

## Original Research Article

# Spectrum of febrile thrombocytopenia among children in a tropical country-a hospital based observational study in South India

Karthikraj T.\*, Jenish Rajma J., Jeyabalaji R. V., Shivani Kuttuva

Department of Pediatrics, Velammal Medical College Hospital, Madurai, Tamil Nadu, India

**Received:** 15 December 2020

**Accepted:** 16 January 2021

### \*Correspondence:

Dr. Karthikraj T.,

E-mail: [karthikrajmmc@gmail.com](mailto:karthikrajmmc@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

**Background:** Febrile thrombocytopenia is a common reason for pediatric admission. Though infections are the major cause, noninfectious causes are not uncommon. This study was done to estimate the prevalence of thrombocytopenia as a presentation in pediatric fever cases, to analyze the various etiologies, presentations and relationship between platelet count and the severity of disease and prognosis.

**Methods:** Retrospective observational study done by collecting data from hospital records of children admitted in Velammal Medical college hospital from January 2016 to December 2017. Children in the age group of 6 months to 15 years with fever and thrombocytopenia at admission were included in the study. Children on treatment with anti-platelet drugs, other chronic diseases and infants less than 6 months were excluded.

**Results:** Out of 2523 fever cases admitted, 372 children fulfilled this criterion. 70% had positive dengue serology, other infectious causes were other viral hemorrhagic fevers, complicated enteric fever, scrub typhus and sepsis. The predominant non-infectious causes were hematological malignancies, Idiopathic thrombocytopenic purpura and Hemolytic uremia syndrome.

**Conclusions:** Febrile thrombocytopenia is a common clinical presentation in children in dengue endemic areas. Most viral fevers have leukopenia but presence of thrombocytopenia with warning signs like pain abdomen, vomiting or oliguria should prompt suspicion of dengue. Infections like enteric fever, scrub typhus or chikungunya may also mimic similar findings. Rarely diseases like leukemia, Idiopathic thrombocytopenic purpura, Hemolytic uremic syndrome or Sepsis may also present as febrile thrombocytopenia. The need for antibiotics or blood products is very minimal.

**Keywords:** Febrile thrombocytopenia, Tropical country, Dengue

## INTRODUCTION

Febrile thrombocytopenia is the thrombocytopenia (platelet count <1,00,000 cells/cu.mm) associated with fever. Diseases which commonly present with fever and thrombocytopenia are infectious diseases like malaria, leptospirosis, rickettsia infections (scrub typhus), septicemia, typhoid, borreliosis, arboviral infections such as dengue or yellow fever, rodent-borne virus infections such as Hanta and Lassa fever, human immunodeficiency virus (HIV), visceral leishmaniasis, leukemia, lymphomas, idiopathic thrombocytopenic purpura and

thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Various infections have been found to be endemic in certain geographic locations and also seasonal epidemics occur every year in different parts of the world.

The study was done by collecting epidemiological data of prevalence of thrombocytopenia in fever cases of pediatric population in South India. This study was intended to know the underlying etiology of febrile thrombocytopenia in children in tropical countries, the various presentations and relationship between platelet

count and severity of disease and its prognosis. This information may be utilized to devise a clinical examination-based investigation protocol for children presenting with febrile thrombocytopenia which will help in developing a cost-effective management strategy with minimum necessary investigations, thereby providing the correct protocol-based management.

The primary objectives of our study were to study the prevalence of thrombocytopenia ( $<1,00,000$  cells/cu.mm) as a presentation in pediatric population in overall fever cases and to analyze various etiology of febrile thrombocytopenia in children in our hospital. We also studied the overall presentation and relationship between platelet count and severity of disease and prognosis.

## METHODS

The study design was a retrospective observational study, done by collecting the data from the hospital records of children admitted in pediatric ward of Velammal medical college hospital, Madurai with fever from January 2016 to December 2017. The patients were to be selected based on inclusion and exclusion criteria. Children in the age group of 6 months to 15 years with fever presentation and thrombocytopenia (platelet count  $<1,00,000$  cells/cu.mm) at admission were included in the study. Children on treatment with anti-platelet drugs and other drugs causing thrombocytopenia, Children who were previously diagnosed to have chronic diseases like malignancy, chronic liver diseases or chronic kidney disease and Infants less than 6 months of age were excluded from the study.

