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Original Research Article

MEAN PLATELET VOLUME AS A PREDICTOR OF CLINICAL OUTCOMES IN DENGUE FEVER: A PROGNOSTIC STUDY

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ABSTRACT

Background: Dengue is the fastest spreading mosquito borne viral disease globally. WHO guidelines use thrombocytopenia to indicate severity. Mean Platelet Volume (MPV), a platelet activation marker, may predict clinical outcomes. This study assessed MPV's prognostic utility in dengue.

Materials and Methods: Hospital based cross sectional study (2019) including 189 children (1 month - 12 years) with confirmed dengue IgM or NS1 positive patients admitted to Government Theni Medical College. Serial platelet counts and MPV were monitored until recovery.

Results: Mean age 6.7±2.72 years, male and female ratio (1.03:1). 38.62 % of the study participants had warning signs of dengue and abdominal tenderness most common 15.34%. The most common finding was a Leukopenia or thrombocytopenia seen in 74.6% of children with dengue fever. Significant inverse correlation between MPV and platelet counts emerged from Day 3 strengthening by Day 5. MPV correlated significantly with platelet counts from day 3 becoming strongly positive by day 5. However, MPV values showed no significant correlation with disease severity or serology. Its role in diagnosing severe disease remains controversial.

Conclusion: While MPV dynamics reflect platelet recovery, it does not predict dengue severity. MPV monitoring aids clinical decisions particularly avoiding unnecessary platelet transfusions in non-bleeding children but should not replace standard severity assessments. It will be useful when there is diagnostic dilemma especially in the decision of administration of platelet transfusion especially among children with dengue without any bleeding manifestations.

Keywords: Dengue, MPV, IgM, NS1.

INTRODUCTION

"If you think you are too small to make a difference, try sleeping with a mosquito" by Dalai Lama, 17% of infectious diseases throughout the world are attributed to vector-borne diseases which account for more than 700000 deaths annually.[1] Of these Mosquito borne diseases are widespread in over 150 countries and have been known to infect over 500 million people resulting in 1 million deaths annually. In India, around 40 million people contract mosquito borne diseases annually.[2] For centuries man has been plagued by mosquitoes as nuisances and as vectors of mosquito borne diseases, resulting in irreplaceable losses in economy and human suffering which is often on the extremes. Mosquitoes are the root cause of numerous illnesses such as dengue, malaria, brain fever, yellow fever and Chikungunya etc.

Since the beginning of the mid twentieth century dengue is a viral disease transmitted by Aedes mosquitoes, which has seen a recent spread

throughout the tropical world. A rapidly spreading mosquito-borne viral disease dengue has seen a 30 fold increase in the last 50 years, with geographic extension to new areas and in recent times a shift from urban to rural settings.[3] Dengue has been placed as the most rapidly spreading vector-borne viral disease globally with a constantly increasing epidemiological determinant.

Dengue inflicts a significant health, economic and social burden on the populations of endemic areas. Globally the estimated number of disability-adjusted life years (DALYs) lost to dengue in 2001 was 528**.** The face of dengue fever has changed from a national to a global concern following drastic climatic changes, the expansion of dengue vectors to new geographic regions, Trans border migration of increasing human population and expansion of global trade and this has subsequently changed the scope of the disease. [4] Having established itself globally in both endemic and epidemic transmission cycles dengue viral infection in humans includes a wide range of clinical manifestations, ranging from mild fever to potentially fatal dengue shock syndrome.[3] No effective antiviral agents yet exist to treat dengue infection and treatment therefore remains supportive.

Although several evidence-based studies exist regarding the historical expansion of this disease is well, there still remains several fallacies across the tropical and subtropical world in terms of the potentially large burden of ill-health attributable to dengue.[5] Knowledge of burden of dengue and distribution is essential to determine optimal allocation of limited resources available for dengue control, patterns of global morbidity and mortality burdens based on prevalence and in evaluating internationally the impact of such activities.[6]

The criteria by WHO guidelines use thrombocytopenia as a potential indicator of clinical severity. Though, bleeding diathesis is an important part of dengue hemorrhagic fever (DHF), the nature of the hemostatic defect has not been defined completely. Three mechanisms have been identified as possible causative factors namely vascular injury, thrombocytopenia and coagulopathy.[7] Two major mechanisms are involved in the pathogenesis of thrombocytopenia in DF and DHF namely decreased production and increased peripheral destruction or increased utilization of platelets.[8] However several studies have shown lack of correlation between the degree of thrombocytopenia and the severity of bleeding. Studies have suggested the hemodynamic abnormalities as due to defects in platelet function reflecting from discrepancies between bleeding times and clot retraction times and platelet counts.[7,9]

The Platelet Indices (PIs) are believed to have a role in predicting the clinical course in various disease states in which platelets are presumed to play a pathogenic role. Among the platelet indices, the most extensively studied platelet activation marker is mean platelet volume (MPV). Furthermore, the value of PIs in suggesting the pathophysiologic mechanism of thrombocytopenia has been well established. It is also helpful in diagnosing and classifying the dengue into Dengue Fever (DF) and Severe Dengue.[10]

The inconsistency with monitoring of platelet counts especially during the course of dengue fever has opened the scope of other parameters as a prognostic factor and to assess the severity of the disease. This study is intended at bringing out the usefulness of one of the Platelet Index namely mean platelet volume whose measurement has become simple in recent times due to availability of automated analyzers. Further the lack of in depth studies in this hematological parameter in a developing country which often sees outbreaks of dengue has laid the foundation for the conduct of this study.

