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Original Research Article

STUDY OF CLINICAL AND HEMATOLOGICAL PROFILE IN PATIENTS OF ACUTE FEBRILE ILLNESS WITH THROMBOCYTOPENIA

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ABSTRACT

Background: Acute febrile illness with thrombocytopenia poses a diagnostic and therapeutic challenge, as it is inversely related to morbidity and mortality in infectious diseases. This study aims to evaluate the clinical and hematological profile of patients presenting with fever and thrombocytopenia.

Materials and Methods: A prospective observational study was conducted on 350 patients (aged ≥13 years) presenting with fever (>99.9°F) and thrombocytopenia (<150,000 cells/cu.mm). A comprehensive clinical examination and laboratory investigations were performed. Treatment was initiated based on the clinical severity and etiology.

Results: The majority of cases (34.8%) were aged 13–20 years, with male predominance (58%). Dengue (44.2%) was the leading cause, followed by typhoid (30%) and sepsis (17.1%). Dengue was the leading cause of nausea, headache, rash, and bleeding tendencies, while typhoid and sepsis contributed to abdominal pain, diarrhea, and impaired consciousness. Most of the patients had mild platelet counts deficiency (50%). The malaria was associated with highest WBC and neutrophil levels on Day 1, while typhoid showed highest hemoglobin and hematocrit levels throughout the observation period. Dengue exhibited lowest WBC and neutrophil counts, while sepsis had persistently low hematocrit and hemoglobin values. Complications included hypotension (22.8%), arrhythmia (17%), acute kidney injury (16%), and metabolic acidosis (8.6%). The overall recovery rate was 93.3%, with a mortality rate of 6.5%, primarily due to sepsis (25%). Platelet transfusion was required in 40 patients (11.4%).

Conclusion: Fever with thrombocytopenia remains a significant challenge in tertiary care. Dengue is the most common etiology, but other infections require further study. Early diagnosis and timely intervention are crucial in reducing morbidity and mortality.

Keywords: Acute febrile illness; Thrombocytopenia; Hematological profile; Etiology; Dengue; Mortality; Platelet transfusion.

INTRODUCTION

Acute febrile illness (AFI) is defined as a fever lasting at least two days with a body temperature of 38°C or above. It is a common clinical presentation in tropical and subtropical regions, often posing diagnostic challenges due to the overlapping manifestations of infectious etiologies. It is characterised by a rapid onset fever, with associated symptoms such as a headache, chills, myalgia, and/or arthralgia.[1] Among the various hematological abnormalities associated with AFI, thrombocytopenia is a frequent finding that can range from mild to life-threatening. Thrombocytopenia, defined as a platelet count of <150,000/mm^3, may result from decreased platelet production, increased destruction, or sequestration,

and its presence in febrile patients necessitates a systematic evaluation to identify the underlying cause and assess the risk of complications such as bleeding and organ dysfunction.[1-3]

Infections such as dengue, malaria, leptospirosis, rickettsial diseases, typhoid/paratyphoid, chikungunya, and viral infections contribute significantly to AFI-associated thrombocytopenia.[1,4] Dengue fever, in particular, has emerged as a major public health concern, with thrombocytopenia being a hallmark laboratory finding, often accompanied by plasma leakage and hemorrhagic manifestations.[5] Malaria, caused by Plasmodium vivax and Plasmodium falciparum, can also lead to thrombocytopenia due to immune-mediated destruction and sequestration in the spleen.6 Similarly, bacterial infections such as typhoid fever and sepsis contribute to platelet consumption through disseminated intravascular coagulation (DIC) and immune-mediated mechanisms.[1,4]

The severity of thrombocytopenia and its clinical implications vary widely among different etiologies. While mild thrombocytopenia is often self-limiting, severe thrombocytopenia (<50,000/mm³) increases the risk of spontaneous bleeding, petechiae, and organ dysfunction, necessitating careful monitoring and targeted interventions.[1,7] Identifying the pattern of hematological changes in AFI patients with thrombocytopenia can help in early diagnosis, appropriate management, and prognosis assessment. This prospective observational study was carried out with the aim to evaluate clinical and hematological profile in patients having fever with thrombocytopenia and its various causes.