Data of selected patients were collected from medical records and complete history; clinical findings and investigations were noted in a structured proforma. The data collected were entered in MS excel software and summary statistics were obtained which are presented below as proportions. Ethical clearance from the institutional ethical committee board was obtained.

## RESULTS

Out of the total 8817 In-patient admissions to the pediatric ward, 2523 children were admitted with a diagnosis of fever in the study period (2016 to 2017), of which, 372 children in the age group of 6 months to 15 years, fulfilled the study criteria for febrile thrombocytopenia. Nearly 45% of these cases (168) were admitted during 2017 dengue epidemic. The predominant age group was 6 to 10 years (34%), followed by 11 to 15 years (29%) and 1 to 5 years (25%). Infants (6 months to 1 year) included were 6.5 % of the total study population. Male:Female ratio was almost equal at 1.1:1.

The most common symptomatology at presentation was fever which was present in all cases. Table 1 nearly half of them (48%) had high grade fever on presentation. The average duration of fever was 4 to 6 days with the

maximum duration being 14 days. Constitutional symptoms and warning symptoms (vomiting, abdominal pain) were the next common symptoms at presentation. Other uncommon presentations included those with respiratory symptoms and loose stools. Around 3% had a neurological symptom like seizure or altered sensorium at presentation.

**Table 1: Common symptomatology of febrile thrombocytopenia.**

Symptoms	Variables
<b>Fever- high grade</b>	182
<b>Low grade (<math>&lt;101^{\circ}\text{F}</math>)</b>	190
<b>Duration</b>	Average 4 to 6 days, max 14 days
<b>Myalgia, poor appetite, headache</b>	152 (40.8)
<b>Cough/cold</b>	48 (12.9)
<b>Pain abdomen and vomiting</b>	164 (44.1)
<b>Loose stools</b>	27 (7.25)
<b>Facial puffiness</b>	98 (26.3)
<b>Melena</b>	70 (18.8)
<b>Hematemesis</b>	13 (3.5)
<b>Oliguria</b>	123 (33.3)
<b>Other mucosal bleeds (gum bleeds/epistaxis/skin bleeds)</b>	74 (19.8)
<b>Atypical CNS (seizures, encephalopathy)</b>	12 (3.2)

Examination showed that erythematous rash was the most common clinical finding seen in almost 51% of the study population at some point of the illness during admission. Table 2 shows hepatomegaly with right hypochondrial tenderness was the next common clinical finding in 45%, followed by fluid leak (ascites, pleural effusion) in 39%, periorbital puffiness (29%), subcutaneous bleeds (20%), conjunctival congestion (11%) and splenomegaly (4.5%) as shown below.

**Table 2: Clinical signs in febrile thrombocytopenia cases.**

Clinical sign	Cases
<b>Periorbital puffiness</b>	108
<b>Conjunctival congestion</b>	43
<b>Petechiae/purpura</b>	76
<b>Erythematous skin rash</b>	190
<b>Hepatomegaly/right hypochondriac tenderness</b>	169
<b>Splenomegaly</b>	17
<b>Ascites/pleural effusion</b>	146

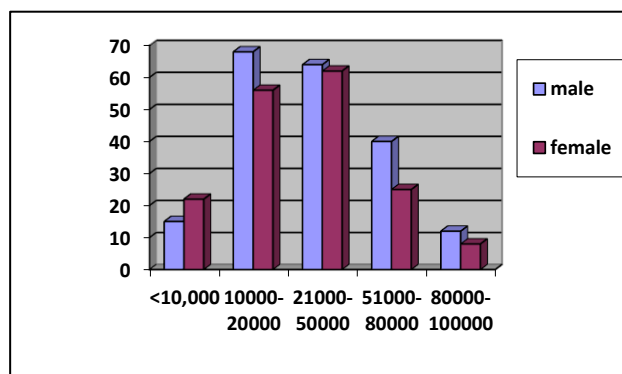
Blood investigations done showed that total leucocyte count below 5000 was more suggestive of viral fever like dengue. Table 3 shows dengue fever with warnings signs also called as dengue hemorrhagic fever (DHF) was mostly associated with hemoconcentration and elevated transaminases. Few children (23/372) had hemoglobin

