## **Original Research Article**

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## Clinicoetiological profile and outcome of acute febrile illness with thrombocytopenia in children: a hospital based prospective study

### Priyanka Agarwal, Ratan Kumar Das\*, Dillip Kumar Dash, Mamta Kumari, M. D. Mohanty

Department of Pediatrics, IMS and SUM Hospital, Bhubaneswar, Odisha, India

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## \*Correspondence:

Dr. Ratan Kumar Das,

E-mail: drratandas88@gmail.com

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### **ABSTRACT**

**Background:** Thrombocytopenia is often the most commonly encountered clinical condition in this routine practice. Etiological causes being numerous, often pose a challenge in evaluating and treating the patients. The objective of this study was to find out the different causes and clinical profile of fever with thrombocytopenia in children aged 1month to 14 year who were admitted in this set up.

**Methods:** This was a prospective study done on 200 patients with thrombocytopenia admitted IMS AND SUM Hospital, BBSR with various complaints, during the period of 01 August 2017 to 01 August 2019. This study includes age group 1months to 14 years.

**Results:** The highest incidence of thrombocytopenia belonged to the age group 11-14 years (22.5%) followed by 6-9 years (19.5%) and 3-6 years (18%). Incidence of thrombocytopenia was more in male child (58.5%) as compared to female child (41.5%). the most common cause of thrombocytopenia was dengue (50%), Scrub typhus (34%) septicaemia (17.5%) followed by malaria (10.5%). Among the infectious aetiology severe thrombocytopenia was seen more in dengue (25%) and scrub typhus (34.5%) but evidence of bleeding was seen more in sepsis (34.2%) even with higher platelet count which may be explained by associated multi organ failure.

**Conclusions:** Infections like malaria, dengue, leptospirosis and septicaemia were the common causes of thrombocytopenia along with scrub typhus. Whenever thrombocytopenia is detected further investigations can help us in reaching a correct diagnosis in the majority of the cases so that appropriate treatment can be given and also to avoid unnecessary platelet transfusion to prevent transfusion related complications.

Keywords: Bleeding Manifestations, Dengue Fever, Malaria, Septicemia, Thrombocytopenia

### INTRODUCTION

Thrombocytopenia is a common presentation of many febrile and few non-febrile illness in children. The common febrile illness in children like dengue, viral fever, malaria and enteric fever are associated with thrombocytopenia. Thrombocytopenia is defined as platelet count less than  $150000/\mu l$  while severe thrombocytopenia is defined as platelet count less than  $50000/\mu l$ . Pesudo-thrombocytopenia can occur due to use of excessive EDTA while sampling. Febrile thrombocytopenia is the thrombocytopenia associated

with fever. Diseases which commonly present with fever and thrombocytopenia are malaria, leptospirosis, rickettsial infections, septicemia, typhoid, borreliosis, arbovirus such as dengue or yellow fever, human immunodeficiency virus (HIV), and TTP-HUS.<sup>5,6</sup> The climatic conditions in tropical countries like India are favourable for the transmission of most of these infections and every year, with onset of monsoons, a rising trend has been observed in the number of cases admitted into wards and intensive care units with febrile thrombocytopenia with a variable clinical course and an unpredictable outcome.<sup>7</sup> The study was intended to know

the underlying aetiology, clinical profile of febrile thrombocytopenia in our community, the various presentations and relationship between platelet level and severity of disease and prognosis.

Aim and objectives of the study is to find out the different causes and clinical profile of fever with thrombocytopenia in children aged 1month to 14 year who were admitted in this set up.

