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THE ASSOCIATION OF IMMATURE PLATELET FRACTION LEVELS WITH BLEEDING MANIFESTATIONS IN PATIENTS WITH SEVERE THROMBOCYTOPENIA IN DENGUE FEVER: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background and objectives: Dengue ranges from asymptomatic to severe forms like dengue haemorrhagic fever. Severe cases often show thrombocytopenia and bleeding. The Immature Platelet Fraction (IPF) indicates reticulated platelets and helps predict platelet recovery in dengue. This study examined the association between immature platelet fraction and bleeding in dengue patients, plus IPF's role in predicting platelet recovery.

Methods: Seventy-five patients with dengue fever and severe thrombocytopenia (platelet count < 25,000 cells/µl) participated after signing the informed consent. IPF was measured and classified as <10 or≥10. Platelet counts were checked after 24 and 48 hours. The correlation between IPF, bleeding manifestations, and platelet recovery was analysed.

Results: Our study showed (M: F 2:1), with 77.3% of patients aged 18-39 years. Common comorbidities were diabetes mellitus and hypertension. Fever affected (98.7%) patients, followed by myalgia (94.6%), fatigue (92%), and gastrointestinal symptoms (64%). Bleeding occurred in (28%), including mucocutaneous (16%), gastrointestinal (8%), and genitourinary (6.7%). Mean platelet count rose from 12,015 (±5,055.05)/µl at baseline to 45,318 (±20,829.83)/µl at 48 hours. Most patients (74.6%) had IPF ≥10, which was associated with lower bleeding risk (p=0.001) but a nonsignificantly higher platelet increment (p=0.262). Blood transfusion was required in 12/75 patients; 3/12 had no bleeding.

Conclusion: The study found that dengue patients with severe thrombocytopenia and an immature platelet fraction (IPF) ≥ 10 had lower bleeding and a faster platelet recovery than those with an IPF < 10, predicting bleeding risk and guiding platelet transfusions, but further research is needed.

KEYWORDS: Immature platelet fraction, Dengue Fever, Severe Thrombocytopenia, Bleeding

INTRODUCTION

Dengue is an arthropod-borne infection caused by the dengue virus (DENV), a member of the Flaviviridae family.[1] The clinical picture following DENV infection ranges from asymptomatic disease to symptomatic disease with varying clinical severity, including: dengue fever (DF), dengue haemorrhagic fever and dengue shock syndrome.[2] Thrombocytopenia is reported in 79–100% of patients admitted with dengue and is often managed inappropriately with platelet transfusions in over 22-23%.[3] Randomised controlled trials have shown that prophylactic platelet transfusions are not superior to supportive care.[4,5] Current guidelines for platelet transfusions address thrombocytopenia in chronic bone marrow failure, thrombocytopenia in the perioperative setting, and sepsis, but may not be appropriate to address thrombocytopenia in dengue.[6]

Immature platelet fraction (IPF) is a blood parameter that measures the level of reticulated platelets in the peripheral blood by identifying the cells' high ribonucleic acid content.[7] Consumptive or recovering thrombocytopenic disorders display a high IPF, while a low IPF favours bone marrow suppression, helping to differentiate between these two processes.[8] A recent study used IPF to predict platelet recovery in DF, with IPF values greater than 10% associated with recovery of platelets within 1-2 days.[9]

Severe thrombocytopenia is one of many factors that predict a higher risk for spontaneous bleeding and severe disease[10-12], but is often over-treated.[4,5,13] IPF, as a surrogate marker of thrombopoiesis, can potentially help in predicting the severity of thrombocytopenia in dengue, thereby identifying individuals at risk for bleeding. This may avoid platelet transfusion in asymptomatic patients with severe thrombocytopenia, reducing the risk of transfusion-related complications and reducing the burden on blood banks in tertiary care centres.[14] This prospective observational study aimed at determining

the association of immature platelet fraction levels and bleeding manifestations in patients with dengue fever and severe thrombocytopenia.

METHODOLOGY

This prospective observational study included patients with dengue who were admitted and treated at our hospital between August 2019 and April 2021. Institutional Ethics Committee (IEC) approval was obtained before the initiation of the study (IEC Reference No 291/2019). Patients were included in the study if 1) they were diagnosed with dengue fever (i.e. patients who tested positive for either NS1 antigen/ IgM Dengue/ both tests),[15] 2) had severe thrombocytopenia i.e. platelet count < 25,000 cells/ µl/ Grade 4 thrombocytopenia based on the Common Terminology Criteria for Adverse Events(CTCAE) classification[16] at the time of admission or any time during their hospitalization and 3) consented to participation in the study. Patients were excluded from the study if 1) they were less than 18 years of age, or if 2) they had a coexisting cause of thrombocytopenia like Immune thrombocytopenia (ITP), aplastic anaemia, or an underlying haematological malignancy or if they were diagnosed with 3) a coexisting infection causing thrombocytopenia.

