Original Research Article

Clinical, etiological and laboratory profile of febrile thrombocytopenia and correlation of platelet count with outcome in a South Indian tertiary hospital

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ABSTRACT

Background: Febrile thrombocytopenia is commonly encountered by doctors especially during monsoon and peri-monsoon period, many of these patients have a turbulent cthisse with multi organ dysfunction and might land up in ICU with significant morbidity and mortality. Infections are the commonest causes of thrombocytopenia and they vary with season and geographical location. A systematic approach, carried out with an awareness of causes, clinical presentation and laboratory profile of febrile thrombocytopenia can shorten the duration of investigations and bring out the diagnosis early, reducing morbidity and mortality of patients and reducing burden on hospital resthisces. The objective of the study is to study the underlying etiology, the various clinical presentations, laboratory profile and complications of fever with thrombocytopenia in this community during monsoon period and to correlate thrombocytopenia with outcome, co morbidities and its etiology.

Methods: The prospective observational study was conducted in tertiary centre in Kolar between June-December 2017. Patients meeting inclusion and exclusion criteria were grouped into 4 groups based on platelet counts, and correlated with comorbidities, etiology and outcome. Detailed clinical and laboratory examination were done in all patients and p value of <0.05 was considered statistically significant.

Results: Among 465 patients were included in the study. Dengue was the most common cause for febrile thrombocytopenia and mortality. Hepatic complications and petechiaes were the most common complications and bleeding manifestations. 135 patients received platelet transfusion but there was no relationship between platelet transfusion and outcome, there were 9 deaths in the study and there was no association between death and platelet count at admission.

Conclusions: There was no relation between platelet count on admission and mortality and also there was no relationship between platelet transfusion and outcome. Knowing the clinical presentation, etiology, complications and its monitoring can significantly reduce the morbidity and mortality due to febrile thrombocytopenia.

Keywords: Dengue, Febrile thrombocytopenia, Fever, Mortality, Outcome, Profile, Thrombocytopenia

INTRODUCTION

Febrile thrombocytopenia is frequently encountered by physicians especially during monsoon and peri-monsoon period.

Fever is one of the most cardinal symptoms of disease; it is an easily noted and a reliable marker of illness. It is defined as an elevation of the body temperature above the normal circadian range as the result of a change in the thermoregulatory center located in the anterior

hypothalamus. An AM temperature of >37.2°C (98.9°F) or a P.M. temperature of >37.7°C(99.9°F) is considered as fever.[1]

Platelets play a central role in normal haemostasis. Thrombocytopenia is defined as platelet count <1,50,000/μL. This is due to decreased production, increased destruction or increased sequestration in spleen.[1]

Infections like Dengue, Leptospirosis, Malaria, Typhoid, ricketssia, Miliary Tuberculosis, HIV, Septicemia are some of the common causes of fever with thrombocytopenia.[2]

The emergence of febrile thrombocytopenia in India has gone into epidemic proportions and outbreaks are frequently engulfing different parts of the country in both urban and rural populations. It may range from simple flu like self-limiting illness to life threatening complication and can be fatal if untreated. Occasionally these patients may have a turbulent cthisse with multi organ dysfunction and might land up in ICU with significant morbidity and mortality.

Therefore, a systematic approach, carried out with an awareness of causes, clinical presentation and laboratory profile of febrile thrombocytopenia can shorten the duration of investigations and bring out the diagnosis early, reducing morbidity and mortality of patients and reduce the burden on hospital resthisces. Hence objective of this study was to

- To study the underlying etiology, the various clinical presentations, laboratory profile and complications of fever with thrombocytopenia in this community during monsoon period.
- To correlate thrombocytopenia with outcome, co morbidities and its etiology.

METHODS

This was a prospective observational study conducted at the department of General Medicine, R.L. Jalappa hospital associated with Sri Devaraj Urs Medical College, Kolar, Karnataka, India.

