



Clinical assessment of fever with thrombocytopenia - A prospective study

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ABSTRACT

Infection is the commonest cause of thrombocytopenia, thrombocytopenia associated with fever helps to narrow the differential diagnosis and management of fever. It also helps to know the various complications of thrombocytopenia and its management. 100 patients, ages >12 years with fever and thrombocytopenia between 1st September 2012 to 31st August 2014 were included for this study. Infection was the commonest cause of thrombocytopenia and Dengue was the commonest infection. Bleeding manifestations were seen in 15% of patients. 14% of patients had Petechiae/purpura as the commonest bleeding manifestation followed by spontaneous bleeding in 10%. Good recovery was noted in 94% while 6% had mortality. septicemia accounted for 5% of deaths, followed by dengue 1%. Infections, particularly Dengue was the commonest cause of fever with thrombocytopenia. In the majority of patients thrombocytopenia was transient and asymptomatic but in a significant number there were bleeding manifestations

Key words: Infection, Dengue, Septicaemia, Petechiae/purpura, Spontaneous bleeding, Mortality.

INTRODUCTION

Fever has been recognized as a cardinal manifestation of disease since ancient times, as recorded by ancient scholars like Hippocrates.^[1] Seen first as a disease but later recognized as an accompaniment to a variety of disease entities, fever is an easily noted and reliable marker of illness.^[2]

Fever is a pervasive and ubiquitous theme in human myth, art and science. Fever is such a common manifestation of illness that it is not surprising to find accurate descriptions of the febrile patients in early-recorded history.^[3] Most cases of prolonged fevers are instances of well-known diseases manifesting them atypically. The actual pattern of graphic recording of fever is variable that it is not helpful in pointing to specific diagnosis at all times an aggressive diagnostic effort is usually justified because curative or palliative measures can so often brought into use once the diagnosis has been achieved.

Fever 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) would define fever.^[3]

Though thrombocytopenia is encountered in various diseases, it is for sure that potentially fatal bleeding due to thrombocytopenia is rare.^[4]

The causes of thrombocytopenia are impaired platelet production, accelerated platelet destruction or dilution and/or splenic sequestration.^[5] Even though there is no absolute relation between platelet counts and bleeding, Certain broad generalizations can be made, with counts less than 10,000/μL, bleeding is usual and may be severe.^[6]

Thrombocytopenia is characterized by bleeding most often from small vessels. This can manifest as petechiae over the skin, hemorrhages from mucosa of gastrointestinal and genitourinary tract. Intracranial hemorrhage is a dangerous consequence in thrombocytopenic patients.

Thrombocytopenia is defined as platelet count $<1,50,000/\mu\text{L}$. This is due to decreased production, increased destruction (immunogenic and non-immunogenic), and increased sequestration in spleen. Of these infections being the commonest cause of thrombocytopenia.^[8,9]

Infections like dengue, leptospirosis, malaria, typhoid, military TB, HIV, septicemia are some of the common causes of fever with thrombocytopenia. Therefore a well-organized systematic approach that is carried out with an awareness of causes of fever with thrombocytopenia narrows the differential diagnosis of the clinical entity and brings out diagnosis.

Timely recognition and treatment of the underlying condition, platelet transfusions are required to prevent fatal outcomes.

Hence a need for study to know the clinical profile and complications of fever with thrombocytopenia

REVIEW OF LITERATURE

HISTORY OF FEVER:

Depicted in the Sumerian pictographs as flaming brazier, fever was recognized as a cardinal feature of disease.^[10] Sir William Osler stated “Humanity has three great enemies: Fever, famine and war; of these, by far the greatest, by far the most terrible is fever”. Like Osler, physicians since antiquity have viewed fever as an entity worthy of unremitting attention.

Hippocrates mentioned that “Heat is the immortal substance of life endowed with intelligence, hence, heat must also be refrigerated by respiration and kept within bounds if the source or principle of life is to persist; for if refrigeration is not provided, the heat will consume itself” The writing of Hippocrates provided the detailed description of febrile disease.^[11]

Although Galileo in the 16th century and Santori S in the 17th century constructed devices to measure body temperature, an effective thermometer was not developed until beginning of the 18th century by Dutch instrument maker Gariel Daniel Fahrenheit.^[12]

Wunderlich in 1868 clearly established that abnormality of temperature was a cardinal sign of diseases and normality a sign of health.¹ Since then physicians have used fever as a reliable guide to the presence of disease and the response of disease to therapy. It is in the diagnosis of febrile illness that the science and art of medicine come together.^[13]

Celsius, of the early Roman Empire first suggested the possible relationship between fever and the cardinal manifestations of inflammation – heat, swelling, redness and pain.

