A Study of Febrile Thrombocytopenia

Radhika B.V.[1], Sooraj C.S.[2], Vasantha Kamath[3]

ABSTRACT

Introduction: Febrile thrombocytopenia is the thrombocytopenia associated with febrile illness. The common causes are dengue, rickettsiae, malaria, typhoid, septicemia and in some cases undifferentiated fever. The present study was intended to know the underlying etiology of febrile thrombocytopenia cases admitted to our hospital, the various presentations and relationship between platelet count and bleeding manifestation and prognosis.

Material and methods: The study was conducted on 855 patients aged 18 years and above who presented with fever and thrombocytopenia and were admitted in MVJ Medical College and Research Hospital, Hoskote, Bengaluru rural district from January 2016 to December 2018.

Results: A total of 855 patients of febrile thrombocytopenia were admitted to our hospital during study period. Majority of patients were in the age group of 18 to 40 years with male to female ratio of 1.15: 1. Most of the cases presented during the months of July to September. Commonest clinical presentation were fever (100%), myalgia (86.5%) and headache (84.7%). In the majority of patients, thrombocytopenia was transient, present for 2 – 3 days, but bleeding manifestations were seen in 24.3% of patients. Petechiae (14%) was the commonest bleeding manifestation. 691 (80.81%) patients had platelet count between 50000 to 1.5 lakh/mm^3 and 164 (19.18%) cases had platelet count less than 50000/mm^3 Only 5.6% had need for platelet transfusion. Dengue (51.9%) was the commonest cause of thrombocytopenia followed by rickettsial fever (27.7%). In 15.6% of patients the etiology could not be ascertained.

Conclusion: Febrile thrombocytopenia is the most common cause for admission to the hospital which requires extensive evaluation and prompt management.

Keywords: Dengue, Rickettsiae, Undifferentiated Fever, Platelet Count, Petechiae

INTRODUCTION

Fever is one of the commonest presentations which is a manifestation of various infections as well as non-infective disease process. An a.m. temperature of >37.2°C (>98.9°F) or a p.m. temperature of >37.7°C (>99.9°F) would define a fever. The normal daily temperature variation is typically 0.5°C (0.9°F).[1] Thrombocytopenia is defined as platelet count below the normal range which is 150, 000–450, 000/mm^3.

Thrombocytopenia results from four processes: deficient platelet production, accelerated platelet destruction, abnormal distribution and artefactual thrombocytopenia.

There is no absolute limit below which thrombocytopenia can lead to spontaneous bleeding. If the patient is hemostatically stable, platelet count more than 30000 will not lead to spontaneous bleeding. Bleeding may occur at higher platelet count if associated with severe anaemia, sepsis, fever etc.[2]

Thrombocytopenia due to decreased platelet production occur in vitamin B12 deficiency and folate deficiency, leukaemia, sepsis and hereditary disease, due to increased platelet destruction which can be nonimmune causes as in thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, and immune causes like autoimmune or alloimmune thrombocytopenia and increased platelet sequestration as in hypersplenism.[3] Drugs which can cause thrombocytopenia are acetaminophen, amiodarone, ceftriaxone, penicillin, piperacillin, diazepam, phenytoin, quinine, ranitidine etc.[4] Diseases which commonly present with febrile thrombocytopenia are dengue, malaria, rickettsial, typhoid, leptospirosis, septicaemia.

The present study was intended to know the underlying etiology of febrile thrombocytopenia cases admitted to our hospital, the various presentations and relationship between platelet count and bleeding manifestation and prognosis.

MATERIAL AND METHODS

This prospective study was undertaken at in the department of general medicine at MVJ medical college and research hospital, Hoskote, Bengaluru rural district, Karnataka, India, from January 2016 to December 2018.

Inclusion Criteria: Patients aged 18 years and above admitted with fever(>99.9 degree F) and thrombocytopenia (<1, 50000/mm^3).

Exclusion Criteria: Patients aged less than 18yrs, who had fever without thrombocytopenia and who had thrombocytopenia without fever.