Patients admitted in medical wards during monsoon and peri-monsoon period (June- December 2017) with fever and thrombocytopenia were recruited with following inclusion and exclusion criteria. Institutional Ethical committee approval was taken. Informed written consent was obtained from all patients participating in the study after clearly explaining the study procedure.

Inclusion criteria

- Age >18 years.
- History of fever > 99.0oF.
- Platelet count < 1,50,000.

Exclusion criteria

- Patients on drugs causing thrombocytopenia.
- Previously diagnosed patients with chronic thrombocytopenia.

Careful history was recorded including history of co-morbidities. General physical examination and detailed examination of all systems was performed. Clinical examination findings of patients with respect to neurological status, respiratory, renal, hepatic and hematological systems was noted based on history and investigations.

Routine investigations such as complete blood count, plasma glucose, blood urea, serum creatinine, serum electrolytes, liver function tests, ECG, Chest X ray and USG abdomen were done in all patients. Dengue serology, peripheral smear for Malaria parasite, Weil Felix test for Leptospira were done. Cause of fever was tabulated accordingly.

Platelet count on day one was classified into 4 groups as shown in Table 1.

Table 1: Platelet group.

Group	Platelet count
1	<20000
2	20000-50000
3	50000-100000
4	>100000

Platelet count was co related with outcome of the patient.

CNS complications like encephalopathy, encephalitis, meningitis, seizures were assessed based on history, lumbar puncture, and CT or MRI brain whenever necessary.

Respiratory complications like pulmonary edema, ARDS, pulmonary hemorrhage were noted based on ABG, chest X-Ray.

Renal complications like acute renal failure, acute tubular necrosis were noted based on urine output, renal function test and urine routine examination.

Hepatic complications like acute hepatitis, fulminant hepatic failure, cholecystits, cholangitis were noted based on liver function test, USG abdomen and coagulation profile whenever needed.

Cardiac complications like myocarditis, pericarditis and conduction block were assessed by ECG, 2D echo and cardiac enzymes whenever necessary.

Hematological complications were noted based on history, petechiae, purpura, bleeding from any orifices

and other complications like intra cranial or intra-abdominal bleeding.

Data was entered into Microsoft excel data sheet and analyzed using SPSS version 20 software. Nonparametric Chi-square ,unpaired t test and one way ANOVA was applied in comparative analysis results between different groups. p value less than 0.05 was considered as statistically significant. Mean values, standard deviation, prevalence was assessed wherever relevant.

RESULTS

A total of 465 patients meeting the inclusion and exclusion criteria were recruited in the study out of which 60% (279) were male and 40% (186) were female. The mean age of presentation was 34.6±14.19 years. Authors classified patients into 3 groups based on their age into 18-30 years, 30-60 years > 60 years as shown in Table 2.

Table 2: Age classification.

Age in years	No of patients	Percentage
18-30	225	48.38%
30-60	217	46.67%
>60	23	4.95%

Average duration of fever at presentation was 4.46±2.86 days.

The average duration of hospital stay was 5.794±2.25 days. Authors correlated hospital duration with platelet count and there was no statistical significance (p value 0.422) 261 patients had headache followed by myalgia (237), arthralgia (187), retroorbital pain (136), pain abdomen (134), vomiting (105), conjunctival suffusion (62), rash (38) and dyspnea in 11 patients as shown in Figure 1.
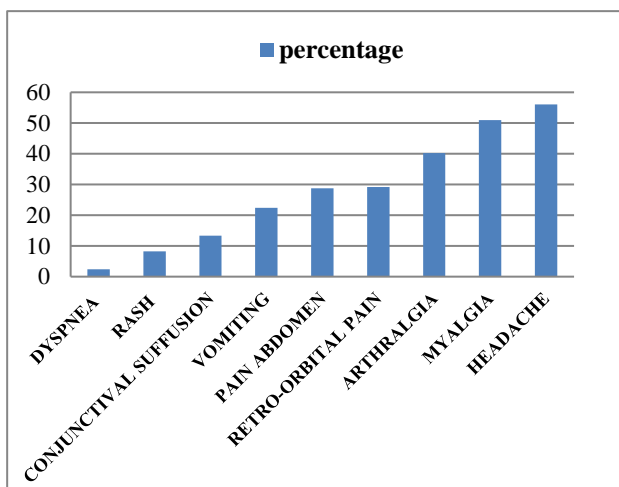

Figure 1: Symptoms.