Aim of the Study

To estimate the prognostic significance of Mean Platelet Volume in Dengue and to study the association of mean platelet volume with severity, serology and treatment outcome to assess its prognostic utility, which can help in predicting the mortality and morbidity associated with dengue fever.

MATERIALS AND METHODS

Type of Study: Observational study

Study population: Children aged 1 month to 12 years of age admitted to the pediatric ward of Government Theni Medical College, Theni.

Study place: Pediatric department, Government Theni Medical College, Theni

Study period: 1 year

Sample size: All children admitted with a diagnosis od Dengue fever / Dengue Haemorrhagic Fever / Dengue Shock Syndrome within the study period.

Inclusion Criteria

Dengue IgM positive or NS1 positive children of age between 1 month to 12 years admitted to pediatric department of Government Theni Medical College Hospital, Theni.

Exclusion Criteria

Parents of children who refuse to give consent for the study. Children who are dengue IgM or NS1 positive and associated with other conditions like aplastic anaemia or Idiopathic Thrombocytopenic Purpura and Child diagnosed as IgM or NS1 positive outside and found to be negative at Government Theni Medical College Hospital.

Method

Basic parameters on age, name of the parent, occupational status, residence and per-capita income were collected. Children below 12 years of age admitted with history of fever and other symptoms included in the case definition of dengue fever, positive serological test of either NS1 antigen or IgM dengue antibodies positivity are included in the study. Serial monitoring of various parameters like

platelet count and mean platelet volume is done until complete recovery of the child occurs.

Case Definition

Probable case of Dengue fever: acute febrile illness with two or more of the below mentioned manifestations such as headache, myalgia, rash, arthralgia, haemorrhagic manifestations, leukopenia, retro-orbital pain and supportive serology (Reciprocal haemagglutination- inhibition antibody titer ≥ 1280, Comparable IgG Enzyme Linked Immuno Sorbent Assay (ELISA) titer and positive IgM antibody test on a late acute or convalescent-phase serum specimen (or) occurrence as other confirmed cases of dengue fever at the same time and location, CONFIRMED CASE: a confirmation of the case provided by laboratory criteria and REPORTABLE CASE: reporting to authorities of any probable or confirmed case (World Health Organization, 1997).

Laboratory criteria for confirmation of dengue fever

Autopsy samples / serum (Dengue virus isolation), Four-fold or greater change in paired serum samples (Demonstration in reciprocal IgG or IgM antibody titers to one or more dengue virus antigens), Autopsy tissue, serum or CSF (Dengue virus antigen demonstration by ELISA, immunofluorescence or immunohistochemistry) and Autopsy tissue, serum or CSF samples (Dengue virus genomic sequence detection by polymerase chain reaction (PCR))**.**

Case definition of Dengue Haemorrhagic fever (DHF)

Biphasic fever or history of acute fever lasting for 2-7 days, Haemorrhagic tendencies as evidenced by at least one of the following (Positive tourniquet test, petechiae, ecchymoses or purpura, mucosal bleed, gastrointestinal bleed, injection sites or other locations and Haematemesis / melena). Thrombocytopenia (100000 cells per mm^3 or less) and Plasma leakage due to increased vascular permeability evidenced by at least one of the following (A rise in hematocrit (20% or greater above average for age, sex, population), a drop in hematocrit of 20% or more of baseline following volume-replacement treatment and signs of plasma leakage: pleural effusion, hypoproteinemia and ascites.

Case definition of Dengue Shock Syndrome (DSS)

In addition to all the four criteria for DHF, evidence of circulatory failure manifested by Weak and rapid pulse, narrow pulse pressure: < 20mmHg (2.7kPa) or manifested by hypotension for age and cold clammy skin and restless patient.

Laboratory Diagnosis of Dengue

Haematological Tests

During the acute stages of dengue infection platelets and haematocrit values are commonly measured carefully using standardized protocols, reagents and equipment. A decrease in the platelet count below 100000 per µL may be rare finding in dengue fever but it is a constant feature of dengue haemorrhagic fever. Following the onset of illness, the period between day 3 and day 8 sees the onset of thrombocytopenia.

