# Etiological Profile of Patients Presenting with Fever and Thrombocytopenia in a Tertiary Care Hospital, Assam, India

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**ABSTRACT**

**Introduction:** Fever is a very common symptom with which the patients presented in hospital outdoors. The association of fever with thrombocytopenia narrows the differential diagnosis of the clinical entity. Many studies were done to evaluate the common causes of febrile thrombocytopenia in different parts of India but data are lacking in our state. Under this backdrop, this study was undertaken to know the etiology of the patients presenting with febrile thrombocytopenia.

**Material and methods:** The present study was conducted in the Department of Medicine, Gauhati Medical College and Hospital, Guwahati, Assam from 1st June 2017 to 31st May 2018. Inclusion criteria: All adult patients with documented fever more than 38.5ºC and thrombocytopenia. Exclusion criteria: Age less than 12 years and Patient with fever and thrombocytopenia other than infectious etiology. Detailed history taking, physical examination and laboratory tests were done as per need of the patients to find out the etiology of the cases. Data was collected and analysed accordingly.

**Results:** A total of 196 patients of fever with thrombocytopenia were included in the present study. The most common age group of patients was 21-30 years 26.02% followed by 31-40 years 21.22%. Male were 57.14% and females were 42.86%. The most common cause of fever with thrombocytopenia were dengue 44.38%, followed by septicemia 18.63%, malaria 12.24% and enteric fever 8.67% respectively. Further, This study revealed 40.72% cases of Dengue, 50% cases of Septicaemia and 8.34% cases of malaria had bleeding manifestations. It was found that out of 196 cases studied, 6.63% cases expired and 93.37% cases were improved and discharged.

**Conclusion:** The fever associated with thrombocytopenia is a common clinical presentation of disease where infection being the commonest cause. Dengue is the most common cause followed by septicemia, malaria and typhoid. A significant number of cases showed bleeding manifestations consists of simple skin bleed to major life threatening bleeding like gastrointestinal bleed and intra cerebral bleed etc. Hence, early evaluation of cause of febrile thrombocytopenia is very important in respect to prompt management and good outcome.

**Keywords:** Fever, Thrombocytopenia, Bleeding, Etiology, Dengue Fever, Septicemia, Mortality

## INTRODUCTION

Fever has been recognized as the cardinal feature of disease since ancient times as stated by the ancient scholars like Hippocrates.[1] Fever was initially seen as a disease but later recognized as variety of disease entities and a reliable marker of illness.[2] Fever is a very common symptom with which the patients presented in hospitals outdoors. Fever is defined as an elevation of body temperature above the normal circadian range; i.e. an A.M. temperature of >37.2ºC (>98.9ºF) or an P.M temperature of >37.7ºC (>99.9ºF).[3] Thrombocytopenia is defined as platelet count less than 1,50,000/µL. This is due to decreased production, increased destruction (immunogenic and non-immunogenic), and increased sequestrations in spleen. Of these, Infection being the commonest cause of thrombocytopenia.[4] Thrombocytopenia is characterized by bleeding most often from small vessels. This can manifest as petechiae over the skin, hemorrhage from mucosal of gastrointestinal and genitourinary tract and sometimes even dangerous consequences like intra cerebral hemorrhage. Though thrombocytopenia is encountered in various diseases, it is fortunate that potentially fatal bleeding due to thrombocytopenia is rare.[5] The risk of complications like bleeding is inversely proportional to the platelet count. Thus, thrombocytopenia correlates inversely with the mortality and morbidity in various febrile illness and serial monitoring of platelet count has prognostic value. This highlights the importance of thrombocytopenia in various febrile disorders.[6] The association of fever with thrombocytopenia narrows the differential diagnosis of the clinical entity. Septicemia and other infections like dengue, leptospirosis, malaria, typhoid, HIV are the common causes of fever with thrombocytopenia.[7] Therefore, a well organized systemic approach can shorten the list of investigations and easily points out the diagnosis and thus timely treatment of the underlying conditions can be done. Many studies were done to evaluate the common causes of febrile thrombocytopenia in different states of India but data are lacking in our state. Under this backdrop, this study was undertaken to know the etiology of the patients presenting with febrile thrombocytopenia.

