



Original Research Article

To determine the various causes of thrombocytopenia and its clinical correlation with bleeding in children and adolescents

Rinu Dwivedi¹, Gyanesh Mishra^{1*}

¹Dept. of Paediatrics, Shri Shankaracharya Institute of Medical Sciences, Durg, Chhattisgarh, India



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ABSTRACT

Introduction: Thrombocytopenia refers to a reduction in platelet count below 1,50,000/cumm. It is the most common cause of defective primary hemostasis that can lead to significant bleeding in children.

Materials and Methods: It was a retrospective observational study conducted in a tertiary care hospital in Bhilai, Chhattisgarh between August to December 2021. Data collection was done from Sept 2018-Sept 2019. The aim of present study was to determine the various causes of thrombocytopenia in children and adolescents and to correlate its severity with etiology and risk of bleeding. Total 112 patients were included from age group 1y-18 yrs.

Results: Out of total 112 patients 59 were males and 53 were females. 27 patients were 1-5 years of age, 30 patients were 6-12 years of age and 55 were 13-18 years. The mean platelet count in my study was 68,340/cumm with a minimum of 4000/cumm. Bleeding was present in total 19 (16.9%) patients. The main bleeding manifestations were petechiae or purpurae, epistaxis, ecchymosis, gastrointestinal bleed and others. Severity of thrombocytopenia correlates significantly with risk of bleeding (The p-value is 0.001**). The most common cause of thrombocytopenia in 69 patients with fever were infective and 43 patients without fever it was vitamin b12 deficiency. Severity of thrombocytopenia (p=0.0528) and bleeding (p=0.121) in patients with fever and without fever was not significant.

Conclusion: Thrombocytopenia in pediatric and adolescent children is caused by both infective and non infective illness. It mainly presents with cutaneous bleeds and mucosal bleeds. Severity of thrombocytopenia is significantly correlated with bleeding.

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1. Introduction

Platelets are non nucleated cellular fragments with a half life of 10-14 days, produced by megakaryocytes within the bone marrow and other tissues. Thrombopoietin (TPO) is the primary growth factor for platelet production.¹ The normal platelet count is 1,50,000 to 4,50,000/cumm. Thrombocytopenia refers to a reduction in platelet count below 1,50,000/cumm. It results from any of the three processes i.e. decreased bone marrow production, sequestration within an enlarged organ like spleen or

increased destruction of normally synthesized platelets on either an immune or non immune basis.¹ However misdiagnosis of thrombocytopenia also occurs, and could be the result of artefactual laboratory errors.²

Thrombocytopenia is the most common cause of defective primary hemostasis that can lead to significant bleeding in children.³ Thrombocytopenia presents with mucocutaneous bleeding, petechiae, cutaneous purpura, gingival bleeding, epistaxis, menorrhagia, gastrointestinal bleeding, and hematuria. Intracranial hemorrhage is the most serious complication but is uncommon. Deep visceral hematomas, hemarthroses, or muscle hematomas are uncommon with thrombocytopenia and suggest a defect in

* Corresponding author.

E-mail address: drgyanesh@gmail.com (G. Mishra).

the coagulation cascade.⁴

There are numerous causes of thrombocytopenia, including infectious causes, immune thrombocytopenic purpura, drug induced, autoimmune, nutritional deficiencies, hypersplenism, malignancy, and many others.⁵ Reduced platelet count is manifestation of disease, but bleeding is clinically important as it affects not only treatment decision but also quality of life of patients especially in chronic conditions.^{6,7} There are many studies on febrile thrombocytopenia in children which covers mostly infective etiology and also many studies on ITP,^{6–11} but very few studies which analyze thrombocytopenia in both febrile and non febrile children and their bleeding correlation. Also the infective causes are different based on region and also season.

Knowledge about the common aetiology of thrombocytopenia in our own region will not only assist clinicians in decision-making and interpretation of laboratory tests but will also help in cost effective patient management. The present study will add on to the existing knowledge about thrombocytopenia causes and clinical presentations in children and adolescents from this region.

2. Materials and Methods

This was a retrospective observational study conducted between August to December 2021 in a tertiary care hospital of Bhilai, Chhattisgarh. Institutional ethical committee approval was taken prior to commencement of study. The data collection was done for a period of 1 year from September 2018 to September 2019 by analysis of patients case sheets from medical record department of the institute.