#### **METHODS**

A hospital based observational study was done with 200 patients to determine the clinical profile and laboratory finding of patient with febrile thrombocytopenia admitted in this hospital. Study design a hospital based observational study. Study conducted duration 01 August 2017 to 01 August 2019 at Department of Paediatric, Institute of medical sciences and SUM hospital Bhubaneswar. Children visiting the paediatric department of this hospital aged 1 month to 14 years. Children between age group of 1 month to 14 years whose hemogram revealed total platelet count <1,50,000 and who were admitted to ward/cabin/ICU were enrolled and patient/parents were informed about the study in details and consent were taken for being enrolled in study. 200 patients included. Considering a confidence level of 98% and confidence interval of 4 the number of patients in this study to achieve statistical significance is 196. This was calculated by Survey System (http://www.surveysystem.com/sscalc.htm#one). Survey System ignores the population size when it is "large" or unknown. Population size is only likely to be a factor when you work with a relatively small and known group of people (e.g., the members of an association). Hence a sample size of 200 was considered adequate for this study.

#### Inclusion criteria

- Children aged 1 month to 14 years of age admitted in this hospital with fever and a total platelet count less than 1.5 lakh/mm<sup>3</sup> on blood picture.
- Parents giving consent to be included in study

### Methodology

After approval by IMS and SUM Hospital ethics committee. Informed and written consent were taken from the cases after explaining the basis of the study. Confidentiality was ensured and participants were informed about the right to discontinue participation.

Presenting symptoms were recorded as per the Performa. Date of onset of symptoms (fever, rash, bleeding, joint swelling etc.), number of days for which symptoms continued, any history of any drug intake, recent vaccination, etc. was asked in detail. Any family history of blood disorder, any previous history of blood transfusion was asked.

Detailed examination of the child was done with special attention to presence of any rash, mucosal bleed, hepatosplenomegaly, lymphadenopathy, sternal tenderness etc. was checked and documented.

### Sample collection and laboratory analysis

Two ml of blood was collected in EDTA vial through a clean venepuncture from children admitted in this hospital. Samples were sent immediately to clinical laboratory. CBC was done using a 6 part autoanalyzer XN-1000 series.

Those with decreased platelet count on CBC 2 ml of blood in EDTA vial was sent for direct smear method examination for confirmation of platelet count using the following formula =  $10n/10^*$  10000 (where n is the number of platelet per high power field examined under microscope). Those showing platelet clumps 2 ml of blood was sent in citrate vial for confirmation of platelet count.

### Statistical analysis

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student's' test and Chi-Square test. 'p' value less than 0.05 is taken as significant. Results were graphically represented where deemed necessary.

Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010.

#### **RESULTS**

A hospital based cross sectional study was conducted with 200 children to find out the different causes and clinical manifestation of febrile thrombocytopenia in paediatric age group.

### Distribution of children according to age

Majority of the children (22.5%) were from the age group of 11-14 years followed by 19.5% from the age group of 6-9 years, 18% from the age groups of 3-6 years and 9-11 years, 12% from the age group of 1-3 years and 10% from the age group of <1 year. The mean age of the children was  $7.62\pm4.20$  years (Table1).

### Distribution of children according to gender

In this study 117(58.5%) children were male while female children constituted 41.5% of the study group (Figure 1).

Table 1: Distribution of children according to Age.

Age (years)	N	%
<1 year	20	10%
1-3 years	24	12%
3-6 years	36	18%
6-9 years	39	19.5%
9-11 years	36	18%
11-14 years	45	22.5%
Total	200	100%
Mean±SD	7.62±4.20	)

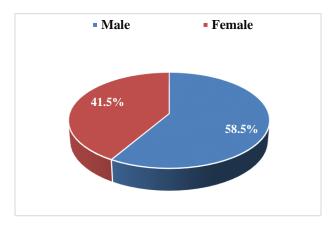


Figure 1: Distribution of children according to gender.

### Distribution of children according to season

It was observed that the febrile thrombocytopenia was more common in rainy season. Out of 200 patients, 93(46.5%) cases were reported in rainy season, 67(33.5%) cases were reported in summer season and number of cases in winter was 40(20%) (Table 2).

Table 2: Distribution of children according to season type.

Type	N	%
Winter	40	20%
Summer	67	33.5%
Rainy	93	46.5%
T0tal	200	100

### Distribution of children according to etiology

It was observed that the commonest cause of febrile thrombocytopenia was Scrub typhus (34.5%) followed by Dengue (25%), septicaemia (17.5) malaria (10.5%), enteric fever (3.5%) and viral fever (3%) (Table 3).

