

A Clinical Study of Febrile Thrombocytopenia with Special Reference to Complications and Seasonal Variation

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ABSTRACT

Background: Infection is the commonest cause of thrombocytopenia. Commonly dengue, malaria, typhoid, septicaemia, and certain viral infections, present as fever with thrombocytopenia. The objective was to determine the aetiology for fever with thrombocytopenia and to study the presentation, laboratory profile, complications, prognosis and seasonal variation of thrombocytopenia.

Methods: This prospective observational clinical study was conducted between November 2015 - May 2017. One ninety patients aged > 18 years with fever and thrombocytopenia were included for this study. A detailed history, general and systemic examination and appropriate investigations were done and recorded.

Results: Out of 190 cases of fever with thrombocytopenia, 115 (60.5%) were males and 75 (39.5%) were females and the most common age group were between 20-30 years 50 (26.3%). The most common presentation was fever 190 (100%). Bleeding manifestations was present in 83(43.7%) cases. Common range of platelet count was in the range of 10000-20000 Lakhs/cumm 61 (32.1%). Infection was the commonest cause of thrombocytopenia and the commonest infection was dengue 131 (68.9%). One seventy nine (94.2%) cases had good recovery and 11(5.8%) patients have expired. Of those 11 mortality cases, all of them died due to septicemia. Among complications Coagulopathy was the most common with 21 (11.05%). Maximum numbers of cases of fever with thrombocytopenia are seen mainly during monsoon season.

Conclusion: Dengue being the commonest cause of febrile thrombocytopenia manifesting with seasonal variation commonly seen in monsoon season with cumulative effect of endemicity of disease in particular geographical region.

Key Words: Dengue, Febrile thrombocytopenia, Multiorgan dysfunction, Septicemia.

INTRODUCTION

From ancient times, fever has been considered as a cardinal manifestation of disease as recorded by scholars like Hippocrates. ^[1] Fever is derived from pyrexia, in Greek “*pyretus*” meaning fire.

The word febrile was originated from the Latin word “*Febris*”, meaning fever. ^[2] It is a cardinal sign that describes increase in internal body temperature to the level above normal. It is seen first as a disease but later recognized as an accompaniment of a

variety of disease entities. [3] It is considered as one of the body's immune mechanisms to attain neutralization of perceived threat inside the body. [4] Fever is an easily noted and reliable marker of illness. Many times fever is associated with thrombocytopenia. [5]

During monsoon and peri monsoon period, febrile patients with thrombocytopenia were commonly encountered by physicians. Patients with acute febrile illnesses in a tropical country like India usually have an infectious etiology and may have associated thrombocytopenia. Infections with bacteria, viruses and protozoa can cause thrombocytopenia. Commonly dengue, scrub typhus, malaria, and other rickettsial infections, meningococci, typhoid, leptospira, military TB, HIV, septicemia and certain viral infections, present fever with thrombocytopenia. Thrombocytopenia is defined as decreased number of platelets below $1.0 \text{ lakh}/\mu\text{L}$. [6] Impaired platelet production, accelerated platelet destruction or dilution and/or sequestration in spleen are the causes of thrombocytopenia. [7] There is no absolute relation between platelet counts and bleeding. Certain broad generalizations can be made, with counts less than $10,000/\mu\text{L}$, bleeding is usual and may be severe. [8]

Thrombocytopenia is characterized by bleeding most often from small vessels. This can manifest as petechiae over the skin, haemorrhages from mucosa of gastrointestinal and genitourinary tract. Intracranial haemorrhage is a serious consequence in thrombocytopenic patients. Thrombocytopenia associated with fever will help to narrow the differential diagnosis and management of fever. Patients present with varied clinical manifestations and these manifestations range from asymptomatic or simple viral illness to severe circulatory shock. So timely recognition and treatment of the underlying condition, platelet transfusions are required to prevent fatal outcomes. Although febrile thrombocytopenia is very common in south

India, studies on febrile thrombocytopenia patients from rural Indian areas are lacking. Therefore, the present was undertaken to assess the etiology, clinical and laboratory profile of febrile thrombocytopenia patients with special reference to complications and seasonal variations.

