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Original Research Article

CLINICAL PROFILE OF ACUTE FEBRILE ILLNESS WITH THROMBOCYTOPENIA IN CHILDREN: A PROSPECTIVE STUDY

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ABSTRACT

Background: Acute febrile illness with thrombocytopenia is a common presentation in children, notably in tropical countries like India during monsoon seasons. It poses a great challenge in diagnosis and management due to varied etiologies, clinical course, and risk of hemorrhagic complications. This study aimed to evaluate the clinical profile, etiological spectrum, and outcomes of febrile thrombocytopenia in children. **Material and Methods:** A prospective descriptive study was conducted over 12 months in a tertiary care pediatric hospital in South India. A total of 250 hospitalized children aged 1 month to 18 years presenting with fever <1 week and platelet count <1.5 lakh/mm³ were included. Children with hematological malignancy, pre-existing thrombocytopenia, systemic lupus erythematosus, or on drugs causing thrombocytopenia were excluded. Clinical features, laboratory parameters, complications, and outcomes were analyzed. **Results:** Of 250 children, 144 (58%) were males. The most affected age group was 6–10 years (36%). Vomiting (54%), abdominal pain (36%), and lethargy (26%) were the most common symptoms; hepatomegaly (69%) was the most frequent examination finding. Dengue was the predominant cause (63%), followed by probable viral fever (18%), enteric fever (8%), malignancy (5%), scrub typhus (3%), sepsis (3%), and malaria (2%). Severe thrombocytopenia (<50,000/mm³) was present in 42%, predominantly associated with dengue (85%). Shock occurred in 18% of cases and there was significant association with severe thrombocytopenia ($p<0.001$). Bleeding manifestations were reported in 11%, most commonly petechiae and melena, also correlating with severe thrombocytopenia ($p<0.001$). Hospital stay was prolonged and PICU admission was higher in children with severe thrombocytopenia. Blood product transfusions were required in 9%. Complications observed were pleural effusion (8%) and respiratory failure (1%). No mortality was recorded. **Conclusion:** Acute febrile thrombocytopenia in children is mostly occurs due to dengue, followed by other viral and bacterial infections. Severe thrombocytopenia correlates strongly with bleeding, shock, and increased duration of hospital stay. Careful monitoring and supportive care, rather than prophylactic platelet transfusions, would ensure favorable outcomes.

INTRODUCTION

Febrile illnesses are common in children, especially in children under 5 years of age. On an average young children experience three to six febrile illnesses per year.[1] Fever is the most common reason for seeking medical attention in the pediatric emergency department.[2] Evaluation of febrile children remains a diagnostic challenge, which requires proper history, clinical examination and appropriate investigations. In recent years in tropical countries like India, an upsurge in number of cases of acute febrile illnesses with thrombocytopenia is seen especially in monsoon season probably due to several emerging and re-emerging infections.[3]

Acute febrile illness with thrombocytopenia is a distinct entity in which platelet count is decreased below 1.5 lakh/mm³ in association with fever <1 week duration with no identified source.[4] Several studies have shown that infections like dengue fever, malaria, rickettsial infections, enteric fever, viral fever, septicemia are associated with febrile illness with thrombocytopenia. Sometimes non infectious causes like primary hematological malignancies, lupus can also present as febrile thrombocytopenia.

As platelets play central role in normal hemostasis and also in thrombosis, patients with

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thrombocytopenia may have bleeding manifestations like petechiae, epistaxis, gum bleeding, hematuria, gastrointestinal hemorrhage, intracranial bleeds. Though patients may initially present with simple fever, in due course thrombocytopenia can lead to variable clinical course and unpredicatble outcomes including death at times. The uncertain course is often a cause of concern to patients and treating physicians and may result in unnecessary prophylactic platelet transfusions in some patients.[5] There is a changing trend in etiology because of varying epidemic trends in different geographical regions. Hence it's imperative that there should be regional studies regarding etiology and clinical profile of fever with thrombocytopenia, correlation between platelet count and hemorrhagic manifestations, as early diagnosis and timely intervention prevent adverse outcomes. This study was carried out to try to determine the etiology, clinical profile and outcome of acute fever with thrombocytopenia in a tertiary care pediatric hospital setting.

