ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 10 | October - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"OBSERVATIONAL STUDY OF FEVER AND THROMBOCYTOPENIA WITH SPECIAL REFERENCE TO COMPLICATIONS AND OUTCOME IN PATIENTS ADMITTED TO A TERTIARY CARE HOSPITAL IN BALLARI, INDIA"

General Medicine

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ABSTRACT

Background: Detection of thrombocytopenia associated with fever helps to narrow differential diagnosis and management of fever. It also helps to know the various complications of thrombocytopenia and its management and outcome of the patient. Infection is a common cause of thrombocytopenia. **Methods:** 100 patients aged > 16 years with fever and thrombocytopenia seen between November 2018 to October 2020, in a medical college hospital, Vijayanagar Institute of medical sciences(VIMS), Ballari, were included for this study. IRB approval was taken before the collection of data for the study. **Results:** Infection was the commonest cause of thrombocytopenia and dengue was the commonest infection. Bleeding manifestations were seen in 12 % of patients. Petechiae/purpura as the commonest bleeding manifestation followed by gum bleeding. Good recovery was noted in 92% while 8% had mortality. 50% of patients with platelet count below 20,000 does not needed platelet transfusion. **Conclusions:** Infections, particularly dengue was the commonest cause of fever with thrombocytopenia. In majority of patients, thrombocytopenia was transient and asymptomatic but in significant number of cases there were bleeding manifestations. Spontaneous bleeding was noted in platelet count of < 20,000/mm3 in majority of patients, petechiae /purpura was seen in platelet count in range of 20,000- 40,000/mm3. On treating the specific cause drastic improvement in platelet count was noted during discharge and further follow-up. Disclosure summary: The authors have no conflicts of interest to disclose that are relevant to this subject matter or materials included in this work

KEYWORDS

Fever, Thrombocytopenia, Infection, Petechiae, Platelets

INTRODUCTION

Pyrexia is from the Greek pyretos meaning fire. Febrile is from the Latin word febris, meaning fever, and archaically known as ague.

As early as the sixth century BC, fever was noted to be a cardinal sign of disease, as Akkadian cuneiform descriptions used a flaming brazier to symbolize both fever and the localization heat that occurs with inflammation (Atkins 1982).(Atkins, 1982)

In the era of Hippocrates, fever was explained with the doctrine of the four humour : blood, phlegm, black bile, and yellow bile. Yellow bile was associated with the element of fire, and thus fever was considered to be caused by an excess of yellow bile. Fever was thought, at the time, to be beneficial sign during infection, because the increased heat or "fire" caused by the excess of yellow bile would cook the infection out of the patient (Atkins 1982, young & brown 1985).

According to Mackowiak et al. ' after over a millennium of clinical investigation, there is not even a generally accepted(clinical) definition of fever' .

The humoral concept of fever was the mainstay of clinical practice until the 17th century, when Harvey discovered that blood circulation through the body. Subsequently, the believe that fever was beneficial changed dramatically, and physicians thought that fever was produced in the body fluid as a result of fermentation and putrefaction or because of friction from increased flow of blood (Atkins 1982).

Fever was then considered to be synonymous with infectious disease as, until the mid- 19 century, most of these diseases were grouped under the generic term of "fever". because patients with fevers were considered to be associated with disease and often death, they were frequently isolated in order to product the community, as a result, fever came to be feared, and thus warranted intervention. Fever is currently treated as 'the origin of, rather than the response to, an illness'.

A growing body of research in immunology and neuro-physiology has led to the recent understanding that fever is generally an adaptive physiology response to some threat. This notion goes against the thinking of the last two centuries that fever was a sinister sign and required intervention to lower or control it.

Fever has many important functions in the healing process:

- Increased mobility of leukocytes.
- Enhanced leukocytes phagocytosis.
- Endotoxin effects decreased.
- Increased proliferation of T cells.

Daniel G. Fahrenheit used human body temperature as a reference point for his temperature scale, defining it to be 96°F in the early 18th century. Later redefinition of his scale to use the boiling point of water as a reference point caused the numerical value for normal body temperature to drift.