Antigen detection

In patients with both primary and secondary dengue infections up to 9 days after the onset of illness demonstrated high concentrations of envelop/membrane (E/M) antigen and the non-structural protein 1 (NS1) antigens in the form of immune complexes. The NS1 glycoprotein which is produced by all flaviviruses, is also secreted from mammalian cells and it produces a very strong humoral response. Commercial kits for the detection of NS1 antigen are now available, though they do not differentiate between dengue serotypes. Detection of dengue virus antigen in acetone-fixed leucocytes and in snap-frozen or formalin-fixed tissues collected at autopsy is facilitated by immunoperoxidase and avidin-biotin enzyme assays and fluorescent antibody.

Serological tests by MAC-ELISA

IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) which measures total IgM in patients sera is captured by anti-µ chain specific antibodies to human IgM coated onto a microplate. Four serotypes of dengue-specific antigens, (DEN-1, -2, -3, and -4), are bound to the captured anti-dengue IgM antibodies. These are detected either directly by monoclonal or polyclonal dengue antibodies or indirectly conjugated with an enzyme which transforms a non-colored substrate into colored products. The optical density of the developed colour is measured by spectrophotometer. If samples are taken within the time frame of five days or more after the onset of fever, serum, blood on filter paper and saliva was used for detection of IgM. Virus-infected cell culture supernatants or suckling mouse brain preparations are used for deriving the dengue virus envelope protein. The sensitivity and specificity of MAC ELISA is good but only when used five or more days after the onset of fever.

Statistical Analysis

Data was collected using the proforma and was entered in Microsoft Excel. Statistical Package for Social Sciences software 16.0 was used for analysis of results. Descriptive statistical analysis has been carried out for discrete variables in the present study. Results on continuous measurements are presented as Mean ± SD and results on categorical measurements are presented in frequencies (%). Differences in the quantitative variables between groups were assessed by means of paired t test. Comparison between groups was made by paired sample t test. One-way ANOVA was used to find the difference between means of groups. To analyze categorical variables Chi square test was used. p value of < 0.05 using a two tailed test was taken as statistically significant. Correlation analysis and scatter plot of dependent and independent variables were also made.

RESULTS

This cross-sectional study involved 189 participants diagnosed with dengue in the age group of 1 month to 12 years. The mean age of the study participants was 6.7±2.72 years. The minimum age was 1 year and the maximum age was 12 years. Of the participants 96 (50.8%) were males and 93 (49.2%) were females.

The proportion of male participants was higher and the male to female ratio was 1.03:1. The mean age difference between male and female children is 0.1630 years. However, this difference is statistically insignificant ($p>0.05$) thereby implying that age distribution among male and female children are uniform and though there is difference, it is statistically insignificant.

The study participant was divided into 3 groups based on the distribution of age. Majority of the children were in the age group of 5 to 10 years followed by the < 5years group. The lowest population group was seen in the < 10 years age group (11.11%). Similar pattern was also observed when stratified among male and female participants.

The mean duration of fever was 3.53±1.17 days and mean duration of stay was 4.71±2.71 days. This could be explained on the fact that children may be afebrile following antipyretics but would have been under admission for correction of hemodynamic instability. Female patients have a longer duration of fever and a longer duration of stay compared to male patients and this was statistically significant. Similarly, children less than 5 years had a longer duration of stay in the hospital compared to other groups and this was statistically significant. However, though there was difference in the duration of fever between age groups it was not statistically significant (Table. 1).

Clinical features of Dengue Fever that were taken into account included Nausea / vomiting, rash, retro-orbital pain, body aches, positive tourniquet test, leucopenia or thrombocytopenia. The most common finding was a Leucopenia or thrombocytopenia seen in 141 (74.6%) of children with dengue fever. This was followed by body aches in 39.2% of children.

Among different age groups leucopenia or thrombocytopenia was the most common presentation. A higher proportion of retro-orbital pain was seen among >10 years age group. None of the children in the age group of above 10 years had a positive tourniquet test. Rashes were noted in 29% of the fewer than 5 age group while body aches were present at a uniform distribution among all age groups. Fever and vomiting was seen among all dengue subtypes. All children with DSS had body pain while rashes were seen with increased frequency among children with dengue fever (Table. 2).

The warning signs of dengue such as abdominal tenderness, persistent vomiting, decreased urine output, fluid accumulation such as pedal edema and anasarca, lethargy / restlessness, enlargement of liver, laboratory derangement of values of platelet and hematocrit were compared among different participants (Fig. 1). 38.62 % of the study participants had warning signs of dengue and more than one warning signs were present in some of the participants. Abdominal tenderness was the most common warning sign (15.34) which was followed by lethargy and restlessness. When stratified though abdominal tenderness was the most common sign, persistent vomiting was seen more commonly in the 5-10 years age group. Clinical fluid accumulation was seen only among <5years and 5-10 years age group (Fig. 2). The most common clinical manifestation was abdominal pain followed by vomiting in dengue fever (Fig. 3).