less than 10 at admission, among which 10 were later diagnosed to have leukemia or hemolytic uremic syndrome. Only 8 of the 23 had positive serology for dengue and they were all stable without any warning signs. The average maximum hematocrit during the hospital stay of all febrile thrombocytopenia cases was 38.9 and it came down to 35.1 at discharge. The hematocrit values were very high in adolescent males (more than 50 in 4 children between 11 to 14 years of age) and all of them had both IgG and IgM for dengue positive.

**Table 3: Basic lab investigations in febrile thrombocytopenia cases.**

Lab investigations	Values
<b>Hemoglobin</b>	5 to 17.2 (mean 12.1±1.85), median 11.9 mode 11.7
<b>Total leucocyte count</b>	Median 5100, range 2200-70300
<b>Hematocrit at admission</b>	37±5.33 (mean/SD)
<b>Maximum hematocrit</b>	38.9±5.23
<b>Hematocrit at discharge</b>	35.1±5.4

Nearly 43 % children were found to have severe thrombocytopenia during hospital stay. Table 4 shows the incidence was more common in boys than girls. Figure 1 shows among the 37 children who had platelet count less than 10,000 only 2 had significant gastrointestinal bleeding manifestation. Others had only mucocutaneous bleeds or skin bleeds only. Nearly 33% had platelet counts 20,000 to 50,000. Significantly low platelet count (<20,000) with high total counts was also noted in scrub typhus, leukemia and sepsis, the latter 2 being associated with poor prognosis. In case of severe sepsis, at admission though the laboratory investigations were not grossly abnormal, these children were more toxic with hemodynamic compromise and the platelet count had more significant fall or clinical bleeds after 48 to 72 hours of admission.



**Figure 1: Severity of thrombocytopenia in children among both genders.**

**Table 4: Platelet count at admission in febrile thrombocytopenia cases.**

Platelet count (per cu.mm)	No. of children
<b>&lt;10000</b>	37
<b>10-20000</b>	124
<b>20000-50000</b>	126
<b>51000-80000</b>	65
<b>80000 to 100000</b>	20

The range of liver enzymes was widely varying from aspartate transaminase 15 to 1119 and alanine transaminase was 13 to 515. The higher the value of liver enzymes, the severe was the course of the disease.

The diagnostic panel done in children with fever less than 5 days included dengue serology (Ns1, IgM, IgG), smear for malarial parasite at admission and they were given supportive care according to the severity of the illness. If fever was persisting beyond 7 days WIDAL, scrub typhus serology, leptospirosis serology was done and antibiotics given according to the diagnosis-doxycycline in scrub typhus and ceftriaxone for enteric fever. Few children who had abnormal finding in the peripheral smear were further evaluated and diagnosed as hemolytic uremic syndrome (HUS) or hematologic malignancy. Only 17 out of the 372 children (4.5%) had non infective cause for febrile thrombocytopenia. Bone marrow study was done in 10 children to confirm leukemia or idiopathic thrombocytopenic purpura (ITP) while in 5 of them there was hyper-leukocytosis or plenty of blasts in peripheral smear itself. Hence flowcytometry was done from peripheral blood itself to confirm the diagnosis.