The aim of present study was to determine the various causes of thrombocytopenia in children and adolescents and to correlate severity of thrombocytopenia with etiology and risk of bleeding.

Total 112 paediatric patients who were admitted in paediatric ICU and ward from age group 1yr-18 yrs were included. The patients were divided into 3 age groups 1-5 yrs, 6-12 yrs and 13-18 yrs. Patients admitted in paediatric surgery and post operative patients, patients with known coagulation disorders or coagulation factor deficiency were excluded from study.

Data included history and thorough clinical findings as mentioned on daily notes regarding fever, cough cold, loose motions, vomiting, hematemesis, malena, seizures or any new symptom during hospital stay. Special emphasis was given on obtaining data related to type and duration of fever and bleeding manifestations present at the time of presentation to our hospital or later during the course of their hospital stay. Investigations included CBC, peripheral blood smear and CRP, rapid diagnostic test for malarial parasites, blood culture, Widal test, ELISA tests for dengue virus, IgM against rickettsial infections. Coagulation studies,

L.F.T, R.F.T, C.S.F analysis, bone marrow aspiration, serum B12 level and radiological investigations were noted as mentioned in records. As many patients had multiple platelet reports in file, the lowest platelet count was entered for study and analysed.

Data was entered in Microsoft excel sheet and analysed using software. SPSS ver.21®. Variables were expressed as mean, standard deviation, and percentage as appropriate. Dichotomous variables were compared using chi-square test or fishers exact test whereas continuous variables were compared using Student t-test. P-value <0.05 was taken as significant.

3. Results

Out of total 112 patients, 59(52.7%) were male and 53 (47.3%) were female patients. 27 patients were 1-5 years of age, 30 patients were 6-12 years of age and 55 patients were 13-18 years age group (Table 1). The mean age was found to be 10.56±5.1 years.

The clinical features were fever in 76 patients (62.2%), weakness in 52(42.6%), progressive pallor with fatigue in 46 patients (37.7%), cough and cold in 8 (6.5%), pain in abdomen in 44(36.1%), headache and body ache in 49(40.2%), joint pains in 35 patients (28.6%), vomiting in 27 patients (22.1%), seizures in 2 (1.6%) and bleeding complaints in 19 patients (8.1%). Examination findings were pallor in 58, icterus in 10, bleeding in 19, edema in 8, bleeding in 19, organomegaly (hepatomegaly or splenomegaly or both) in 48 patients.

Platelet counts were divided into 4 groups. 55 patients had platelets between 1,50,000/mm³-1,00,000/cumm, 28 patients had platelets 1,00,000/cumm to 50,000/cumm, 15 patients had platelets between 50,000-20,000/cumm and 14 patients had less than 20,000/cumm platelet counts as shown in Table 2. The mean platelet count was 68,340/cumm with a minimum of 4000/cumm.

Bleeding was present in total 19 (16.9%) patients out of which 12 had platelet counts <20,000/cumm, 4 had platelet count between 20,000-50,000/cumm and 3 had platelets 50,000-1,00,000/cumm. None of patients had bleeding with counts > 1,00,000/cumm (table no 2). (table no 2) This was significant with The p-value 0 .00001 using fishers exact test. Severity of thrombocytopenia correlates significantly with risk of bleeding. Patients with platelets less than 20,000/cumm showed significant bleeding.

Bleeding was present in 19 patients and there were 40 bleeding episodes in these 19 patients were as shown in table no 3. The petechie or purpurae were seen in total 15 patients, epistaxis in 5, ecchymosis in 8, gastrointestinal bleed in 6 patients and other bleeding manifestations include hematuria in 4 patients, pulmonary bleed in 1 and intracranial bleed in 1 patient. Maximum bleeding was seen in patients with platelet counts less than 20,000/cumm (50%).(Table no- 3)

Table 1: Age distributions of patients with thrombocytopenia

Age	Male	Female	Total
1-5 years	17	10	27(24.1%)
6-12 years	11	19	30(26.8%)
13-18 years	31	24	55(49.1%)
Total	59	53	112(100%)

Table 2: Distribution of platelet count and bleeding

Platelet counts/cumm	Male	Female	Bleeding present	Bleeding absent	Total
1,50,000-1,00,000	29	21	0	50	50
1,00,000-50,000	11	17	4	24	28
50,000-20,000	10	7	4	10	17
<20,000	9	8	12	5	17
Total	59	53	19	93	112(100%)

Table 3: Site of bleeding manifestations and platelet counts.