The mean age among dengue fever, dengue shock syndrome is lower compared dengue haemorrhagic fever and dengue fever subtypes. The pattern of mean duration of stay and duration of fever did not show any specific pattern or increase (Table. 2). Dengue fever is the most common presentation among all age groups, but it is seen more commonly among male participants (82.3%). However, a greater percentage of female participants present with decompensated DSS (4.3%) than male patients (1%). Compensated DSS was not seen among children >10 years and a higher percentage of decompensated DSS was seen among participants <5 years and >10 years (Table. 3).

The mean platelet volume and platelet counts among study participants over 5 days shows an increasing trend in both parameters except on day 5 when there is a sudden fall probably due to development of hemorrhagic manifestations (Table. 4). The trends depict a fall in platelet values for dengue fever and DHF grade 4 on day 4 and 5. For all other dengue types the platelet count increases from day 3 onwards. There is no significant correlation between MPV and Platelet count during the first 2 days of dengue fever, however the correlation becomes significant from day 3 onwards with the positivity gradually increasing from correlation present to strong positive correlation towards the 5th day (Table. 5; Fig. 4 and 5).

The different ranges of MPV with the severity of dengue. MPV at day 5 values does not however correlate with the severity of the disease (Table. 6). Similarly increasing MPV values does not have and significance with severity of disease. Hence the role of MPV as a diagnostic tool in diagnosis of severe disease remains controversial. There was difference in MPV values between DF, DHS and DSS and this inter difference was statistically significant. This difference was however over a period of 5 days and the difference in periods beyond this was not statistically significant (Table. 7). The mean difference in MPV values at the time of discharge for dengue fever, DHS and DSS was however not statistically significant, thereby demonstrating the utility of the diagnostic test during the early phase of

the disease when sufficient thrombocytopenia has not occurred (Table. 7).

Table 1: Duration of fever and hospital stay and Distribution of symptoms of dengue among age groups and gender

Duration of fever and hospital stay					Distribution of symptoms of dengue among age groups and gender					
Parameter	**Fever duration Mean ± SD**	**p value**	**Hospital stay Mean ± SD**	**p value**	**Nausea / Vomiting n (%)**	**Rash n (%)**	***ROP n (%)**	**Body aches n (%)**	***PTT n (%)**	***L/T n (%)**
Age Group										
< 5years	3.50 ± 1.10	0.0069	5.13 ± 2.95	0.0001	13 (19.1)	20 (29.4)	16 (23.5)	30 (44.1)	16 (23.5)	50 (73.5)
5-10 years	3.52 ± 1.21		4.52 ± 2.75		18 (18.0)	18 (18.0)	22 (22.0)	36 (36.0)	18 (18.0)	76 (76.0)
> 10 years	3.67 ± 1.24		4.29 ± 1.19		3 (14.3)	6 (28.6)	7 (33.3)	8 (38.1)	0	15 (71.4)
Gender										
Male (96)	3.59 ± 1.19	0.0007	3.46 ± 1.15	<0.0001	15 (15.6)	22(22.9)	19 (19.8)	35 (36.5)	11 (11.5)	70 (72.9)
Female (93)	4.49 ± 2.26		4.95 ± 3.10		19 (20.4)	22 (23.7)	26 (28.0)	39 (41.9)	23 (24.7)	71 (76.3)

ROP- Retro orbital pain, PTT-positive tourniquet test, L/T- leucopenia / thrombocytopenia

Table 2: Common clinical manifestations among dengue affected children and Age, hospital stay and fever duration among different dengue types

	Dengue fever	DHF	DSS
Common clinical manifestations among dengue affected children			
Fever	142 (100)	38 (100)	9 (100)
Nausea / vomiting	142 (100)	38 (100)	9 (100)
Rash	31 (21.8)	3 (7.9)	9 (100)
ROP	38 (26.8)	5 (13.2)	1 (1.1)
Body pain	36 (25.4)	9 (23.7)	9 (100)
Torniquet test positive	65 (45.8)	7 (18.4)	2 (22.2)
Leucopenia / thrombocytopenia	141 (99.3)	28 (73.7)	5 (55.6)
Age, hospital stay and fever duration among different dengue types			
Age	6.87 ± 2.74	6.30 ± 2.44	5.44 ± 3.28
Mean duration of fever	3.59 ± 1.21	3.21 ± 0.91	3.89 ± 1.167
Mean duration of hospital stay	4.80 ± 2.69	4.45 ± 2.89	4.44 ± 2.35