Carl Reinhold August Wunderlich (Wunderlich, C. A. (Carl August), n.d.) released his summary of the armpit, or axillary, temperatures of twenty-five thousand people in 1861, and reported the mean to be 37.0 °C (98.6 °F), with a range of 36.25 °C (97.25 °F) to 37.5°C (99.5 °F), reaching its nadir between 2 AM and 8 AM and its zenith between 4 and 9 PM. (Mackowiak & Worden, 1994)

Fever is defined as an elevation of the normal body temperature that above the normal circadian variation as a result of the changes in the thermoregulatory centre, located in the hypothalamus and occurs in conjunction with an increase in hypothalamic set point e.g. 37°c to 39°c.

Thrombocytopenia is defined as platelet count <1,50,000/microliter. This is due to decreased production, increased destruction, increased sequestration in spleen. Of this infection is the most common cause. Fever with thrombocytopenia narrows the differential diagnosis of the clinical entity. Infection like malaria, dengue, leptospirosis, typhoid, HIV, and miliary tuberculosis are some of the common causes of fever with thrombocytopenia.

As a result, employing a structured and systematic approach, while remaining cognizant of the underlying causes of fever with thrombocytopenia, has the potential to expedite the investigative process and facilitate accurate diagnoses. Consequently, there exists a compelling need for comprehensive research to elucidate the etiological factors and associated complications of this condition.

MATERIALS AND METHODS

The present study was done in patients admitted to VIMS, Ballari, over a period of two year. Patients presenting with fever and thrombocytopenia comprised the study population. The primary objective of the current study was to evaluate the various etiological factors and clinical presentations of fever with thrombocytopenia. The secondary objective was to assess the outcomes and complications associated with the same. Ethical clearance was obtained from the Institutional Ethics Committee prior to the start of the study. Written informed consent was taken from all the participants before enrolling them into the study and strict confidentiality over relevant patient information was maintained throughout the study. The study was executed in accordance with the principles of International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.

Considering a mortality rate of 13% based on previous literature by Nair et al, sample size was calculated using the formula $n = 4pq / d^2$ where p=disease prevalence, q=1-p and d=loss to follow-up which was set at 7%. This resulted in a total sample size of 92 which was rounded off to 100 for the sake of easy calculations.

The patient details collected on the case record form were later entered into Microsoft Excel sheet. All the data were analysed using SPSS v20.0. Numerical data were expressed in terms of mean and standard deviation. Categorical data was expressed in terms of frequency (n) and percentage (%). Appropriate statistical tests were applied and any difference was considered statistically significant at $p<0.05$.

Number of patients selected: 100

Inclusion Criteria:

1. Patients age group more than 16 years.
2. Patients with fever. Fever defined as 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.
3. Patients with platelet count less than 150,000/µL.

Exclusion Criteria:

1. Patient presenting with thrombocytopenia without fever
2. Diagnosed case of immune thrombocytopenic purpura.
3. Patient with thrombocytopenia already diagnosed to have haematological disorder/ malignancy or on treatment with chemotherapy and another immunosuppressive agent.
4. Diagnosed cases of platelet disorder and dysfunction
5. Drug induced thrombocytopenia
6. Patients with cirrhosis and chronic liver disease.

Period Of Study:

The current study was a prospective observational study conducted over a period of two years from November 2018 to October 2020 in the Department of General Medicine of VIMS, Ballari.

Study Design: Prospective observational study

All patients admitted in VIMS Ballari, India with fever and thrombocytopenia were evaluated. History was taken regarding duration of fever, occupation and history of travel. Symptoms like fever, headache, nausea, vomiting, abdominal pain, diarrhea, cough, anorexia, myalgia, gum bleeding, hematemesis, conjunctival suffusion, oliguria, haematuria, loss of weight, etc., were noted.

Signs like rashes, signs of dehydration, petechiae, jaundice, lymphadenopathy, hepatomegaly, splenomegaly, anaemia, abdominal tenderness, added sounds in lungs, altered sensorium, etc., were also noted. Investigations which includes complete hemogram, ESR, Liver function tests, routine urinary examination, Renal parameters like blood urea, serum creatinine, serum electrolytes, peripheral smear, X-ray chest, USG abdomen were done on admission.