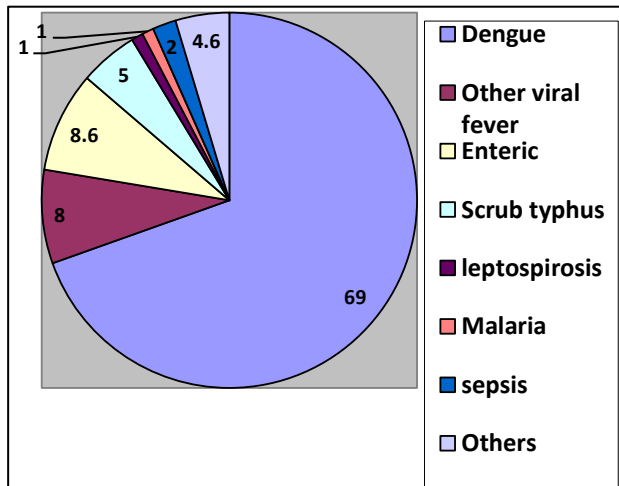
**Table 5: Diagnostic investigations.**

Diagnosis	Findings
<b>Dengue NS1 Ag +ve</b>	129
<b>Dengue NS1 Ag and IgM +ve</b>	94
<b>Dengue IgM and IgG +ve</b>	33
<b>VHF (serology negative)</b>	30
<b>PS for malaria positive</b>	5
<b>WIDAL (&gt;1:320) +ve</b>	32
<b>Scrub typhus serology +ve</b>	19
<b>Leptospirosis serology +ve</b>	5
<b>PS/BMA suggestive of leukemia</b>	8
<b>PS suggestive of HUS</b>	5
<b>Sepsis with DIC</b>	8
<b>ITP</b>	4

Diagnosis was reached in almost 80% of the cases with the initial panel of investigations (CBC with peripheral smear, dengue serology). When fever persisted beyond 5 to 7 days or child had some atypical symptoms like splenomegaly, eschar or abnormal peripheral smear the second line investigations were done.

The predominant diagnosis was dengue fever in 253 children (69%), followed by other viral haemorrhagic

fevers (8%), scrub typhus fever (5%), malaria (1%), leukemia (2%), sepsis with disseminated intravascular coagulation (DIC) (2%), HUS (1.3%) and leptospirosis (1%) Figure 2.



**Figure 2: Percentage distribution of the various diagnoses of febrile thrombocytopenia among children.**

Among dengue those with warning signs were 152 (53%) were the majority, followed by those without warning signs-101 (35%). 29 children (10.2%) were diagnosed to have severe dengue. Among this 29, 15 (50%) had significant bleeding, 8 (27.5%) had Dengue shock syndrome and 6 (20.6%) had severe respiratory distress with metabolic abnormalities.

All the viral fever cases were managed as per protocol (WHO dengue protocol) and others according to their specific diagnoses.

A total of 246 cases (66%) required fluid challenge. 45 cases (12%) required platelet rich plasma (PRP) transfusion for whom the diagnoses were Dengue with warning signs (71%) in PICU care, dengue shock syndrome (DSS) (6.6%) and leukemia (33.3%). The average hospital stay was 8 days and the maximum duration was 22 days. 124 (33.33%) children required PICU care during their course of treatment. The clinical outcome was positive in 367 cases, while 5 children (3-DHF, 2-sepsis) expired in the course of their treatment.

## DISCUSSION

Fever is one of the commonest presenting symptoms for most of the hospital visits in children. Thrombocytopenia may be an important laboratory finding in a febrile child as it needs further evaluation regarding the etiology. Various infectious agents like dengue, chikungunya, *Plasmodium* species and *Salmonella typhi* can present with febrile thrombocytopenia in tropical countries. Identifying the exact etiologic agent is important as the management protocol is different for different infections.

In addition to infections, noninfectious causes for febrile thrombocytopenia, though rare, do exist in all countries. Thrombocytopenia is defined as platelet count less than 150000/ $\mu$ l while severe thrombocytopenia is defined as platelet count less than 50000/ $\mu$ l.<sup>1</sup>

In our study, out of the total fever cases admitted (2523) in the pediatric wards, around 15% had febrile thrombocytopenia at admission. Some children had normal platelet counts at admission but they developed thrombocytopenia during the hospital stay but they were not included in this study. Almost 70% of the children who were included in the study had positive dengue serology. Incidence of dengue has increased 230-fold with increasing geographic expansion and the rapidly expanding global footprint of dengue is a public health challenge in many developing countries.<sup>2</sup> Though it occurs in seasonal epidemics, many areas have also become endemic to dengue virus resulting in cases throughout the year. In the age distribution, almost two third were between 6 years to 15 years of age. Two third of these children improved with fluid therapy alone, either oral or intravenous, given according to WHO protocol for dengue management. Antibiotics were not started in children with fever less than 4 days duration, if the blood counts had evidence of leucopenia along with thrombocytopenia at admission and clinical evidence of viral fever with no foci of bacterial infection. This sort of antibiotic stewardship is essential in developing countries to prevent antibiotic resistance and misuse of antibiotics in viral infections. Also imaging studies like ultrasound abdomen were not routinely done in all cases of fever more than 3 days. It was done only in sick children and if the initial diagnostic workup was not confirmatory.