MATERIALS AND METHODS

A prospective observational study was conducted at a tertiary care hospital over a period of 18 months, from July 2022 to January 2024. The study population included 350 patients aged 13 years and above presenting with fever (temperature >99.9°F) and thrombocytopenia (Platelet count <150,000 cells/cu.mm) at the medicine outpatient department (OPD). Patients less than 13 yrs of age, with thrombocytopenia without fever, pregnant female, patient with alcoholic liver disease, diagnosed cases of platelet disorders and dysfunction and patients on drugs causing thrombocytopenia were excluded from the study. Patients who fulfilled the inclusion and exclusion criteria and provided written informed consent were enrolled in the study.

A detailed history was obtained from each patient, focusing on the duration of illness, fever pattern, and associated symptoms. This was followed by a comprehensive clinical examination, including general physical, per abdomen, and systemic examination. All patients underwent laboratory investigations, including routine blood tests such as complete blood count, peripheral smear, liver and kidney function tests, inflammatory markers (CRP, ESR), blood sugar levels, and screening for HIV, HBsAg, and HCV. Urine routine microscopy, urine culture, blood culture, chest X-ray, ultrasonography (USG), ECG, and coagulation profiles (BT, CT, PT-INR, APTT) were also performed. Specific diagnostic tests included Dengue ELISA (IgM Ab, IgG Ab, NS1 Antigen), malaria peripheral smear, Widal titre for typhoid (O and H antigen), Leptospira IgM Ab for leptospirosis, and Weil-Felix test (OXK, OX19, OX2) for scrub typhus. Additional tests such as sputum study, arterial blood gas (ABG) analysis, d-Dimer, and CPK-MB were conducted when indicated.

Treatment- Physician often must balance the need for empirical antibiotic treatment with the patient's clinical condition. When clinically feasible it is best to obtain relevant samples for culture prior to administration of antibiotics. As antibiotic treatment often makes subsequent diagnosis more difficult. Although general dictum is to use the antibiotic with narrow spectrum as possible. Empirical regimen used is somewhat broad spectrum. Once a specific diagnosis is made, this regimen should be narrowed accordingly.

Dengue is categorized into three groups based on severity. Category A includes dengue without warning symptoms, managed on an OPD basis with hydration maintenance, paracetamol for fever every six hours, tepid sponging, and immediate hospital reporting if warning signs develop. Category B includes dengue with warning symptoms or risk factors (infants, elderly >65 years, diabetes, CKD), requiring IPD admission with four-hourly vitals and input-output monitoring. Crystalloids (NS or RL) are administered at 5-7 ml/kg/hr for 2 hours, followed by 3-5 ml/kg/hr for 2 hours. If hematocrit (Hct) is reduced and clinical features improve, IV fluids continue at 3 ml/kg/hr for 4 hours before switching to oral fluids. If Hct increases but clinical improvement is seen, IV fluids are given at 10 ml/kg/hr for 2 hours. Category C involves dengue with plasma leakage, bleeding, or organ dysfunction, requiring ICU admission and frequent Hct monitoring. If Hct increases significantly, a bolus of 10 ml/kg/hr is given for 1 hour, and if no improvement is seen, another bolus at 10 ml/kg/hr for 15 minutes is administered before shifting to colloids like albumin. If Hct decreases with bleeding, PRBC or blood transfusion was required. A sudden fall in hematocrit indicates internal bleeding, necessitating packed RBC or blood transfusion.

Discharge criteria include being afebrile for 24 hours without antipyretics, having a good appetite and clinically improved condition, maintaining adequate urine output, and having a stable hematocrit level. Additionally, the patient must have recovered from shock for at least 48 hours, show no signs of respiratory distress (such as pleural effusion or ascites), and have a platelet count greater than 50,000 cells/µL.

Statistical Analysis: Sample statistics like mean, median and standard deviation were calculated for

Quantitative data. Tests of significance Chi-square test and difference of proportion was applied for categorical data. Mean and standard deviation was compared by Student T test. Statistical significance was set up at $p \leq 0.05$.

RESULTS

A total of 350 patients were enrolled in the study. The majority of the patients were in the age range of 13-20 years (34.8%), followed by 31-40 years (18.3%) with male predominance (58%), as shown in table 1. [Table 1]

Dengue (44.2%) was the leading cause, followed by typhoid (30%) and sepsis (17.1%) as depicted in figure 1.

