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# Comparison of platelet indices in dengue fever patients based on platelet transfusion: A prospective observational study in a tertiary care center

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## Abstract:

**CONTEXT:** Dengue fever is the most prevalent mosquito-borne viral disease in humans. Platelet indices (PIs) are given by the cell counters but are often not reported which is possibly due to under-recognition of the utility of these parameters.

**AIMS:** This study aimed to compare PI in patients with dengue fever to assess their role in the outcome such as hospital stay and platelet transfusion requirements.

**SETTINGS AND DESIGN:** Prospective observational study in a tertiary care center, Thrissur, Kerala.

**SUBJECTS AND METHODS:** A group of 250 dengue patients was studied over a period of 18 months. The platelet parameters (platelet count, mean platelet volume [MPV], platelet distribution width [PDW], platelet large cell ratio [PLCR], plateletcrit [PCT] and immature platelet fraction [IPF]) were measured with Sysmex XN-1000 and followed up every 24 h. The clinical features, duration of hospital stay and platelet transfusion requirements details were collected.

**STATISTICAL ANALYSIS USED:** Independent *t*-test, Chi-square test, Karl Pearson correlation coefficient.

**RESULTS:** A total of sample size was 250. The study showed normal PDW and MPV, low platelet count and PCT, and high PLCR and IPF in dengue patients. There were significant differences in PIs (lower platelet count and PCT, higher MPV, PDW, PLCR, and IPF) in comparison between dengue patients based on platelet transfusion.

**CONCLUSIONS:** PIs may act as a predictive tool in the diagnosis and predicting outcomes in dengue fever. Low platelet count and PCT, high PDW, MPV, PLCR, and IPF in transfused dengue patients were found to be statistically significant. Clinicians need to be sensitized about the utility and limitations of these indices and rationalize the need for red cell and platelet transfusions in dengue.

## Keywords:

Dengue, immature platelet fraction, mean platelet volume, platelet count, platelet distribution width, platelet large cell ratio, platelet transfusion, plateletcrit

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## Introduction

Dengue fever is an acute infectious disease caused by four serotypes of dengue virus, DEN 1–4 of the Flavivirus family

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transmitted through *Aedes Aegypti* mosquito and is the most prevalent mosquito-borne viral disease in humans, occurring in tropical and subtropical countries of the world where over 2.5 billion people are at risk of infection.<sup>[1]</sup> In the majority of people, the illness is self-limiting and called simple

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dengue. However, dengue can be complicated by dengue shock syndrome (DSS) or dengue hemorrhagic fever (DHF) which warrants proper recognition and treatment without which, outcomes may be severe.

Platelet indices (PI) are a group of platelet parameters obtained automatically as a part of the complete blood count, without any extra cost. Hence, simultaneous measurement of all PIs (platelet count, mean platelet volume [MPV], platelet distribution width [PDW], platelet cell large ratio [PCLR], plateletcrit [PCT], and immature platelet fraction [IPF]) will provide a valid instrument for measuring disease. The clinical significance, reference values, and usefulness of some of these parameters are still under investigation.

The aim of this study was to investigate the PIs in patients who are dengue NS1 or IgM positive and to assess the role of it in the severity of dengue infection, diagnostic significance and outcome of dengue fever (duration of hospital stay and transfusion requirements) which can be of great help in limiting morbidity and mortality associated with dengue fever.

## Subjects and Methods

This was a prospective observational study done at the Department of Transfusion Medicine and General Medicine at a Tertiary Care Center in Kerala. The data collection was done from December 2017 to May 2019 from dengue patients who were admitted to the General Medicine wards at this hospital. A total of 250 samples were taken up for this study.

This study was approved by the Institutional Research and Ethics Committee. Written informed consent was obtained from each patient/guardian included in the study after informing them about their role in the study.

The platelet parameters (platelet count, MPV, PDW, PCLR, PCT and IPF) were measured all the days in the hospital with Sysmex XN-1000, Automated Hematology Analyzer.