MATERIALS AND METHODS

This was hospital based prospective observational study. Febrile patients who fulfill the inclusion and exclusion criteria admitted at Adichunchanagiri hospital and research centre, B.G. Nagara, during the period of November -2015 to May 2017 were considered for this study. 190 cases who presented with fever and thrombocytopenia were studied over the period of 18 months. Ethics committee approval was taken for the study. After taking consent, patients were subjected for blood investigations. Study protocol included detailed clinical history and examination and investigations. Routine investigations were done for all patients which includes, complete haemogram, random blood sugar, peripheral smear, serum electrolytes, liver function test, BT, CT, PT, APTT, renal function test, chest X Ray, blood culture, and ultrasound abdomen. Special investigations like HIV-Elisa, Widal, Dengue NS1, IgM and IgG, Leptospira IgG and IgM, and smear for malaria parasite were also done. D Dimer, bone marrow, ABGA, TROP I, CPKMB and 2D ECHO were done in required patients.

Inclusion Criteria

- Platelet count $< 1,50,000$.
- Both male and female aged > 18 years.
- Fever of < 2 weeks duration.

Exclusion Criteria

- Chronic illness causing thrombocytopenia like idiopathic thrombocytopenic purpura, systemic lupus erythematosus.
- Drug induced thrombocytopenia.
- Pregnancy.

Statistical Methods: Data were compiled and tabulated by using standard appropriate statistical techniques, which includes numbers and percentages.

RESULTS

In this study 190 patients were included. The maximum cases were found to be in age group of 20-30 years and Mean \pm SD: 41.11 \pm 16.94 (Table 1). In this study 115 (60.5%) were males and 75 (39.5%) were females. Among patients of fever with thrombocytopenia dengue fever (DF) was present in 131 (68.9%) followed by septicaemia 18 (9.5%) (Table 2). In 131 cases of Dengue infection, DF was the commonest with 51 (38.93%), followed by Dengue Hemorrhagic Fever (DHF) III 26 (19.84%), DHF II 25 (19.08%), DHF I 24 (18.32%) and DHF IV 5 (3.8%). In 16 cases of Malaria, *P.vivax* was the commonest species with 7 cases, followed by *P.falciparum* 3 cases and mixed type (*P.vivax* and *P.falciparum*) 6 cases. Amongst 190 cases in the study, all of them presented with fever, 147 complained of headache, 140 of Vomiting, 139 of Arthralgia, 137 Retro orbital pain, 125 of Myalgia, 100 of Rashes, 94 of Pain abdomen, 83 of bleeding manifestations, 81 of Chills, 62 of Giddiness, 51 of Breathlessness, 43 of Cold clammy skin, 31 of Diarrhea and 11 of acutely altered mental status. (Table 3).

Table 1: Age distribution of patients

Age (years)	Number of patients (percentage)
<20	14(7.4)
20-30	50(26.3)
31-40	43(22.6)
41-50	27(14.2)
51-60	26(13.7)
61-70	21(11.1)
>70	9(4.7)
Total	190(100.0)

Table 2 : Distribution of cases based on aetiology

Diagnosis	Number of patients (percentage)
Dengue fever	131 (68.9)
Septicaemia	18(9.5)
Viral fever other than Dengue	17(9.0)
Malaria	16(8.4)
HIV	4(2.1)
Typhoid fever	4(2.1)
Total	190(100)

Table :3 Distribution of cases based on symptomatology

Symptoms	No. of patients	Percentage
Headache	147	77.4
Vomiting	140	73.7
Arthralgia	139	73.2
Retro orbital pain	137	72.1
Myalgia	125	65.8
Rashes	100	52.6
Pain abdomen	94	49.5
Bleeding manifestations	83	43.7
Chills	81	42.6
Giddiness	62	32.6
Breathlessness	51	26.8
Cold clammy skin	43	22.6
Diarrhea	31	16.3
Altered mental status	11	5.8

Out of 190 cases, 115 had conjunctival congestion, 74 edema, and 16 had pallor (Table 4).