# Distribution of children according to clinical presentation

The most common clinical presentation was fever (91%) followed by Organomegaly (72.5%), Jaundice (66%),

Lymphadenopathy (52.5%), abdominal pain (43%), Rash (31.5%), vomiting (21%) and bleeding tendency (12.5%) (Table 4).

Table 3: Distribution of children according to etiology.

Etiology	N	%	
Dengue	50	25%	
Septicaemia	35	17.5%	
Malaria	21	10.5%	
Scrub typhus	69	34.5%	
Enteric Fever	7	3.5%	
Viral Fever	6	3%	
Others	12	6%	
Total	200	100%	

Table 4: Distribution of children according to clinical presentation.

Clinical presentation	N	<b>%</b>
Fever	182	91%
Organomegaly	145	72.5%
Jaundice	132	66%
Lymphadenopathy	105	52.5%
Abdominal pain	86	43%
Rash	63	31.5%
Vomiting	42	21%
Bleeding tendency	25	12.5%

# Distribution of children according to site of bleeding manifestations:

Among 38(19%) children had bleeding manifestations. Petechiae was the most common site of bleeding manifestation (42.1%) followed by Epistaxix (21.1%), Malena (15.5%), Haematuria (13.2%), Haematemesis (5.2%) and Gum bleed (2.6%) (Table 5).

Table 5: Distribution of children according to site of bleeding manifestations.

Site of bleeding manifestations	N	%
Petechiae/purpura	16	42.1%
Epistaxis	8	21.1%
Malena	6	15.8%
Haematuria	5	13.2%
Haematemesis	2	5.2%
Gum bleed	1	2.6%

### Distribution of children according to platelet count

In this study 135(67.5%) children had platelet count of >50,000/ $\mu$  Followed by 39(19.5%) children with platelet count of 21,000-50,000/ $\mu$ L, 14(7%) children with platelet count of 11,000-20,000/ $\mu$ L and 12(6%) children with platelet count of  $\leq$ 10,000/ $\mu$ L (Table 6).

Table 6: Distribution of children according to platelet count.

Platelet count	N	0/0
≤10,000/µL	12	6%
$11,000 - 20,000/\mu L$	14	7%
$21,000 - 50,000/\mu L$	39	19.5%
>50,000/µL	135	67.5%
Total	200	100%

## Association of bleeding manifestations and platelet count

In the present study, out of the 38 children who had bleeding manifestations, 9(23.7%) children each had platelet count  $\leq\!10000/\mu L$  and  $11000\text{-}20000/\mu L$ , 13(34.2%) children had platelet count  $21000\text{-}50000/\mu L$  and 7(18.4%) children had platelet count  $>\!50000/\mu L$ . There is no significant association between bleeding manifestations and platelet count as per Chi-Square test (p<0.05) (Table 7).

Table 7: Association of bleeding manifestations and platelet count.

Platelet count (/µl)	Total		eding nifestations 38)	p Value
10,000	12	9	23.7%	
11,000-20,000	14	9	23.7%	
21,000-50,000	39	13	34.2%	< 0.05
50,000	135	7	18.4%	
Total	200	38	100%	

### Association of bleeding manifestations and etiology

Out of the 38 children who had bleeding manifestations, 21(55.4%) children had dengue, 4(10.5%) and 3(7.9%) children had *septicaemia* and *vivax* malaria respectively and 5(13.1%) children each had falciparum malaria and viral fever. There is significant association between bleeding manifestations and etiology as per Chi-Square test (p<0.05) (Table 8).

Table 8: Association of bleeding manifestations and etiology.

