Original Article

Analysis of Clinical and Etiological Spectrum of Febrile Thrombocytopenia and correlation of Platelet Indices with Recovery

Vennila Muniswamy[1] Lokesh P[2] and Yogambal Muthureddy[3]

[1]Associate Professor, Department of Pathology, Government Vellore Medical College, Vellore, India.
[2]Post Graduate, Department of Paediatrics, Institute of Child Health and Hospital for Children, Madras Medical College, India.
[3]Associate Professor, Department of Pathology, Govt Kilpauk Medical College, Chennai, India.

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Corresponding Author:

Vennila Muniswamy
Associate Professor
Department of Pathology
Government Vellore Medical
college, Vellore, India.
8939958993
vennilapatho@gmail.com

ABSTRACT

Introduction: Patients with severe thrombocytopenia must be admitted to the hospital in order to be monitored and treated since they may require immediate platelet transfusions. Reduced platelet production, aberrant distribution, or accelerated platelet degradation can all lead to thrombocytopenia.

Materials and Methods: This study was conducted in Department of Pathology, Department of General Medicine and Department of Microbiology, Government Vellore Medical college, Vellore. During this period 60 cases of fever (oral or axillary temperature of more than 380C at time of admission with Platelet count less than 1.5 lakhs /cu.mm at any point of hospital stay were included in the study.

Results: Among the 268 fever cases admitted in our centre during the month of August and September 2018, 60 patients had febrile thrombocytopenia accounting for 22.3%. The study group showed steady rise in platelet count, mean platelet volume, platelet distribution width in majority of patients during the follow up period. statistically significant correlation was found between platelet count and other platelet indices such as mean platelet volume and plateletcrit. The mean platelet volume and platelet crit showed statistically significant correlation with platelet count. Duration of hospitalisation showed negative correlation with platelet count and plateletcrit. Among those with rising trend in platelet count during recovery significant correlation was found between the trends of MPV and PDW.

Conclusion: Undifferentiated fevers predominate in our geographic area which needs further research. Platelet count and plateletcrit has inverse relationship with hospitalization duration while MPV and PDW do not have significant association with hospitalization or fever duration.

Keywords: *Etiological Profile, Clinical Profile, Thrombocytopenia, Fever, Platelet Indices.*

INTRODUCTION

The most frequent reason for seeking medical care is continues to be infections. A clinical disorder known as febrile thrombocytopenia is characterized by low platelet counts during an acute feverish illness. While individuals with severe thrombocytopenia come with potentially fatal bleeding episodes, those with mild thrombocytopenia heal even without any help. Patients with severe thrombocytopenia must be admitted to the hospital in order to be monitored and treated since they may require immediate platelet transfusions. Reduced platelet production, aberrant distribution, or accelerated platelet degradation can all lead to thrombocytopenia. In India, rural populations are affected by outbreaks of several illnesses, including dengue fever and malaria, which can lead to febrile thrombocytopenia. Repeated platelet transfusions, studies of different fever profiles, and inpatient intensive care medical services put a greater financial strain on lower socioeconomic populations, depleting their savings. Therefore, a predictive marker is required to evaluate patients' recuperation from disease in order to prevent excessive platelet transfusions and medical costs.

Platelet count and platelet indices can be easily measured in all cell counters without any extra cost or blood requirements along with complete blood count. The clinical utility of platelet indices in various infective and inflammatory conditions is reported to be significant.[1-4] Platelet distribution width (PDW) reflects the size distribution, Mean platelet volume (MPV) reflects the level of platelet function/activation.[5,6]

The main pathogenesis of thrombocytopenia in dengue is suggested to be due to bone marrow depression, immune mediated destruction or sequestration. MPV and PDW levels are lower in hypo-proliferative thrombocytopenia and higher in destructive immune thrombocytopenia. In the setting of thrombocytopenia with low MPV, rising trend in MPV may herald recovery as the thrombocytopenia is due to bone marrow depression in these cases. In contrary, persistently elevated MPV along with ongoing thrombocytopenia suggests immune destruction and deterioration of illness.[8-14]

The data regarding etiological spectrum that cause febrile thrombocytopenia in the given geographical area is limited in available literature. The predictive role of various platelet indices in differentiating recovering and detoriating disease progression would greatly aid in the development of management protocols for febrile thrombocytopenia patients.