MATERIALS AND METHODS

This Prospective descriptive study was conducted in the department of pediatrics at a tertiary care hospital in south India over a period of 12 months. A total of 250 hospitalized Children in age group 1 month to 18 years who presented with fever for < 1 week and with platelet count less than 1.5 lakh/mm3 were included in the study. Children who presented with thrombocytopenia without fever, preexisting thrombocytopenia (ITP, Platelet disorder or dysfunction), previously diagnosed case of hematological malignancy/ marrow dysfunction/ preexisting conditions associated with thrombocytopenia like SLE, patients on antiplatelet drugs/ drugs causing thrombocytopenia were excluded from the study. The objectives of this study was to study various clinical presentations of acute febrile illness with thrombocytopenia in children of age group 1 month to 18 years, identify etiology of acute fever with thrombocytopenia and study the relationship between platelet count and severity of disease. After obtaining an informed consent from parent or legal guardian or from the child if age > 12 years, detailed history of illness was noted. Thorough clinical examination was done and relevant clinical findings, laboratory investigations, clinical course and outcome were noted. Baseline investigations like Complete blood count to look into other cell lineages and PCV, renal function tests, liver function tests were done for all the patients. Etiological work up included Dengue IgM, NS1Ag, Smear for Malarial parasite, Scrub typhus IgM, Blood culture, Widal test, Bone marrow examination (in case of suspected malignancies), Bone marrow culture. Other relevant Tests for etiology were done as needed based on clinical presentation and examination findings. Children were periodically followed up till discharge for complications like shock, major hemorrhagic manifestations, hepatic and renal failure, pulmonary edema, multiorgan dysfunction, DIC. Discharge criteria were hemodynamic stability, afebrile period for more than 24 hours, recovery from complications if any, documented increasing trend of platelet count. Data was analyzed using SPSS software 20 version. Descriptive analysis was done for background variables. Etiological factors for thrombocytopenia was described as percentages and 95% confidence interval was calculated. Association between categorical variables was tested for significance by Chi-square test. Association between continuous variables was tested for significance by Unpaired t test/ Anova test. P value of <0.05 was considered statistically significant.

RESULTS

This study included 250 children aged 1 month–18 years, of whom 144 (58%) were males and 106 (42%) females (M:F ratio 1.4:1). The age distribution was <1 year (23, 9%), 2–5 years (72, 29%), 6–10 years (89, 36%), and >10 years (66, 26%).

Fever was the universal symptom. Vomiting was most common (135, 54%), followed by abdominal pain (90, 36%), lethargy (65, 26%), cough and cold (37, 15%), oliguria (30, 12%), rash (19, 8%), loose stools (15, 6%), and facial puffiness (12, 5%). Less frequent were breathing difficulty, myalgia, and abdominal distension (3% each), and headache (2%) [Table 1].

Bleeding manifestations were seen in 24 children (10%): melena in 12, hematemesis in 6, epistaxis in 4, gum bleeding in 3, and hematuria in 1. On examination, hepatomegaly was most frequent (171, 69%), followed by splenomegaly (44, 18%) and hepatosplenomegaly (41, 17%). Other findings included pallor in 19 (8%), petechiae in 15 (6%), and eschar in 5 (2%). Shock occurred in 44 children (18%)—25 with compensated and 19 with hypotensive shock.