Table 3: Distribution of dengue among various age groups and gender

Parameter	DF	DHF-1 n (%)	DHF-2 n (%)	DHF-3 n (%)	DHF-4 n (%)	C- DSS n (%)	DC- DSS n (%)
Age Groups							
< 5years	47 (69.1)	10 (14.7)	3 (4.4)	2 (2.9)	1 (1.5)	2 (2.9)	3 (4.4)
5-10 years	78 (78.0)	12 (12.0)	3 (3.0)	2 (2.0)	2 (2.0)	2 (2.0)	1 (1.0)
> 10years	17 (81.0)	0	2 (9.5)	1 (4.8)	0	0	1 (4.8)
Male	79 (82.3)	7 (7.3)	5 (5.2)	1(1.0)	1 (1.0)	2 (2.1)	1 (1.0)
Female	63(67.7)	15 (16.1)	3 (3.2)	4 (4.3)	2 (2.2)	2 (2.2)	4 (4.3)

DF- dengue fever, DHF-dengue haemorrhagic fever, C-DSS- compensated dengue shock syndrome, DC-DSS- decompensated dengue shock syndrome

Table 4: Mean Platelet Volume (MPV) and Platelet counts among study participants

	Platelet count	SD	MPV	SD
Day 1	81385.19	29808.69	9.33	0.91
Day 2	102352.38	158282.35	9.61	1.00
Day 3	106400.53	50265.78	9.73	1.85
Day 4	114614.81	66495.08	9.12	3.52
Day 5	87556.61	82244.64	6.55	5.15

Table 5: Pearson Correlation between platelet and MPV values for dengue fever and dengue hemorrhagic fever

Pearson Correlation between platelet and MPV values for dengue fever					
MPV	**Day 1 Plt**	**Day 2 Plt**	**Day 3 Plt**	**Day 4 Plt**	**Day 5 Plt**
Day 1	0.050 (0.551)	0.091 (0.281)	0.084 (0.319)	-0.007(0.936)	-0.194(0.21)
Day 2	0.060 (0.475)	0.141 (0.094)	0.153 (0.069)	0.042 (0.623)	-0.248 (0.003)
Day 3	-0.274(0.001)	-0.450 (0.000)	0.577 (0.000)	0.369 (0.000)	0.089(0.290)
Day 4	-0.462 (0.000)	-0.293 (0.000)	-0.219 (0.009)	0.843 (0.000)	0.374 (0.000)
Day 5	-0.314 (0.000)	-0.177 (0.036)	-0.482 (0.000)	-0.016 (0.852)	0.943 (0.000)
Pearson Correlation between platelet and MPV values for dengue hemorrhagic fever					
MPV	Day 1 Plt	Day 2 Plt	Day 3 Plt	Day 4 Plt	Day 5 Plt
Day 1	0.510 (0.001)	0.389 (0.016)	0.222 (0.181)	0.279 (0.089)	0.260 (0.115)

Day 2	0.323 (0.048)	0.520 (0.001)	0.408 (0.011)	0.413 (0.010)	0.427 (0.008)
Day 3	0.385 (0.017)	0.461 (0.004)	0.340 (0.037)	0.312 (0.056)	0.381 (0.018)
Day 4	0.366 (0.024)	0.454 (0.004)	0.464 (0.003)	0.580 (0.000)	0.634 (0.000)
Day 5	0.316 (0.053)	0.415 (0.010)	0.443(0.005)	0.631 (0.000)	0.691 (0.000)

Table 6: MPV and severity of Dengue (MPV at time of admission, MPV at time of discharge and Association of MPV with DF and other severe types

MPV at time of admission				
MPV (fL)	**Dengue Fever n (%)**	**DHF n (%)**	**DSS n (%)**	**Chi-square test**
< 8	1 (12.5)	2 (25.0)	5 (62.5)	62.94 with 2dF and p value (<0.001)
8-12	141 (77.9)	36 (19.9)	4 (2.2)	
> 12	0	0	0	
MPV at time of discharge				
< 8	0	0	0	0.419 with 2dF and p value of 0.811
8-12	133 (75.1)	36 (20.3)	8 (4.5)	
> 12	9 (75.0)	2 (16.7)	1 (8.3)	
Association of MPV with DF and other severe types				
MPV (fL)	Dengue Fever n (%)	Severe Dengue	Odds Ratio	p value
8-12	133 (75.1)	44 (24.9)	0.99 (0.257 – 3.82)	0.9913 (NS)
> 12	9 (75.0)	3 (25.0)		

Table 7: Association of mean difference in Mean Platelet Volume with severity of disease (MPV at time of admission and MPV at time of discharge)

MPV at time of admission					
Severity			**Number**	**Mean**	**SD**	**ANNOVA**
DF			142	9.49	0.826	
DHF			38	9.07	0.937	
DSS			9	8.011	0.909	
Total			189			2.743 (p<0.001)
MPV at time of discharge						
DF			142	10.87	0.691	
DHF			38	11.09	0.572	
DSS	9	10.822	0.826	0.369 (NS)		

