Original Article

Clinical Profile of Febrile Thrombocytopenia: A Hospital-Based Cross-Sectional Study

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ABSTRACT

Background: Thrombocytopenia is the most common cause of abnormal bleeding. Thrombocytopenia develops when there is profound disequilibrium in the balance between platelet production, distribution and destruction. More than one component may be affected in some disorder.

Aim: To evaluate clinical profile, etiological profile and outcome of febrile thrombocytopenia and to determine the relationship between platelet count and the occurrence and severity of bleeding

Materials and Methods: 393 patients, aged more than 12 years, presented with febrile thrombocytopenia were observed for occurrence of bleeding manifestations, investigated in detail and treated symptomatically and specifically after definite diagnosis.

Results: Age and Sex distribution: Febrile thrombocytopenia affects all age groups but was more common in 12-30 years age group (62.34%).Male (69.97%) outnumbered Female (30.07%) in this study. Its incidence increased 71.24% during the month of September to December, 2015. Etiology of disease: Dengue fever (55.98%), Malaria (25.95%) were the common etiologies of febrile thrombocytopenia in present study. Platelet count and bleeding manifestations: 45.29% patients with platelet count >50000/mm^3 mild thrombocytopenia); 38.17% with platelet count 20000-50000/mm^3 (moderate thrombocytopenia) and 16.54% with platelet count less than 20000/mm^3 (severe thrombocytopenia) were recorded. Bleeding manifestations were recorded in 98.46%, 54%, 17.97% cases of severe, moderate and mild thrombocytopenia respectively. Outcome: 94.15% patients had good recovery.

Conclusion: Risk of bleeding increase when platelet count decreases below 20000.There was no absolute relationship between platelet count and severity of bleeding.

Key words: Thrombocytopenia, Fever, Bleeding, Platelet

INTRODUCTION

Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in hypothalamic set point. An A.M. temperature of > 37.2 ℃ (>98.9℉) or a P.M. temperature of >37.7 ℃(>99.9℉) would define fever. [1] Thrombocytopenia is defined as a reduction in the peripheral blood platelet count below the lower normal limit of 150000 /mm^3. [2]Despite the number and diversity of disorders that may be associated etiologically, thrombocytopenia results from only four processes: Artifactual thrombocytopenia, deficient platelet production, accelerated platelet destruction and abnormal distribution or pooling of the platelets within the body. [3] It is the most common cause of abnormal bleeding. Thrombocytopenia develops when there is profound disequilibrium in the balance between platelet production, distribution and destruction. More than one component may be affected in some disorder. [4]With normally functioning platelets, the following is expected:

1.Platelet count ≥100000 per microliter : patients have no abnormal bleeding even with major surgery.2.Platelet count between 50000 to 100000 per microliter : patients may bleed longer than normal with severe trauma.3.Platelet count of 20000 to 50000 per microliter : bleeding occurs with minor trauma, but spontaneous bleeding is unusual.4.Platelet count <20000 per microliter : patient may have spontaneous bleeding.5.Platelet count <10000 per microliter : patients are at high risk for severity bleeding.[5]

This study aims to evaluate clinical and etiological profile of febrile thrombocytopenia and to determine the relationship between platelet count and the occurrence and the severity of bleeding.

MATERIAL AND METHODS

We have conducted this prospective cross-sectional observational study at PDUMC and civil hospital, Rajkot, Gujarat, India from 1st November 2014 to 31st March 2016 after taking clearance from the Ethical committee. The patients were selected as per protocol based on inclusion and exclusion criteria.

- **Inclusion Criteria :**

All new patients aged more than 12 years, with fever (Temperature >99.9°F) and thrombocytopenia (Platelet count less than 150000/mm^3).