In children where available etiological investigations were negative or in whom further etiological workup could not be done because of logistic reasons and with decline of fever over 1 week were labelled as probable viral fever. The most common etiology was dengue (158, 63%), followed by probable viral fever (44, 18%), enteric fever (19, 8%), malignancy (11, 5%), scrub typhus (7, 3%), sepsis (7, 3%), and malaria (4, 2%). Dengue predominated across all age groups: 70% in <1 year, 44% in 2–5 years, 67% in 6–10 years, and 75% in >10 years[.Thrombocytopenia was graded as mild in 78 (31%), moderate in 68 (27%), and severe in 104 (42%). In mild thrombocytopenia, dengue and probable viral fever were equally common (37% each).In moderate thrombocytopenia, dengue predominated (60%).In severe thrombocytopenia, dengue accounted for 85%(figure 1)

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Shock was not observed in mild thrombocytopenia. It was present in 9% of children with moderate and 36% with severe thrombocytopenia ($p<0.001$). Dengue was the sole cause of compensated shock (25 cases). Among hypotensive shock cases (n=19), etiologies included dengue (10), malignancy (3), sepsis (2), enteric fever (2), malaria (1), and scrub typhus (1).

Bleeding was documented in 27 children (11% of the study population), most frequently petechiae (6%) and melena (5%). By age, bleeding manifestations occurred in 13% of <1 year, 8% of 2–5 years, 12% of 6–10 years, and 11% of >10 years, with no significant association with age group. Petechiae and hematemesis were more frequent in 6–10 years, melena and gum bleeds in 2–5 years, and epistaxis/hematuria in >10 years (Figure 2).

Etiologically, bleeding was most often due to dengue (23, 85%), followed by malignancy (3, 11%) and sepsis (1, 4%). Among dengue patients, 15% had bleeding, compared to 27% with malignancy and 14% with sepsis (figure 3). Bleeding correlated strongly with thrombocytopenia severity ($p<0.001$). It was absent in mild cases, present in 6% with moderate, and 22% with severe thrombocytopenia. Of 28 children with platelet count <20,000/mm³, nine (32%) had bleeding.

There was no statistically significant association between thrombocytopenia severity and leucopenia. However, bleeding manifestations correlated with lower platelet counts, lowest platelet nadir during admission, and elevated liver enzymes (SGOT, SGPT). No association was noted with PCV.

Duration of hospitalization was <5 days in 71%, 5–10 days in 23%, and >10 days in 6%. Severe thrombocytopenia was significantly associated with longer hospital stay and need for PICU admission ($p<0.001$). Thirteen percent required PICU care, predominantly those with severe thrombocytopenia (table 3).

Blood product transfusions were given to 23 children (9%), including packed cells in 14, platelets in 13, and FFP in 12. Of these, 21 had severe thrombocytopenia and two had moderate. Most transfused children had dengue (12), malignancy (8), or sepsis (3). Colloid infusions were needed in 16 children with dengue who presented in refractory hypotensive shock. Inotropes were required in 7 children, all with hypotensive shock. Nineteen children developed pleural effusion, confirmed radiologically. Two with severe dengue required mechanical ventilation for respiratory failure. Importantly, no mortality was recorded during the study period. Children diagnosed with malignancies were started on appropriate therapy.

Table 1: Symptoms and signs of acute febrile illness with thrombocytopenia in children

Parameter	Number/ percentage
Symptoms	
Vomiting	135 (54%)
Abdominal pain	90 (36%)
Lethargy	65 (26%)
Cough & cold	37 (15%)
Oliguria (decreased urine output)	30 (12%)
Bleeding manifestations	24 (10%)
Rash	19 (8%)
Loose stools	15 (6%)
Facial puffiness	12 (5%)
Breathing difficulty	7 (3%)
Myalgia	6 (3%)
Abdominal distension	7 (3%)
Headache	5 (2%)
Signs	
Hepatomegaly	171 (69%)
Splenomegaly	44 (18%)
Hepatosplenomegaly	41 (17%)
Petechiae	15 (6%)
Pallor	19 (8%)
Eschar	5 (2%)

Table 2: Etiological profile of febrile thrombocytopenia

Etiology	Number of cases/ percentage
Dengue	158 (63%)
Probable viral fever	44 (18%)
Enteric fever	19 (8%)
Scrub typhus	7 (3%)
Malignancy	11 (5%)
Sepsis	7 (3%)
Malaria	4 (2%)