In this study there were 46 Diabetics and 15 hypertensive patients, 8 patients had hypothyroidism, 4 were known

seizure disorder and 4 had COPD, one patient had CVA and SLE as shown in Table 3.

Table 3: Co-morbidities.

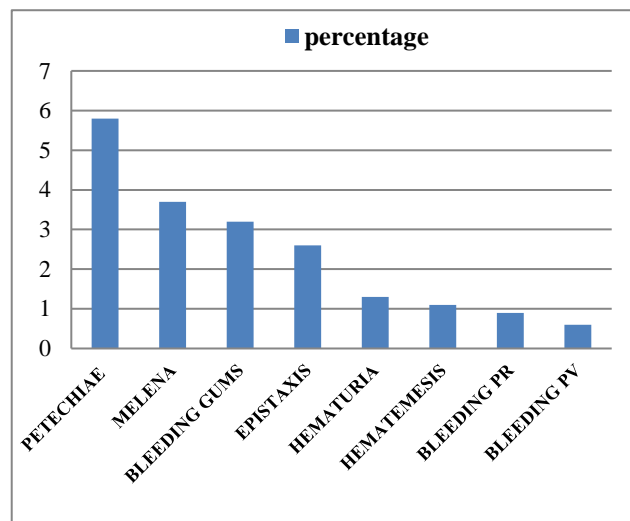| Comorbidities	Total
T2DM	46
HTN	15
Hypothyroid	8
COPD	4
CVA	1
Seizure	4
SLE	1

Figure 2: Bleeding manifestations.

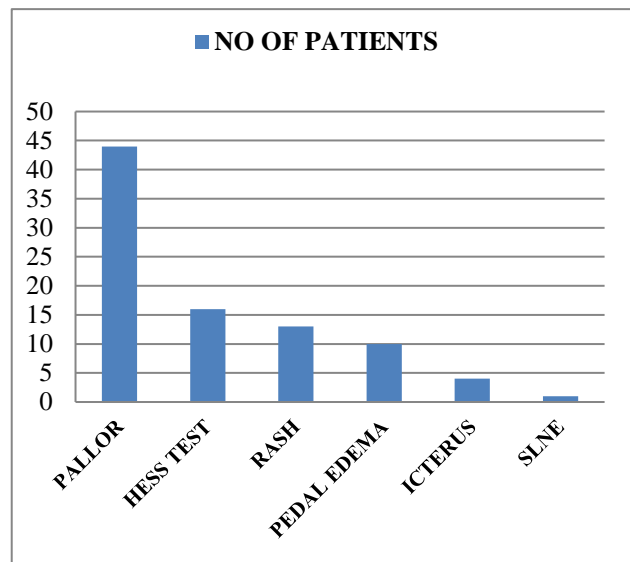### Figure 3: General physical examination.

Bleeding manifestations were also tabulatedand 81 patients had bleeding manifestations. In this study 27 patients had petechiae which were the most common presentation followed by melena (17), bleeding gums

(15), epistaxis (12), hematuria (6), hematemesis (5) bleeding PR (4) and bleeding PV in 3 patients. None of the patients in this study had life threatening bleeding manifestation like intracerebral or Intra-abdominal bleed as shown in Figure 2.

Vital parameters were measured in all patients and 36 patients had BP < 90, 116 patients had PR > 100/min and 4 had PR < 60/min, 117 patients had RR > 20/minute as shown in Table 4.