Bleeding manifestation	1,00,000-50,000/cumm	50,000-20,000/cumm	<20,000/cumm	Total
Petechie, purpurae	2	6	7	15
Epistaxis	1	1	3	5
Ecchymosis	5	1	2	8
Gi bleed	0	2	4	6
Others	1	1	4	6
	9(22.5%)	11(27.5%)	20(50%)	40(100%)

Table 4: Etiology of thrombocytopenia -age wise distribution, platelet counts and bleeding in patients with fever

Etiology	Age in years			Total	Platelet counts (/cumm)				No of patients with Bleeding
	1-5	6-12	13-18		1,50,000-1,00,000	50,000-20,000	<20,000		
Septicemia	9	6	4	19	8	5	1	5	0
Enteric fever	0	2	7	9	4	3	2	0	0
Sickle cell with fever	4	4	1	9	1	1	3	4	2
Dengue fever	1	1	5	7	0	2	1	4	1
Viral fever	5	4	2	11	9	2	0	0	0
UTI and pyelonephritis	4	3	4	11	7	3	1	0	5
Malaria	0	1	1	2	0	1	1	0	1
Ricketssia	0	0	1	1	0	0	1	0	0
Total	23	21	25	Total 69(100%)	29	17	10	13	Total15

Table 5: Etiology of thrombocytopenia -age wise distribution, platelet counts and bleeding in patients without fever

Etiology	Age in years			Total	Platelet counts (/cumm)				No of patients with Bleeding
	1-5	6-12	13-18		1,50,000-1,00,000	1,00,000-50,000	50,000-20,000	<20,000	
Vitamin B12 deficiency	1	4	24	29	19	8	2	0	0
Sickle cell with painful crisis	1	3	1	5	1	1	3	0	0
Leukemia	0	0	2	2	0	1	1	0	1
Thalassemia with hypersplenism	0	1	1	2	1	0	1	0	0
ITP	1	1	2	4	0	1	0	3	2
Fanconi anemia	1	0	0	1	0	0	0	1	1
Total	4	9	30	Total 43(100%)	21	11	7	4	Total 4

Table 6: Correlation of age with etiology of thrombocytopenia in children with and without fever

Age group	With fever	Without fever	Total	P value- 0.00129 Significant
1-5 years	23	4	27	
6-12 years	21	9	30	
13-18 years	25	30	55	
Total	69	43	112	

Table 7: Correlation of thrombocytopenia (<50,000/cumm) severity in children with fever and without fever

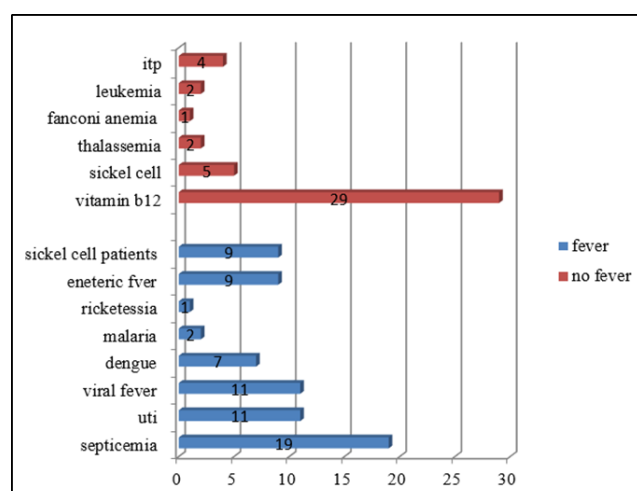
Platelet count	With fever	Without fever	Total
<50,000	22	11	33
>50,000	47	32	79
Total	69	43	112

P value =0.0528 non significant

Table 8: Correlation of bleeding with different parameters

Parameters	Bleeding present	Bleeding absent	P value	Significance
1. Bleeding in patients of thrombocytopenia with fever and without fever				
With fever	15	54	0.121	Non significant
Without fever	4	39		
2. Bleeding among patients with septicemia as compared to other causes with fever				
septicemia	6	13	0.3264	Non significant
Other causes	9	41		
3. Bleeding among patients with ITP as compared to other causes without fever				
ITP	2	2	0.0373	Significant
Other causes	2	37		

Common causes of thrombocytopenia were divided into two based on history of fever. Fever was present in 69 (61.6%) patients and 43(38.4%) patients had no fever. (Figure 1).