The following parameters were analyzed – patients' demographics, clinical features, laboratory parameters, transfusion requirements, and hospital stay. Patients were categorized into different groups based on their platelet count on each day. The mean and median of all the PIs were calculated for each day. The mean of a platelet count of patients who required and not required a transfusion was calculated and checked its significance. Other PIs such as PDW, MPV, platelet large cell ratio (PCLR), PCT and IPF were also categorized as low, normal, and high values. Patients were grouped based on their values of different indices and found their

mean and median values. A comparison of PIs based on their transfusion requirement was done and checked its significance.

## Selection and description of participants

### *Inclusion criteria*

All patients with clinical features and serologically positive dengue infection (dengue NS1/IgM positive) with more than 12 years of age admitted under general medicine department and who had given consent for taking part in this study.

### *Exclusion criteria*

All patients with coinfections or antiplatelet drugs.

## Statistical tests

Categorical and quantitative variables were expressed as frequency (percentage) and mean  $\pm$  standard deviation, respectively. Independent *t*-test was carried out to compare quantitative data between groups. Chi-square test was used to compare categorical parameters with selected variables. Karl Pearson correlation coefficient was used to find out the relationship of quantitative parameters.  $P < 0.05$  was considered the threshold for statistical significance. Statistical analyses was performed using a statistical software package SPSS, version 20.0 IBM Corp. IBM SPSS Statistics for Windows [Internet]. Armonk, NY: IBM Corp; 2017. Available from: <https://hadoop.apache.org>.

## Results

### Outcome of patients with dengue fever

In this study, 41% of the patients were within the age limit of 25–44 years. The majority (55.8%) of patients were male. In the month of June, 47.6% of the patients were reported as dengue positive and 0.8% in February. We found out that 91.6% of the patients had no hemorrhagic manifestations. The mean hospital stay of patients was  $5.4 \pm 1.8$  days and 74.1% of the patients had stayed  $\leq 6$  days in the hospital. About 13.5% of the patients required platelet transfusion.

### *Platelet count*

Study population with 250 patients was divided into five groups based on the platelet count as  $\leq 20,000/\mu\text{l}$ , 21,000–50,000/ $\mu\text{l}$ , 51,000–100,000/ $\mu\text{l}$ , 101,000–150,000/ $\mu\text{l}$  [Table 1], and  $\geq 150,000/\mu\text{l}$ . The median platelet value is 60,000/ $\mu\text{l}$  (range 9000–281,000/ $\mu\text{l}$ ). The mean platelet count on the 1<sup>st</sup> day was 78,700/ $\mu\text{l}$  and 2<sup>nd</sup> day was 80,900/ $\mu\text{l}$ . An increasing trend in platelet count was observed in patients from day 1 to day 9. The majority (92.3%) of patients who had platelet count  $\leq 20,000/\mu\text{l}$  did not have any hemorrhagic manifestation. However, statistical significance

was not found for these two variables ( $P > 0.001$ ). Patients with lower platelet count were found to have a statistically significant association with platelet transfusion ( $P < 0.001$ ).

In the current study, 16% of the patients had platelet count  $<20,000/\mu\text{l}$  among which 41% of the patients required platelet transfusion. The correlation between lower platelet count and transfusion requirement was found to be statistically significant ( $P < 0.001$ ) [Table 2].

**Platelet distribution width**

The normal value of PDW is in between 8.3 and 56.6 fL. The majority (99.6%) of patients had normal PDW value as the baseline. From day 1 to 10, more than 90% of the patients were having PDW values within the normal range. The mean PDW was  $20.4 \pm 11.3$  fL and median PDW was 12.3 fL (range 8.4–18.05 fL). Patients who required platelet transfusion had higher values of PDW when compared to the group which did not require transfusion. There was no statistically significant association for the same [Table 3].