Sample Size: A total of 855 patients admitted in department of medicine were included based on the above inclusion and exclusion criteria.

Protocol

Informed written consent was taken from all patients. Patients were evaluated with history and examination at

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How to cite this article: Radhika B.V., Sooraj C.S., Vasantha Kamath. A study of febrile thrombocytopenia. International Journal of Contemporary Medical Research 2019;6(9):I21-I25.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.9.20

admission and all basic investigations like complete blood count, renal function test, liver function test, chest x ray, ultrasonography abdomen, urine routine with necessary specific investigations like dengue serology(NS1AG, IgG, IgM Antibody), weil Felix, smear for malarial parasite, rapid card test, widal test, IgM Leptospira, Blood culture, peripheral smear, CSF analysis and bone marrow studies (when needed) for evaluation of febrile thrombocytopenia were done. Baseline platelet counts at presentation and repeat platelet counts were done until normal and near normal values were reached. Bleeding manifestations if present were recorded. All patients received appropriate symptomatic and where necessary specific treatment.

STATISTICAL ANALYSIS

Data was tabulated and charts and tables were generated using MS Excel and MS Word. Qualitative variables were presented using ratios and percentages. Quantitative variables were presented using mean ± Standard Deviation

RESULTS

Male to female ratio was 1.15:1 for total three years (graph-1).
Majority of patients 92.5% belonged to the age group of 18-40 years (graph-2).
Majority of patients 564(65%) presented during July, august, September months (graph-3).
The commonest symptom after fever (100%) was myalgia (86.5%) and headache (84.7%) and the least common symptom was seizures (0.35%) (graph-4).
Pallor is the commonest sign in 120 (14%) cases after fever (100%) and the least common sign was bradycardia in 3 (0.35%) cases (graph-5).
In all three years dengue fever (51.9%) was commonest cause of febrile thrombocytopenia and the least common cause was retroviral (0.11%) disease and malignancy (0.23%). In our study there is increase in trend of dengue fever in first and second year and decline in third year. Rickettsial fever (27.7%) showed increasing trend in second and third year.

Aetiology	2016		2017		2018	
	No	%	No	%	No	%
Undifferentiated Febrile thrombocytopenia(134)	68	29.3	30	9	36	12.2
Dengue fever(444)	93	40	201	60	150	51.1
Rickettsial Fever (237)	51	21.9	88	26	98	33.4
Enteric fever (14)	7	3	3	0.9	4	1.3
Malaria fever(8)	5	2.15	2	0.6	1	0.34
Septicemia (17)	7	3	6	1.8	4	1.3
HIV (1)	1	0.43	0	0	0	0
Malignancy(2)	1	0.43	1	0.3	0	0
Total cases(855)	232		330		293	

Table-1: Distribution of cases based on etiology

Platelet count per mm^3	Number of patients	Bleeding manifestations in number	Skin bleeding in number	Mucosal bleeding in number	Platelets Transfusion in number
1lakh- 1.5 lakh	182(21.28%)	26 (14.2%)	24 (92.3%)	02 (7.6%)	0
50000-1lakh	509(59.53%)	59 (11.5%)	39(66.1%)	20 (33.8%)	5
20000-50000	129(15.08%)	98 (75.9%)	54 (55.1%)	44 (44.8%)	18
<20000	35(4%)	25 (71.4%)	03 (12%)	22 (88%)	25
TOTAL	855	208 (24.3%)	120(57.6%)	88 (42.3%)	48(5.6%)

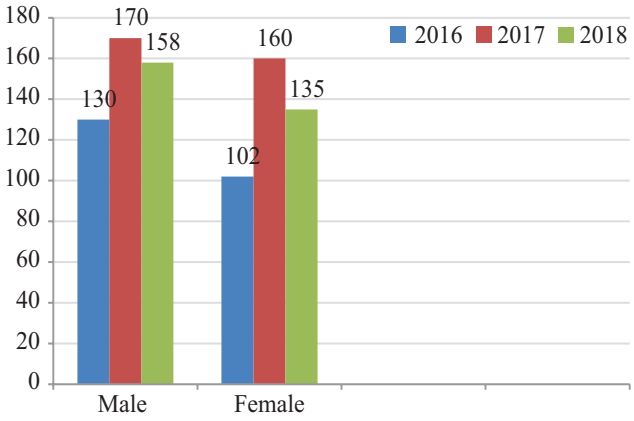
Table-2: Distribution of patients based on platelet count