Carl Reinhold August Wunderlich (1815 –1877), in his book, *Das Verhalten der Eigen warm in Krankheiten* (the course of temperature in diseases) gave $98.6^{\circ}\text{F}(37^{\circ}\text{C})$ its special significance Vis-à-vis the normal temperature. He described the normal diurnal variation of the body temperature.^[13]

He described the normal diurnal variation of the body temperature, established $100.4^{\circ}\text{F}(38^{\circ}\text{C})$ as the upper limit of the normal range and gave the first quantitative definition of fever. Wunderlich is generally regarded as the father of clinical thermometry.^[14]

He also wrote that “Fever can give more certainly than anything else information as to the grade of disease”. Because of his work, fever, which has previously been viewed as a disease, came to be recognized more appropriately as a clinical sign.^[12]

The mercury thermometer had been perfected in Holland in the early 18th century by Gabriel Daniel Fahrenheit. The work “thermometer” surfaced in the literature of Leurechon’s “*Recreation Mathematique*” (1624) which mentioned the use instrument “to test the intensity of fever”.^[12]

The concept of central set-point temperature was introduced by H.T.Hammel who proposed an original neuronal model to explain regulation of a set-point temperature, by preoptic. Heat production responses were shown to regulate near a set-point of 37°C by the respective effector neurons.

In 1961, Pittendrigh enumerated all of the characteristics required to explain temporal organization in living organism. He proposed that internal time keeping is achieved by a self-sustained oscillator(s) with a temperature compensated period that can be entrained by the external environment. These characteristics of circadian temporal organization were described in detail by a group of scientists meeting at the Cold Spring Harbor symposium (1960) on biological clocks.

The term “Circadian” (derived from circa or “about” and dies or “day”) was proposed by Dr. Franz Harberg in the late 1950s to denote these daily cycles.^[15]

In 1948, Kleitmann and Ramsaroop provided some of the first detailed information concerning endogenous and exogenous influences on the diurnal rhythm of core (oral) temperature. In most of their subjects, there was a 12 hour difference between the maximum and minimum observed temperatures.

The current concept of fever physiology is that, host cell-derived molecules induce fever, which usually occurs in the context of an overall inflammatory response directed against pathogenic microbes. The host derived molecules responsible for fever used to be known as endogenous pyrogens, as first demonstrated by Paul Beeson in 1948. He described temperature-elevating effect of a substance obtained from polymorphonuclear leucocytes.

Patrick Murphy and late Barry Wood were the first to obtain a purified form of endogenous pyrogen from rabbit peritoneal exudate cells.

The late Phyllis Bodell described an intracellular form of Endogenous pyrogen (EP) and reported production of EP by both a murine macrophages and human lymphoma cell.

In 1972, Gery and Waksman described the chemical nature of “Lymphocyte-activating factor” which showed striking similarity with endogenous pyrogens.^[16] Kluger and co-workers provided proof that endotoxin-induced fever is mediated by IL-1 B induction of IL-6, suggesting that IL-6 might be the final common pathway for such fever.^[16]

Milton and Wendlandt originally proposed that E-series prostaglandins (PGE) might mediate the febrile response to pyrogens. This consensus of opinion still favors the proposition that PGE₂, the endogenous isoform of PGE, plays an essential role in production.^[17]

Rotondo et al proposed that the PGE₂ involved in fever might be generated peripherally, transported to the Pre Optic/Anterior Hypothalamus (POAH) by the blood stream, and then, being Lipophilic, either cross the BBB at this site or diffuse to the POAH through the Organum Vasculosum Laminae Terminalis (OVLT) to cause the induction of fever.^[17]

HISTORY OF THROMBOCYTES:

In 1877, Osler coined the term thrombocytes or haematoblasts of Deetjen and Dekhuyzen (1901) and elucidated the role of these third corpuscles as fibrin formers in coagulation.