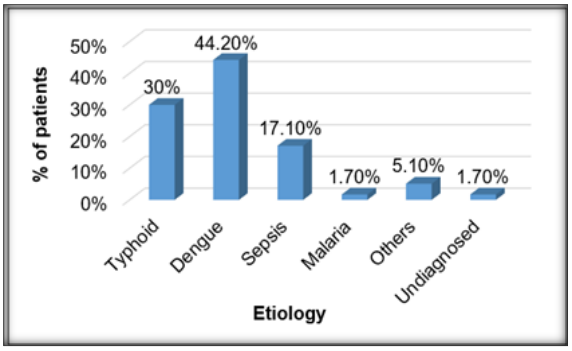

Figure 1: Etiology

Table 2 presents the clinical features observed across various etiologies, including malaria, dengue, sepsis, typhoid, other infections, and undiagnosed cases. Dengue was the most common cause of symptoms like nausea (100), headache (81), rash (78), and bleeding tendencies (40), while typhoid and sepsis also contributed significantly to abdominal pain, diarrhea, and impaired consciousness. Malaria was less frequent but associated with splenomegaly, whereas undiagnosed cases accounted for minimal presentations. [Table 2]

Mild platelet counts (1,00,000-1,50,000 cells/cu mm) deficiency were seen in 50% of the patients (175 cases). Moderate platelet counts (50,000-1,00,000 cells/cu mm) deficiency were seen in 34.8% of patients (122 cases). Severe platelets count (<50,000 cells/cu mm) deficiency were seen in 15.1% of cases (53%).

Table 3 presents the hematological profile across various diseases. The malaria was associated with the highest WBC and neutrophil levels on Day 1, while typhoid showed the highest hemoglobin and hematocrit levels throughout the observation period. Dengue exhibited the lowest WBC and neutrophil counts, while sepsis had persistently low hematocrit and hemoglobin values. [Table 3]

The most common complications were hypotension (22.8%) followed by arrhythmia (17%) acute kidney injury (16%), and metabolic acidosis (8.6%) as depicted in figure 2. [Figure 2]

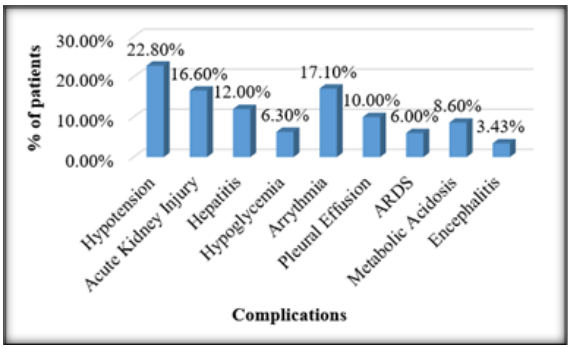

Figure 2: Complications

Out of 350 patients, 327 patients (93.3%) were recovered, and mortality were seen in 23 patients (6.5%). The overall recovery rate was 93.3%, with a mortality rate of 6.5%, primarily due to sepsis (25%), [Figure 3]

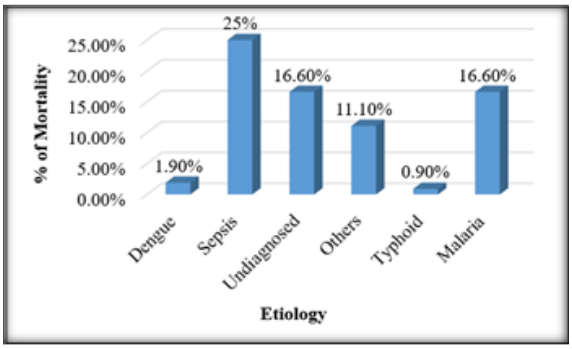

Figure 3: Mortality related to etiology

Out of 350 patients, 40 patients required platelet transfusion. Platelet transfusion was most commonly required in sepsis (25%) and malaria (33.3%), followed by dengue (12.9%) as shown in table 4.