Table :4 Distribution of cases based on clinical signs at the time of presentation

Signs	No. of patients	Percentage
Conjunctival congestion	115	60.5
Edema	74	38.9
Facial flush	65	34.2
Ascites	57	30
Tachycardia	55	28.9
Hypotension	54	28.4
Tachypnoea	44	23.2
Hepatomegaly	37	19.47
Splenomegaly	36	18.94
Icterus	33	17.4
Pallor	16	8.4

In the 190 cases of fever with thrombocytopenia, 47 (24.7%) of them had fever <4 days, 143 (75.3%) had fever 4-8 days.

Table :5 Distribution of cases based on Systemic involvement

Systemic involvement	No. of patients	percentage
Cardiovascular system		
Myocarditis	2	1.1
Hypotension	54	28.4
Respiratory system		
Pleural effusion	49	25.8
Pneumonia	18	9.5
ARDS	3	1.6
Gastrointestinal system		
Ascites	57	30
Organomegaly	70	36.8
Central nervous system		
Encephalitis	2	1.1

Cardiovascular system involved in the form of myocarditis (1.1%) and Hypotension (28.4%). Respiratory system involved in the form of Pleural effusion (25.8%), pneumonia (9.5%) and ARDS (1.6%). Gastro intestinal system involved in the form of Ascites (30%), organomegaly

(36.8%). Central nervous system involvement was present in 1.1% cases in the form of encephalitis (Table 5). Eighty three (43.7%) patient had signs of bleeding manifestation. Among the cases which had bleeding manifestations, Venepuncture bleed 32 (16.8%) was the most common presentation, followed by Gum bleed 28 (14.7%), haematuria 21 (11.1%), Petechiae 17(8.9%), Epistaxis15 (7.9%), haematemesis 3 (1.6%), and Melena 3 (1.6%) (Table 6). Leucopenia (<4000 cells/cumm) was present in 18.9% of cases. Leucocyte count was normal (4000-11000 cells/cumm) in 74.21% cases. Leucocytosis (>11000 cells/cumm) was present in 6.8% cases. Elevated heamatocrit (> 45%) was observed in 25.8% cases.

Table :6 Distribution of cases based on mode of Bleeding manifestations

Bleeding manifestations	Total	Percentage
Venepuncture bleed	32	16.8
Gum bleed	28	14.7
Haematuria	21	11.1
Petechiae	17	8.9
Epistaxis	15	7.9
Haematemesis	3	1.6
Melena	3	1.6

Seventeen (8.9%) patients had platelet count below 10000/ μ L, 61(32.1%) patients had platelet count between 10000 to 20000/ μ L, 40 (21.1%) had between 20000/ μ L to 50000 / μ L, 72 (37.9%) had

platelet count above 50000/ μ L. Seventeen (8.9%) had prolonged Bleeding time and clotting time and 21(11.05%) had prolonged Prothrombin time, APTT and INR (Table 6). Dengue NS1 was positive in 55.5% cases. Malaria test was positive in 8.4% cases, Widal test was positive in 2.1% cases and HIV Elisa was positive in 2.1% of cases (Table 7). Total Bilirubin was elevated in 33.7% cases. SGOT and SGPT were elevated in 39.5% and 37.4 % cases respectively. Low serum albumin level observed in 46.8% cases. Urea was elevated in 20.5 % of cases. Elevated creatinine level observed in 23.7% of cases.

Table :7 Distribution of cases based on Dengue serology and other serological test

Investigation	No. of patients	Percentage
Dengue NS1	96	55.5
Dengue IgM	86	45.3
Dengue IgG	18	9.5
Malaria	16	8.4
Widal	4	2.1
HIV	4	2.1

Out of the 83 cases who had bleeding manifestations, 15(18.1%) patients had platelet count below 10000/ μ L, 32(38.6%) patients had platelet count between 10000 to 20000/ μ L, 23(27.7%) had platelet count between 20000/ μ L to 50000 / μ L, 13(15.7%) had platelet count above 50000/ μ L. The difference was statistically significant (p value < 0.001).