PATHOPHYSIOLOGY OF FEVER

1. Endogenous Regulation

Thermoregulation is closely related to various non-thermal regulatory systems and thus, changes in the body temperature can affect these other systems, just as changes in non-thermal parameters can affect these other systems, just as changes in non-thermal parameters can affect thermoregulation.^[18]

2. Exogenous Pyrogens

The current concept of fever physiology is that host cell – derived molecules induce fever, which usually occurs in context of an overall inflammatory response directed against pathogenic microbes.

Three different cytokines – interleukin-1, (IL-1), Tumor Necrosis Factor (TNF) and Interleukin-6 (IL-6) account for endogenous pyrogen activity, and it is clear that exogenous pyrogens by themselves do not cause fever unless they elicit cytokine release.

Like interferon (IFN), TNF and IL-6, IL-1 is produced by many different (non-leucocytic) cells and acts on many non leucocytic targets, hence these polypeptides are regarded as a special class of substances called “Cytokines”.^[19]

There are many different substances capable of causing fever in human :microorganisms (primary cell wall components), microbial toxins, antigen antibody complexes, activated complement components (C3a, C5a), pyrogenic steroids (Etiocortanalone), Drugs, Polynucleic acids.

Gram negative bacteria possesses two known pyrogens: Lipopolysaccharide (LPS), which is component of the bacterial outer membrane and peptidoglycan, which forms cross link lattice below the outer membrane.

LPS is the most potent stimulus known for TNF production and release. TNF causes fever by affecting brain prostaglandin production. LPS binds to Lipopolysaccharide Binding Protein (LBP) which is present in the normal

human sera and its concentration rises 100-fold during acute phase response. LBP catalyses the binding of LPS to LPS receptor known as CD14, which is present on macrophages and granulocytes. This markedly enhances LPS induced inflammatory cytokine production by cells.

Heat shock proteins (HSP):

One of the most interesting events in the febrile response is the heat shock stress or response. HSP participates in the development and maintenance of the thermotolerant state. Thermotolerance describes the phenomenon by which cells and animals previously exposed to a single intense but sub-lethal conditioning heat stress, become tolerant to a subsequent otherwise lethal heat stress.^[20]

The inducers of Heat Shock Response are: Temperature (Hyperthermia and hypothermia), Ischemia, Hypoxia, Accident stress, endotoxin, cytokines (IL-1 and TNF), chemotherapeutic agents etc.

HSP confers protection against ischemic injury to the kidney, liver, and heart. HSP 70 gene have shown tolerance to both thermal and hypoxic stress.^[20]

Definitions of Febrile Patterns:

The types of febrile patterns have been traditionally grouped according to the definitions listed below. Often, within these groups, specific infectious diseases may occur.^[21]

1. Continuous (sustained):

Fever does not fluctuate more than about (1.5°F) during 24 hours, but at no time touches the normal. eg: Pneumonia, Rickettsial diseases, Typhoid fever central nervous system disorders, Tularemia, and Falciparum (malignant tertian malaria).^[3]

2. Intermittent fever:

When fever is present only for several hours during the day, it is called intermittent fever.

When a paroxysm of intermittent fever occurs daily, the fever is described as Quotidian, when on alternate days, it is tertian, when two days intervene between consecutive attacks, it is quartan.^[3]

Eg: Localized pyrogenic infections and bacterial endocarditis; Malaria (commonly with leukopenia) may present as quotidian (daily spike), tertian (spike every third day), or quartan (spike every fourth day) types.

A double quotidian pattern with two daily spikes occurs sufficiently often to be helpful in salmonella, miliary tuberculosis, double malarial infections, and gonococcal and meningococcal endocarditis.

3. Remittent Fever: Fever with daily fluctuation exceeding 2°C in 24 hours without touching the baseline.

4. Relapsing fever:

Short febrile periods punctuating one or several days of normal temperature. Eg: Pel-Ebstein fever - Hodgkin's disease, brucellosis of the Brucella melitensis type, Rat-bite fever, Dengue fever, Yellow fever, etc.

5. Saddleback (biphasic fever):

With several days of fever, a gap of reduced fever of about 1 day, and then several additional days of fever. This type characterizes dengue and yellow fever, Colorado tick fever. Rift Valley fever and viral infections such as influenza, poliomyelitis, and lymphocytic choriomeningitis.

Fever should be regarded as a reliable clinical sign and with the fever pattern mentioned above, it is possible to suggest a diagnosis within the group of disease and this can lead to specific therapy and ultimate cure.