Table 4: Vital parameters.

	Temperature (0F)	Respiratory rate/min	Pulse rate/min	Systolic BP (MMHG)
Mean	99.61	18.23	89.75	113.63
SD	0.74	4.31	14.88	15.52

In this study 44 patients had pallor, 4 had icterus, 10 patients had pedal edema, 1 patient has significant lymph node enlargement, 13 patients had maculopapular rash and 16 patients had positive HESS test as shown in Figure 3.

On clinical examination authors found that 30 patients had abdominal tenderness, 20 patients had decreased air entry and 12 had crepitations on auscultation of lungs. 12 patients had distension of abdomen, 4 were in altered senosorium, 3 had hepatomegaly, 2 had splemomegaly and 3 patients were pregnant on abdominal examination. 1 patient had raised JVP and 1 patient had meningitis signs like neck stiffness, Kernig and Brudzinski sign as shown in Figure 4.
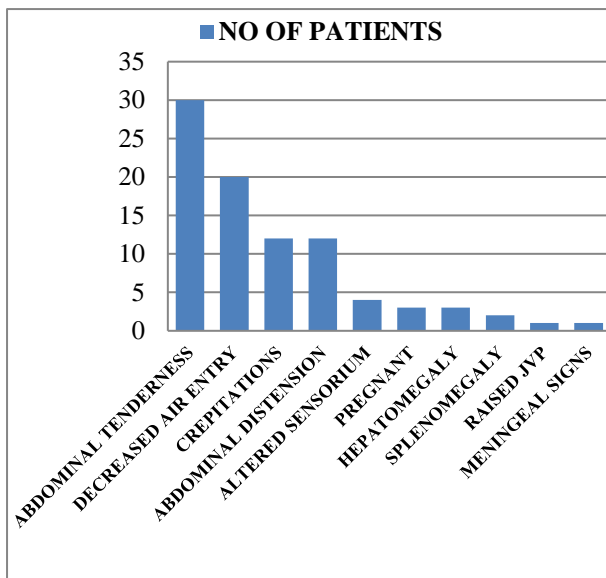

Figure 4: Clinical examination findings.

Authors also divided patients according to their day 1 platelets into 4 groups.

The average platelet count at admission was 60116, the lowest platelet count with which patient presented to us was 2000 as shown in Table 5.

Table 5: Platelet groups.

Classification	Platelet count	Frequency	%
1	<20000	96	20.64
2	20000-50000	146	31.39
3	50000-100000	128	27.52
4	>100000	95	20.43

Authors correlated platelet group with age group and found no significant association between them (p value 0.913) as shown in Table 6.

Authors correlated platelet group with Hess test and found no significant association between them (p value 0.811) as shown in Table 7.

The cause for febrile thrombocytopenia was found and tabulated. The most common cause for febrile thrombocytopenia in this study was Dengue followed by sepsis, Malaria, Typhoid, Leptospira, Ricketssia and HIV. 322 patients had dengue out of which 204 were NS1Ag positive, 64 were IgM, 51 patients had both NS1Ag and IgM. 2 patients had IgM and IgG, and one patient was positive for both NS1Ag and IgG. 11 patients had Malaria, and all were peripheral smear positive for Plasmodium Vivax, 7 patients were Typhi dot Positive, 4 patients had rickketsia, 6 were leptospira positive.

Cause of thrombocytopenia was sepsis in 34 patients and in 84 patients cause could not be determined.

Fthis patients had co infection - one was both VCTC and NS1Ag positive, 1 patient had Plasmodium vivax and dengue NS1Ag positive, 2 patients were positive for typhi dot and dengue NS1Ag as shown in Table 8.

Authors correlated etiology with platelet group and found statistically significant association between dengue positivity and platelet group. There was significant association between Ricketssia positivity and platelet group also we found a significant association between platelet group and undetermined cause of febrile thrombocytopenia as shown in Table 9.