Parameter	Number of patients
Increased SGOT/SGPT	285 (35%)
Increased Urea /Creatinine	100 (11.7%)
Hypoalbuminemia	52 (6%)
Hyperbilirubinemia	76 (9%)

Table-3: Distribution of other lab parameters in patients

Ultrasonography abdomen	Number of patients	% of patients
GB wall oedema	186	21.7%
Splenomegaly	167	19.5%
Hepatomegaly	93	10.8%
Ascites	87	10.1%

Table-4: Ultrasonography findings of patients



Graph-1: Distribution of patients based on sex

Complication	Number	Percentage
Non-oliguric acute renal failure	16	1.8
Pleural effusion	24	2.8
Meningoencephalitis	5	0.58
Liver cell failure	18	2.1
Acute respiratory distress syndrome	4	0.46
Dengue myositis	2	0.23
Hypokalemic periodic paralysis	1	0.11
Viral myocarditis	10	1.1
Total	80	9.3

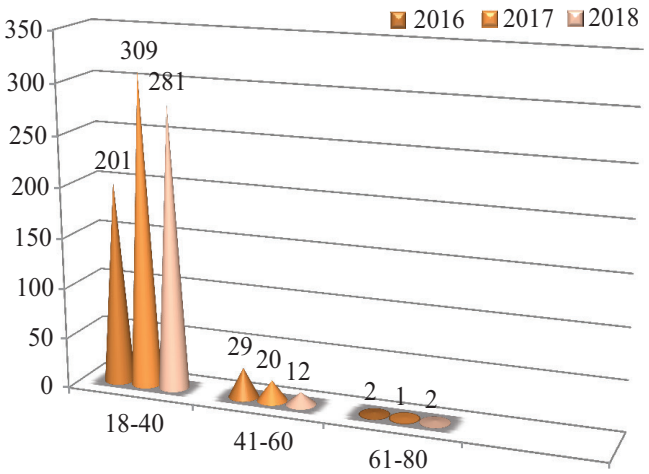
Table-5: Complications of patients

Outcome	No of patients	Percentage
Recovered	781	91.3
Discharge against medical advice	49	5.7
Referral	21	2.4
Death	4	0.4
Total	855	99.8%