Etiology	Total		Bleeding manifestations (n=38)	
		N	%	Value
Dengue	50	21	55.4%	
Septicaemia	35	4	10.5%	
Malaria	21	3	7.9%	
Scrub Typhus	79	5	13.1%	< 0.05
Enteric Fever	9	0	-	
Viral Fever	6	5	13.1%	
Total	200	38	100%	

### Association of etiology and platelet count

27(13.5%) children of dengue had platelet count >50,000/while 11(5.5%) children had platelet count  $21,000-50,000/\mu$ L. 6(3%) children each had platelet count of  $11,000-20,000/\mu L$  and  $\leq 10,000/\mu L$ . 23(11.5%)children with septicaemia had platelet count >50,000/ while 8(4%) had platelet count 21,000-50,000/μL. 2(1%) children each had platelet count  $11,000-20,000/\mu L$  and ≤10000/µL. Among the cases malaria, 19(9.5%) children had platelet count  $21,000-50,000/\mu L$  while 2(1%) and 0children had platelet count  $11,000\text{-}20,000/\mu L$  and ≤10000/ respectively. Among the cases of Scrub typhus, 69(34.5%) children had platelet count >50,000/μL while 8(4%) children had platelet count 21,000-50,000/μL and no one had platelet count between 11,000-20,000/μL. There is significant association between etiology and platelet count as per Chi-Square test (p<0.05) (Table 9).

# Association of thrombocytopenia with deranged liver function test

All patients with total bilirubin level >2 mg/dl and alanine transaminase level more than 2 fold rise of upper limit of normal for age were considered to have deranged liver function test. In this study out of 32 cases of scrub typhus 23(71.8%) had deranged LFT. Similarly 42.4% and 16.2% of patients of sepsis and dengue had deranged LFT. 4 children (23.5%) with enteric fever had abnormal LFT (Table 10).

Table 9: Association of etiology and platelet count.

Etiology	Platelet Co	unt (/µL)			— Total	n Volue
Euology	≤10,000	11,000-20,000	21,000-50,000	>50,000	Total	p Value
Dengue	6 (3%)	6 (3%)	11 (5.5%)	27 (13.5%)	50 (25%)	
Septicaemia	2 (1%)	2 (1%)	8 (4%)	23 (11.5%)	35 (17.5%)	
Malaria	0	2 (1%)	5 (2.5%)	14 (7%)	21 (10.5%)	
Scrub Typhus	0	2 (1%)	8 (4%)	69 (34.5%)	79 (39.5%)	< 0.05
Enteric Fever	0	0	0	9 (4.5%)	9 (4.5%)	
Viral Fever	0	1 (0.5%)	2 (1%)	3 (1.5%)	6 (3%)	
Total	8 (4%)	13 (6.5%)	34 (17%)	145 (72.5%)	200	

Table 10: Association of thrombocytopenia with deranged liver function test.

Etiology	AST/ALT	Sr. bilirubin	Total
Dengue	6	2	6 (16.2%)
Septicaemia	14	14	14 (42.4%)
Malaria	2	2	2 (100%)
Scrub typhus	23	5	23 (71.8%)
Enteric fever	4	0	4 (23.5%)
Viral fever	0	0	0
Meningitis	0	0	0
Uti	0	0	0
Encephalitis	0	1	1 (16.6%)
Leukemia/lymphoma	3	4	4 (26.6%)
Hypersplenism	1	0	1 (12.5%)
Hus	2	1	3 (22.3)
Secondary hlh	2	2	2 (100%)

# Association of thrombocytopenia with deranged renal function test

Patients with Serum creatinine >0.5 mg/dl, or more than 2 times of upper limit of normal for age or 2fold increase in baseline creatinine value were considered to have deranged renal function test. In this study 4 (10.8%) children of dengue, 15 (45.45%) of sepsis, 1 (50%) of malaria, 2 (6.25%) of scrub typhus, 1 (16.6%) of encephalitis had abnormal RFT (Table 11).

Table: 11 Association of thrombocytopenia with deranged renal function test.

Etiology	Creatinine	Total
Dengue	4	4 (10.8%)
Septicaemia	15	15 (45.45%)
Malaria	1	1 (50%)
Scrub typhus	2	2 (6.25%)
Enteric fever	0	0
Viral fever	0	0

### Mortality among children

In this study 183(91.5%) children had complete recovery while 17(8.5%) children died (Figure 2).