The current study we evaluated the clinical presentation and causes of febrile thrombocytopenia among the study population to analyse the relationship of variation in trends of platelet indices with outcome of illness.

MATERIALS AND METHODS:
This study was conducted in Department of Pathology, Department of General Medicine and Department of Microbiology, Government Vellore Medical college, Vellore. The study was undertaken between June 2018 to September 2019 after getting clearance from Institutional Ethics Committee. The current study was undertaken as part of the ICMR-STS project (Reference Id:2018-01441). During this period 60 cases of fever (oral or axillary temperature of more than 38^0C at time of admission with Platelet count less than 1.5 lakhs /cu.mm at any point of hospital stay were included in the study.

Initial assessment
Information sheets were provided and informed consent was sought from all study participants. On recruitment to the study, detailed history regarding various symptoms, examination findings and investigation results were collected. The study population were subjected to relevant fever profile investigations and infective aetiology of illness was confirmed as per the following operational definitions.
1. Malaria and filaria – presence of parasites in peripheral smear.
2. Enteric fever – presence of salmonella typhi/ Para typhi in blood culture or by a 4-fold increase in titres of Widal test.
3. Dengue fever – presence of NS1Antigen or Dengue IgM antibody positivity by ELISA
4. Scrub typhus – scrub IgM titre of more than 0.5 by ELISA with or without eschar
5. Leptospirosis - Leptospirosis Ig M antibody positivity by ELISA
6. Chikungunya fever – chikungunya antibody positivity by ELISA
7. Human immunodeficiency virus – ELISA and Western blot assay for HIV 1 AND HIV 2
8. Tuberculosis –presence of Acid-fast bacilli in sputum
9. Undifferentiated fever - Diseases that were not confirmed by the abovesaid investigations.

Haematological Assessment:
Peripheral smear examination was done to all participants to rule out non infective causes such as leukaemia and pancytopenia. The platelet indices of study population were analysed in EDTA preserved venipuncture samples using automatic cell counter (Sysmex XP 100). Mean platelet volume, platelet distribution width and plateletcrit are the indices measured. The normal range of platelet indices used in our study are as follows: Mean platelet volume (MPV)=8 to 12 fL; Platelet distribution width= 9 to 14 fL; Plateletcrit=0.22 to 0.24%; Platelet count= 1,50,000 to 4,50,000 cells/cu.mm.

The study participants were followed up during their period of hospitalisation and their alternate day platelet count and platelet indices were monitored. The outcome of illness in the form of recovery, prolonged hospitalisation more than 2 weeks with or without platelet transfusion, patients left hospital against medical advice and death were recorded.

Statistical Analysis:
The relationship between variation in trends of platelet indices and outcome of illness were statistically analysed. Data were analysed using EPIINFO software version 7.0. Continuous variables such as platelet indices of study group were presented as Mean and standard deviation. Categorical variables such as different aetiologies were presented as proportions. The correlation between variation in trends of platelet indices and outcome of febrile thrombocytopenia cases was done using Pearson correlation coefficient. A p value of less than 0.05 is considered to be statistically significant.

RESULTS:

Out of 268 fever cases admitted in our centre during the month of August and September 2018, 60 patients had febrile thrombocytopenia accounting for 22.3%. Males were in higher proportion compared to females with male female ratio of 2:1. Age group of 20 -40 years were more frequently affected. Undifferentiated viral fever is the most common cause of febrile thrombocytopenia in our geographic area followed by malaria, scrub typhus and mixed infections.

Myalgia, headache and nausea were the commonest clinical presentation of febrile thrombocytopenia. Bleeding manifestations were seen in 30% of the study participants. Anaemia was observed in 33.3% of the patients, 38.3% had leukopenia, 6.66% had leucocytosis associated with febrile thrombocytopenia. We observed that 41.6% of the study group presented with severe thrombocytopenia and 8.3% of the group had very severe thrombocytopenia. Clinical recovery of patients from illness was associated with improvement in platelet count in 90% of our study group while 10% showed mild reduction in platelet count.