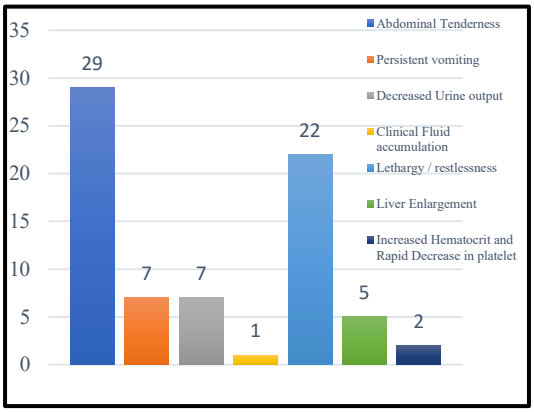

Figure 1: Warning signs of Dengue among study participants

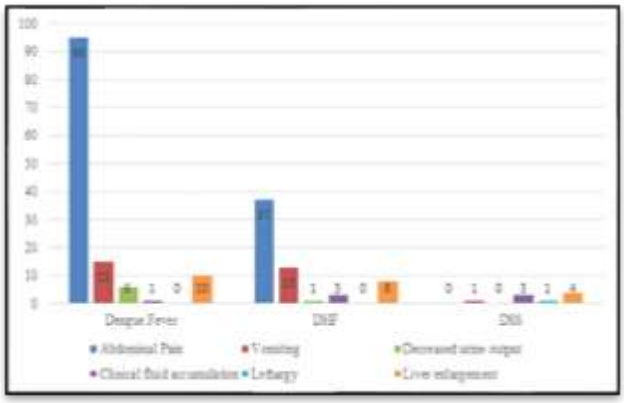

Figure 3: Warning signs among different dengue types

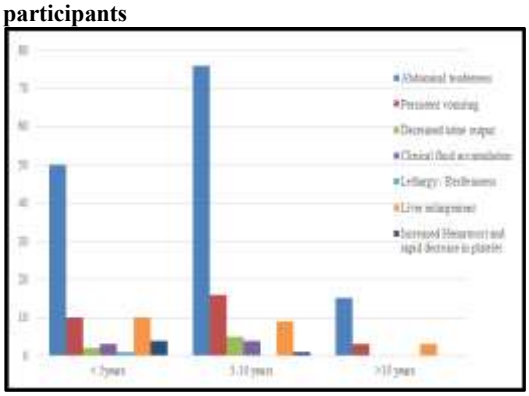

Figure 2: Warning signs of dengue among study participants stratified on basis of age.

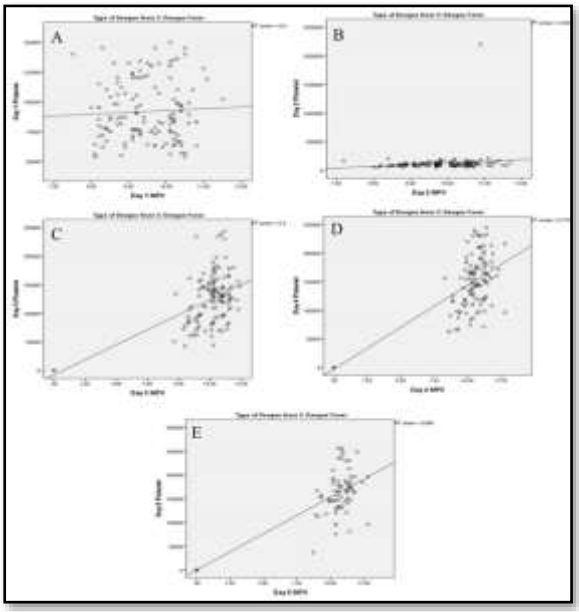

Figure 4: Correlation between DF and MPV on day 1, day 2, day 3, day 4 and day 5

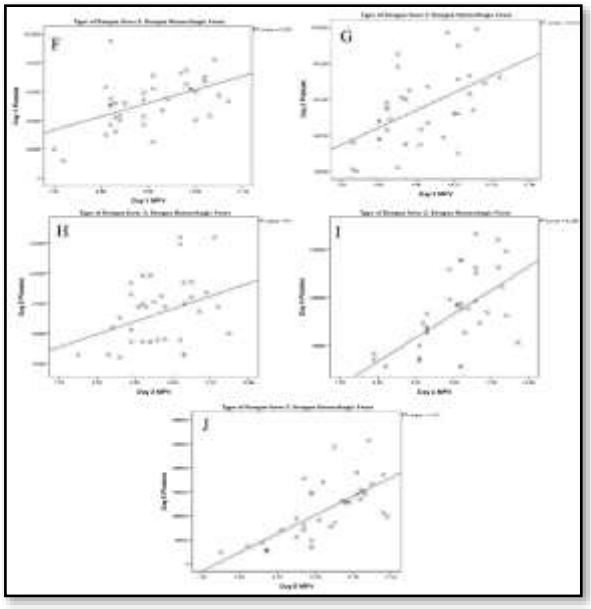

Figure 5: Correlation between DHF and MPV on day 1, day 2, day 3, day 4 and day 5