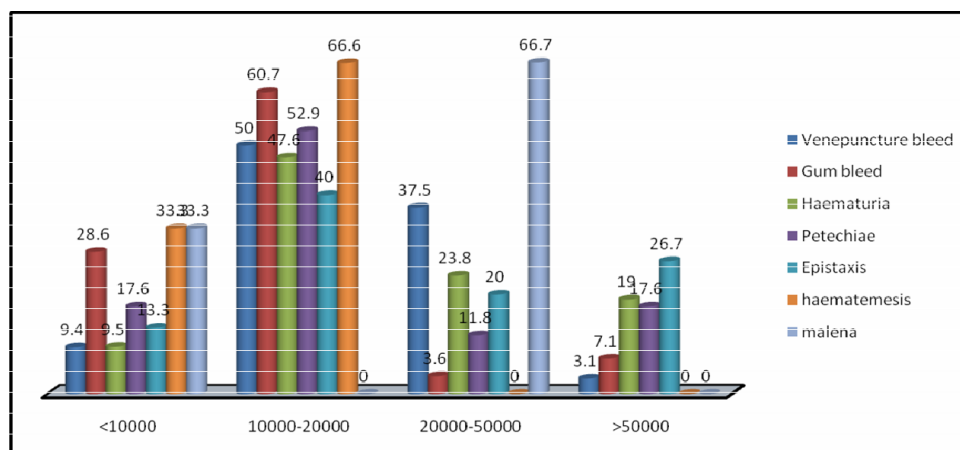


Figure: 1 Distribution of cases with respect to platelet count and various bleeding manifestations

In 131 cases of Dengue fever 28 had Gum bleed, 21 had Haematuria, 17 had Venepuncture bleed, 16 had Petechiae, 5 had Epistaxis, 3 had Haematemesis and 3 had melena. In 18 cases of Septicemia, 15 had Venepuncture bleed and 1 had Petechiae. In 17

cases of Viral fever other than Dengue, 10 had epistaxis. Plasma leakage manifested as Hypoalbuminemia 89(46.8%), Ascites 57(30%), hypotension 54(28.4%), Pleural effusion in 49(25.8%) cases, Increased haematocrit 49(25.8%), Gallbladder wall edema in 6(3.16%). Among the cases which had complications, Coagulopathy was the most common with 21(11.05 %) followed by multi organ dysfunction (MODS) 18(9.5%), (Figure 2).

