. also demonstrated clinically useful associations between IPF measured early in the course of illness and subsequent platelet recovery.[8]

But the present finding should not be interpreted as a higher IPF simply indicates better immediate recovery. IPF reflects platelet formation and the circulating platelet count reflects the balance between formation and peripheral loss. In dengue, peripheral consumption or destruction may be high even when marrow production is increasing. Thus it is possible to have a relatively high IPF and a considerably low platelet count in a patient.

This is important clinically and may explain why IPF should be considered a complementary marker of platelet kinetics rather than a replacement for platelet-count monitoring.

IPF and platelet regeneration

The second significant finding was the difference in IPF between platelet-recovery categories. The mean IPF for those recovering in <24 hours was 5.48% as compared to 6.01% for those recovering in 24-48 hours and 6.38% for those requiring > >48 hours.

This result needs to be interpreted with care. A higher IPF doesn't mean the platelets bounce back faster." Rather, we found that in this cohort, patients with longer time to platelet normalization had higher IPF values. One explanation is that higher IPF indicates greater compensatory marrow response to greater or more prolonged platelet loss. Such patients may have increased production but not enough to cause a rapid normalization of the circulating platelet count.

Previous studies have shown IPF can increase before platelet recovery. Dadu et al reported that most patients had platelet recovery within 24–48 hours after elevation of IPF.[6] Similarly, Looi et al. reported that IPF increased in the period before platelet recovery.[7] Chuansumrit et al. reported that IPF ≥10% after defervescence was associated with subsequent recovery to a hemostatic platelet level within 72 h.[9] Abeysuriya et al. reported day of illness specific IPF thresholds predictive of subsequent platelet recovery and highlighted that the predictive performance of IPF is time dependent .[8]

Unlike these studies, the analysis of the current study was based on the observed IPF value and recovery categories rather than serial peak-IPF measurements or a validated prediction model. Therefore, the present findings should not be used to set a threshold for clinical prediction of IPF.

Contemporary evidence comparison

The evidence base for IPF in dengue has continued to grow. A longitudinal study of 667 dengue patients in 2026 found that higher baseline IPF was associated with faster subsequent platelet-recovery trajectories and that IPF dynamically changed during the course of the disease.[11] These results support the biological rationale for longitudinal study of IPF.

Meanwhile, the literature shows a great heterogeneity in the proposed thresholds. Ahmad et al. identified an IPF cutoff of 10.55% for predicting platelet recovery with moderate sensitivity and specificity.[10] Abeysuriya et al. reported thresholds of about 7.15-7.25% depending on the day of illness.[8] Chuansumrit et al. described a threshold of ≥10% after defervescence.[9]

These differences point to why a universal IPF cut-off cannot be extrapolated from the present study. Factors that can influence IPF values include platelet recovery and population characteristics, disease severity, timing of sample collection and analyzer characteristics. The current study is therefore rightly concerned with associations and not the determination of a predictive threshold.

Implications for the clinic

When interpreted with serial platelet counts, IPF may have clinical value in that it may provide

additional information regarding platelet production. In a patient with dengue and severe thrombocytopenia, a rising IPF may suggest that marrow platelet production is active even before a significant improvement in the absolute platelet count is seen.

Ultimately this may allow for more rational interpretation of platelet trends and possible reduction in unnecessary interventions. However, this study did not assess platelet-transfusion decisions, bleeding outcomes or mortality and therefore cannot support a recommendation to use IPF alone to guide transfusion or discharge decisions.

The current evidence supports the use of IPF as an adjunctive biomarker rather than a stand-alone parameter for clinical decision making.[6-11]

Limitations and Strengths

Strengths:

1. The study included 100 laboratory-confirmed adult dengue patients.
2. Clinical and hematological data were prospectively collected.
3. Analysis was limited to two clinically relevant relationships: IPF with platelet count severity and IPF with time to platelet recovery.
4. The study provides data from the tertiary-care hospital population in India.

Limitations

There are a few caveats that must be recognized.

First, this was a single-center study with a relatively small sample size and thus limited generalizability.

Secondly, the analysis did not have a healthy control group. Therefore, the study cannot tell if the observed IPF values are different from those in dengue-negative individuals.

Third, the study did not longitudinally analyze serial IPF values Thus, it cannot determine whether an increasing or decreasing IPF precedes platelet recovery.

Fourth, ROC analysis, sensitivity/specificity analysis or multivariable regression was not performed in the study. Thus it cannot establish an independent predictive effect or validated IPF cutoff.

Fifth, the number of observations in the platelet-count table is different for 48 hours and discharge. The study reports 35 participants at 48 h and 12 at discharge. These denominators have been preserved, rather than assuming an artificial complete follow-up.

Sixth, the study categorized recovery by time to normalization but did not include day of illness in the main analysis. This could have resulted in heterogeneity, as IPF is known to vary significantly between the febrile, critical and recovery phases.[7,8]

Finally, the study did not specifically examine the impact of platelet transfusion, bleeding, severity of disease or treatment on IPF and recovery. Future studies should address these factors in a prospective manner.

Conclusion

Among adult dengue fever patients, immature platelet fraction was significantly associated with severity of thrombocytopenia at admission and time needed for platelet counts to return to normal range.

Higher IPF values were associated with lower platelet counts on admission, suggesting increased thrombopoietic activity in the setting of more severe thrombocytopenia. Higher IPF was also seen in those participants who took longer to reach platelet normalization, suggesting that increased platelet production might be a compensatory mechanism for more extensive or prolonged platelet loss, rather than immediate platelet recovery.

Thus, IPF may be a useful adjunctive marker of platelet kinetics in dengue fever when interpreted along with serial platelet counts and clinical status.

The findings do not define a predictive cutoff or prove that IPF independently predicts platelet recovery. Future multicenter prospective studies should collect serial IPF measurements at predefined days of illness and apply longitudinal

and multivariable statistical approaches to determine if IPF can provide clinically actionable prediction of platelet recovery.

Funding

None

Conflict of interest

Nil

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