PLATELETS AND THROMBOPOIESIS

Platelets are small, nucleated cells, they are formed in the bone marrow by megakaryocytes and subsequently released into the vascular compartment where they play an essential role in hemostasis. Platelets are the terminal stage of development of megakaryocyte series.

The most immature is the megakaryoblast which accounts for less than 8% of megakaryocyte population. The megakaryocyte population in total forms less than 1% of Bone marrow cells.

Next stage is promegakaryocyte, these make up 25% of megakaryocyte population. These cells are nucleated and have basophilic cytoplasm.

Next stage is the mature megakaryocytes which range from 30-90 μm in diameter and contain 4-16 nuclear lobes. Platelets appear to be formed by protrusion in to the bone marrow sinusoids of pseudopods of megakaryocyte cytoplasm.

Morphology of Platelets

A mature platelet is 2-4 micrometer in diameter. Volume is $7.06 \pm 4.85 \text{ micro m}^3$.

Thickness is $0.9 \pm 0.3 \mu\text{m}$.

The normal life span is 8-12 days.

In the stored blood life span is 1-2 days.

Platelet turnover is $1.2-1.5 \times 10^{11} / \text{day}$

Once released from the marrow platelets are trapped in the marrow for 36 hours. 60-75% of the circulating platelets are in the blood. The remainder are in the spleen.

Normal values for platelet numbers in peripheral blood vary with the method used for their estimation.

Normal range is 1.5-4.5 lakhs/ μL . Thrombocytopenia may be defined as subnormal.

FUNCTIONS OF PLATELETS

1. Hemostasis:-Following vascular injury, immediate reaction is vasospasm. Next reaction is formation of platelet plug.

Following endothelial injury, platelets come in contact with subendothelial collagen, proteoglycans and vWF in the vessel wall. They exhibit 3 general reactions

a. **Adhesion,**

b. **Secretion and activation.** The activated platelets change shape, put out pseudopodia and discharge their granules.

c. **Aggregation.** The activated platelets stick to one another which is called aggregation.

Aggregation is also fostered by platelet activating factor. Primary platelet plug gets formed which gets reinforced by fibrin to form stable platelet plug.

2. Platelets secrete growth factors which cause vascular endothelial cells, vascular smooth muscle cells and fibroblasts to multiply and grow that helps repair damaged vascular walls. They maintain the capillary integrity. This is evident by the fact that in thrombocytopenia due to any cause endothelium thins out with development of more fenestrations.

The major components of the hemostatic system, which function in concert, are

- (1) Platelets and other formed elements of blood, such as monocytes and red cells;
- (2) Plasma proteins (the coagulation and fibrinolytic factors and inhibitors); and
- (3) The vessel wall itself.

Platelet Plug Formation

On vascular injury, platelets adhere to the site of injury, usually the denuded vascular intimal surface. Platelet adhesion is mediated primarily by von Willebrand factor (vWF), a large multimeric protein present in both plasma and in the extracellular matrix of the subendothelial vessel wall, which serves as the primary "molecular glue," providing sufficient strength to withstand the high levels of shear stress that would tend to detach them with the flow of blood. Platelet adhesion is also facilitated by direct binding to subendothelial collagen through specific platelet membrane collagen receptors.

Platelet adhesion results in subsequent platelet activation and aggregation. This process is enhanced and amplified by humoral mediators in plasma (e.g., epinephrine, thrombin); mediators released from activated platelets (e.g., adenosine diphosphate, serotonin); and vessel wall extracellular matrix constituents that come in contact with adherent platelets (e.g., collagen, vWF). Activated platelets undergo the release reaction, during which they secrete contents that further promote aggregation and inhibit the naturally anticoagulant endothelial cell factors. During platelet aggregation (platelet-platelet interaction), additional platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is anchored and stabilized by the developing fibrin mesh. The platelet glycoprotein (Gp) IIb/IIIa complex is the most abundant receptor on the platelet surface. Platelet activation converts the normally inactive GpIIb/IIIa receptor into an active receptor, enabling binding to fibrinogen and vWF. Because the surface of each platelet has about 50,000 GpIIb/IIIa fibrinogen binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. Since this receptor is the key mediator of platelet aggregation, it has become an effective target for antiplatelet therapy.