The primary objective of the study was to correlate IPF levels with clinical bleeding in patients with dengue and severe thrombocytopenia. The secondary objective was to study the role of IPF in predicting the rise in platelet counts in 24-48 hours. The estimated sample size for our study was based on a study by Dadu et al.[9] and powered to determine the estimated outcome of platelet recovery at a relative precision of 10% and at 95% confidence level. It was estimated that the minimum sample size required for the study would be 75.

Patients fulfilling both inclusion criteria were then monitored as follows: 1) An IPF level was sent on the day the patient fulfilled the inclusion criteria. Patients were further classified into two groups: patients with an IPF value < 10 and ≥ 10. [9] Three platelet count readings, 24 hours apart, were analysed to determine platelet count increment. A manual platelet count assessment was performed by a pathologist by reviewing the peripheral blood smear.

Patients included in the study also underwent a detailed clinical examination and details of their illness, including: the duration of fever and hospitalisation, presence of a co- morbid illness, symptomatology, use of medications that may affect platelet counts or platelet function, such as antiplatelets and anticoagulants, presence and degree of bleeding manifestations, and use of blood product transfusions. The IPF was correlated with bleeding manifestations. The severity of bleeding manifestations was graded according to the World Health Organisation classification of bleeding[17], with bleeding manifestations broadly grouped into the following: genito-urinary, gastrointestinal, mucocutaneous and intracranial bleeding.

All statistical data were analysed using Statistical Package for the Social Sciences (SPSS v). Descriptive statistics were computed with frequency and percentage for categorical variables. Continuous variables were assessed using mean and standard deviation. Pearson's chi-square test and independent t-tests were used to analyse the association.

RESULTS

The study showed a male preponderance (M: F ratio of 2.:1). Most of the study population, 40/75 (77.3%), was in the age group of 18-39 years. Most of the patients, 55/75 (70.7%), included in the study did not have any comorbidities. The most common comorbid illness was diabetes mellitus (11/75), followed by hypertension (8/75) and hypothyroidism (3/75). The most common symptom was fever in 74/75 (98.7%) patients, followed by myalgia 71/75 (94.6%), fatigue 69/75(92%) and gastrointestinal symptoms 48/75 (64%).

More than half of the patients, 60% (45/75), had a platelet count between 5,000 and 15,000 cells/µl when they were included in the study. Only 66/75 patients had platelet count assessments on all three days and could be analysed for platelet increment. Mean platelet counts on day 1, day 2(after 24 hours) and day 3(after 48 hours) were 12015.15 ± 5055.05 cells/microL , 22969.70 ± 11760.38 cells/microL, 45318.18 ± 20829.83 cells/microL respectively.

Bleeding was noted in 21/75 (30.7%) patients, of which 12/75(16%) had mucocutaneous bleeding, 6/75(8%) had gastro-intestinal bleeding and 5/75(6.7%) had genito-urinary bleeding. No patient had intracranial bleeding. Two patients had bleeding from two sites: (mucocutaneous and gastrointestinal) and (mucocutaneous and genito-urinary). Most patients, 56/75 (74.6%), had an IPF of greater than or equal to 10, whereas 19 patients (25.4%) had an IPF less than 10. Patients who had mucocutaneous bleeding had a lower mean platelet count (11916.66 cells/µL) on the day of inclusion into the study compared to the patients who had gastrointestinal (15333.33 cells/µL) and genitourinary bleeding (14600 cells/µL). An IPF greater than or equal to 10 had a lower incidence of bleeding compared to patients who had an IPF less than 10 (p=0.01) Table1. The increase in platelet counts from baseline in 24 hours and 48 hours between the two groups (IPF < 10 and ≥10) is shown in Table 2. The mean platelet count increment at 24 hours and 48 hours was higher in patients with an IPF ≥ 10. however, this was not statistically significant. Of the 75 patients, 63 were not transfused with platelet units. Of the 12/75 patients that did receive platelet transfusions (9/75 with bleeding and 3/75 without bleeding), 8/75 patients received 2 units of random donor platelets (RDP), 3/75 received 4 units of RDP, and one patient received 6 units of RDP. Three patients who did not bleed but received platelet transfusions had platelet counts of 6,000 cells/µl, 7,000 cells/µl and 9,000 cells/µl on the day of transfusion.