**Mean platelet volume**

The normal value of MPV is between 8.6 and 15.5 fL. The majority (97.6) of patients had normal baseline values, while 1.2% had low and only 2% had high baseline values. Mean MPV on day 1 was  $10.8 \pm 1.6$  fL which was within the normal range. Median MPV was 10.55 fL (range 7.9–21.6 fL) on day 1. The mean MPV of patients who required transfusion was 12 fL and who did not need platelet transfusion was 10.6 fL. When comparing both the groups with their mean value, the platelet transfusion

required group had a higher value of MPV and was statistically significant with a  $P < 0.01$  [Table 4].

**Platelet large cell ratio**

PLCR's normal value is in between 15% and 35%. In this study, 36.3% of the patients had higher PLCR values and 62.5% of the patients had normal PLCR and 1.2% have a lower value as the baseline. The median of PLCR is 31.4% (range 12.4%–52.4%) and the mean value of PLCR on day 1 was  $32\% \pm 9.3\%$ . In comparison, patients with high PLCR required platelet transfusion, which was found statistically significant. The mean value of PLCR in transfusion-required patients was 36.3% and nontransfused patients were 31.3%, respectively. High PLCR associated with thrombocytopenia was observed in patients who required transfusion and it was found statistically significant [Table 5].

**Plateletcrit**

The normal value of PCT is in between 0.22% and 0.24%. The majority (98%) of patients have low PCT as the baseline value. From day 2 to 10, more than 90% of the patients have a low PCT value. The median PCT was 0.06% (range 0.01%–0.06%), and the mean PCT was  $0.08\% \pm 0.07\%$  on day 1. PCT of the patients who had transfusion were found to be low with a mean value of 0.04%, and this had a statistically significant association ( $P < 0.001$ ) [Table 6].

**Immature platelet fraction**

The normal IPF value is in between 1.1% and 6.1%. More than two-third (68.4%) of patients have high IPF, 30.8% have normal and 0.8 have low IPF values as the baseline. From day 2 to 10, the majority of patients have high IPF values [Figure 1]. On day 5, there was a decrease in the percentage of patients having IPF  $>6.1\%$ . The median value of IPF is 8 (range 0.7%–28%) and the mean value was  $10.1\% \pm 6.9\%$ .

An increased IPF suggests increased immature platelets and low IPF shows suppressed thrombopoiesis.

**Table 1: Percentage distribution of the study population according to platelet count**

	Platelet count	Percentage of patients
Day 1	$<20,000/\mu\text{l}$	8.8%
	21,000-50,000/ $\mu\text{l}$	3.2%
	51,000-100,000/ $\mu\text{l}$	28.7%

**Table 2: Comparison of Platelet count based on platelet transfusion requirement**

Days	Platelet transfusion						t	P
	Yes			No				
	Mean Platelet count	SD	Number	Mean platelet count	SD	Number		
Day 1	43,600/ $\mu\text{l}$	34,700	34	84,200/ $\mu\text{l}$	56,300	216	4.08	$P < 0.001$
Day 2	39,400/ $\mu\text{l}$	20,800	34	87,400/ $\mu\text{l}$	58,500	216	4.73	$P < 0.001$
Day 3	55,700/ $\mu\text{l}$	34,200	33	95,300/ $\mu\text{l}$	57,400	211	3.91	$P < 0.001$

**Table 3: Comparison of platelet distribution width based on platelet transfusion requirement**

Day	Platelet transfusion				t	P
	Yes		No			
	Mean PDW (fL)±SD	Frequency	Mean PDW (fL)±SD	Frequency		
Day 1	$14.9 \pm 4.0$	34	$21.3 \pm 121.7$	216	0.31	0.758
Day 2	$15.0 \pm 3.5$	34	$13.3 \pm 2.8$	217	3.23	0.001
Day 3	$14.6 \pm 3.4$	34	$14.8 \pm 9.7$	211	0.11	0.909

SD=Standard deviation, PDW=Platelet distribution width

Patients who had platelet transfusion with high IPF (14%) could have been managed without platelet transfusion.

PIs have no statistical correlation with hospital stay [Table 7].