Table 1: Demographic data of patients

Demographic data		No. of patients	Percentage
Age range (years)	13-20	122	34.8
	21-30	30	8.6
	31-40	64	18.3
	41-50	62	17.7
	51-60	44	12.5
	>60	28	8.0
Sex	Males	203	58.0
	Females	147	42.0

Table 2: Clinical features of various etiologies

Clinical features (Present)	Etiologies						Total
	Malaria	Dengue	Sepsis	Typhoid	Others	Undiagnosed	
Nausea	04	100	24	63	14	02	207
Headache	03	81	18	55	08	02	167
Rash	02	78	18	26	08	02	134
Abdominal pain	04	55	24	30	07	04	124
Diarrhoea	02	12	06	20	08	02	50
Bleeding tendencies	01	40	10	11	07	02	71
Pallor	03	51	36	30	09	02	131
Torniquet Test	02	65	14	30	09	02	122
Petechie/Purpura	01	53	12	22	04	01	93
Splenomegaly	04	15	15	11	11	01	57
Hepatomegaly	02	08	08	07	06	01	32
Ascitis	01	31	04	10	00	01	47
Impaired consciousness	01	14	10	07	00	00	32

Table 3: Hematological profile in various diseases

Hematological profile		Etiologies					
		Malaria	Dengue	Sepsis	Typhoid	Others	Undiagnosed
WBC	Day 1	9133.0±8544.7	4369.2±1842.7	4265.2±1942.7	6781.2±3788.1	5671.4±1876.5	4987.1±1987.2
	Day 3	3966.6±1824.7	3871.4±1682.1	3678.2±1567.0	4155.2±1871.0	4671.1±1541.1	3897.1±1432.1
	Day 5	5325.0±2211.3	5720±1451.9	5346 ±1422.1	5345 ±2200.1	4999.1±2100.1	5132.1±1321.1
Mean neutrophils	Day 1	77.6±13.2	66.4±9.2	68.9±8.9	65.27±16.69	70.8±11.1	68.9±9.8
	Day 3	62.4±15.5	47.3±10.9	49.4±9.0	49.1±10.1	58.1±9.8	56.7±8.9
	Day 5	63.2±9.7	54.9±14.9	52.1±10.1	56.1±10.1	60.1±9.1	57.7±10.1
Lymphocytes	Day 1	18.3±11.5	24.6±9.2	23.2±8.7	27.07±15.67	26.5±11.2	23.1±8.9
	Day 3	28.1±12.4	40.0±9.4	30.2±8.9	43.2±7.6	41.2±8.7	30.7±7.1
	Day 5	24.5±9.4	31.3±10.7	29.1±9.1	34.1±9.9	34.9±9.1	28.7±8.8
Hemoglobin	Day 1	9.4±1.0	12.9±2.3	10.12±2.1	13.37 ± 1.48	12.12±2.2	11.4±2.4
	Day 3	10.3±2.4	11.3±2.0	10.3±2.9	13.4±2.3	12.1±2.9	11.4±2.3
	Day 5	9.5±1.5	11.5±1.4	10.11±1.3	13.9±3.2	12.1±2.2	11.9±3.2
Hematocrit	Day 1	26.6±4.8	39.8±6.2	25.1±4.1	40.70 ± 4.36	39.1±4.4	37.1±3.9
	Day 3	29.2±7.0	35.3±7.1	31.1±6.9	36.5±7.8	33.4±6.9	32.4±5.9
	Day 5	28.3±6.6	35.2±5.4	30.1±4.9	36.3±5.2	32.21±4.9	30.12±3.9

Table 4: Platelet transfusion

Etiology	Platelet Transfusion	
	Yes	No
Dengue	20 (12.9%)	135 (87.09%)
Sepsis	15 (25%)	45 (75.0%)
Malaria	02 (33.3%)	04 (66.6%)
Others	02 (11.1%)	16 (88.8%)
Undiagnosed	01 (16.6%)	05 (83.3%)