Fibrin Clot Formation

Plasma coagulation proteins (clotting factors) normally circulate in plasma in their inactive forms. The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a waterfall or a cascade. Two pathways of blood coagulation have been described in the past: the so-called extrinsic, or tissue factor, pathway and the so called intrinsic, or contact activation, pathway.

Coagulation is normally initiated through tissue factor (TF) exposure and activation through the classic extrinsic pathway, but with critically important amplification through elements of the classic intrinsic pathway. These reactions take place on phospholipid surfaces, usually the activated platelet surface. Coagulation testing in the laboratory can reflect other influences due to the artificial nature of the in vitro systems used.

THROMBOCYTOPENIA

Thrombocytopenia may be defined as subnormal number of platelets in circulating blood, which is a count below the normal limits of 1.5lakhs.

Thus despite the number and diversity of disorders associated with thrombocytopenia,

Thrombocytopenia results from 4 processes.

1. Accelerated platelet destruction
2. Deficient platelet production
3. Abnormal distribution or pooling of platelets within the body.
4. Artifactual Thrombocytopenia

A single platelet count that is lower than normal should always be confirmed by a second count. Thrombocytopenia should also be confirmed by the examination of blood film. The electronic particle counters now widely employed gives accurate results.

PATHOPHYSIOLOGIC CLASSIFICATION OF THROMBOCYTOPENIA

- A. Artifactual Thrombocytopenia
- B. Increased platelet destruction
 - i) Immunologic process
 - ii) Nonimmunologic process
- C. Decreased platelet production
- D. Abnormal platelet pooling.

AIMS AND OBJECTIVES

- 1.To study the **Clinical Presentation and Profile** of Febrile illnesses causing Thrombocytopenia mainly under **Etiological basis**.
- 2.To study the **Complications and Prognosis** of the illnesses.

MATERIALS AND METHODS

The prospective study was conducted in the Department of Medicine, Pravara Rural Hospital, Loni, from 1st September 2012 to 31st August 2014.

- **Sample size(100)** –Randomly 100 patients were selected for the study.

- **Inclusion Criteria**

- a. All the patients more than 12 years of age.
- b. All the patients presenting with the complaints of fever. ($>99.9^{\circ}\text{F}$) with thrombocytopenia. (less than 1,50,000/ μL)

- **Exclusion Criteria**

- a. Patients less than 12 years of age.
- b. Patients having afebrile thrombocytopenia.
- c. Congenital thrombocytopenia.

- **Observational methodology**

The study was approved by the Ethical and Research Committee of Rural Medical College, Loni. During the study period, all the patients presenting with Fever and Thrombocytopenia were screened for eligibility.

Informed Consent was obtained and a Proforma based Study included in Annexure.

The diagnostic work up of patients with fever and thrombocytopenia included battery of investigations including biochemical tests; haemograms; peripheral blood smear etc.

- Once the patients are admitted with fever and those who have thrombocytopenia confirmed by peripheral smear, a careful history was recorded, general physical examination and detailed examination of various systems was done.
- Routine investigations and specific investigations were done as and when indicated.

Procedure

1. Details of history, general physical examination and laboratory and technical investigation reports were noted down from time to time.
2. Once the specific diagnosis was reached, patients were treated for it specifically and symptomatically (Mechanical ventilations, haemodialysis etc.)
3. For bleeding complications platelet transfusions was done if platelet count was $<20,000/\mu\text{L}$

The causes of fever with thrombocytopenia are numerous, a simple workable classification is presented in –