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## MATERIAL AND METHODS

The present study was conducted in the Department of Medicine, Gauhati Medical College and Hospital, Guwahati, Assam over a period of 1 year from 1st June 2017 to 31st May 2018. It iwas a hospital based, observational, cross-sectional, descriptive study. Ethical clearance for the study protocol was obtained from ethical committee of Gauhati Medical College, Guwahati. The data for this study was collected by detailed history taking, clinical examination and relevant investigation using a proforma specially designed for this study. Inclusion criteria: All adult patient (age more than 12 years) admitted in Department of Medicine with documented fever more than 38.5ºC and thrombocytopenia (platelet count less than 1,50,000/µL) of infectious etiology. Exclusion criteria: Age less than 12 years and Patient with fever and thrombocytopenia other than infectious etiology like -Immune thrombocytopenic purpura (ITP), Myeloproliferative disease or any hematological malignancy etc. The patients fulfilling the above mentioned criteria were selected for the study and consent was obtained. A detailed clinical history, general examination, systemic examinations and laboratory tests were done as per need of the patients to find out the etiology of the cases. Following laboratory tests were done: 1) Complete hemogram: Thrombocytopenia was defined as mild(platelet count>50,000/µL), moderate (platelet count 20,000-50,000/µL) and severe (platelet count <20,000/µL).[8] 2) Peripheral blood smear: Peripheral blood smear was used for estimation of manual blood counts. Spurious thrombocytopenia was ruled out after careful peripheral smear examinations.3) Bone marrow examination: It was done only in cases where cause of fever was unexplained with routine investigations. 4) Other investigations were done: Liver function test, Serum creatinine, blood glucose, serum electrolytes, prothrombin time /INR, ESR, urine analysis and culture, Blood culture -as and when indicated, CSF analysis, CBNAAT to rule out TB as and when required. 5) Specific microbiological investigations to rule out specific etiology are: Dengue(CDC,2015): NS1 ELISA – NS1 Ag has been detected in the serum of dengue infected person as early as day 1 of appearance of symptoms up to day 18. Ig M (MAC ELISA) for Dengue, IgG ELISA- samples with a positive IgG in the acute phase and a 4 fold rise in IgG titre in the convalescent phase (with at least a 7 day interval between the two samples) is a secondary dengue infection. Malaria- PBS for MP/ Rapid Diagnostic kit test,. Enteric fever- widal test /Rapid diagnostic kit test,. Leptospirosis-IgM ELISA for Leptospira, Scrub typhus- IgM ELISA for Scrub typhus, Japanese Encephalitis (JE) –IgM ELISA for JE in CSF sample, Sputum for AFB and CBNAAT. Radiological investigations done were: Chest X ray done in all cases. Ultrasound of the abdomen and CT scan (Brain) - done only when indicated. All the patients selected for the study were investigated in a systematic manner to find out the etiology. Statistical analysis was performed using GraphPad Software, SanDiego California USA, www.graphpad.com.

## RESULTS

A total of 196 patients of fever with thrombocytopenia were studied and the results and observations were presented in the table-1.