- **Exclusion Criteria :**

Patients with fever without thrombocytopenia, patients with thrombocytopenia without fever,
Already diagnosed cases of hematologic disorder/malignancy or on chemotherapy/other immunosuppressive agent presented/admitted with febrile thrombocytopenia, diagnosed cases of platelet disorder and dysfunction, patients on drug causing thrombocytopenia, patients with cirrhosis and chronic liver disease, patients not giving consent -were excluded from this study. Details of clinical history including symptoms of bleeding e.g. rash/purpura/petechiae/ Ecchymosis, bleeding gum, subconjunctival hemorrhage, hemoptysis, hematemesis, melena, bleeding per rectum, abnormal bleeding per vaginum, menorrhagia; drug history, past history, personal history, family history were recorded. Thorough physical examination for vital signs, general examination, and systemic examination were done and noted. The bleeding manifestations on admission or developed during hospital stay were recorded. All patients were subjected to routine laboratory evaluation like Complete blood count, Platelet count, peripheral smear for cell morphology, peripheral smear for malarial parasite, Dengue NS1 Ag /Dengue IgM Ab test, Prothrombin time with International Normalized Ratio(INR),activated partial Thromboplastin time, RBC indices(Mean Corpuscular Volume MCV, Mean Corpuscular Hemoglobin MCH, Mean Corpuscular Hemoglobin Concentration MCHC),liver function test, renal function test, urine routine, Electrocardiograph (ECG),X ray chest, Ultrasonography (USG) abdomen. Other investigations were done to achieve diagnosis such as Thyroid Stimulating Hormone (TSH), S.widal, D-dimer, serum vitamin B12 level, Anti-Nuclear Antibody (ANA), bone marrow trephine biopsy, serological study for Human Immunodeficiency Virus (HIV) infection, Real-time Reverse Transcriptase-Polymerase Chain Reaction (rRT-PCR) of nasal and pharyngeal swab for H1N1 (novel) swine flu influenza, RT-PCR for Crimean Congo Hemorrhagic Fever (CCHF), whenever indicated. Baseline platelet counts were done on the day of admission repeated on alternate days until normal or near normal platelet count reached. In patients with bleeding manifestations or with platelet count <50000/mm^3 ,repeat platelet count were done daily/as and when required till rising trends of platelet was achieved. All patients were given supportive symptomatic treatment and specific treatment after definitive diagnosis. Patients with platelet count less than 10000/mm^3 and/or bleeding manifestations were treated with platelet concentrate. Patients were followed for their duration of stay in hospital and outcomes were analyzed. Statistical analysis was performed by using SPSS 14.3 which involves paired and unpaired T-tests. Mean value and ±SD were calculated for each group and compared with other studies. P value <0.05 were taken as a point of minimal statistical significance.

Results

During the period of 1st November 2014 to 31st March 2016, 393 patients were included in the study. Age and Sex distribution: Out of 393 patients with febrile thrombocytopenia, 275 were male and 118 were female. (Refer**TABLE-1**)Male were affected more than female in present study.12 to 30 year age group were affected the most 62.34% followed by 30 to 50 year age group(24.17%),50 to 70 year age group(10.43%); more than 70 year age group(3.05%).(refer **TABLE-2**)Effect of Seasonal variation on incidence of Febrile thrombocytopenia In the present study, 280(71.24%) of 393 cases of febrile thrombocytopenia were seen during rainy and early winter season (September to December).Etiology of febrile thrombocytopenia (refer **TABLE-1**)

Table 1: Etiological Profile of Febrile Thrombocytopenia

Etiology	Male (N=275)	Female (N=118)	Total (N=393)	Total (%)
Dengue Fever	168 (61.09)	52(44.06)	220	55.97
P.Falciparum Malaria Fever	31(11.27)	22(18.64)	53	13.48
P.Vivax Malaria Fever	33(12)	9(7.62)	42	10.68
P.Falciparum + P.Vivax Malaria Fever	3(1.09)	4(3.38)	7	1.78
Septicemia	11(4)	11(9.32)	22	5.59
Viral Fever Other Than Dengue*	14(5.09)	7(5.93)	21	5.34
Megaloblastic Anaemia	5(1.81)	6(5.08)	11	2.79

*Viral fever other than dengue includes H1N1 (novel) swine flu influenza, Human Immunodeficiency Virus (HIV) and Crimean Congo Hemorrhagic Fever (CCHF).