DISCUSSION

Dengue virus infection occurs through a dengue virus (four serotypes) transmitted by the bite of female Aedes aegypti mosquito. Asymptomatic infection or classic symptoms of dengue fever are caused by all four serotypes which may vary from fever with body pain to more severe manifestations such as altered vascular endothelial permeability, leakage of plasma, thrombocytopenia, bleeding, hypotension and shock leading to death (Castilho *et al*., 2020). One of the most important coagulation components of blood, namely platelets are destroyed in patients infected with DENV and the resulting thrombocytopenia renders them vulnerable to bleeding manifestations and other severe complications.[11]

The development of haemorrhagic conditions in the event of severe thrombocytopenia is common, though increased bleeding tendency with severe thrombocytopenia is not always the rule. In such conditions, platelet number alone may not predictor the tendency to bleed. The role of platelet size in affecting the haemostatic potential has been proposed by few authors, because of the influence of the platelet size particularly in thrombocytopenic patients on platelets function.[12]

Demographic pattern among study participants

In our study male participants were on the higher side (50.8%) and most of the study participants were in the age group of 5 to 10 years. The mean age among male children were 6.62±2.69 years while among female children it was 6.78±2.71 and the difference between the two gender does not have statistical significance implying the fact that being male or female does not increase the risk of developing dengue fever. A greater prevalence among male population has been reported by several authors,[13] with some differing on this aspect with a greater female prevalence.[14] In a study by Celia et al in comparing the clinical features and hematological abnormalities between dengue fever and dengue hemorrhagic fever among children in Philippines had observed differences in the male female distribution with higher male predominance and a male female ratio of 1.49. The mean age group among children with dengue fever was 6.87±2.74 years, among DHF it was 6.30±2.44 years and among DSS it was 5.44±3.28 years. Similar age distribution was observed in a study by Kabra *et al*., in 1999,[15] which showed a lower prevalence of age group among children affected with dengue. In the study a mean age of 5.12 years was seen among children affected by dengue fever while DHF children were in the mean age of 7.6 years.

Male predominance was seen among all dengue subtypes which were similar in comparison to our study. The predominance of severe forms of dengue among children of 5-10 years age group in this study can be explained on the diurnal adaptation of Aedes mosquito in stored water. Further the day biting mosquitoes frequent in schools and absence of completely covered clothing makes this disease more prone among male children than female children who wear covered clothes. Similar age distribution and male pattern of predominance was seen in a study by Mishra *et al*., in 2016,[16] among children with dengue from southern Odisha.

Duration of fever and duration of hospital stay among children with dengue fever

The mean duration of fever among children with uncomplicated dengue fever was 3.59±1.221 days, among DHF was 3.21±0.905 days and among DSS it was 3.89±1.17 days. In a study by Mishra *et al*., in

2016,[16] the mean duration of hospital stay was 3.8 days, while among severe dengue it was 5.8 days. The mean duration of stay was however higher for children less than 5 years which was 5.13 days and this difference was statistically significant. This increase could be explained on the fact that children less than 5 years experience more complications and require more duration of hospitalization for transfusion and these findings are similar to studies by Archuleta *et al*., in 2020.[13] Longer hospitalizations are recommended for patients with poor platelet recovery especially for clinical bleeding by pediatricians in order to provide close monitoring. Early hospitalization might have not manifested the full course of the illness as a result of which longer hospitalization results from an earlier presentation with an earlier hospitalization. An ongoing peripheral destruction of platelets might be responsible for absent platelet recovery following an earlier platelet transfusion during the febrile phase.

The mean duration of fever was 3.8±1.2 days which had similar distribution pattern among different age groups. However, when stratified children greater than 10 years had longer duration of fever especially in those with DSS with a mean duration of 5.0 days of fever. In another study by Manjith in 2022,[17] in an epidemic outbreak of Dengue in Chennai had a mean duration of fever of 4.89 days and the average duration of fever was lesser in Dengue Shock Syndrome group but the difference was not statistically significant. This was similar in comparison to our study but however, the mean duration of fever among other studies conducted elsewhere in India had a longer duration of 6 to 7 days. [16] This decreased duration of fever in our present study could be attributed to the administration of antipyretics at an earlier period of the illness as per the treatment guidelines by the Government of Tamil Nadu.

Clinical features among children with dengue

Fever, nausea and vomiting were seen among all groups. The most common clinical manifestation was body pain (39.2%) among all children. Among children affected by dengue fever, the most common clinical manifestation besides fever and vomiting was retro-orbital pain (26.8%) while among DHF and DSS it was body pain (23.7%). The other symptoms in varying degrees of severity included rash and retro-orbital pain. Positive tourniquet test was seen in 45.8% of children with DF, 18.4% of children with DHF and among 22.2% of children with DSS. Leucopenia and thrombocytopenia was noted in 99.3% of children with DF. However the percentage of thrombocytopenia decreases in DHF and further in DSS reflecting the impact of platelet size on the function of platelets rather than the number. However abdominal pain was noted with decreasing frequency among DF, DHF and DSS which is in contrast to our study. Similarly in a study by Kiitigul *et al*., in 2007,[18] the most common clinical presentation among children was vomiting followed by headache. Studies have reported the increased occurrence of vomiting and retro-orbital pain among patients with DSS and DHF. This highlights the fact that the clinical presentation of dengue could be varied and depends on the age at presentation and the gender along with the coexisting conditions. In our study most of the children were in the 5-10 years age group but in the above study most of the children were in the above 10 years age group.