**Figure 1:** Etiology of thrombocytopenia in patients with fever and without fever.

The common causes of thrombocytopenia in 69 patients with fever were mainly infective, the most common was septicemia in 19 cases., followed by urinary tract infection (UTI) in 11 which included 1 patient with pyelonephritis,

viral fever (excluding dengue) in 11, enteric fever in 9, dengue fever in 7, sickle cell patients with infections in 9, malaria in 2, rickettsial fever in 1 patient. Blood culture was positive in 14 cases of septicemia; however it was negative in 5 cases. Viral fever included 2 cases of viral hepatitis A, 5 cases with upper respiratory illness and 4 of acute gastroenteritis. Sickle cell patients with infections causes included sepsis in 4, viral fever in 3 patients and pneumonia in 2 patients (Table 4)

The most common cause of thrombocytopenia in total 43 patients without fever was vitamin b12 deficiency which was found in 29 cases. Other causes were sickle cell anaemia with painful crisis or hypersplenism in 5, ITP in 4, thalassemia with hypersplenism in 2, fanconi's anemia in 1, leukemia in 2 patients. The mean vitamin b12 levels was found to be 74.3 pg/ml.(Table 5)

Among children of age 1-5 years, 23 patients had thrombocytopenia with fever and 4 patients without fever. The most common cause in this age group was septicemia which was seen in 9 patients

Among children of age 6-12 years, 21 patients had thrombocytopenia with fever and 9 patients had without fever and most common cause was septicemia in total 6 patients

Among adolescent age group 13-18 years, 25 patients had thrombocytopenia with fever and 30 patients had without fever and the most common cause was vitamin b12 deficiency which was seen in 24 patients.

The number of patients with thrombocytopenia with fever was significantly higher than thrombocytopenia without fever in children 1-5 years and 6-12 years as compared to 13-18 years age group .chi square test p-value is .00129. The result is significant at $p < .05$.(Table 6)

Severity of thrombocytopenia (platelets $< 50,000$) in patients with fever and without fever was non significant with $p=0.0528$ using fishers exact test.(Table 7)

Bleeding in children of thrombocytopenia with fever and without fever was not significant with $p=0.121$. The most common cause of bleeding in patients with fever was septicaemia; however it was not statistically significant with fishers test p value was 0.326. The most common cause of bleeding in patients without fever was ITP and it was statistically significant. The Fisher exact test statistic value is 0.0373. (tTable 8)

Out of 112 patients 2 patients with leukaemia were referred to oncology centres. Out of remaining 110 patients, 6 patients succumbed to illness. The outcome in terms of mortality was 5.45%. 6 patients who died included 1 patient with sickle cell anaemia with painful crisis, 2 sickle cell patients with septicaemia and 3 other patients with septicaemia.

4. Discussion

In the present study there were a total of 112 patients out of which, 59 patients (48.3%) were male and 53 patients (43.4%) were female .The maximum cases of thrombocytopenia were seen in the age group 13 - 18 years and minimum cases were seen in the 1-5years age group.

Cohn J. et al in their study on thrombocytopenia in childhood in Denmark found that there was a peak incidence of thrombocytopenia in the age of 3-4 years.¹² Another study done by Mahvish K. et al, at patna bihar which included 120 children with febrile thrombocytopenia found that Mean age of the study group was 6.9 years. Most of the children were in 5-10 years age group ($n=52$, 43.3%). Males (69) patients were more than females (51) with a male: female ratio of 1.35:1.¹³

Subramanian V. et al in their study in Chennai found that out of 644 children admitted with thrombocytopenia, 213 had bleeding manifestations Among the Bleeding manifestations, cutaneous(49.1%) and mucosal bleeds(27.1%) were the most common presentations. 23% of children either had bleeding in various forms like Haematemesis, melena and epistaxis, haematuria, subconjunctival haemorrhage or intracranial haemorrhage.¹⁴