Table 2: Age Incidence of Febrile Thrombocytopenia

	Dengue (N=220)	Malaria (N=102)	Septicemia (N=22)	Other Viral Fever* (N=21)	Megaloblstic Anaemia (N=11)	Hematological Malignancy (N=11)	Enteric Fever (N=6)	Total (%)
12-30	168 (76.36)	60(58.82)	0	5(23.80)	5(45.45)	3(27.27)	4(66.66)	245(62.34)
30-50	41(18.63)	30(29.41)	9(40.90)	9(42.85)	2(18.18)	2(18.18)	2(33.33)	95(24.17)
50-70	9(4.09)	11(10.78)	7(31.81)	7(33.33)	2(18.18)	5(45.45)	0	41(10.43)
>70	2(0.9)	1(0.98)	6(27.27)	0	2(18.18)	1(9.09)	0	12(3.05)

*"viral fever other than dengue" is mentioned as "other viral fever" in table-2 (Figures in parenthesis are percentages

Viremia 241(61.32%)constitutes the commonest a etiology of febrile thrombocytopenia of which 220(55.98%) were of dengue fever and 21(5.34%)viral infection other than dengue, followed by Malaria 102(25.95%),Septicemia 21(5.34%), Megaloblastic anemia 11(2.79%), Hematological malignancy 11(2.79%) and Enteric fever 6(1.58%).Similar results were observed in Raikar et al study[6],while Gandhi et al study[7], Patil et al study[8] and Dash et al study[9] had malaria and Nair et al study[10] had septicemia as the major cause of Febrile thrombocytopenia. (Refer **TABLE-3**).

Table 3: Percentagewise Comparison of Etiology of Febrile Thrombocytopenia

Etiology	Present Study	Nair et al	Patil et al	Dash et al	Gandhi et al
Dengue Fever	**55.97 (N=220)**	13.80	15	20	26.79
Malaria (P.F And P.V)Fever	25.95 (N=102)	9.20	**54**	**45**	**41.07**
Septicemia	5.59 (N=22)	**26.60**	4	21	4.46
Viral Fever Other Than Dengue	5.34 (N=21)	---	---	---	16.07
Megaloblastic Anaemia	2.79 (N=11)	11.90	---	1	5.36
Hematological Malignancy	2.79 (N=11)	3.70	---	1%	1.79
Enteric Fever	1.53 (N=6)	14.70	6	10	4.46
Others/ Unknown	---	18.30	21	2	---

Clinical profile:In the present study, symptoms observed in descending order of frequency were: fever(393), Headache(195, 49.61%), Bodyache (143, 36.38%), Backache (129, 32.82%), Vomiting(101, 25.69%), Retroorbital pain(94,23.91%), Nausea(61,15.52%), Joint pain(56,14.24%), abdominal pain (44,11.19%), respiratory symptoms: cough and breathlessness (32, 8.14%), giddiness (28, 7.12%), loose motion (19, 4.83%), gastrointestinal bleed (hematemesis with/ without melena) (18,4.58%), altered sensorium (14, 3.56%) and convulsion (5, 1.27%)

Degree/severity of thrombocytopenia in various diseases (refer **TABLE-4**):

Table 4: Etiology of Febrile Thrombocytopenia in Different Platelet Count Range

	Platelet Count (/MM^3)				
Disease	>50000	20000-50000	10000-20000	<10000	Total
Dengue Fever	90 (50.56)	85 (56.66)	32 (72.72)	13 (61.90)	220 (55.97)
P.F Malaria Fever	15 (8.42)	30 (20.00)	5 (11.36)	3 (14.28)	53(13.48)
P.Vivax Malaria Fever	24 (13.48)	16 (10.66)	2 (4.54)	---	42 (10.68)
P.F + P.V Malaria Fever	2 (1.12)	3 (2.00)	---	2 (9.52)	7 (1.78)
Septicaemia	18 (10.11)	4 (2.66)	---	---	22 (5.59)
Viral Fever Other Than Dengue	17 (9.55)	2 (1.33)	1 (2.27)	1 (4.76)	21 (5.34)
Megaloblastic Anaemia	3 (1.68)	7 (4.66)	1 (2.27)	---	11 (2.79)
Hematologic Malignancy	3 (1.68)	3 (2)	3 (6.81)	2 (9.52)	11 (2.79)
Enteric Fever	6 (3.37)	---	---	---	6 (1.52)
Total	178	150	44	21	393