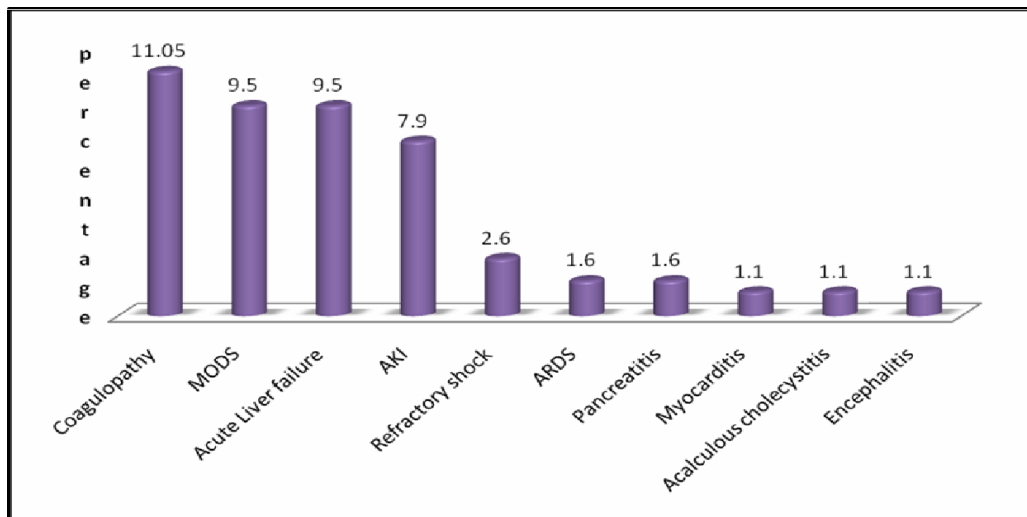


Figure 2. Distribution of cases based on complications

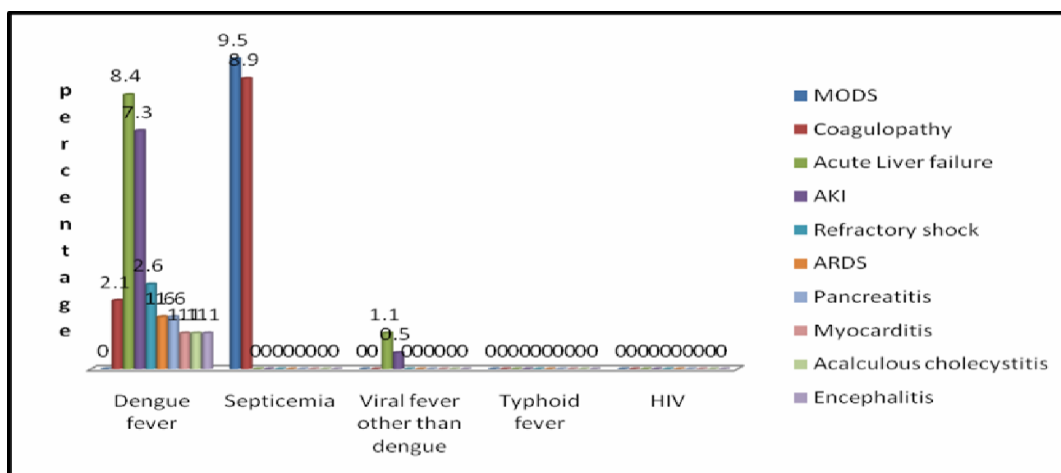


Figure 3 Complications with respect to aetiology

Platelet was transfused in 84 patients. Out of which 21 patients received platelets <5 units, 43 patients received 6-10 units and 20 patients received >10 units of platelets. Fresh frozen Plasma (FFP) given to 17 patients. Out of which 10 patients received FFP <5 units and 7 patients received 6-10 units. Plasma concentrate given for 84 patients. Out of which 21 patients received Plasma concentrate <5 units. Forty three patients received Plasma concentrate 6-10 units and 20 patients

received Plasma concentrate >10 units. 16 required mechanical ventilatory support.

Out of the 190 cases, 179(94.2%) cases had recovered and were discharged while 11 (5.8% patients expired during their period of hospital stay. Out of 11 deaths, 2 cases is found in the age group of 31-40 years, 2 in age group of 41 to 50 years, 3 in age group of 51 to 60 years, 3 in age group of 61 -70 years and 1 in >70 years. In septicaemia, there were 11 mortalities out of 18 cases. P value is <0.001-statistically significant.

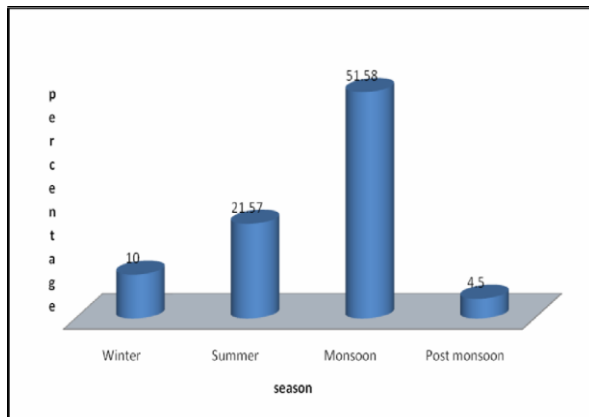


Figure:4 Seasonal distribution of cases

Maximum number of cases of fever with thrombocytopenia (51.58%) are seen mainly during monsoon season, during the month of June to September followed by 41(21.57%) cases in summer, 32(10%) cases in post monsoon and 19 (4.5%) cases in winter (Figure 4).