Table 1 Characteristics of the study population

Variable	Frequency (n=60)	Percentage
Age (in years)		
13-20 years	11	18.3
20-40 years	29	48.3
40-60 years	12	20
>60 years	8	13.3
Gender		
Male	40	66.7
Female	20	33.3
Etiology of febrile thrombocytopenia		
Malaria	7	11.67
Dengue	3	5
Typhoid	3	5
Scrub typhus	4	6.66
Leptospirosis	2	3.33
Pneumocystis pneumonia	1	1.67
Mixed infections		
Malaria + Dengue	1	1.67
Malaria + Typhoid	1	1.67
Scrub typhus + Typhoid	1	1.67
Scrub typhus + Leptospirosis	1	1.67
Undifferentiated viral fever	36	60
Clinical presentation		
Headache	24	40
Body pain	36	60
Nausea/vomiting	26	43.3
Cough/ dyspnoea	20	33.3
Chills/ rigor	15	25
Joint pain	7	11.67
Loose stools	12	20
Abdominal pain	12	20
Altered sensorium/convulsions	11	18.3
Weight loss	5	8.3
Petecheial rashes	5	8.3
Gum bleed	12	20
Hematuria	3	5
Gastrointestinal bleed	2	3.33

Table 2 Characteristics of platelet indices among the study population

Variable	Frequency (n=60)	Percentage
Severity of Thrombocytopenia		
<20,000 (Very severe)	5	8.3
20,000 to 50,000 (Severe)	25	41.6
50,000 to 1,00,000 (Moderate)	20	33.3

>1,00,000 (Mild)		10	16.6

Mean platelet indices in relation to hospitalisation

Platelet indices	Mean on day of admission (SD)	Mean value on day 3 admission (SD)	Mean value on day of discharge (SD)
Platelet count/cu.mm	67367 (35084)	82668 (48543)	111000 (50316)
Mean platelet volume(fL)	10.18 (1.2)	10.4 (1.3)	10.4 (0.9)
Platelet distribution width(fL)	14 (3.2)	14.5 (3.3)	14.2 (2.6)
Platelet count/cu.mm	67367 (35084)	82668 (48543)	111000 (50316)
Plateletcrit (%)	0.1(0)	0.1(0)	0.1(0)

Mean platelet indices in relation to hospitalisation

Platelet indices	Rising trend	Declining trend	No change
Platelet count	54	6	0
Mean platelet volume	30	27	3
Platelet distribution width	36	24	0
Plateletcrit	56	3	1

Degree of thrombocytopenia with period of hospitalisation

Degree of thrombocytopenia	Hospitalisation <3 days	Hospitalisation 3 to 7 days	Hospitalisation >7 days
Very severe	0	5	0
Severe	2	22	1
Moderate	0	20	0
Mild	5	5	0

Mean platelet volume(fL)

<8	1	2	0
8-12	5	45	1
>12	1	5	0

The study group showed steady rise in platelet count, mean platelet volume, platelet distribution width in majority of patients during the follow up period. On the day of lowest platelet count, 51 cases had normal mean platelet volume, 3 cases had low MPV and 6 cases had high MPV. During the follow up period, 30 cases showed rising trend in mean platelet volume while 27 cases showed declining trend and 3 cases showed no change in their mean platelet volume. Platelet distribution width showed rising trend in 36 cases and declining trend in 24 cases. Among those with rising trend in platelet count, there is statistically significant correlation between the trends of mean platelet volume and platelet distribution width.