(Figures in parenthesis are percentages)

In present study, Dengue fever presented with mild thrombocytopenia in 90(40.9%),moderate thrombocytopenia in 85(38.64%);severe thrombocytopenia in 45(20.45%).P.falciparum malaria fever presented with mild thrombocytopenia in 28.3%,moderate thrombocytopenia in 56.6%,severe thrombocytopenia in 15.9%.P.vivax malaria fever presented with mild thrombocytopenia in 57.14%, moderate thrombocytopenia in 38.04% and severe thrombocytopenia in 4.76%. Combined P.falciparum and P.vivax malaria presented with mild thrombocytopenia 28.57%, moderate thrombocytopenia in 42.86% and severe thrombocytopenia in 28.57%. Platelet count and bleeding manifestations (refer **TABLE-5**)

Table 5: Correlation of Bleeding Manifestation with Severity of Thrombocytopenia*and Statistical Analysis**

Bleeding Manifestation	Platelet Count (/MM^3)			Total
	<20000	20000-50000	>50000	
Petechiae	41 (64.06)	56 (70.88)	22 (64.70)	119 (67.23)
Subconjunctival Hemorrhage	0	1(1.26)	1(2.94)	2(1.12)
Gum Bleeding	8(12.5)	3(3.79)	0	11(6.21
Hematuria	1(1.56)	1(1.26)	0	2(1.12)
Abnormal Bleeding Per Vaginum	0	1(1.26)	2(5.88)	3(1.69)
Bleeding Per Rectum	1(1.56)	3(3.79)	1(2.94)	5(2.82)
Hemoptysis	1(1.56)	1(1.26)	1(2.94)	3(1.69
Hematemesis	1(1.56)	1(1.26)	0	2(1.12)
Melena	5(7.81)	5(6.32)	6(17.64)	16(9.03)
Epistaxis	6(9.37)	7(8.86)	1(2.94)	14(7.90)
Total	64	79	34	177

*Platelet Count <20000/Mm^3, 20000-50000/Mm^3,>50000/Mm^3 Were Classified As Mild, Moderate And Severe Thrombocytopenia.

	A	B	C	Total
Bleeding Manifestation	64	79	34	177
No Bleeding	1	71	144	216
Total	65	150	178	393

**Platelet Count <20000/Mm^3, 20000-50000/Mm^3,>50000/Mm^3 Were Labelled As Group A, B And C For Statistical Analysis. Chi Square Value=126.845, P Value<0.0001, Degree Of Freedom (Df) 2 Indicates Significant Difference Between All The 3(A, B And C) Groups. Chi Square Value (A Vs. B+C) =89.795, P Value<0.0001, Df=1 Indicates Very Strong Association Of Occurrence Of Bleeding At Platelet Count <20000/Mm^3.

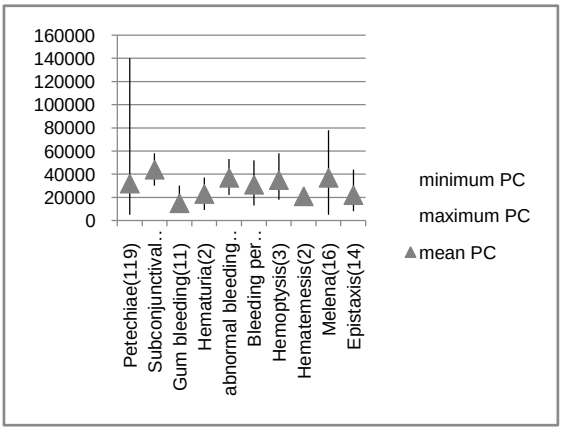
In present study, 45.29% patients had platelet count >50000/mm^3, 38.17% had platelet count in range of 20000-50000/mm^3,11.19% had platelet count in range of 10000-20000 and 5.34% had platelet count less than 10000/mm^3.These findings correlate with Nair et al study[10] and Bhalara et al study[11]. Bleeding manifestations were recorded in 98.46%, 54%, 17.97% cases of severe, moderate and mild thrombocytopenia respectively. Platelet count <20000/mm^3, 20000-50000/mm^3,>50000/mm^3 were labelled as group A, B and C for statistical analysis. Chi square value=126.84, p value<0.0001, degree of freedom (DF) 2 indicates significant difference between all the 3(A, B and C) groups. Chi square value (A vs. B+C) =89.79, p value<0.0001, DF=1 indicates very strong association of occurrence of bleeding at platelet count <20000/mm^3.