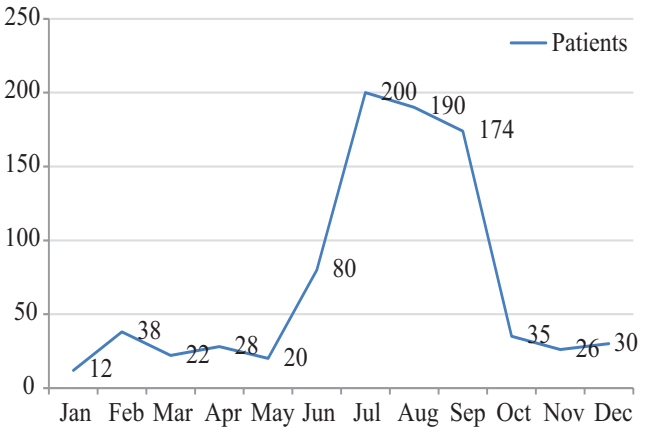
Table-6: Outcome of patients

Causes	Number of patients
ARDS	2
Myocarditis	1
Septicemia	1

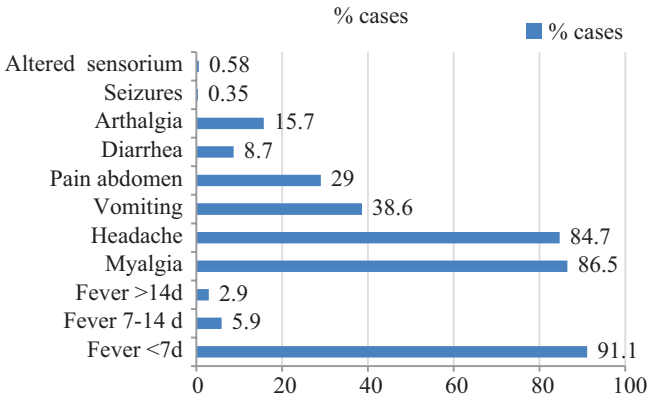
Table-7: causes of death



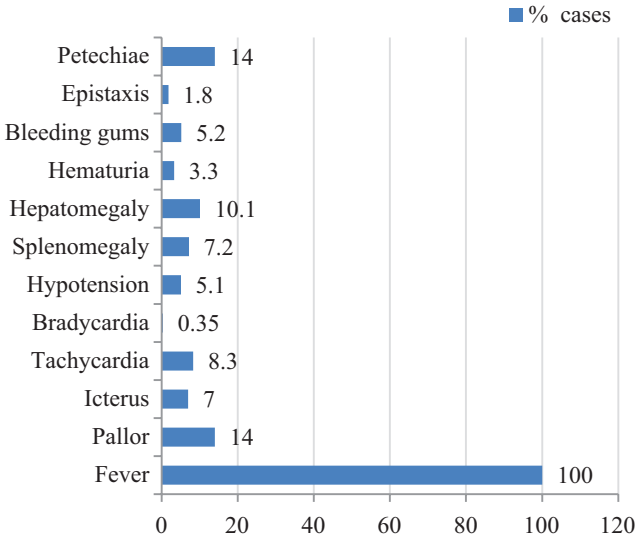
Graph-2: Distribution of patients based on age



Graph-3: Seasonal distribution of patients



Graph-4: Symptom wise distribution of cases



Graph-5: Signs wise distribution of patients

Undifferentiated fever (15.6%) trend was high in first year compared to second and third year which was diagnosed after excluding other causes by investigations (table-1).

Amongst 855 cases, 509 (59.53%) cases had platelet count between 50000-1 lakh and 35 (4%) cases had platelet count less than 20000. 208 (24.3%) cases had bleeding manifestations in the form of skin bleeding in 120 (57.6%) patients and mucosal bleeding in 88 (42.3%) patients and 48(5.6%) cases had platelet transfusion. (Table-2)

Transaminitis (raised SGOT/ SGPT) was present in 285 (35%) patients, altered renal function tests in 100 (11.7%) patients, hypoalbuminemia in 52(6%) patients and hyperbilirubinemia in 76 (9%) patients. (Table-3)

In ultrasonography, Gall bladder wall oedema was commonest finding in 186(21.7%) patients and ascites in 87(10.1%) patients was the least common finding. (Table- 4)

80 (9.3%) patients of febrile thrombocytopenia had complications. Commonest complication was pleural effusion in 24 (30%) patients since it was found in three predominant aetiologies of our study dengue, rickettsial and undifferentiated fever. The least common complication hypokalemic periodic paralysis in 1(1.25%) patient was atypical presentation of dengue fever (Table-5).

781 (91.3%) patients recovered, 49(5.7%) patients were discharged against medical advice, 21(2.4%) patients were

referred to higher centre, mortality was seen in 4 (0.4%) patients. (Table- 6)

Mortality was seen in 4(0.4%) patients, 2 had acute respiratory distress syndrome, 1 patient had myocarditis and 1 patient had septicemia. (Table- 7)

DISCUSSION

This study was conducted on 855 patients of febrile thrombocytopenia in MVJ Medical College and Research Hospital in Bangalore Rural District during the study period from January 2016 to December 2018.