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Table 3: Association of thrombocytopenia with complications

parameter	Complication	P value
Thrombocytopenia Mild Moderate Severe	**Shock (%)** 0 9 36	**<0.001**
Thrombocytopenia: Mild Moderate Severe	Bleeding (%) 0 6 22	<0.001
Thrombocytopenia: Mild Moderate Severe	Hospital stay in days (mean±sd) 3.32±1.39 3.9±2.11 5.4±4.14	<0.001
Thrombocytopenia: Mild Moderate Severe	PICU stay in days(mean±sd) 0.03±0.23 0.1±0.47 1.1±2.6	<0.001

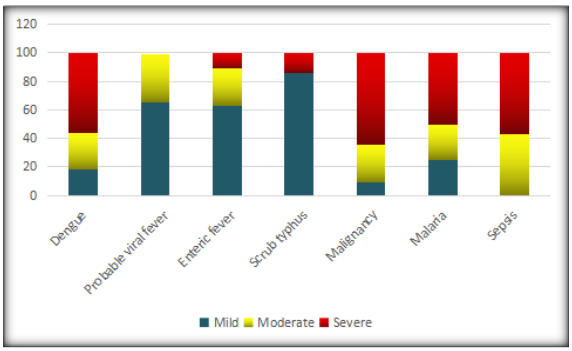

Figure 1: Grades of thrombocytopenia in different etiologies

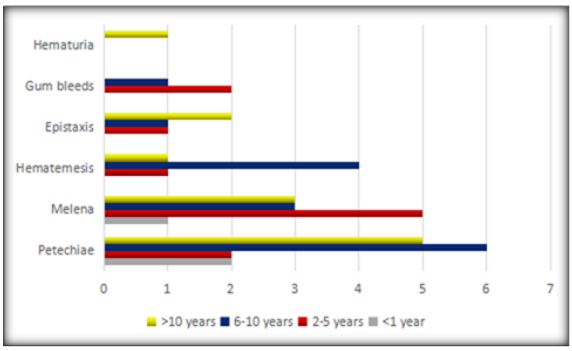

Figure 2: Common bleeding manifestations in different age groups

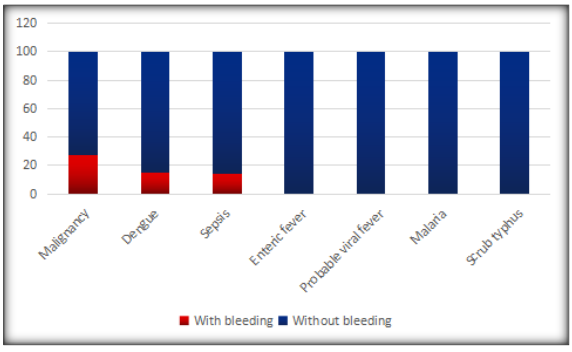

Figure 3: Bleeding manifestations shown in percentage in different etiologies

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DISCUSSION

Fever with thrombocytopenia has varied clinical presentation and diverse etiology. In this study which is a prospective descriptive study, clinical profile, etiological profile and severity of illness in relation to thrombocytopenia, outcome of children with acute febrile illness with thrombocytopenia were studied.

The sex ratio in our study was 1.4:1 which is similar to previous studies.[6] Vijapura et al observed in his study that commonly affected age group was 6 -10 yrs age. The age distribution was in similar percentages in our study.[7] This can be attributed to increased outdoor activity in this particular age group of children and increased exposure to mosquito vectors.