177 of 393 patients presented with or developed bleeding manifestations. Petechiae were seen in 119 patients as a major bleeding manifestation followed by melena(16),epistaxis(14), gum bleeding(11), bleeding per rectum(5),Hemoptysis(3),abnormal bleeding per vagina (3), Hematuria(2) and subconjunctival hemorrhage(2). Petechias, gum bleeding, epistaxis, hematemesis, hemoptysis, bleeding per rectum, hematuria, abnormal bleeding per vaginum, melena, subconjunctival hemorrhage occurred at an average (mean in 10^3) of 32000/mm^3,15000/mm^3,22000/mm^3,21000/mm^3,35 000/mm^3,31000/mm^3,23000/mm^3, 37000/mm^3,37000/mm^3,44000/mm^3 respectively.(refer **GRAPH-1 WITH TABLE**)

- Outcome

370 of 393 patients had good recovery with increasing trend of platelet count at the time of discharge. Out of 23 mortality cases, 13 were due to septicemia with multiorgan dysfunction, 2 were due to complicated malaria, 1 was due to hematological malignancy and 7 were due to H1N1 (novel) swine flu influenza virus infection with adult respiratory distress syndrome.

Figure1: Spectrum of Bleeding Manifestation with Maximum, Minimum and Mean Platelet Count



DISCUSSION

The most common etiology responsible for newly diagnosed febrile thrombocytopenia in present study was found to be viremia (61.32%) including dengue fever (55.98%) and other viral infection (5.34%) like H1N1 swine flu (novel) influenza, Human Immunodeficiency Virus infection and Crimean Congo Hemorrhagic fever. Thrombocytopenia in Dengue fever is caused by bone marrow suppression (i.e., decreased platelet synthesis and increased immune mediated destruction of platelets). [12]Autoimmune thrombocytopenia occurs during or immediately after acute viral infections. HIV associated thrombocytopenia arise through multiple mechanisms, including decreased platelet production, increased platelet destruction due to HIV-mimetic antiplatelet antibodies and increased use of activated platelets.[13]

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%).Malaria is commonly accompanied by mild to moderate thrombocytopenia (88.23%) (78.4% by Jadhav et al study). [14]Thrombocytopenia in malaria is probably due to increased splenic sequestration, immune-mediated destruction, and a shortened platelet survival and consumption by DIC. [15]