In the current study on dengue patients, platelet count was positively correlated with PCT and negatively correlated with PDW, MPV, PLCR, and IPF. All the correlations were found statistically significant.

### Discussion

Dengue fever is one of the major public health problems. Defects in dengue fever/dengue hemorrhagic fever (DF/DHF) are multifactorial mechanisms that include thrombopathy, coagulopathy, and vasculopathy. Many factors can contribute to the onset of thrombocytopenia in DF, varying from a reactive immune response against platelets to decreased platelet production. To our knowledge, there are only a few studies investigating changes in PIs during dengue infection.<sup>[2-4]</sup> PIs give information on whether the platelet destruction is ongoing (necessitating an impending platelet transfusion) or whether the bone marrow is responsive [Table 8] and platelet transfusions can be put on hold.<sup>[5]</sup>

The mean age of the study population was 41 years. Another study also reported an increased incidence of dengue in the age group of 21–30 years.<sup>[6]</sup>

In the current study, nearly 55.8% of the subjects were male. Corresponding studies also found that males constituted 68% of the study cases<sup>[7-9]</sup> with a male: female ratio of 1.6:1. This has been attributed to the Asian culture whereby males spend more time outside their houses and are more likely to be exposed to mosquitoes compared to females.<sup>[6,8-11]</sup>

In the present study, 8.4% of the patients had fever with hemorrhagic manifestations (Grade 1 category).<sup>[12]</sup> Bleeding diathesis is a known feature of dengue fever because of low platelet count and leakage from blood vessels. Bone marrow suppression, immune-mediated

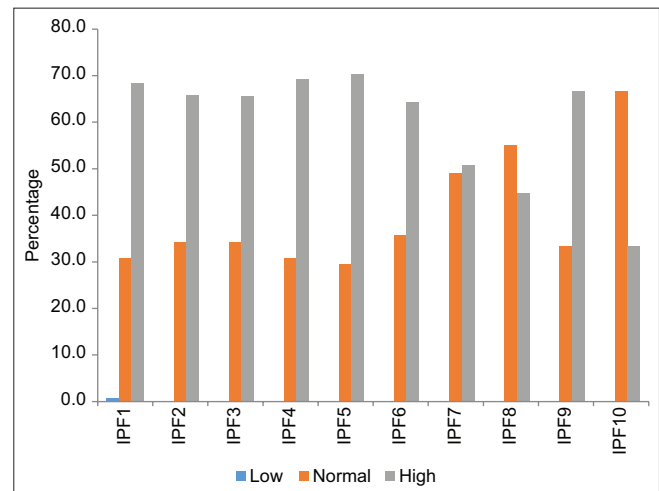


Figure 1: Percentage distribution of the sample according to immature platelet fraction

Table 4: Comparison of MPV based on platelet transfusion requirement

Days	Platelet transfusion						t	P
	Yes			No				
	Mean MPV (fL)	SD	Frequency	Mean MPV (fL)	SD	Frequency		
Day 1	12.0	2.8	34	10.6	1.2	216	5.28	P<0.01
Day 2	11.5	1.3	34	10.7	1.1	217	3.74	P<0.01
Day 3	11.8	1.5	34	10.9	1.1	210	4.32	P<0.01

Table 5: Comparison of PLCR based on platelet transfusion requirement

Days	Platelet transfusion						t	P
	Yes			No				
	Mean PLCR(%)	SD	frequency	Mean PLCR(%)	SD	frequency		
Day 1	36.3	9.6	34	31.3	9.1	217	2.95**	0.003
Day 2	38.1	9.1	34	32.1	8.5	217	3.82	P<0.001
Day 3	36.0	9.3	34	33.3	8.3	211	1.72	0.087