In a pediatric study done by Ramabhatta et al at Bangalore, 20% of children with fever had associated thrombocytopenia.<sup>3</sup> A total of 306 children were included in the study and 280 children definite diagnosis was made out, of which more than 80% had dengue fever. A study done at the university of Munich hospital by Herbinger et al showed increased incidence of EBV, CMV along with arboviral infections.<sup>4</sup> Another study by Malik et al showed that complicated Enteric fever is an important cause for febrile thrombocytopenia in developing countries.<sup>5</sup> In our study, 69% of the children had dengue fever while enteric fever was the second common cause for febrile thrombocytopenia. In a similar pediatric study done by Nair et al published from North India, viral fevers other than Dengue and chikungunya were more common while Enteric fever had an incidence of around 12%.<sup>6</sup> We did not evaluate for other viruses like chikungunya, *Ebstein Barr* virus due to cost issues and unavailability of the tests in our institute. But most of the cases of febrile thrombocytopenia had positive dengue serology in our study (69%) and only 8% were viral fever with negative dengue serology.

In a study by Phakhounthong most significant factor in predicting severe dengue was low hematocrit, followed



by a GCS of 11 or hematocrit was greater than 28 or platelet count of 146,000 per mm<sup>3</sup>.<sup>7</sup> The correlation between degree of thrombocytopenia and severity of the disease is not directly analyzed in our study but skin bleeds were seen in only 20% of the study group and it was mostly present when platelet counts was less than 20,000. But in children with features of severe dengue, 50% had significant bleeding manifestations like hematemesis, Malena and pulmonary hemorrhage. The tendency to bleed was not correlating to the platelet count as few children had bleeding manifestations in spite of having platelet counts more than 50,000. The bleeding manifestations were not directly proportional to the degree of thrombocytopenia and the need for blood products transfusion was predominantly for hemodynamic compromise. We could also infer that sick children had significant rise in transaminases, hematocrit and deranged coagulation profile. Nair et al.<sup>6</sup> also had similar findings in their study. Also, in few adult studies like those done by Harsha and Radhika et al showed that infections like dengue, septicemia and malaria were the predominant causes of febrile thrombocytopenia.<sup>8,9</sup> In a study by Subramanian et al bleeding manifestations were noted predominantly in children with counts 20000 to 100000/ $\mu$ l and they contributed to nearly 70% of all the bleeding manifestations.<sup>10</sup> In a study by Kshirsagar et al thrombocytopenia, elevated serum hepatic enzymes, abnormal renal function tests, low sodium, hypoalbuminemia, hypoglycemia, abnormal radiological findings were found to be the predictors of severity.<sup>11</sup> Our study was not designed to develop the predictors for disease severity but the severe cases had evidence of fluid overload or multiorgan dysfunction like oliguria, respiratory distress or encephalopathy or shock within the first 24 to 48 hours of admission itself.

The mortality rate in our study was 0.01% (5 out of 372) which was both due to severe dengue and severe sepsis with disseminated intravascular coagulation. Dengue shock syndrome was recognized in 22 cases at admission and most of them responded well to intravenous fluids given as per WHO protocol and only few required colloid or platelet rich plasma (PRP) for further resuscitation.

The duration of hospital stay was 8 to 12 days in most of the dengue serology positive cases. In a study done by Selvan et al the duration of hospital stay was similar and male children in the age group of 10-18 years were more affected.<sup>12</sup> Few children with other alternative diagnosis, who required further investigations or those who had secondary problems during the hospital stay like abscess, sepsis with blood culture positivity or infection associated hemophagocytic syndrome had a prolonged stay lasting 2 to 3 weeks on an average.