It was observed that the most common age group of patients

| Age groups (years) | No. of cases | Percentage(%) |
|---|---|---|
| 13-20 | 35 | 17.85% |
| 21-30 | 51 | 26.02% |
| 31-40 | 42 | 21.22% |
| 41-50 | 40 | 20.40% |
| 51-60 | 16 | 8.16% |
| 61-70 | 8 | 4.08% |
| >70 | 4 | 2.04% |
| Total | 196 | 100 |

**Table-1:** showing age wise distribution of patients with febrile thrombocytopenia.

| Cli nical features | No. of cases (N= 196) | Percentage (%) |
|---|---|---|
| Fever | 196 | 100% |
| Chills and rigor | 47 | 23.98% |
| Headache | 133 | 67.86% |
| Body ache/myalgia | 101 | 51.53% |
| Retro-orbital pain | 83 | 42.34% |
| Pain abdomen | 58 | 29.56% |
| Loose motion | 47 | 23.98% |
| Jaundice | 49 | 25% |
| Coughand breathlessness | 41 | 20.92% |
| Bleeding manifestations | 45 | 22.96%% |
| Weight loss | 11 | 5.61% |
| Altered sensorium | 13 | 6.63% |

**Table-2:** Showing clinical features of the cases with febrile thrombocytopenia.

| Etiology | No. of caeses | Percentage |
|---|---|---|
| Dengue | 87 | 44.38% |
| Septicaemia | 36 | 18.36% |
| Malaria | 24 | 12.24% |
| P.vivax | 6 | 3.06% |
| P.falcipaum | 14 | 7.14% |
| Mixed | 4 | 2.04% |
| Enteric fever | 17 | 8.67% |
| Disseminated tuberculosis | 2 | 1.02% |
| Undiagnosed cases | 6 | 3.06% |
| Leptospirosis | 4 | 2.04% |
| Hiv | 4 | 2.04% |
| Japanese encephelitis (je) | 3 | 1.53% |
| Malaria + dengue | 4 | 2.04% |
| Hiv +tb | 2 | 1.02% |
| Hepatitis b | 2 | 1.02% |
| Hepb + hiv | 2 | 1.02% |
| Hep c +hiv | 1 | 0.51% |
| Scrub typhus | 1 | 0.51% |
| Mumps | 1 | 0.51% |
| Total | 196 | 100 |

**Table-3:** Showing Etiologies of Patients presenting with febrile thrombocytopenia.

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presenting with febrile thrombocytopenia was 21-30 years (26.02%) followed by 31-40 years(21.22%). The mean age of the patients were found to be 36.01±14.87.

It was seen that majority of patients presenting with febrile thrombocytopenia were male 112 cases (57.14%) and females were 84 cases (42.86%). The male to female ratio was 1.34:1

Table-2 showed the common symptoms associated with patients having febrile thrombocytopenia were headache in 67.86%, followed by body ache in 51.53%, retro-orbital pain 42.3%, pain abdomen 29.5% and bleeding manifestations 22.9% cases.

In this study, we observed that most common cause of fever with thrombocytopenia were dengue fever 44.38% followed by septicemia 18.63%, malaria 12.24% and enteric fever 8.67% respectively (table-3).

| Etiology | no. of caeses n=196 | Bleeding tendencies n=62 | Percentage | $\chi^2$ | p-value |
|---|---|---|---|---|---|
| Dengue | 87 | 35 | 40.22% | 4.656 | <0.05 |
| Septicaemia | 36 | 18 | 50% | 5.878 | <0.05 |
| Malaria | 24 | 2 | 8.34% | 5.692 | <0.05 |
| Enteric fever | 17 | 0 | 0% | 7.086 | <0.05 |
| Disseminated Tuberculosis | 2 | 0 | 0% | 0.041 | >0.05 |
| Undiagnosed cases | 6 | 2 | 33.34% | 0.0082 | >0.05 |
| Leptospirosis | 4 | 3 | 75% | 1.799 | >0.05 |
| HIV | 4 | 0 | 0% | 0.6912 | >0.05 |
| Japanese encephelitis (JE) | 3 | 0 | 0% | 0.3155 | >0.05 |
| Malaria + Dengue | 4 | 2 | 50% | 0.065 | >0.05 |
| HIV +TB | 2 | 0 | 0.% | 0.037 | >0.05 |
| Hepatitis B | 2 | 0 | 0% | 0.037 | >0.05 |
| Hep B + HIV | 2 | 0 | 0% | 0.037 | >0.05 |
| Hep C+ HIV | 1 | 0 | 0% | 0.465 | >0.05 |
| Scrub Typhus | 1 | 0 | 0% | 0.465 | >0.05 |
| Mumps | 1 | 0 | 0% | 0.465 | >0.05 |