In our study the male to female ratio was 1.15:1, out of which 458 were males and 397 were females. Majority of patients (92.5%) were in the age group of 18- 40 years constituting 92.5% with mean±SD was 39.8±20.1 In our study seasonal variation was seen in 564 (65%) patients during July to September especially in cases of rickettsial fever. In study by Modi T et al[6], 71.24% patients of febrile thrombocytopenia were seen during rainy and early winter season.

In our study fever(100%) was the commonest symptom followed by myalgia(86.5%), headache (84.7%), vomiting (38.6%), pain abdomen (29%), arthralgia (15.7%), diarrhoea (8.7%), altered sensorium (0.58%), seizures (0.35%).In study by Gondhali M P et al[12] 90% had headache, 92% had bodyache, 43% nausea, 24% abdominal pain, 15% altered sensorium.

The commonest sign after fever was pallor and rash in 14% each and other signs seen in our study were icterus (7%), hepatomegaly (10.1%), splenomegaly (7.2%), tachycardia(8.3%), hypotension (5.1%), Bleeding manifestations in the form of petechiae (14%), bleeding gums(5.2%), haematuria (3.3%), epistaxis (1.8%) were seen. Pallor, hepatomegaly, splenomegaly were seen in patients of malaria and undifferentiated febrile illness. Bleeding manifestations were predominantly seen in patients of dengue fever and few cases of undifferentiated febrile thrombocytopenia. In study by Gondhali M P et al[12] 22% had pallor, 28% had icterus, 12% had hepatomegaly, 19% had splenomegaly.

In our study dengue fever was the commonest cause of febrile thrombocytopenia in all the three years, 40%, 60%, 51.1% in 2016, 2017, 2018 respectively. Dengue fever was the commonest cause of febrile thrombocytopenia in studies by Gandhi A A et al 26.7%[5], Modi T et al 55.97%[6], Fawas M N et al 54.5%.[7]

Rickettsial fever was the second common cause of febrile thrombocytopenia with increasing trend from 21.9% in 2016 to 26% in 2017 and 33.4% in 2018.Rickettsial fever was suspected in 6.6% patients of study by Suneetha et al[8] conducted in Mysuru, and also reported in 2.5% patients in study by Hariprasad S et al[9] conducted in raichur, Karnataka.

Undifferentiated fever was the third common cause of febrile thrombocytopenia and was 29.3% in 2016, 9% in 2017 and 12.2% in 2018.Undifferentiated fever was reported as most commonest cause in studies by Suneetha et al (61.4%)[8], Naveen Kulkarni et al(62.5%)[10], Yadav and Singhai et al(35.6%)[11],

The other causes of febrile thrombocytopenia in our study was septicemia in 1.9%, enteric fever in 1.6%, malaria in 0.9%, malignancy in 0.23% with 2 cases of acute leukemia, HIV in 0.11%.

The incidence of septicemia was 0.8% in the study by Fawas M N et al[7], 8% each in the studies by suneetha et al[8], Naveen Kulkarni et al[10], 12.5% in the study by Hariprasad S et al.[9]

The incidence of enteric fever was 6.5% in the study by Naveen Kulkarni et al[10], 2% in the study by suneetha et al[8], 1.8% in the study by Yadav and Singhai et al[11], 0% in the studies by Fawas M N et al[7] and Hariprasad S et al.[9]

The incidence of malaria is 28.5% in the study by Hariprasad S et al[9], 24.4% in the study by Yadav and Singhai et al[11], 13% in the study by Naveen Kulkarni et al[10] and lower incidence of 2% in the study by Suneetha et al.[8]

The incidence of hematological malignancy was reported of 0.6% in the study by Yadav and Singhai et al[11], 1.79% in the study by Gandhi A A et al[5] which was 0.23% in our study.

HIV was reported as viral fever in the study by Modi T et al[6], 5% patients of study by Gondhali MP et al[12] and which was reported as 1(0.11%) patient in our study.