Dengue and Malaria were the more frequent causes(81.93%) due to the higher prevalence of these infections during rainy and early winter season as well as their endemicity.71.24% of Dengue and Malaria were reported during the month of September to December 2015(rainy and early winter season) in present study. Septicemia (5.59%) was the third common cause in the study. Thrombocytopenia is an independent prognostic marker. The etiology of thrombocytopenia in sepsis is multifactorial. It is commonly associated with DIC and is caused by splenic destruction of immune complex coated platelets, platelet adherence to damaged vascular surfaces and by direct platelet toxicity caused by microorganism.[16]It is also probably related to impaired production of platelets from within the bone marrow, active phagocytosis of megakaryocytes and other haemopoietic cell by monocytes and macrophages hypothetically due to stimulation with high levels of macrophage colony-stimulating factor(M-CSF) in sepsis and platelet consumption due to ongoing generation of thrombin. Megaloblastic anemia due to Vitamin B12 and folic acid deficiency was found in 2.79% patients in which thrombocytopenia was believed to be due to impaired DNA synthesis resulting in ineffective thrombopoesis. [17]In patients with Leukemia (2.79%) particularly in acute leukemia, patients have petechiae, ecchymosis and nose bleeding associated with thrombocytopenia because of bone marrow infiltration. [3] Petechiae was the major bleeding manifestation (67.23%) followed by spontaneous bleeding (32.77%) in present study which was consistent with Patil et al study [8]and Gandhi et al study[7]. In Srinivas et al study[18], purpura (63%) was the commonest bleeding manifestations followed by spontaneous bleeding (37%).In Nair et al study[10] spontaneous bleeding in 77.78% was a major manifestation followed by petechiae/purpura accounting for 22.22%. When bleeding due to thrombocytopenia does occur, it usually begins in the skin or mucous membranes. [4]A platelet count of approximately 5000-10000/microL is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankle and feet in an ambulatory patient. Petechiae are pinpoint, non-blanching hemorrhages and are usually a sign of decreased platelet number and not platelet dysfunction. [19] Petechiae, gum bleeding, epistaxis, hematemesis, hemoptysis, bleeding per rectum, hematuria, abnormal bleeding per vaginum, melena, subconjunctival hemorrhage occurred at an average (mean in 10^3) of $32000/mm^3$,$15000/mm^3$,$22000/mm^3$, $21000/mm^3$, $35000/mm^3$, $31000/mm^3$, $23000/mm^3$, $37000/mm^3$, $37000/mm^3$, $44000/mm^3$. Bleeding manifestations were recorded in 98.46%, 54%, and 17.97% in severe, moderate and mild thrombocytopenia respectively. Platelet count $<20000/mm^3$, $20000-50000/mm^3$,$>50000/mm^3$ were labelled as group A, B and C for statistical analysis. Chi square value=126.845, p value<0.0001, degree of freedom (DF) 2 indicates significant difference between all the 3(A, B and C) groups. Chi square value (A vs. B+C) =89.795, p value<0.0001, DF=1 indicates very strong association of occurrence of bleeding at platelet count $<20000/mm^3$. Spontaneous bleeding is rare at platelet counts above 30000/microL. The risk of bleeding increases exponentially as the platelet count falls below 20000/microL, at which point patient may begin to complain of easy bribability. Spontaneous bruising and petechiae, generally starting in dependent areas, gingival bleeding after bruising, menorrhagia and epistaxis become progressively more common if the platelet count falls below 10000 to 20000/microL. Bleeding may occur at higher platelet counts when qualitative platelet defects, such as those caused by medication that impair platelet function, have been superimposed or when underlying anatomic defects that predispose to bleeding are present. [4] Out of 23 mortality cases, 13 were due to septicemia with multiorgan dysfunction, 2 were due to complicated malaria, 1 was due to hematological malignancy and 7 were due to H1N1 swine flu (novel) influenza virus infection with adult respiratory distress syndrome.60.86% patients were having platelet count$>50000/mm^3$indicating that mortality was not directly related to severity of thrombocytopenia but related to underlying etiology leading to multi organ dysfunction syndrome. Mortality due to septicemia was observed in 56.52%, 60%, and 78% in present study, Patil et al study [8] and Srinivas et al study [18] respectively.

CONCLUSION AND RECOMMENDATIONS

1. Maximum prevalence of febrile thrombocytopenia due to infectious etiology are in young, in male, in rainy and early winter season with summative effect of endemicity of disease in particular geographical region.

2. Dengue is the commonest cause of febrile thrombocytopenia followed by malaria and septicaemia. 3. Thrombocytopenia has no correlation to mortality and morbidity.
3. Thrombocytopenia due to infectious diseases shows seasonal variation with peak of incidence in rainy and winter season.
4. Risk of bleeding increase when platelet count decreases below 20000.There is no absolute relationship between platelet count and severity of bleeding.
5. Prompt diagnosis and immediate specific treatment of underlying etiology of febrile thrombocytopenia with maintenance of platelet count and haemostatic function gives good recovery.

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