The limitations of our study were that we did not include children admitted with fever who developed thrombocytopenia in the course of hospital stay and we also did not attempt to diagnose the exact etiology of other viral hemorrhagic fevers.

## CONCLUSION

Febrile thrombocytopenia is a common clinical presentation in children especially during rainy seasons in dengue endemic areas. In addition to dengue, few other infections like enteric fever, scrub typhus or chikungunya may also mimic similar findings. Rarely diseases like leukemia, idiopathic thrombocytopenic purpura, hemolytic uremic syndrome or sepsis may present as febrile thrombocytopenia, but a proper peripheral smear or serial hemograms will help us to arrive at the right diagnosis. In our study 15% of children with fever had febrile thrombocytopenia of which around 70% were confirmed to be dengue and less than 5% had underlying noninfective etiology. Two third of the children required only fluid therapy and the degree of thrombocytopenia was not directly related to the severity of the viral fever. Most sick children had significant rise in transaminases, hematocrit and deranged coagulation profile. Though most of the viral fevers can have leukopenia, presence of thrombocytopenia along with warning signs like pain abdomen, vomiting or oliguria should prompt the treatment protocol as advised by WHO. Judicious use of antibiotics and radiologic tests will result in a cost-effective management of the common prevalent infections in tropical countries.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee on 04/04/2017, IEC REF NO:VMCIEC/23/2017*

## REFERENCES

1. Nagler M, Keller P, Siegrist D, Alberio L. A case of EDTA dependent pseudo-thrombocytopenia: simple recognition of under diagnosed and misleading phenomenon. *BMC Clin Pathol.* 2014;14:19.
2. Simmons CP, Farrar JJ, Nguyen V, Wills B. Dengue. *N Engl J Med.* 2012;366:1423-32.
3. Sujatha R, Pushpalatha K, Bharathi K, Udaya R, Hareesh S. An aetiological profile of febrile thrombocytopenia in children. *Sri Lanka J Child Health.* 2018;47:146-8.
4. Herbinger KH, Schunk M, Nothdruff HD, Von Sonnenburg F, Loscher T, Bretzel G. A comparative study on infection induced thrombocytopenia among returned travellers. *Infection.* 2012;40:373-9.
5. Malik AS. Complications of bacteriologically confirmed typhoid fever in children. *J Trop Paediatr.* 2002;48:102-8.
6. Nair Bindu T, Kuldeep S, Sandeep PD. A study of clinical and laboratory profile of febrile children presenting with thrombocytopenia. *Int J Contemp Pediatr.* 2017;4(6):2114-9.
7. Phakhounthong K, Chaovalit P, Jittamala P. Predicting the severity of dengue fever in children on admission based on clinical features and laboratory

- indicators: application of classification tree analysis. *BMC Pediatr*. 2018;18:109.
8. Harsha NS, Thimma Reddy TR, Shruthi M, Ravishankar SN, Madhuvan HS. A Study of Clinical and Laboratory Profile of Fever with Thrombocytopenia. *J clin biomed sci*. 2016;6:121-4.
  9. Radhika BV, Sooraj CS, Kamath V. Section: Medicine A Study of Febrile Thrombocytopenia Section. *Medicine*. 2019;6:21-5.
  10. Subramanian V, Santosh K. Thrombocytopenia in children: a clinico-etiological profile in an urban tertiary care hospital. *Int J Contem Pediatr*. 2018;6:131.
  11. Kshirsagar P, Chauhan S, Samel D. Towards Developing a Scoring System for Febrile Thrombocytopenia. *The J Asso Physicians India*. 2016;64(2):14-8.
  12. Selvan T, Nagaraj MV, Saravanan P, Somashekar. A study of clinical profile of dengue fever in children. *Int J Contemp Pediatr*. 2017;4:534.

**Cite this article as:** Karthikraj T, Rajma JJ, Jeyabalaji RV, Kuttuva S. Spectrum of febrile thrombocytopenia among children in a tropical country-a hospital based observational study in South India. *Int J Contemp Pediatr* 2021;8:354-9.