Other special investigations like peripheral smear for MP, dengue serology, widely study, IgM antibody for leptospirosis, sputum AFB, ELISA for HIV1 and 2, blood culture and urine culture, bone marrow aspiration.

During the hospital stay, all the patients were subjected repeat CBC once in 2 days. The renal function tests were repeated every third day unless the patient developed ARF for whom the tests were done daily. Follow up of all patients regarding treatment and outcome were done during the hospital stay.

The causes of fever with thrombocytopenia are so numerous, a simple workable classification was adopted

1. Viral :Cytomegalovirus, Herpes Simplex virus, HIV, dengue, parvo-B19
2. Bacteria: Gram positive and gram-negative septicaemia, miliary tuberculosis, leptospirosis, typhoid.
3. Protozoal causes: Malaria

Patients were monitored until their discharge or demise, and the data was systematically collected and organized for the study.

RESULTS

Our study encompassed an analysis of clinical symptoms, laboratory profiles, and complications among 100 patients admitted to VIMS Ballari, India, between November 2018 and October 2020, who met the predetermined inclusion criteria.

The most prevalent cause of fever with thrombocytopenia was infectious in nature.

Among infectious conditions, dengue emerged as the predominant cause, accounting for 42% of cases, followed by malaria at 21%, and leptospirosis at 11%. Etiological distribution is given in table 1. The majority of affected individuals fell within the 25 to 35-year age group. Males were notably more affected, with a male-to-female ratio of 2.3:1. Demographic information is tabulated in table 1.

Besides fever, patients commonly reported symptoms such as myalgia (63%) and chills and rigor (62%).Among bleeding manifestations, purpura was the most frequent at 12%, followed by bleeding gums (10%), with gastrointestinal bleeding being less common (3%).

Among the cohort, 38 patients presented with dehydration upon admission, of which 11 patients exhibited hypotension during admission. Signs and symptoms are elucidated in table 1.

Table 1 : Demographics And Patient Characteristics

Characteristics	No. Of Patients	Percentage (%)
AGE		
16-25	22	22
26-35	38	38
35-45	32	32
>45	8	8
SEX		
FEMALE	70	70
MALE	30	30
CAUSE OF FEVER WITH THROMBOCYTOPENIA		
DENGUE	42	42
MALARIA	21	21
LEPTOSPIROSIS	11	11
TYPHOID	8	8
SEPTICEMIA	7	7
HIV	4	4
UNSPECIFIED	5	5
MORTALITY		
CURED	92	92
DEATH	8	8
SYMPTOMS		
FEVER	100	100
CHIILS AND RIGOR	62	62
MYALGIA	63	63
ABDOMINAL PAIN /VOMITING	28	28
COUGH	8	8
BREATHLESSNESS	25	25
BLEEDING GUMS	10	10
RASHES	12	12
GI BLEEDING	3	3
CONJUCTIVAL SUFFUSION	12	12
LOSS OF WEIGHT	9	9
ALTERED SENSORIUM	12	12
SIGNS		

DEHYDRATION	38	38
PALLOR	12	12
JAUNDICE	10	10
HYPOTENSION	11	11
HEPATOMEGALY	10	10
SPLENOMEGALY	9	9
PLEURAL EFFUSION	9	9
HEMMORHAGIC FUNDUS	4	4

Assessment of blood urea nitrogen and serum creatinine levels revealed elevated renal parameters in 12 patients. Notably, 8 of these patients demonstrated improvement in renal function through hydration alone, while 4 patients necessitated nephrology consultation and dialysis.