### Association of etiology and mortality

It was observed out of 17 children that died 11(5.5%) children had septicaemia, 4(2%) children had dengue and 1(0.5%) child each had vivax malaria and falciparum malaria. There is significant association between etiology and mortality as per Chi-Square test (p<0.05) (Table 12).

### Association of platelet count and mortality

It was observed out of 17children that died, 3(17.6%) children had platelet count  $\leq 10,000/\mu L$  while 6(35.2%)

and 8(47.2%) children had platelet count in the range of  $21,000-50,000/\mu L$  and  $>50,000/\mu L$  respectively.

There is significant association between platelet count and mortality as per Chi-Square test (p<0.05) (Table 13).

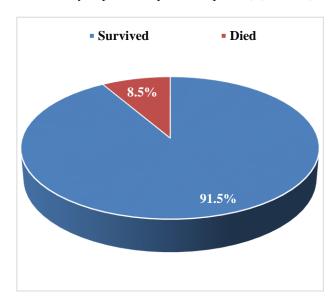


Figure 2: Mortality among children.

Table 12: Association of etiology and mortality.

Etiology	Mortality		Tot	p Value
Littology	Survived	Died	al	p value
Dengue	46 (23%)	4 (2%)	50	
Septicaemia	24 (12%)	11 (5.5%)	35	
Malaria	20 (10%)	1 (0.5%)	21	
Scrub typhus	78 (39%)	1 (0.5%)	79	< 0.05
Enteric fever	9 (4%)	0	9	(0.05
Viral fever	6 (3%)	0	6	
Total	183	17	200	-
10181	(91.5%)	(8.5%)	200	

#### **DISCUSSION**

Thrombocytopenia is defined as a platelet count below the  $150\times109/L$ , the  $25^{th}$  lower percentile of the normal platelet count distribution.<sup>7</sup>

Table 13: Association of platelet count and mortality.

Platelet count	Total	Mortality (n=17)		р
(/μL)	1 Otal	N	%	Value
≤10,000	8	3	17.6%	
11,000-20,000	13	0	-	
21,000-50,000	34	6	35.2%	< 0.05
>50,000	145	8	47.2%	
Total	200	17	100%	·

Typically, platelet counts higher than 50×109/L do not lead to clinical problems unless platelet dysfunction coexists with the low count. Medical help is usually sought by a patient with platelet counts less than 30×109/L, suffering from spontaneous bruising and purpura or with continuous/relatively long-lasting bleeding from injuries and wounds. Clinically significant spontaneous bleeding does not usually occur until the platelet count is less than 10×109/L.8 In this study more, children were between age group of 3-6years because they are more exposed to infectious aetiology (Table 1). Saba Ahmed et al, and Shah G.S. et al, also observed male predominance and similar results were seen in my study.8 Out of 200 patients 58.5% consisted of male population (Figure 1). In the present study, majority of cases were reported in rainy season (58%) followed by 24% in winter season and 18% in summer season (Table 3). whereas Praveen Kumar et al, reported majority of cases during summer season. More number of cases during rainy season in this study could be explained by more exposure to mosquito bite in this grown up children.9 Scrub typhus which is a common aetiology found in this study is more prevalent during rainy and winter season due to increasing humidity during these seasons. This favour hatching of the mite egg into chigger which is responsible for disease transmission. As per Mathai and Isac R et al, Recently it seems that there is resurgence of scrub typhus in this region.<sup>10</sup>

Increased prevalence may be attributed to expansion of human into previously uninhabited area, widespread use of beta lactum antibiotics, over population and climate change (et al, Mathai and Isac R et al, In the present study among the infectious causes Dengue was the commonest etiology (18.5%) followed by Septicaemia (16.5%), Scrub typhus (16%), Enteric fever (8.5%) malaria (1%), Encephalitis (3%) meningitis (4%), UTI (0.5%) (Table 3). Prithvi Raj et al, Rekha MC et al, and Nikhalje Anand et al, study results shows undiagnosed fever was the commonest etiology followed by dengue fever and enteric fever. These studies were comparable with present studies. Shankar Raikar et al, and Shruti K Bhalara et al, studies revealed that Dengue fever was the

commonest etiology followed by sepsis, these studies were also comparable with present study in reference to diagnosable etiology. <sup>12</sup> In contrast Putta Suresh et al, Praveen Kumar et al, and Amita G Gandhi et al, studies showed malaria as commonest etiology followed dengue and undiagnosed fever. <sup>13</sup>