Table 1. Association between Bleeding Manifestations and IPF

Bleeding Manifestations	Immature platelet fraction		P value (Chi-square test)
	<10	≥10	

Absent	5	49	0.001
Present	14	7	

Table 2. Platelet count increment and IPF

Interval increase in platelet counts	IPF	Number of patients (N=75)	Mean ± Std. Deviation (cells/µl)	Independent t-test (p-value)
Increase in platelet count in 24 hours (First sample – second sample)(N=75)	<10	19	9947.36 ± 9640.61	0.262
	≥ 10	56	13339.28 ± 11787.93	
Increase in platelet count in 48 hours (First sample -third sample)(N=66)	<10	17	27705.88 ± 21905.37	0.188
	≥ 10	49	35244.89 ± 19512.31	

DISCUSSION

Dengue fever has emerged as a global public health disease over the last few decades due to population growth, unplanned urbanisation, ineffective mosquito control and a lack of health care infrastructure.[18,19] In India, dengue is now one of the leading causes of hospitalisation in both rural and urban settings, with a steady rise in mortality.[20] Dengue deaths are driven by profound capillary permeability and plasma leakage and cause life-threatening bleeding and profound shock. The resultant organ dysfunction usually manifests in the critical phase.[21] Bleeding in severe dengue occurs because of endothelial dysfunction, thrombocytopenia, and platelet dysfunction.[22] Current treatment guidelines are directed towards early identification of "warning signs" that portend a poor outcome and mitigating their progression with adequate fluid resuscitation.[2,13,15,23]

Demographics and Clinical Profile:

Dengue fever affects individuals of all age groups, with the highest incidence noted in children and young adults.[24-26] A similar preponderance for younger adults was noted in this study. Mortality and severe disease, however, are usually seen in the extremes of age, with the elderly and children at greatest risk.[10,11,21-22,27] This study also showed a male preponderance comparable to findings in other studies.[24,28] Studies have noted a higher incidence of mortality in women, and the female gender has been noted as an independent risk factor for bleeding.[11-12,27] The most common symptoms reported by patients in this study were fever, myalgia and gastrointestinal symptoms. The presence of biphasic fever and gastrointestinal symptoms has been noted to be associated with a higher incidence of bleeding, though no definitive pattern exists.[10,11,12]

Nearly one-third (30%) of our patients had bleeding manifestations, of which mucocutaneous bleeding was the most common. Lower numbers were reported in studies by Looi et al. (24%) and Wayez et al. (3%).[24,26] Chuansumrit et al reported bleeding in 60 % (38/64) of their patients (pediatric population), of which petechiae was the most common manifestation, seen in 76% (29/38) (28). Our study only included patients with severe thrombocytopenia (platelet counts < 25,000cells/microL), which may have contributed to the higher percentage of patients with bleeding in this study. This study noted that the most common comorbid illnesses were diabetes mellitus, followed by hypertension. Comorbid illnesses like diabetes mellitus and hypertension have been noted to be independent risk factors for progression to severe disease.[11] A study in Taiwan assessing mortality in older patients with dengue noted that pre-existing cardiac disease was a significant risk factor.[21]

IPF and its role as a predictor of platelet recovery:

The role of IPF in dengue fever to predict platelet recovery has been evaluated in multiple studies.[9,24-26,28-31] Dadu et al. showed that there was a dramatic improvement in platelet counts within 24 hours of the IPF peak when values were trended over time.[9] Over 90% of patients recovered their platelet count within 24-48 hours of their IPF, increasing by over 10%.[9] Other studies showed platelet count recovery was at its highest within 24 hours after IPF values began to decrease from their peak.[31] Similar findings of good correlation between IPF value increment and platelet recovery in dengue have been noted. Although these studies differed on a specific IPF value to predict platelet recovery, all studies noted that platelet recovery was seen once IPF values were above the lab reference range for their specific population.[24-26,28-31]

This study showed a higher increment in platelet count in patients who had IPF values ≥10, though this association was not statistically significant. The lack of statistical significance in this study could be attributed to the small sample size

and a single IPF value measured at the time of inclusion into the study. Serial IPF values were a better predictor of platelet increment as seen in the studies.