In this study, 54% of participants reported vomiting as a frequent symptom and the next common symptom was abdominal discomfort. The common signs observed were hepatomegaly (69%), splenomegaly(18%) and hepatosplenomegaly(17%),

According to the Gutthi et al. study, the most prevalent symptoms were bleeding in 45% of cases, vomiting in 38%, and stomach discomfort in 43%. The most prevalent symptom, pallor, was observed in 69% of the research participants, followed by hepatomegaly in 41%, splenomegaly in 32%, and hepatosplenomegaly in 55%. This could be as a result of the study's prevalent etiology being malaria.[3]

The Nair BT et al. research, on the other hand, revealed that the most prevalent symptom was myalgia at 66%, followed by headache at 61%, joint pain at 51%, vomiting at 19%, stomach discomfort at 19%, bleeding symptoms at 19%, and rash at 8%. The differences in prevalent causes of febrile thrombocytopenia may be the reason for the diversity in symptoms and signs between studies.[8]

Of the 250 cases in this trial, 44 (18%) experienced shock. Twenty-five children (10%) experienced compensated shock, whereas nineteen (8%) experienced hypotensive shock. There was a substantial statistical correlation (P value<0.001)

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between shock and severe thrombocytopenia. According to a research by Palange et al., 35% of patients suffered shock, with 17% experiencing compensated shock,18% had hypotensive shock.[9]

Dengue fever accounted for 63% of the children in the current research who had acute febrile illness with thrombocytopenia, followed by probable viral fever (18%), enteric fever (8%), scrub typhus (3%), malignancy (5%), sepsis (3%), and malaria (2%). According to studies conducted on children by Sujatha et al,[59] and Subramanian V et al,[60] dengue was the most prevalent cause, followed by likely viral fever.[6,10] According to the Gutthi et al.research, dengue and malaria are the two most prevalent etiologies. This can be because the epidemics vary by area. Various Studies done in adults by also showed dengue as common etiology.[11]

Dengue was the most frequent cause of thrombocytopenia in our research, accounting for 44–75% of cases across all age categories. Across all age categories, probable viral fever was the second most frequent cause, accounting for 9% to 22% of cases.

The proportion of severe thrombocytopenia (41%) in the current research was greater than that of mild and moderate thrombocytopenia. With the exception of the Naikwadi et al,[67] research, where proportion of cases was high in moderate thrombocytopenia group, this result is consistent with other previous investigations.[12]

Among the cases with severe thrombocytopenia, predominant causes were malignancy, sepsis and dengue. Sepsis, probable viral fever, malignancy were the common causes in cases with moderate thrombocytopenia. Infections like Scrub typhus, probable viral fever, enteric fever, malaria and dengue, accounted for majority of the cases with mild thrombocytopenia . This was comparable with few studies done previously.[13] According to the Nair BT et al. research), severe thrombocytopenia was present in 80% of dengue patients, 47% of malaria patients, 32% of enteric fever patients, and 100% of sepsis and cancer patients.[8] Severe thrombocytopenia was seen in 15% of patients with malaria, 40% of patients with dengue, and 10% of patients with viral fever in a different investigation.[12] Infections like sepsis and dengue were reported as frequent causes of severe thrombocytopenia in some studies.[14]

In this investigation, 25 infants who presented with compensated shock had dengue as their only aetiology. Ten of the 19 children who experienced hypotensive shock had dengue, three had cancer, two had sepsis, two had enteric fever, one had malaria, and one had scrub typhus. Dengue was the most frequent cause of shock in this research (80%).

In this study, bleeding manifestations were seen in 11% of study population. The most frequent sign of bleeding was petechiae, which occurred in 15 children (6%), followed by melena by 5%, haematemesis by 2.5%, epistaxis by 2%, gum bleeding by 1.5%, and haematuria by 0.5%. Bleeding symptoms varied in different age groups. The 6–10 age group was more likely to experience petechiae and bleeding, the 2–5 year age group to experience gum and melena haemorrhage, and the >10 year age group to experience epistaxis and haemorrhage. The findings of this study are comparable to those of many research studies , where petechiae was the most common bleeding symptom.[3,14] Some studies reported melena as common bleeding manifestation.[11]