Nair BT. et al also found that 57.7% children had spontaneous bleeds and 42% had cutaneous bleeds.¹⁵ Another study done by Patil P. et al studied bleeding manifestations and found petechiae was the major manifestation (73.9%) followed by spontaneous bleeding (26.9%).¹⁶ Lohitashwa S.B. et al, however found that

purpura (63%) was the commonest bleeding manifestations followed by spontaneous bleeding (37%) in his study.¹⁷

In the present study the bleeding manifestations were similar to Subramanian v et al and also severity of thrombocytopenia correlates significantly with risk of bleeding. Patients with platelets less than 20,000/cumm showed significant bleeding in present study. Alam S.et in their study also found that bleeding manifestation was invariably present in children with platelet count $<20,000$ /cumm. Bleeding manifestation had a significant association with the degree of thrombocytopenia ($p=0.036$).¹⁸

In the present study the leading cause of thrombocytopenia in children with fever was infective in 69 patients, most common being septicemia and in 43 children without fever most common was vitamin b12 deficiency.

Subramanian V et al in their study regarding etiology of thrombocytopenia found that most of the causes were due to infectious (86.6%), Other causes included connective tissue disorders, hematological problems, drug induced thrombocytopenia. Among the infective causes for thrombocytopenia that were analysed predominant children were affected by Viral fevers including dengue (78%).¹⁴

However one adult study done by Nair P.S. in New Delhi, showed septicaemia (26.6%) to be the major cause of thrombocytopenia.¹⁹

In a study done by Ramabhattacha S.et al, in bengluru, the most common cause of thrombocytopen in febrile children aged 1-18 years patients was found to be dengue fever in 83%, followed by viral fever, enteric fever, malaria and hepatitis.²⁰

The difference in etiology in various studies could be regional and seasonal variations, which determine the outbreaks of viral illness.

There are very few studies on thrombocytopenia in non febrile patients. In the present study among the thrombocytopenia patients without fever vitamin b12 deficiency was most common cause which was significantly high in children of the age group 13-18 years. However none of the patients showed bleeding. There are many studies and case reports regarding vitamin b12 deficiency with thrombocytopenia and bleeding manifestations.²¹⁻²⁴ However few studies did find thrombocytopenia in patients with vitamin b12 deficiency but it was not significantly associated.^{25,26}

Marwaha RK, et al reported 10 children with megaloblastic anemia and a hemorrhagic diathesis . Four of them had life-threatening bleeds necessitating an emergency blood transfusion. Seven had platelet counts of less than 30,000/cu mm. Vitamin b12 deficiency was most common etiology in their study.²⁷

One adult study done by Nafil H. et al in 120 patients of anaemia with vitamin b12 deficiency, noted that

thrombocytopenia was present in 34 patients (28%). The average vitamin B12 was 72 pg/ml.²⁸

In present study mortality was seen in 5 children. Karthikraj T et al in their study found that out of 372 children with thrombocytopenia 5 children died which included 3 with dengue hemorrhagic fever and 2 with septicaemia.²⁹ A study done by Gowd K.P. et al measured outcome in terms of morbidity in children with fever and thrombocytopenia and found that late visit to hospital with prolonged fever and warning symptoms were associated with poor outcome. They also found that children presenting with hepatomegaly, platelet count less than 1 lakh, elevated hematocrit, abnormal renal function test, elevated liver enzymes and abnormal coagulation profile at the time of admission had poor outcome.³⁰

Limitations of present study were that being a single institution based study, results cannot be generalised and we could not evaluate etiology for all viral illness. Another limitation was that it is one year data; there is need for long duration studies for better understanding of all causes of thrombocytopenia in children.

5. Conclusion

Thrombocytopenia in children below 13 years was mainly infective in etiology, most common cause was septicemia, and however in adolescent children it was non infective and vitamin b12 deficiency was the most common cause. It mainly presents with cutaneous bleeds and mucosal bleeds. Severity of thrombocytopenia is significantly correlated with bleeding. There was no significant difference in severity of thrombocytopenia and also incidence of bleeding in children with thrombocytopenia with fever and without fever. Among children with thrombocytopenia without fever ITP was significant cause of bleeding,

6. Conflict of Interest

None.

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Medical record department of Shri Shankaracharya Institute of Medical Sciences Bhilai. C.G.

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Author biography

Rinu Dwivedi, Associate Professor  <https://orcid.org/0000-0003-0612-9238>

Gyanesh Mishra, Associate Professor

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