TABLE 2.1: LABORATORY INVESTIGATIONS AND IMAGING		
CHARACTERISTICS	NO. OF PATIENTS	PERCENTAGE (%)
PLATELET COUNT (/µl)		
<1,50,000	100	100
>40,000	60	60
20,000-40,000	17	17
<20,000	23	23
RENAL FUNCTION		
BLOOD UREA (mg/dl)		
<40	88	88
40-60	5	5
60-100	2	2
>100	5	5
SERUM CREATININE(mg/dl)		
0.5-1.2	50	50
1.2 – 1.5	30	30
>1.5	20	20
ULTRASOUND ABDOMEN		
Hepatomegaly	10	10
Splenomegaly	8	8
Hepatosplenomegaly	2	2
Free fluid	4	4
Thickened Gallbladder	4	4
Other	2	2
Normal ultrasound	74	74
X RAY CHEST PA VIEW		
BILATERAL PLEURAL EFFUSION	7	7
CONSOLIDATION	1	1
ARDS	2	2
MILIARY TB	2	2
NORMAL FINDING	88	88

13 patients exhibited elevated liver function test results. Among these, 6 patients had bilirubin levels exceeding 5.0mg/dl, and 3 of them succumbed to the condition. The mean serum bilirubin was 2.14 mg/dl. Mean levels for haematocrit and haemoglobin was 32.05 and 11.8 gm%.

TABLE 2.2: LABORATORY INVESTIGATIONS AND IMAGING		
CHARACTERISTICS	MEAN	RANGE
LIVER FUNCTION TEST		
Serum Bilirubin (mg/dl)	2.14	0.8-18.0
SGOT(U/L)	53.10	21-360
SGPT(U/L)	57.54	23-336
ALP(IU/L)	82.53	54-179
HEMATOCRIT	32.05	21-55
HEMOGLOBIN (gm%)	11.8	5.5-14.4

Among the 100 patients with thrombocytopenia (platelet count <150,000/µl), 60 had platelet counts exceeding 40,000/µl, while 17 fell in the range of 20,000/µl to 40,000/µl.

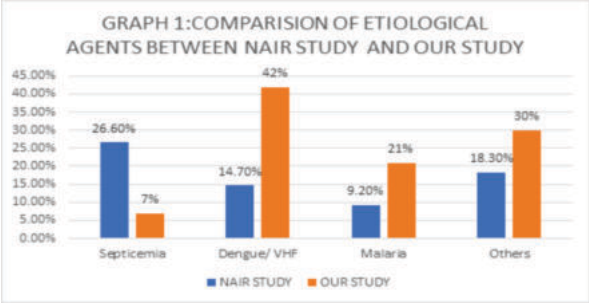
A subset of 23 patients exhibited platelet counts below 20,000/µl. Among the 17 patients with platelet counts between 20,000/µl and 40,000/µl, 15 demonstrated improvement without requiring blood transfusion, whereas only 2 needed such intervention.

Among the 23 patients with platelet counts below 20,000/µl, 12 showed improvement without platelet transfusion, while 11 required blood transfusion. Of these 11 patients, 5 showed improvement with fresh frozen plasma (FFP) alone, while 6 necessitated platelet transfusion as shown in the table 3.

Table 3: Requirement Of Blood Transfusion For Clinical Improvement			
PLATELET COUNT (/ µL)	NO. OF CASES	NO. OF CASES IMPROVED WITHOUT BLOOD TRANSFUSION	NO. OF CASES IMPROVED AFTER BLOOD TRANSFUSION
40,000-1,50,000	60	60	0
20,000-40,000	17	15	2
<20,000	23	12	11

Despite appropriate treatment, 8 patients in the study cohort ultimately died due to complications associated with their underlying diseases. The overall mortality rate for this study stood at 8%.

A similar type of study conducted in India by Nair Ps, Jain A at St. Stephen's hospital, New Delhi, for period of one and half year. A total study of 109 cases were studied with same criteria as in our study(Saini et al., 2018).



In this study, septicaemia emerged as the leading cause of fever with thrombocytopenia, accounting for 29% of cases, followed by enteric fever, dengue, and malaria.

In our study, we observed that Infection was the most common cause of fever with thrombocytopenia, with dengue being the predominant infectious cause. The next frequently encountered cause was malaria, with a higher prevalence of P. vivax infections.Petechiae was a common bleeding manifestation, and it was observed that not all patients with platelet counts below 20,000 required blood transfusion.