Table 6: Age and platelet groups correlation.

Age group* platelet group cross tabulation						
		Platelet group				Total
		<20000	20000-50000	50000-100000	>100000	
Age group	< 30 Years	49	70	62	44	225
	> 60 Years	6	5	6	6	23
	30-60 Years	41	71	60	45	217
Total		96	146	128	95	465

Table 7: Hess test and platelet group crosstbulation.

Hess test * platelet group cross tabulation						
		Platelet group				Total
		1.00	2.00	3.00	4.00	
Hess test	No	92	140	124	93	449
	Yes	4	6	4	2	16
Total		96	146	128	95	465

All patients underwent complete blood count, renal function tests, liver function test (LFT) and GRBS, fasting and post prandial blood sugars were done whenever necessary. LFT was deranged in 132 patients among them 15 patients had elevated bilirubin 50 patients had increased Aspartate amino transferase(AST) and Alaninie amino transferase(ALT) and 60 patients had elevated alkaline phosphatase (ALP) and 45 patients had elevated Gamma Glutamyl transferase (GGT). 28 patients had deranged renal function test (RFT) 2 patients needed hemodialysis during admission. 73 patients (15.7%) had leucopenia and 45 (9.7%) had leucocytosis in this study.

Table 8: Causes for febrile thrombocytopenia.

Cause	Total	Percentage
Dengue	318	68.3
Sepsis	34	7.31
Malaria	10	2.1
Typhoid	5	1.07
Rickketsia	4	0.86
Leptospira	6	1.29
Malaria +Dengue	1	0.21
Typhpoid+Dengue	2	0.43
Hiv + Dengue	1	0.21
Undetermined	84	18.06
Total	465	100

Authors correlated Co-morbidities with platelet group but did not find any significant association as shown in Table 11.

There were 9 deaths in this study. Patients who died in this study had a initial platelet presentation between 2,000 to 105,000 (platelet counts were 2000, 5000, 9000, 19000, 40000, 41000,77000,88000,105000) and their scores were between 17 to 24 with average score of 19.22.

Among 8 patients had dengue (3 patients had Ns1Ag+ IgM and 5 had IgM positivity) and cause could not be determined in one patient as shown in Figure 5.
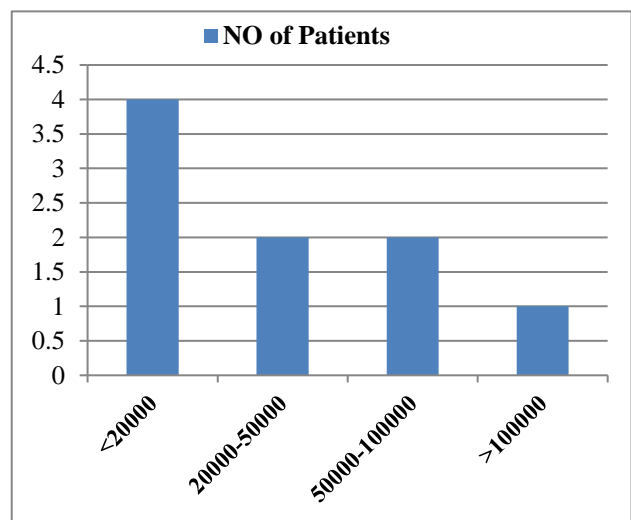

Figure 5: Platelet distribution in mortality cases.

Among 5 patients received platelet transfusion, but platelet transfusion did not have any effect on the mortality of these patients. 2 patients were both diabetic and hypertensive and rest did not have any co morbidities as shown in Table 12.