Table 6: Comparison of PCT based on platelet transfusion requirement

Days	Platelet transfusion						t	P
	Yes			No				
	Mean PCT(%)	SD	frequency	Mean PCT(%)	SD	frequency		
Day 1	0.04	0.04	33	0.1	0.1	217	3.81	P<0.001
Day 2	0.05	0.04	33	0.1	0.1	217	3.61	P<0.001
Day 3	0.06	0.04	34	0.2	0.7	211	1.1	0.272



clearance, and spontaneous aggregation of platelets to virus-infected endothelium may be responsible. Another study found that bleeding in form of petechiae, ecchymosis, and epistaxis was documented in 5.43% of the DF cases.<sup>[13]</sup>

In this study, 13.5% of the patients required platelet transfusion as a part of treatment. The majority (76.7%) of patients showed an increase in the platelet count 24 h after transfusion while 23.3% did not. The transient increase in platelet count from the transfusion could have caused a reduction in serum thrombopoietin level, thereby slowing the endogenous production of platelets from megakaryocytes.<sup>[14]</sup> This may be the reason for no increase in platelet count after transfusion for a minority group. In one study, platelet transfusion in absence of bleeding in adult dengue patients with platelet count <20,000/mm<sup>3</sup> did not reduce bleeding or expedite platelet recovery.<sup>[15]</sup> There was potential harm by slowing recovery of platelet count to >50,000/mm<sup>3</sup> and increasing the length of hospitalization.

The correlation between lower platelet count and transfusion requirement was found statistically significant ( $P < 0.001$ ). In one of the review articles, thrombocytopenia was attributed to autoantibodies which

induce platelet lysis through complement activation.<sup>[16]</sup> Another study concluded that thrombocytopenia was a persistent finding in dengue, however, an absence of thrombocytopenia should not rule out the possibility of dengue infection.<sup>[17]</sup> The exact pathophysiology of thrombocytopenia in dengue is uncertain. It could be due to direct bone marrow suppression of thrombopoiesis by the modulation of endothelial cells by dengue virus destruction of platelets by anti-NS1 antibodies directed against the virus cross-reacting with the platelets. However, transfused platelets are as much likely to be destroyed by these antibodies as one's own platelets, and hence, platelet transfusions have a limited role in the management of dengue.<sup>[18]</sup>

In this study, the majority of patients have normal baseline MPV values and MPV is inversely related to platelet counts. According to one study, increased MPV can be used as a marker of production rate and platelet activation.<sup>[5]</sup> High MPV with ongoing thrombocytopenia represents peripheral destruction. We got a higher MPV value in patients who required platelet transfusion. Low MPV indicates underproduction/bone marrow suppression. MPV is inversely related to platelet counts, which is similar in our study. When marrow depression is the cause of thrombocytopenia, a rising trend in MPV heralds platelet recovery, and platelet transfusions may be put on hold.<sup>[19]</sup>

**Table 7: Correlation of platelet indices on day 1 and hospital stay**

Variables	Hospital stay		
	n	Correlation coefficient	P
PLT count	250	0.053	0.403
PDW 1	250	-0.132	0.037
MPV 1	250	-0.146	0.021
PLCR 1	250	-0.202	0.001
PCT 1	250	0.023	0.720
IPF 1	250	-0.191	0.003

PDW=Platelet distribution width, PLT=Platelet, MPV=Mean platelet volume, PLCR=Platelet large cell ratio, PCT=Plateletcrit, IPF=Immature platelet fraction

**Table 8: Platelet indices<sup>[5]</sup>**

Platelet indices	Definition	Normal range
MPV (fL)	Measure of platelet volume expressed in femtoliter	8.6-15.5
PDW (fL)	Measure of variability in platelet size/anisocytosis	8.3-25
PDW (%)	The distribution width at the level of 20% in platelet histogram	8.3-56.6
PCT (%)	Volume of platelets expressed as a percentage of total blood volume	0.22-0.24
IPF (%)	Percentage of immature platelets released into the circulation	1.1-6.1
P-LCR (%)	Percentage of circulating larger platelets (>12 fL)	15-35

PDW=Platelet distribution width, MPV=Mean platelet volume, P LCR=Platelet large cell ratio, PCT=Plateletcrit, IPF=Immature platelet fraction

*Platelet distribution width*

In this study, the PDW value of the majority (99.6%) of patients comes within the normal range. High PDW is a marker of DHF and thus its severity. However, we could not involve any DHF/DSS in this study as a subject. In another study, there is a direct relation between MPV and PDW, that is, a high PDW is associated with a high MPV,<sup>[6]</sup> which is similar to the current study. MPV and PDW have no value in predicting dengue infection<sup>[20]</sup> in another study which is against our study results.