DISCUSSION

Patients with acute febrile illnesses in a tropical country like India usually have infectious etiology and may have associated thrombocytopenia. Present study showed higher incidence of dengue 44.2% followed by Typhoid 30%, sepsis 17.1%, Others 5.1% (Pulmonary Tuberculosis, Viral hepatitis, Leptospira, Scrub Typhus, Rickettsia, Leukaemia), 1.7% Malaria and 1.7% remain undiagnosed. In Dash et al,[8] study more number of cases were recorded in the age group 30-40 years (35%) whereas in current study more cases were seen in the age group of 13-20 years (34.8%). They found most common cause was malaria (38%) followed by dengue, sepsis, typhoid, viral hepatitis, alcoholic liver disease, unknown bite, which was not so in our study as mentioned above. In Kumar et al,[9] study most common cause was malaria (62 cases), followed by sepsis (60 cases), dengue (30 cases), viral infection (12 cases), enteric fever (7 cases), pulmonary tuberculosis (2 cases); which was contradictory to our study. This difference from other studies might be explainable due to geographical and climatic differences among the regions where the studies were conducted.

Dengue and typhoid were the more frequent causes (74.2%) due to the higher prevalence of these infections during rainy and early winter season as well as their endemicity. 70% of Dengue and typhoid were reported during the month of September to December 2023 (rainy and early winter season) in our study. Sepsis was the third common cause in the study. Most common clinical symptom among the patients included in our study was nausea-vomiting (59.1%), headache (47.7%), rash (38.2 %) and abdominal pain (35.4.4%) apart from others. This finding correlated with the Malaysian study by Tong et al10 while contradicts the Indian study by Kumar AS.[11] The patients in dengue group more frequently ($p < 0.05$) had rash, bleeding tendencies, tourniquet

test positivity, ascitis and respiratory abnormalities while malaria patients ($p<0.05$) presented more frequently with abdominal pain, diarrhoea, pallor, icterus, hepatomegaly and splenomegaly.

In dengue patients there was a gradual fall in the mean WBC count and platelet count till day 3 and started rising thereafter, while in malaria there was initial rise in WBC count on 2nd day which gradually settled to normal by 5th day. Malaria patients had significantly low haemoglobin and hematocrit values as compared to their dengue counterparts that can be explained by hemolysis in malaria. Thrombocytopenia was the most marked finding in both dengue and malaria but there was a continuous fall in platelet count till day 3 in dengue patients and rise thereafter while in malaria platelet fall was noticed early on 2nd day of fever which gradually recovered

Duration of illness and stay in hospital, both were higher among malaria group as compared to their dengue counterparts. This is similar to a study done by Bhatnagar MK et al.[12] The changes observed in typhoid can be as a result of hemophagocytosis, which is one of the major means of evasion by the causative agent, Salmonella typhi patients infected with typhoid fever.[13] There was an observed decrease in hematocrit, hemoglobin and platelet in typhoid fever patients. Reduction in the levels of hematocrit and WBC can be as a result of metabolic process in Salmonella which is common in most bacteria, and this causes the release of toxins on the bone marrow which serves as the main site of myelopoiesis. The invasion of organs affected during hematopoiesis such as lymph nodes, bone marrow, spleen, tonsils can be the main reason for the reduction in the hematological parameters and this drastically lowers the rate of hematopoiesis.[14] In most Patients, Hemoglobin is normal in the initial stages but drops with progressing illness. Studies report anemia in 34-42.9% of cases, with severe anemia being rare unless complications like intestinal hemorrhage or hemolysis occur.[15,16]

The observed changes in typhoid fever were anemia, bone marrow suppression, and hemaphagocytosis. These factors are major mechanisms in the production of hematological changes. Some hematological parameters have been affected due to typhoid fever as this illness affects several body systems including the bone marrow and this can be the cause of lowered neutrophil levels, packed cell volume and platelet count. The result obtained in this work is in agreement with those of Anusuya et al,[17] and Okafor et al,[18] in which haematological alterations due to typhoid fever were evaluated. These changes may be attributed to suppression of bone marrow activity and haemophagocytosis which are the major attacking mechanism of Salmonella typhi in typhoid patients.

CONCLUSION

Fever with thrombocytopenia is a challenging condition in tertiary care, with dengue being a major cause. Other infections and non-hematologic conditions can also lead to thrombocytopenia. Thrombocytopenia is a diagnosis, not a disease, requiring comprehensive clinical and laboratory assessment. A thorough evaluation, including laboratory tests and detailed history, is essential for identifying the underlying cause. Timely intervention and early diagnosis can help reduce mortality, morbidity, and severe complications. Proper management leads to better patient outcomes.

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