Platelet counts did not have any significant relationship with outcome of the patient as shown in table. We correlated platelet count and complications as shown in the Table 13.
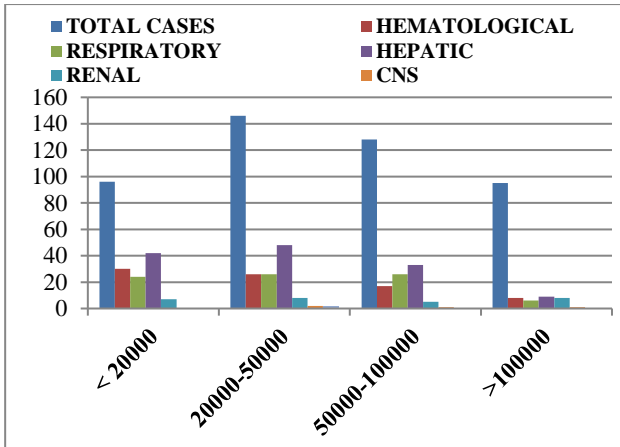
Figure 6: Platelet distribution with complication.

Among 17.63% patients had respiratory complications, 6.02% renal, 28.38% hepatic, 17.41 hematological and 0.86% CNS complications, there was no association between platelet count and organ system complications. Hepatic complications are more common in this study. 2 patients had myocarditis and 1 patient had meningitis as shown in Figure 6.

Platelets were transfused to patients with bleeding manifestations or platelets count less than 10000/cumm. Among 135 patients received platelet transfusion in this study. On an average 3.8 RDPs were transfused. 5 patients who died during study received platelet transfusion and remaining 4 did not require any platelet transfusion.

Authors correlated Platelet group and platelet transfusion; maximum platelets were transfused in patients with platelet count <20000. 76 (56.29%) of 135 patients who received platelets were having platelet count <20000 as shown in Table 14.

Table 9: Causes for febrile thrombocytopenia and platelet group correlation.

Etiology	<20000	20000-50000	50000-100000	>100000	p value
Dengue	86	101	73	58	<0.001
Sepsis	6	12	8	8	0.453
Malaria	0	3	5	2	0.287
Typhoid	1	2	0	2	0.155
Rickketsia	0	0	4	0	0.015
Leptospira	0	2	3	1	0.518
Malaria +Dengue	0	1	0	0	0.533
Typhpoid+Dengue	0	1	1	0	0.702
Hiv + Dengue	1	0	0	0	0.233
Undetermined	2	24	34	24	<0.001

Table 10: Biochemical parameters.

	Minimum	Maximum	Mean	SD
HB%	5.1000	19.4000	13.647414	2.2283915
PCV	17.5000	60.0000	40.691185	6.3900077
WBC	1.1700	29.8000	6.665989	3.4956990
TB	0.4000	7.6500	0.848147	0.6270187
DB	0.1000	6.8000	0.489224	0.5476364
AST	10	750	59.63	111.700
ALT	2.0	501.0	36.697	46.8991
ALP	20	750	106.00	59.312
TP	3.3000	8.4000	6.744397	0.7736556
Albumin	1.3000	5.3000	3.486638	0.8230969
Globulin	1.7000	4.2000	2.959698	0.4690792
A:G	0.6000	1.8000	1.160453	0.2913260
GGT	10	804	44.51	69.454
BU	4	125	22.72	14.717
SC	0.2000	11.0000	0.841207	0.6258136
Na+	122	165	138.27	5.022
RBS	20	625	107.64	61.424
FBS	71	565	169.32	81.545
PPBS	78	625	215.12	99.454
GHB	5.0000	12.1000	7.671930	1.6397685

Table 11: Platelet group and co-morbidities correlation.

Co-morbidities	<20000	20000-50000	50000-100000	>100000	p value
HTN	3	3	4	5	0.591
DM	6	12	15	12	0.436
Hypothyroidism	0	3	3	2	0.541
COPD	0	0	0	2	0.059
CVA	0	0	0	1	0.272
Seizure	1	1	1	1	0.987
SLE	0	0	0	1	0.272

Table 12: Causes for febrile thrombocytopenia.