*Platelet large cell ratio*

Nearly 1/3<sup>rd</sup> (36.3%) of patients had a higher PLCR value and 62.5% of the patients had normal PLCR and as the baseline value. Platelet larger cell ratio (PLCR) is inversely related to platelet count and directly related to PDW and MPV. High PLCR is highly sensitive and specific for DF in one study which is in accordance with our study.<sup>[21]</sup> A greater increase in PLCR is seen in destructive thrombocytopenia than in those with hypo proliferative thrombocytopenia.<sup>[2]</sup> In dengue peripheral destruction is one of the proposed mechanisms behind thrombocytopenia.

*Plateletcrit*

The majority (98%) of patients had low PCT as the baseline value. PCT values of patients who require

transfusion were low with a mean value of 0.04%, which was found statistically significant ( $P < 0.001$ ). In one of the studies, they found that low PCT in DF which is highly sensitive and specific for DF, which is a similar finding as this study.<sup>[21]</sup> Another study says that PCT parallels the platelet count.<sup>[19]</sup>

### *Immature platelet fraction*

Nearly (2/3<sup>rd</sup>) 68.4% of the patients had high IPF, and 30.8% had normal IPF values as the baseline. From day 2 to 10, more than 90% of the patients had high IPF values. IPF of patients who require transfusion was high (mean 14.6%) and statistically significant with a  $P < 0.01$ . An increased IPF is seen as the production of platelets increases as in the patient group who require no transfusion which is the majority in number. Low IPF shows suppressed thrombopoiesis. Thus, IPF can be used as a tool to not only diagnose and monitor the severity of thrombocytopenia, but also a predictor of recovery of thrombopoiesis, in a previously thrombocytopenic patient.

Published data from various institutions<sup>[12,22,23]</sup> and countries have put varying figures as the trigger for platelet transfusion in hospitalized dengue patients. The DHS guidelines stipulate that platelet transfusion should be given to patients with platelet count  $< 20,000/\text{cumm}$ . In our study, 34 of the 250 patients receiving platelet transfusion, 18 patients had a platelet count  $> 20,000/\text{cumm}$ , out of which only one patient who had hemorrhagic manifestations that necessitated the use of platelet transfusion. Another study had found 56.2% of inappropriate platelet transfusions during dengue epidemics in Delhi during 1999.<sup>[20]</sup> Many times, the prescription for this blood component is not based on medical rationale, but as a response to an intense social pressure on the treating physicians by the patients and their relatives.

### **Conclusions**

- PIs may act as predictive tools in the diagnosis and predicting outcomes in dengue fever
- PIs give information on whether the platelet destruction is ongoing (necessitating an impending platelet transfusion) or whether the bone marrow is responsive and platelet transfusions can be put on hold
- In transfused dengue patients, low platelet count and PCT, high PDW, MPV, PLCR, and IPF were found to be statistically significant
- PIs are not having an important role in determining the hospital duration of dengue fever patients
- Clinicians need to be sensitized about the utility and limitations of these indices in day-to-day clinical practice. Transfusion decisions based

on these indices may also help in rationalizing the need for red cell and platelet transfusions in dengue and thereby allay the of anxiety clinicians and improving the preparedness of the blood center to provide necessary blood components for transfusion

- Most of these studies are retrospective in small study populations and the cutoff values have not been validated prospectively. Hence, large epidemiological, randomized, control studies are needed to establish the utility of these parameters in dengue beyond doubt.

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### **Conflicts of interest**

There are no conflicts of interest.

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