**Table-4:** showing distribution of cases with correlation of etiology and bleeding tendencies.

| Outcome | No. of cases | Percentage (%) |
|---|---|---|
| Expired | 13 | 6.63%%% |
| Improved | 183 | 93.37% |
| Total | 196 | 100 |

**Table-5:** Distribution of cases according to outcome of the patients

| Etiology | No. of cases (n=196) | Mortality (n=13) | Percentage (%) | X 2 | P-value |
|---|---|---|---|---|---|
| Septicaemia | 36 | 8 | 61.53% | 14.361 | 0.0002 |
| Malaria (falciparum) | 14 | 1 | 7.62% | 0.006338 | >0.05 |
| Enteric fever | 17 | 1 | 7.62% | 0.01692 | >0.05 |
| HIV | 4 | 2 | 15.38% | 6.282 | 0.0122 |
| Leptospirosis | 4 | 1 | 7.62% | 0.2270 | >0.05 |

**Table-6:** showing distribution of cases according to causes of mortality.

| Diagnosis | Pritviraj et al (2014) n=100 | Nair PS et al (2003) n=109 | Srinivas et al (2009) n=100 | Saini KS et al (2018) n=1217 | Raikar S et al (2013) n=100 | Gondhali et al (2015) n= 100 | Present Study n=196 |
|---|---|---|---|---|---|---|---|
| Place of study | Kohlapur, Maharastra | New Delhi | Davangere Karnataka | Bikaner, Rajasthan | Bhavnagar, Gujrat | Loni, Uttar Pradesh | Guwahati, Asssam |
| Year of study | 2012-2013 | 2001-2002 | 2004-2005 | 2013-2014 | 2012-2013 | 2012-2014 | 2017-2018 |
| Dengue | 15% | 14% | 14% | 47% | 52% | 56% | 44.7% |
| Malaria | 54% | 09% | 41% | 20% | 45% | 15% | 12.24% |
| Septicaemia | 4% | 27% | 19% | 10.5% | 00 | 17% | 18.36% |
| Enteric fever | 6% | 15% | 24% | 1% | 3% | 3% | 8.67% |
| Leptospirosis | 00 | 00 | 00 | 0.5% | 00 | 00 | 2.04% |
| Others | 21% | 18% | 02% | 16.5% | 00 | 9% | 14% |

**Table-7:**

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Table-4 revealed that 40.72% cases of Dengue had bleeding manifestations, 50% cases of Septicaemia and 8.34% cases of malaria had bleeding manifestations. There was no bleeding manifestations seen in Enteric fever, Disseminated tuberculosis, HIV, Japanese encephalitis and Hepatitis B etc. The bleeding manifestations in Dengue, Septicemia and Malaria are statistically significant (P value < 0.05).

In this study, it was found that out of 196 cases studied 6.63% cases expired and 93.37% cases were improved and discharged. The outcome of patients was assessed during hospital stay. No cases were followed up after being discharged from hospital (table-5).

It was observed that Septicemia was the most common cause of mortality, seen in 61.53% cases followed by HIV (15.38%). By applying Chi-Square test, the mortality associated with septicemia and HIV are statistically significant. (P value < 0.05) (table-6).