	<20000	20000-50000	50000-100000	>100000	Total
Survived	92 (95.84%)	144 (98.63%)	126 (98.43%)	94 (98.95%)	456
Died	4 (4.16%))	2 (1.37%)	2 (1.57%)	1 (1.05%)	9
Total	96	146	128	95	465

Table 13: Platelet group and complications.

Complications	<20000	20000-50000	50000-100000	>100000	Total
Respiratory	24	26	26	6	82 (17.63%)
Renal	7	8	5	8	28 (6.02%)
Hepatic	42	48	33	9	132 (28.38%)
Hematological	30	26	17	8	81 (17.41%)
CNS	0	2	1	1	4 (0.86%)
Cardiac	0	2	0	0	2(0.43%)

Table 14: Platelet groups and platelet transfusion.

Platelet group	Total cases	No of people platelet transfused	Percentage
<20000	96	76	79.1%
20000-50000	146	40	27.3%
50000-100000	128	17	13.28%
>100000	95	2	2.10%

Table 15: Complications and blood transfusion.

Complications	No of patients	Patients receiving platelets	No of platelets transfused	Average no. of platelet transfused
Respiratory	82	33 (40.24%)	132	4
Renal	28	7 (25%)	28	4
Hepatic	132	57 (42.22%)	233	4.08
Hematological	81	43 (53.08%)	168	3.9
CNS	4	2 (50%)	7	3.5

Table 16: Average platelet at admission.

	Patients	Average platelet at admission
Survived	456	60456
Dead	9	42888
Platelet transfused	135	26725
No platelet transfusion	330	73775
Hematological complication	81	41851
No hematological complications	384	63968

Among 40.24% patients with respiratory complications, 53.08% with hematological, 25% with renal, 42.22% with hepatic and 50% with CNS complications were transfused platelets as shown in Table 15. Among 135 patients were transfused platelets; mean platelet count among transfused patients was 26725 and 73775 among non-transfused patients. The average platelet count among the patients who died was 42888 and those who survived was 60456. Average no of platelets transfused in patients who died was 3.8 bags of platelets and in those who survived was also 3.8 RDPs. 5 Patients who died had hematological complications and received platelet transfusion but there was no change in outcomeAmong 81 patients had hematological complications 45 patients received platelet transfusion. The mean platelet count at admission with hematological complications was 41851 and those without any hematological complication were 63968 as shown in Table 16.

ECG, chest X-ray and USG abdomen features

Among 41 patients had ECG changes, 10 had sinus bradycardia, 15 sinus tachycardia 6 patients had LVH, 3 patients had poor R wave progression and 7 patients had ST depression in anterior leads but none of the patient had myocarditis in this study. Among 83 out of 465 had Chest X ray changes, 56 patients had pleural effusion, 15 had non homogenous opacities, 6 patient had cardiomegaly 2 had COPD changes and 2 patients had X ray features of ARDS.

Among 336 patients had normal USG abdomen, 89 patient had ascites, 87 patients had thickened and edematous gall bladder, 30 patient had splenomegaly, 22 patient had hepatomegaly, 2 patient had features of cholecystitis and 3 had gravid uterus. CT and MRI brain was done for patients in altered sensorium, no abnormalities were detected. 1 patient was diagnosed as dengue encephalitis.

DISCUSSION

Febrile thrombocytopenia is one of the most common diseases encountered by physicians especially during monsoon period. Infections like Dengue, Leptospirosis, Malaria, Typhoid, ricketssia, Miliary Tuberculosis, HIV, Septicemia are some of the common causes of fever with thrombocytopenia.[1]

These patients come with varied clinical presentation and it may range from simple flu like self-limiting illness to life threatening complication and can be fatal if untreated. Occasionally these patients may have a turbulent cthisse with multi organ dysfunction and might land up in ICU with significant morbidity and mortality.[3]

Infections cause decrease in platelet count both due to effects on platelet production and platelet survival.[4] This study was conducted as there is a need to know the etiology, clinical presentation and laboratory profile of febrile thrombocytopenia during monsoon and peri-monsoon period in this community.