DISCUSSION

Definition Of Fever

According to studies of healthy individuals 18-40 years of age, the mean oral temperature is 36.8°C ± 0.4°Celsius (98.2°± 0.7°F), with low levels at 6am and higher levels at 4-6 pm. The maximal normal oral temperature is 37.2°C (98.9°F) at 6am and 37.7°C (99.9°F) at 4pm;these values define the 99th percentile for healthy individuals. In light of these studies 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 fever(Kasper, 2015).

Pathophysiology Of Fever

A febrile response is a complex physiologic reaction to a particular disease involving number of endocrinological and immunologic systems. Understanding this basic mechanism underlying the phenomenon helps to plan rational approaches for treatment and interventions. A basic elucidation of the pathophysiology of fever is given in the Figure 1.

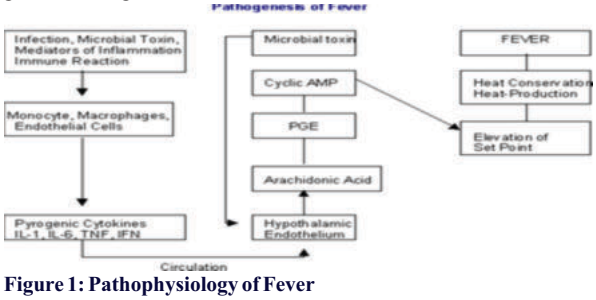


Figure 1: Pathophysiology of Fever

Thrombocytopenia Definition:

The lower limit of the reference interval for platelets is approximately 150×109/L.

The clinical significance of borderline thrombocytopenia (100-150 ×

109/L) is unclear. However, severe thrombocytopenia is usually associated with clear clinical complications(Marder, 2013).

Platelets or **thrombocytes** (from Greek, "clot" "), are small, irregularly shaped clear cell fragments (i.e. cells that do not have nucleus containing DNA), 2–3 μm in diameter, which are derived from fragmentation of precursor megakaryocytes. The average lifespan of a platelet is normally just 5 to 9 days.

- The physiological range for platelets is (150–400) $\times 10^9$ per liter.
- Around 10^{11} platelets are produced each day by an average healthy adult.

Megakaryocyte and platelet production are regulated by thrombopoietin, a hormone usually produced by the liver and kidneys.

Fever With Thrombocytopenia

Fever with thrombocytopenia can be caused by various viral, bacterial, and protozoal infections.

In the context of viral infections, dengue fever, caused by four dengue viruses, is a significant concern, especially in tropical regions like India(Guzman et al., 2010). Dengue can lead to persistent thrombocytopenia due to secondary immune thrombocytopenic purpura, which is characterized by low platelet counts and skin-mucosal bleeding(Rothman & Ennis, 1999). In HIV infection, thrombocytopenia can occur due to immune thrombocytopenic purpura (ITP), which is characterized by low platelet counts and may result in easy bruising and bleeding(Nascimento & Tanaka, 2012).

Thrombotic thrombocytopenic purpura (TTP) is a rare complication of HIV characterized by fever, hemolytic anemia, and thrombocytopenia, requiring immediate treatment.

Kyasanur Forest Disease, Severe Fever with Thrombocytopenia Syndrome, and Heartland Virus are emerging viral hemorrhagic fevers that can cause fever with thrombocytopenia. These infections are associated with high mortality rates and multiorgan failure(McMullan et al., 2012)(Sreenivasan et al., 1986).

Malaria, caused by Plasmodium parasites transmitted through mosquito bites, is a widespread protozoal disease that can lead to fever with thrombocytopenia(Mohanty et al., 1988). The mechanisms of thrombocytopenia in malaria are multifactorial, involving platelet destruction, increased cytokine levels, and sequestration in non-splenic areas(Kreil et al., 2000).

Bacterial infections like septicemia, tuberculosis, leptospirosis, and typhoid can also cause fever with thrombocytopenia (Kahn, 1982)(Clerke et al., 2002)(Edwards et al., 1986). Thrombocytopenia in tuberculosis can occur due to marrow suppression or immune-mediated platelet destruction(Cockcroft et al., 1976).

Scrub typhus, caused by Orientia Tsutsugamushi, is transmitted by mites and can present as fever with thrombocytopenia. Rickettsial infections, such as ehrlichiosis and anaplasmosis, transmitted by ticks, can lead to similar symptoms and require prompt treatment with doxycycline(Adem, 2019)(Tello-Martin et al., 2018) (Satjanadumrong et al., 2019).