In our study 59.53% patients had platelet count within 50000-100000/ mm^3 range compared to 57.14% in study by Gandhi A A et al[5], 53% in Fawas M N et al[7], 53.8% in Yadav and Singhai et al.[11] In our study 4% of patients had platelet count less than 20000, compared to study by Gandhi A A et al[5] which is 13.39%, in Fawas M N et al[7] 5% and in Yadav and Singhai et al[11]

11.8%.

Bleeding manifestations were seen in 24.3% patients in our study as compared to study by Yadav and Singhai et al[11] which is 7.8%, in Fawas M N et al[7] 17%, in Gondhali MP et al[12] 24%.Petechiae was the commonest bleeding manifestation of 14% in our study followed by mucosal bleeding in 10.3%patients which is similar to study by Gondhali MP et al.[12]

In our study when the platelet count was between 20000-50000 / mm^3. 75.9% had bleeding manifestation, 71.4% had bleeding when platelet count less than 20000 and 12.3% had bleeding manifestations with platelet count more than 50000/ mm^3. Hence thrombocytopenia less than 50000/ mm^3 had more bleeding manifestations.

In our study 48(5.6%) patients had platelet transfusion according to WHO guidelines. Majority of patients were transfused depending on bleeding manifestations with respect to platelet count. For example 4 Patients developed Bleeding gums on the third day of fever with platelet count <50000/mm^3, 1 patient developed epistaxis on Second day of fever with platelet count 56, 000/mm^3, another patient developed haematuria on the 3rd day of fever with a platelet count of 18, 000/mm^3 also had platelet transfusion.

Transaminitis (raised SGOT, SGPT) was present in 285 (35%) patients, hypoalbuminemia in 52(6%), hyperbilirubinemia in 76 (9%) patients of febrile thrombocytopenia in our study as compared to the study by Gondhali MP et al[12] where abnormal SGOT was found in 45%, abnormal SGPT in 38%, hyperbilirubinemia in 39% patients of febrile

thrombocytopenia. Hypoalbuminemia in rickettsial fever in our study was a predictor of complications.

In our study renal function tests were altered in 100 (11.7%) patients of febrile thrombocytopenia as compared to 24% in study by Gondhali MP et al.[12]

Dengue fever and undifferentiated fever patients suggestive of dengue had GB wall oedema in 21.7% patients.[13] The other ultrasonography findings present in dengue, rickettsial fever, undifferentiated fever were splenomegaly in 19.5%, hepatomegaly in 10.8%, ascites in 10.1%. Hepatosplenomegaly was also a feature of malaria and acute leukemia.

In our study 9.3% patients of febrile thrombocytopenia had complications. They are non-oliguric acute renal failure in 1.8%, pleural effusion in 2.8%, liver cell failure in 2.1%, meningoencephalitis in 0.58%, acute respiratory distress syndrome in 0.46% in patients of dengue and rickettsia fever. Complications predominantly seen in dengue were myositis in 0.23%, hypokalemic periodic paralysis in 0.11%, myocarditis in 1.1%.

In the majority of patients, thrombocytopenia was transient, present for 2 – 3 days and duration of stay in our hospital ranged from 2 to 7 days.

91.3% patients of febrile thrombocytopenia improved both clinically and by lab parameters.5.7% patients had left against medical advice.2.4% patients were referred to higher centre especially those with malignancy.

There were 4 (0.4%) deaths. 2 were acute respiratory distress syndrome, 1 due to dengue and 1 due to rickettsial fever, the other two deaths were, 1 in dengue myocarditis and 1 in septicemia.

CONCLUSION

Febrile thrombocytopenia is the most common cause for admission to the hospital which requires extensive evaluation and prompt management. Dengue infection(51.9%) was commonest followed by Rickettsial fever(27.7%).

Undifferentiated fever(15.6%) forms the third commonest cause in our study diagnosed on exclusion after investigating for known causes were normal.

There is decline in the incidence of dengue fever and raise in the incidence of rickettsial fever during the course of three years of our study. Rickettsial infection and dengue fever both form important causes of community acquired undifferentiated febrile illness.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 15-08-2019; **Accepted:** 30-08-2019; **Published:** 17-09-2019