DISCUSSION

Out of 190 cases included in this study 115(60.5%) were males and 75 (39.5%) were females. In a study done by Gondhal et al showed similar results with male preponderance with males 56% and females 44%.^[9] In another study conducted by Durbesula et al 88(58.7%) were male and 62(41.3%) were female patients.^[10] The most common age group was between 20-30 years 50(26.3%) in our study which is comparable to Gondhali et al study which showed 26(26%).^[9] In the present study Dengue with 131 (68.9%) cases was leading cause of fever associated with thrombocytopenia. Second common cause was Septicaemia 18(9.5%). Similar results were obtained in Gondhali et al study.^[9] In the present study there are 16 cases of malaria, out of which plasmodium vivax are 7(43.8%) cases, plasmodium falciparum are 3(18.8%) cases and mixed infections are 6 (37.5%) case compared to Gondhali study in which 15 cases of malaria, out of which, plasmodium vivax 10 (66.67%), plasmodium falciparum 4(26.66%) cases and mixed infection were 1(6.67%) cases.^[9] In present study, 37.9% patients had platelet count $>50000/\text{mm}^3$ it is not

concordance with Gondhali et al study and Modi et al study.^[9,11] In Gondhali et al study, 78% patients had platelet count $>50000/\text{mm}^3$, 15% had platelet count in range of $20000-50000/\text{mm}^3$, 4% had platelet count in range of $10000-20000$ and 3 had platelet count less than $10000/\text{mm}^3$. In Modi et al study, 78% patients had platelet count $>50000/\text{mm}^3$, 15% had platelet count in range of $20000-50000/\text{mm}^3$, 4% had platelet count in range of $10000-20000$ and 3 had platelet count less than $10000/\text{mm}^3$. Bleeding manifestations were recorded in 60%, 57%, 18% cases of severe, moderate and mild thrombocytopenia respectively. These findings correlate with Modi et al study, where bleeding manifestations were recorded in 98.46%, 54%, and 17.97% cases of severe, moderate and mild thrombocytopenia respectively.^[11] In present study out of 190 patients 83 had thrombocytopenic signs accounting for (43.7%) where as In Gondhali study out of 100 patients 15 patients had thrombocytopenic signs accounting for 15%.^[9] The most common bleeding manifestation in our study was Venepuncture bleed in 32 (16.8%) followed by Gum bleed 28 (14.7%), Compared to study by Gondhali et al petechiae / purpura was the commonest bleeding manifestation with 14 cases (14%) followed by spontaneous bleeding accounting for 10 cases(10%).^[9] In study done by Patil et al petechiae was the major manifestation 73.9% followed by spontaneous bleeding (26.9%).^[12] Mortality was noticed in 5.8% of patients which is consistent with Patil et al study 5%. In both studies major incidence of mortality was seen in patients of septicemia.^[12] In present study multi organ dysfunction (61.1%) was the common complication associated with mortality which is comparable to Nakhale et al study(100%) and Kumar et al study(83.3%).^[13,14] In present study maximum number of cases of fever with thrombocytopenia was seen during monsoon season. In Kumar et al, Modi et al study and Raiker et al study febrile thrombocytopenia

was common in monsoon and early winter seasons. [11, 15, 16] The limitation of our study was small sample size.

CONCLUSION

Now a days febrile thrombocytopenia is an emerging problem in the field of medicine. Dengue being the commonest cause of febrile thrombocytopenia manifesting with seasonal variation commonly seen in monsoon season with cumulative effect of endemicity of disease in particular geographical region. Common complication of Dengue fever being varied bleeding manifestations secondary to thrombocytopenia showing no direct correlation between platelet count and severity of bleeding as well as to mortality and morbidity. Prompt diagnosis and appropriate treatment of underlying etiology of febrile thrombocytopenia with maintenance of platelet count, adequate hydration and symptomatic management gives good recovery and better outcome. More population based studies with large sample size needed in future; various geographical areas and populations should be considered.

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