Previous studies showed malaria was commonest etiology of fever with thrombocytopenia but in this study malaria contributes to only 1% of cases. This may be due to increased awareness, proper preventive measure and ongoing DAMAN (Durgama Anchalare Nirakaram) program in this state. Putta Suresh et al. Malaria (25.95%) was the second common cause responsible for febrile thrombocytopenia which includes P. falciparum (13.48%), P. Vivax (10.68%) and Combined P. falciparum - P. Vivax malaria (1.78%).14 Malaria is commonly accompanied by mild to moderate thrombocytopenia (88.23%) (78.4% by Jadhav et al, study) study showed that thrombocytopenia in Malaria due to sequestration and immune mediated destruction with elevated platelet activated immunoglobulins and thrombocytopenia in Dengue fever due to immune mediated mechanism.<sup>15</sup>

Muhammed Ayub et al, study revealed marrow depression in acute stage of Dengue infection causes thrombocytopenia and also in other infectious etiology. 183 (91.5%) children had complete recovery while 17 (8.5%) children died (Figure 2). 16 11 children had septicaemia, 4 child had dengue had malaria and 1 had suffered from scrub.Pankaj K Palange et al, Kriti Mohan et al, Shah G.S et al, Nikalje Anandh et al, Shankar Raikar et al, study results revealed that there was no relation between platelet count and mortality, according to them it only depends upon severity of disease and other co-morbid conditions. 17-21

In this study out of 32 cases of scrub typhus 23 (71.8%) had deranged LFT (Table 10). Similarly, 42.4% and 16.2% of patients of sepsis and dengue had deranged LFT. Similar findings were seen in study by MP Gondhali et al.<sup>22</sup> Deranged RFT was observed mostly in septicemic cases (Table 11). Mortality was high in septicaemia (5%) even if moderate with thrombocytopenia (Table 12). Evidence of complications and bleeding was seen more in sepsis even with higher platelet count (47.2%) which may be explained by associated multi organ failure (Table 13).

### **CONCLUSION**

Thrombocytopenia is a common haematological finding in many febrile children's. Infectious diseases are the most common cause of febrile thrombocytopenia in children. Fever with thrombocytopenia narrowed down clinical diagnosis and management in children. Dengue is the most common etiology followed by septicaemia and scrub typhus.

Scrub typhus is an emerging infectious disease in this region and should be suspected in a child with history of prolonged fever, oedema, lymphadenopathy, organomegaly with deranged liver function test and thrombocytopenia. Malaria was found as a leading infectious cause of thrombocytopenia in many previous studies but in this study, it accounted for only 1% of cases. This variation in results may be explained by increased awareness and early treatment by healthcare workers and ongoing DAMAN program (Durgama Anchalare Malaria Nirakaran) in odisha.

Petechiae are the commonest bleeding manifestation in children with thrombocytopenia but it can also be an incidental finding in many asymptomatic children. Among the infectious aetiology severe thrombocytopenia was seen more in dengue but evidence of bleeding was seen more in sepsis even with higher platelet count which may be explained by associated multi organ failure. Patient suffering from infectious diseases had thrombocytopenia which was transient i.e. it improved as the disease process subsided.

Treatment of primary condition improves the platelet count in infectious cause of thrombocytopenia hence aggressive platelet transfusion should be avoided to prevent transfusion related complications. Any child presenting with a febrile illness having a blood picture of thrombocytopenia should be given early treatment at a health care facility to prevent morbidity and mortality. Majority of patients have full and sustained recovery within 1-2 month of presentation with appropriate treatment.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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