Among warning signs, abdominal pain was seen commonly among DF and DHF children while Liver enlargement was noted with increased frequency among DHF (16%) and DSS (99.3%) affected children. Clinical fluid accumulation was also noted among DHF and DSS patients but not among DF patients. The incidence of hepatomegaly was less frequent among DHF and DSS groups than in other groups by studies reported in Philippines and Delhi.[19] The bleeding manifestations like epistaxis and melena were not observed in our study. However, hematemesis was noted with increased frequency in other studies on Indian children. In studies from south-east Asian countries, the most common bleeding manifestation is the tourniquet test positivity.[20] In our study a positive tourniquets test was seen among 45.8% of children with DF, 18.4% of children with DHF and among 22.2% of children with DSS. The lower proportion of tourniquet test in studies among children with dengue in India may be the result of different strains of Dengue virus affecting the Indian subcontinent and the impact of the darker skin among children leading to difficult interpretations of the tourniquet test.

Platelet count and Mean Platelet Volume among children with dengue

In our study the mean platelet concentration among all dengue types had a lower level on day one and had a gradual increase from day 2 and reached normal values by day 5. However, among children with DF, the platelet counts after an initial increase started to decrease on day 4 reflecting the increased destruction of platelets caused by the antibodies. The similar pattern was also observed among children with DHF grade 4 wherein the decrease in platelet count was observed on day 5. The mean platelet concentration among DHF and DSS was <50,000 and all showed an upward rising trend probably as a result of interventions in the form of platelet transfusions. In DSS, DHF grades 2, 3 and 4 the platelet count shows a fall on day 2 compared to baseline values but shows a progressive increase.

In this study, when comparing patients with MPV values between different types of dengue, it was observed that children with dengue fever had a fall in values of MPV as early as 3rd day despite the normal levels of platelet during the same period. The trend among various dengue types and MPV values do not show any specific patterns. For children with DF the correlation values with platelet values show a strong positive correlation on day 3, 4 and 5 and this was statistically significant. In DHF

the strength of correlation was significant from day 1 onwards for platelet values. However, in DSS there was no significant correlation between MPV values and platelet values for all 5 days. In our study the difference in mean platelet volumes among different types of dengue fever was statistically significant ($p<0.001$).

Similar findings are observed by Khatri *et al*., in 2018,[21] where variations in platelet indices like Mean Platelet Volume, Platelet Distribution widths and PCT. The mean platelet distribution width (PDW) was observed to be on the upper limit of the normal laboratory reference range and among patients with mean plateletcrit (PCT) was low and correlated with linear relationship with MPV. In a study by Mohamed *et al*., in 2015,[22] MPV and Platelet counts were found to be lower in dengue fever patients compared to controls. In this study a value of <9 fl MPV levels had considerable sensitivity for dengue fever.

One of the major problems in dengue haemorrhagic fever management among patients with severe thrombocytopenia is the clinical decision on timing of platelet transfusions to avert life threatening haemorrhages. The routine management of thrombocytopenic patients who exhibit a bleeding tendency is to give platelet transfusions. The difficulty however arises when dealing with patients with platelet counts of less than 20000 without bleeding tendency on deciding the timing of platelet transfusions, which might be difficult for an experienced pediatrician. The utility of mean platelet volume lies in the observation that it helps to differentiate between those patients with dengue fever who do not experience any bleeding manifestations and those exhibit bleeding manifestations. Further it may also serve as a guideline for predicting the danger of life threatening haemorrhage and the timing for prophylactic transfusion of platelets.

CONCLUSION

MPV, one of the platelet indices which is a routine test performed during blood morphology, can provide valuable information on the course and prognosis in conditions associated with thrombocytopenia in particular Dengue fever. The diagnostic dilemma especially in the decision of administration of platelet transfusion especially among children with dengue without any bleeding manifestations. In such scenarios, the role of MPV values in aiding the treating physicians for management of thrombocytopenia cannot be ignored. However, several other factors such as standardization of laboratory procedures influence the measurement of MPV. Further with the increased availability of automated analyzers, the measurement of platelet indices becomes a reality which was not possible especially in a rural setting.

Limitations

A difference in measurement techniques of MPV and Platelets by different analysers was a major issue. Quantification of antibody and antigen titres could have provided more information on progression of the condition. Only few children with DSS and DHF were included in the study.

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