## DISCUSSION

The present study showed that most common age group of the patients presenting with febrile thrombocytopenia was 21-30 years 26.02% followed by 31-40 years of age group (21.22%). The mean age group was found to be 36.01±14.87. This was almost similar to the study conducted by Gondhali et al who found most common age group was 21-30 yrs (26%).[7] This findings were also comparable to various studies carried out by different authors from time to time like Raikar S et al found 65% cases, in age group of 12-30 years and another study by kumar P. et al found the most common age group was 18-40 years 52%.[10,11] In our study, out of 196 patients, 57.14% were male and 42.86% female, with a sex ratio of 1.34:1. This finding was similar with other studies Gondhali et al found that male to female ratio-1.27:1.[7] and Jacob K et al found that the sex ratio was 1.19:1.[12] The most common symptoms that associated with patients of febrile thrombocytopenia were headache (67%), followed by body ache (51%). This observations were similar to other studies done by other authors like Gondhali et al, observed body ache (92%) and headache (90%) as the most common symptoms and Mohammad F N et al also found headache (52%) was the most common symptoms next to fever.[7,13] In our present study, diagnosis was established in 190 cases (96.9%), out of 196, whereas in 6 cases (3.06%) the cause remain unexplained even after extensive search for the etiology with the help of available investigation modalities. The most common cause was Dengue 44.38%. It was followed by septicemia 18.36%, malaria 12.24% and enteric fever 8.67% respectively.

The three most common causes of fever with thrombocytopenia and it comparison among different studies are summarized in tabular form (Table 7):

Analysis of the above table showed that the findings of our study corresponds to many studies conducted by different authors in other states of India like Gondhali et al in Uttar Pradesh, Raikar S et al in Gujrat and Saini KS et al in Rajasthan as Dengue being the most common cause, but varies with other studies.[7,10,14] This may be due to seasonal variation. Nair PS et al showed Septicaemia as the most common cause in their study in New Delhi but it was 2nd most common cause in our study.[15] The incidence of Malaria in our study was less comparative to other studies. The incidence and prevalence of various infections vary seasonally and geographically. Some infectious diseases occur cyclically in a particular season. A Study conducted during epidemic of a disease shows high incidence of that disease. Therefore, the time and duration of study conducted also affect the study results. Available resources also affect the diagnosis of a disease. Table:4 showed the correlation of etiology and bleeding manifestations. In our study, 40.72% cases of Dengue, 50% cases of septicaemia and 8.34% cases of Malaria had bleeding manifestations. The bleeding manifestation in Dengue, Malaria and septicaemia were statistically significant in our study (P value <0.05). This findings were comparable with Saini KS et al where 55.3% of dengue had bleeding manifestation.[14] But their study showed lesser incidence of bleeding due to septicemia (23.80%) and higher incidence of bleeding due to malaria (27.12%) compare to our study. The present study showed that out of 196 patients, 93.37% had good clinical outcome, whereas 6.63% had expired and septicemia (61.53%) was the most common cause of mortality. This observation was similar to the previous studies. Like, Gondhali et al reported 6% cases of mortality and Septicemia (83%) being most common cause of mortality.[7] Saini KS et al also reported 5% mortality with septicemia being the most common cause.[14]

**Limitation of study:** This was a hospital based study with a small sample size over a period of one year only. Hence, more studies with large sample size and large population based study with long term follow up from this part of the country are welcomed in the future.

## CONCLUSION

The fever associated with thrombocytopenia is a common clinical presentation of disease where infection being the commonest cause. Dengue is the most common cause followed by septicemia, malaria and typhoid. Other less common diseases are leptospirosis, Scrub typhus, disseminated TB, HIV and Hepatitis B infection etc should also be considered and investigated accordingly. Most of the patients with febrile thrombocytopenia don't show bleeding manifestations. But a significant number of cases showed bleeding manifestations consists of simple skin bleed to major life threatening bleeding like gastrointestinal bleed and intra cerebral bleed etc. Early diagnosis and treatment results in good clinical recovery and reduces mortality. Septicemia is the most common cause of mortality and it must be treated promptly and adequately. Hence, early evaluation of cause of febrile thrombocytopenia is very important in respect to prompt management and good outcome.

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