Hemophagocytic lymphohistiocytosis (HLH) is a rare but critical syndrome associated with various conditions, including infections. It results from uncontrolled hypercytokinemia due to defects in inflammatory signals. Early treatment is crucial to prevent end-organ failure and death (Janka, 2012).

Research in this field should focus on improving diagnostic methods for these infections, especially in regions where they are endemic, and developing targeted therapies to manage fever with thrombocytopenia, particularly in cases of emerging viral hemorrhagic fevers with high mortality rates.

Investigations For Fever With Thrombocytopenia

In the investigation of patients presenting with fever and thrombocytopenia, a comprehensive workup is essential to determine the underlying cause. This workup includes a complete hemogram, where various parameters like ESR, leukocyte count, and peripheral smear examination can provide valuable insights. A high ESR (>30mm per hour) may suggest conditions such as tuberculosis or malignancy, though it is non-specific. Leucopenia might be an early sign of dengue, while leukocytosis with predominance of neutrophils could indicate septicemia. Rapid spot tests for Plasmodium vivax and Plasmodium falciparum are highly sensitive for diagnosing malaria. The Widal tube method is useful for identifying enteric fever, while IgM ELISA tests for dengue and leptospirosis antibodies are crucial for confirming these infections. Blood cultures should be taken to detect septicemia, and in cases with abnormal renal and liver parameters, conditions such as leptospirosis, malaria, dengue, and septicemia with multi-organ failure should be considered. Platelet counts should be closely monitored, and platelet transfusions are indicated when counts fall below 20,000. Treating the underlying condition is vital for improving platelet counts and preventing complications.

Future research in this field should focus on developing more accurate and rapid diagnostic tests for these infections, especially in regions where they are prevalent. Additionally, studies aimed at improving the understanding of the pathophysiology of fever with thrombocytopenia and identifying novel treatment strategies are essential for better patient management and outcomes.

CONCLUSION

In our study involving 100 patients presenting with fever and thrombocytopenia, we have arrived at a significant conclusion highlighting the formidable challenges encountered in the realm of medical practice. It is evident that fever accompanied by thrombocytopenia often constitutes an occult presentation of common diseases, rather than being associated with rare conditions. Notably, our findings underscore the prevalence of infections as the leading causative factor in fever with thrombocytopenia, with diseases such as dengue, malaria, and leptospirosis manifesting in atypical and concealed forms, thus complicating the diagnostic process. As a result, a heightened level of clinical suspicion is imperative for accurate identification. In addition to routine investigations, our study recommends the inclusion of specific tests such as rapid spot tests, IgM ELISA for dengue, IgM ELISA for leptospirosis antibodies, and the Widal test to facilitate precise diagnosis.

Remarkably, the majority of our patient cohort exhibited thrombocytopenia without any discernible bleeding manifestations. While spontaneous bleeding tended to occur in individuals with platelet counts below 20,000 cells per cubic millimeter, it is noteworthy that a subset of patients did not exhibit bleeding symptoms . Owing to qualitative platelet defects, some patients showed bleeding manifestation with platelet counts as low as 40,000 cells per cubic millimeter. Furthermore, our study suggests that platelet transfusions may not be warranted for all cases with platelet counts below 20,000, unless complicated by sepsis. Importantly, the overall mortality rate observed in patients presenting with fever and thrombocytopenia in our study was found to be 8%. These findings shed light on the intricacies of managing this challenging medical condition and emphasize the need for a nuanced approach in clinical practice.

Limitations

One of the major limitations of this study was the small sample size of 100 patients.

Acknowledgements

The authors acknowledge the contributions of all general medicine physicians who have contributed to the management of this patient.

Contributors

All authors made individual contributions to authorship. All authors reviewed and approved the final draft.

Funding

None associated with this study

Disclosures

The authors have no conflicts of interest to disclose that are relevant to this subject matter or materials included in this work

Informed Patient Consent For Publication

Signed informed consent obtained directly from the patient or their guardians.

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