In this study there was male preponderance 60% compared to females similar to study by Sujata S. Kumbhar et al, where 59% males had fever with thrombocytopenia.[5] Nikalje Anand et al, in their study found that highest number of cases was seen in the age group of 18 - 40 years (75%) followed by 40 - 60 years (16%) and then above 60 years were 9% but in this study authors found 48.38% cases were seen in 18-30 years and between 30-60 years 46.67% cases and > 60 years 4.94% cases.[6]

Average duration of fever at presentation was 4.46±2.86 days. The average duration of hospital stay was 5.794±2.25 days in this study.

Incidence and prevalence of causes of febrile thrombocytopenia vary seasonally and geographically. In studies conducted by Srinivas et al, and Prithviraj Patil et al, malaria was the common cause for febrile thrombocytopenia and in study conducted by Nair et al, septicemia was the common cause and in a recent study in North India dengue was the common cause for febrile thrombocytopenia as shown in Table 17.[7-10]

Table 17: Comparison of etiology.

Diagnosis	Srinivas study[7] (%)	Prithviraj study[8] (%)	Nair study[9] (%)	Saini study[10] (%)	Present study (%)
Dengue	14	15	14	47	68.3
Malaria	41	54	09	20	2.1
Septicemia	19	4	27	10.5	7.31
Enteric Fever	24	6	15	1	1.07
Leptospirosis	0	0	0	0.5	1.29
Ricketsial	-	-	-	-	0.86
HIV + Dengue	-	-	-	-	0.21
Malaria + Dengue					0.21
Typhoid + Dengue					0.43
Others	2	21	18	16.5	18.06

Comparison of cause of fever with thrombocytopenia

In this study dengue was the most common cause for febrile thrombocytopenia and in 84 patients cause of febrile thrombocytopenia could not be identified. The most common presenting complaint in this study was fever with headache and the most common bleeding manifestation was petechiaes similar to study by Srinivas et al, (63%), there was no life threatening bleeding in this study.[7] Authors correlated Co morbidities and platelet count and found no significant association. There was no association between platelets group with age or Hess test in this study. 31.39% of patients were having platelets count between 20000 to 50000/mm^3.

In this study 132 patients had deranged LFT and 45 had deranged RFT parameters, 35 patients required ICU care and 2 patients underwent hemodialysis and 12 patient had mechanical ventilator support. Hepatic complications were most common in this study. 2 patients had ARDS and 1 patient had meningitis in this study. 94 patients had features suggestive of polyserosis, 56 had pleural effusion and 89 had ascites in this study.

Total 135 patients were transfused platelets in this study and there was no relationship between platelet transfusion and outcome in this study. Maximum platelets were transfused in patients with platelet count < 20000 /mm^{3}There were 9 deaths in this study and there was no statistical relationship between platelet count at admission and death in this study. Most common cause of mortality was dengue in this study.

CONCLUSION

Febrile thrombocytopenia is one of the most commonly encountered disease by a physician especially during monsoon and peri- monsoon period, the varied clinical presentation from a self-limiting disease to life threatening condition with varied etiology and management cause a lot of burden on the hospital resthisces.

The Incidence and prevalence of the etiology of febrile thrombocytopeniachange seasonally and geographically which contribute to significant morbidity and mortality which also depends on the time of diagnosis, severity of disease, time of initiation of treatment and also monitoring the patients for complications.

There was no relation between platelet count on admission and mortality in this study and also there was no relationship between platelet transfusion and outcome.

Knowing the clinical presentation, etiology, complications and its monitoring can significantly reduce the morbidity and mortality due to febrile thrombocytopenia.

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