In our study, 59 cases recovered well and discharged, while 1 patient died due to multiorgan failure and associated ailments such as diabetes mellitus and shock. On linear regression analysis, statistically significant correlation was found between platelet count and other platelet indices such as mean platelet volume and plateletcrit (correlation coefficient =0.92). There was no significant association found between fever duration and platelet indices on the day of lowest platelet count by linear regression analysis. Duration of hospitalisation showed statistically significant negative correlation with platelet count and plateletcrit on the day of lowest platelet count (Table7 & Table 9). No association was found between hospitalisation duration and mean platelet volume as well as platelet distribution width. Only one case had unfavourable outcome of death. The platelet indices of one patient with unfavourable outcome had lower platelet indices when compared to the mean of platelet indices of the favourable outcome group.

DISCUSSION:
Febrile thrombocytopenia is a clinical condition with varied causes but to be monitored cautiously with lab parameters to avoid severe bleeding complications. In this study, febrile thrombocytopenia occurred in 23.3% of fever cases admitted in our tertiary care centre that is consistent with the study conducted by Geetha et al.[16]

In this study male outnumbered female accounting for 60%. Cases were highest in 20 -40 years age group as compared to study conducted by Choudhary et al.[17] Myalgia, headache and nausea/vomiting were the common clinical findings in our study which is similar to the study conducted by Hariprasad et al[18] and Fah et al[19]. Undifferentiated viral fevers account for 60% of cases in the present study similar to study conducted by Kulkarni at al,[15] while Geetha et al[16](20.9%) and Hariprasad et al (26%)[18] had reported a lesser prevalence. In this study, 11% were positive for Malaria and 5% were positive for dengue which is lesser than the studies conducted by Geetha et al[16] who reported them to be 41.86% and 32.55% and

Hariprasad et al who reported them to be 28.5% and 27%.[18] This may be attributed to the geographic differences and climatic changes resulting in various epidemic and endemic outbreaks.

We observed that 50% of our study group had platelet count less than 50,000 while study conducted by Yadav et al showed it to be 25.6%.[20] Bleeding manifestations were observed in 30% of our cases which was higher than reported by Yadav et al (11.5%). During the follow up period, the platelet count showed rising trend in 90% patients while Patil et al had observed a rising trend of platelets in 61% patients.[8]

Statistically significant negative correlation was found between platelet count and mean platelet volume similar to study conducted by Coelho et al[21] and Mukker et al[22]. No significant relation found between platelet count and platelet distribution width which is consistent with study conducted by Vishnuram et al.[23]

In our study group, the mean values of Platelet count, mean platelet volume and platelet distribution width increased between the values noticed on the day of minimal platelet count and at discharge while no significant difference was observed in Mean between MPV at the time of minimal platelet counts and at discharge in the study conducted by Sharma et al.[24]

In this study, patients with normal and low MPV showed rising trend in MPV while patients with high MPV on the day of minimal platelet count showed declining trend in MPV, both indicates recovery pattern as suggested by Khandal et al.[11] This observation supports the role of MPV in suggesting progression of illness while statistical analysis could not be performed due to small sample size. The patient who had mortality had MPV in normal range with rising trend of MPV and platelet count during follow up.

Hospitalisation period shows significant inverse relationship with platelet count and plateletcrit on the day of minimal platelet count. As all the cases were well managed with good surveillance, 98.3% of our cases recovered well without any adverse outcomes, while 1 case died of multiorgan failure, shock and associated diabetes mellitus complications. This is similar to the study done by Patil et al in which 95% cases recovered [8]

The mean platelet count and mean platelet indices on the day of minimal platelet count were lesser in mortality group than the favourable group who had good recovery from illness. This corresponds to the observation made by Sharma et al[24].

CONCLUSION AND RECOMMENDATIONS
The mean values of platelet indices were lower in mortality group when compared with favourable group who had good recovery. Based on our observations we also conclude that platelet count and plateletcrit have an inverse relationship with hospitalisation duration while MPV and PDW do not have significant association with hospitalisation or fever duration.

Studies with longer duration that cover entire year are required to assess various etiological causes and clinical presentations of febrile thrombocytopenia in our geographical area in relation to different monsoon period. Larger sample size would provide more evidence regarding the role of serial monitoring of platelet indices in predicting the outcomes of febrile thrombocytopenia patients.

Conflict of interest: None declared

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