Out of the 27 children in this research that had bleeding symptoms, dengue was the cause in 85% of cases, followed by cancer in 11% and sepsis in 4%. Of the children who had bleeding, four (15%) had a platelet count between 50,000- 100,000, fourteen (52%) had a platelet count between 20,000 -50,000, and nine (33%) less than 20,000. Eighty-five percent of children with bleeding symptoms had severe thrombocytopenia, with a statistically significant correlation ($p<0.001$). According to study, there were greater instances of clinical thrombocytopenia in platelet counts between 20,000 and 50,000.it was observed in few studies that bleeding symptoms was frequent when platelet counts were below 20,000 in investigations.[14,15]

On the other hand, research by Nikalje et al found no connection between bleeding symptoms and platelet count. This may be due to the lower frequency of severe thrombocytopenia (15%) compared to other grades of thrombocytopenia .16

The WBC count in this investigation ranged from 700 to 3300,000 cells/mm3. 38% of children had leucopenia, while 6% had leucocytosis. Leucopenia and thrombocytopenia grades did not significantly correlate ($P=0.44$). There was statistically significant difference between the least platelet count, platelet count at admission in bleeding and non-bleeding groups. (<p 0.05)

The study population's SGOT and SGPT ranges were 30–2500 IU/L and 25–1100 IU/L, respectively. Half of the children had elevated liver enzymes. There was a statistically significant correlation between these liver enzyme levels, and bleeding symptoms in both the bleeding and non-bleeding groups. Five percent of the study population had a deranged coagulation profile.

The length of hospital stay in this research group ranged from one to thirty days. Thirty-three cases needed a PICU stay of one to eighteen days. The length of hospital stay, the need for PICU stay, and the severity of thrombocytopenia were all statistically significantly ($P<0.001$). Children with severe thrombocytopenia needed PICU stay and a longer hospital stay.

Of the 23 (9%) children in this research who had blood product transfusions, 14 received PRBC transfusions, 13 received platelet transfusions, and 12 received FFP transfusions. Blood product transfusions were administered to 12 children who had dengue, 8 who had cancer, and 3 who had sepsis. Two of the 23 children who needed blood products had mild thrombocytopenia, and 21 of them had severe thrombocytopenia. Twenty percent of patients in a study had platelet transfusions, including those

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with septicaemia, dengue shock syndrome, and platelet counts below 100,000.[3]

All the patients in this research had recovered well from their acute febrile illnesses. There was no fatality reported. Children who had been diagnosed with cancer were referred to oncology speciality for further treatment. Mortality was reported in other studies. According to a study, 6% of patients died due to septicaemia , complex malaria and cancer. 3Sepsis was the cause of all 3% of fatalities in the Vijapura et al, investigation. According to the Gondhali et al, sepsis accounted for 5% of deaths, dengue for 1%, and mortality for 6%.[14]

CONCLUSION

Acute febrile illness with thrombocytopenia is common in children, most often due to dengue, other viral infections, enteric fever, or malaria. In this study, males were more frequently affected, particularly in the 6–10 years age group, while infants showed no sex predisposition. Gastrointestinal symptoms were frequent, and hepatomegaly was present in about two-thirds. Shock occurred mainly with severe thrombocytopenia, predominantly due to dengue.

Severe thrombocytopenia was the most common presentation, followed by mild and moderate grades. Dengue accounted for most severe and moderate cases, whereas mild thrombocytopenia was often due to probable viral illness, enteric fever, or scrub typhus. Petechiae were the most common bleeding manifestation, significantly associated with severe thrombocytopenia, especially in dengue. Elevation of liver enzymes was noted in half the children, with higher levels among those with bleeding. Severe thrombocytopenia correlated with prolonged hospital stay and PICU admission, though most children recovered platelet counts spontaneously without prophylactic transfusion. Outcomes were favorable, and mortality was not directly linked to platelet count.

This hospital-based study had limitations: exclusion of outpatients, underrepresentation of mild cases, lack of confirmatory tests for some infections, and incomplete etiological workup in a few children. Improved diagnostic facilities are needed for complete work up to reach diagnosis.

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