IPF as a Predictor of Bleeding Manifestations:

Of the 75 patients in this study, approximately 2/3rd had an IPF ≥ 10 at the time of inclusion into the study. This indicates that although patients had severe thrombocytopenia, there was an appropriate compensatory thrombopoietic marrow response. From the single IPF value obtained, patients with a value ≥10 were significantly less likely to bleed over the next 48 hours(p=0.001). Following an extensive literature search, no other studies have compared IPF and bleeding in patients with dengue. IPF has been studied in patients with ITP and is an independent predictor of bleeding. [32,33] Higher IPF and absolute immature platelet counts were also associated with a lower incidence of severe bleeding. McDonnell et al reported that an IPF < 10.4% was an independent predictor of bleeding risk at severe thrombocytopenia (platelet counts <10000 cells/µl) in patients with ITP.[33] This study demonstrated that a single IPF value in patients with severe thrombocytopenia was sufficient to predict bleeding.[33] This may be useful in low-resource settings where obtaining a single reading may be more feasible than trending IPF. A recent large retrospective study from India, evaluating predictors of severe bleeding in dengue treated in the intensive care unit, found that only 1/3rd of thrombocytopenic patients bled. In contrast, factors like a maximal temperature of > 38.3 °C, deranged activated partial thromboplastin time and presence of organ dysfunction as determined by the SOFA(Sequential organ function assessment) score were independent predictors of bleeding.[34] Studies have identified varying factors besides thrombocytopenia, such as elevated liver enzymes, degree of lymphopenia, hematocrit percentage, and presence of abdominal symptoms/signs such as vomiting and abdominal tenderness, as potential independent early clinical predictors of bleeding tendencies.[10,12] Hence, IPF alone should not be used as the sole predictor of bleeding without considering the entire clinical context.

Bleeding and Platelet Transfusions:

Studies have shown a lack of evidence for prophylactic transfusions in severe thrombocytopenia and that they may likely harm.[35] This includes transfusion reactions, transfusion-related infections and in some highly endemic areas, transfusion-related transmission of dengue from asymptomatic viremic donors. Studies also show that prophylactic transfusions delay platelet count recovery and prolong hospitalisation. [35] Prophylactic platelet transfusions also threaten the availability in resource-poor countries where dengue is endemic, as more potential donors are turned away due to recent dengue infection.[14]

The role of platelet transfusions in patients with bleeding has been controversial. WHO guidelines state that blood transfusions should be limited to life-threatening bleeding in the setting of severe bleeding and managed with fresh packed red cells/fresh whole blood, with equal importance given to adequate fluid resuscitation and treating shock.[15] The Indian guidelines make similar recommendations with the additional caveat that use of platelet products can be considered in bleeding patients with thrombocytopenia. Testing for coagulopathy is also recommended in the setting of massive haemorrhage.[36] In a study of coagulation abnormalities of 48 children with bleeding in dengue, a decrease in procoagulant factors like protein C, protein S and antithrombin III was noted with worsening shock. This was associated with a proportionate rise in plasminogen activator inhibitor type I. This was reflected in coagulation tests demonstrating mildly prolonged prothrombin and activated partial thromboplastin times and decreased fibrinogen levels.[22] The study postulated bleeding in severe dengue was likely due to a hyperfibrinolytic process with secondary activation of the hemostatic response. This raises the question if severe bleeding in dengue should be managed on lines like those of DIC.[22] Given the multiple coagulation abnormalities noted, studies have also explored the use of Anti-D globulin and IVIG as possible alternatives to platelet transfusions.[37] Smaller cohorts of patients have been treated with recombinant factor VIIa (rFVIIa), interleukin-1 (IL-1), or tranexamic acid with little overall benefit.[13]

In this study, 12/75 patients received platelet transfusions (9/75 with bleeding and 3/75 without bleeding). The 3 patients who received platelet unit transfusions without bleeding could likely have been avoided. Platelet transfusions should likely be reserved for patients with bleeding in the setting of severe dengue as an adjunct to packed cell transfusion and, more urgently, adequate fluid resuscitation.

The small sample size limits this study. A larger cohort of patients may add strength to the association found in this study. The second limitation is that a single IPF value was taken into consideration to determine its ability to predict bleeding and platelet recovery, in contrast to existing studies that examined the trend of IPF. This study also did not analyse the role of other potential risk factors for bleeding and their relationship with IPF in determining bleeding outcomes in patients. These limitations could be addressed in further studies, examining the role of IPF in predicting bleeding manifestations in dengue fever.

CONCLUSION

In conclusion, this study showed that dengue with severe thrombocytopenia with an IPF ≥ 10 had a lower incidence of bleeding compared to patients with an IPF < 10. IPF can be regarded as an important predictor of bleeding in patients with severe thrombocytopenia due to dengue and likely helps in the judicious use to transfuse platelet units. Further studies to further elucidate this relation and to examine the role of IPF as an independent predictor of bleeding are warranted.

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List of Abbreviations: (In alphabetical order)
IPF - Immature platelet fraction
DF – Dengue Fever
CTAE – Common Terminology Criteria for Adverse Events
SOFA - Sequential organ function assessment
IEC - Institutional Ethics Committee
SPSS - Statistical Package for Social Sciences