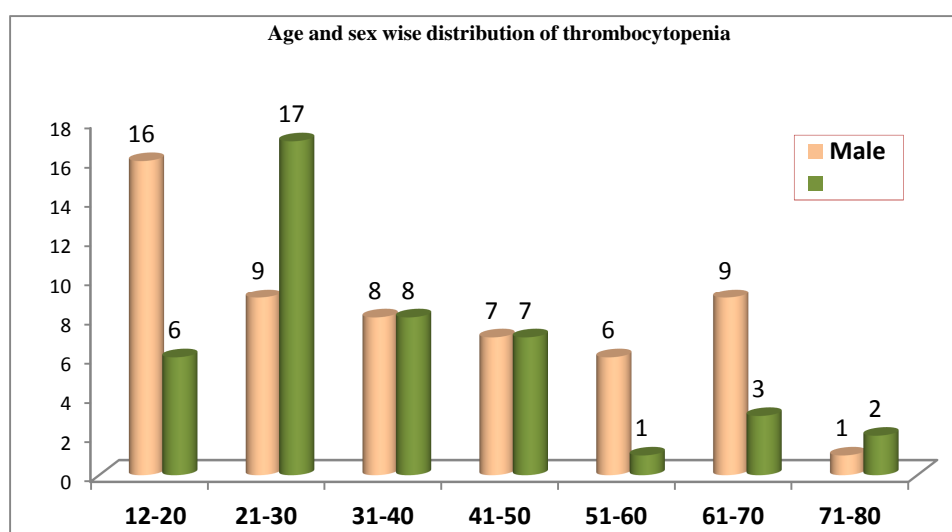
- 1) **Viral causes** : CMV; Dengue; Parvo-B19; HSV, HIV, Hantana etc.
- 2) **Bacterial causes**: Gram +ve and –ve Septicaemia, Miliary Tuberculosis, Leptospirosis, Typhoid etc.
- 3) **Protozoal causes**: Malaria.
- 4) **Others**: Leukemia, lymphoma, etc.

RESULTS

A] CLINICAL FINDINGS

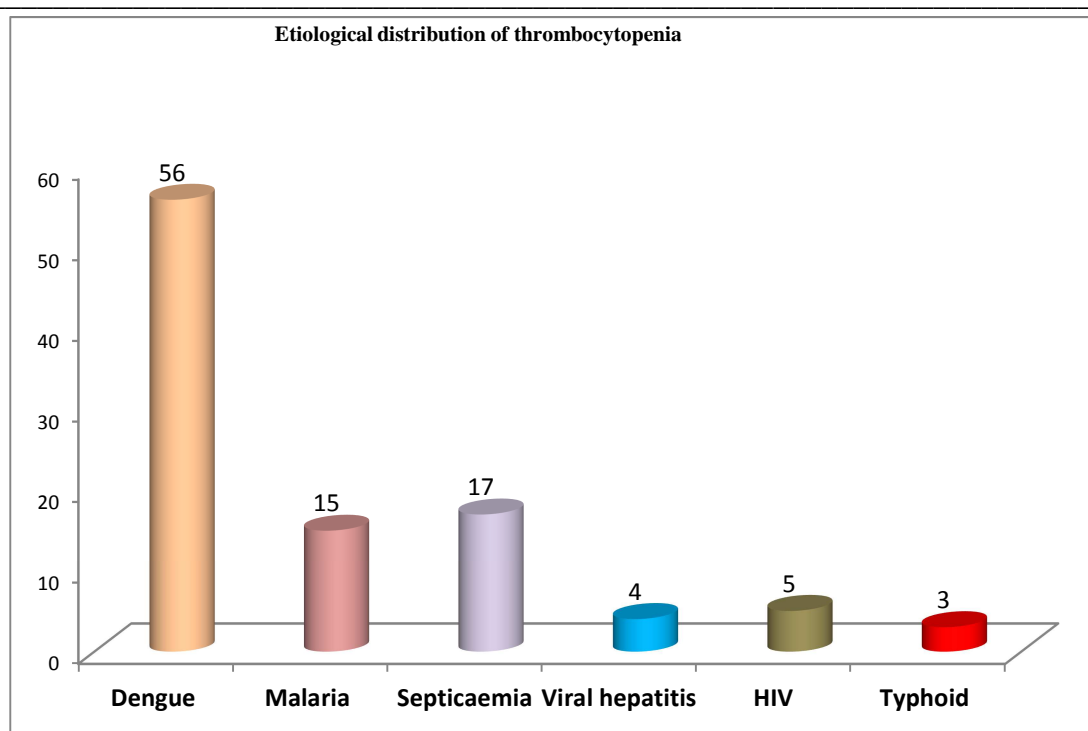
1. Age and Sex Distribution

In our study, a total of 100 cases were selected as per the criteria. Out of the 100 cases 56 were males and 44 were females. The cases included in the study were divided into 7 age groups, 22 in the age group of 12-20 years, 26 in age group of 21-30 years, 16 in age group of 31-40 years, 14 in age group of 41 to 50 years, 7 in age group of 51-60 years, 12 in age group of 61-70 years, 3 in age group of 71-80 years. The maximum cases were found to be in age group of 21-30 years.



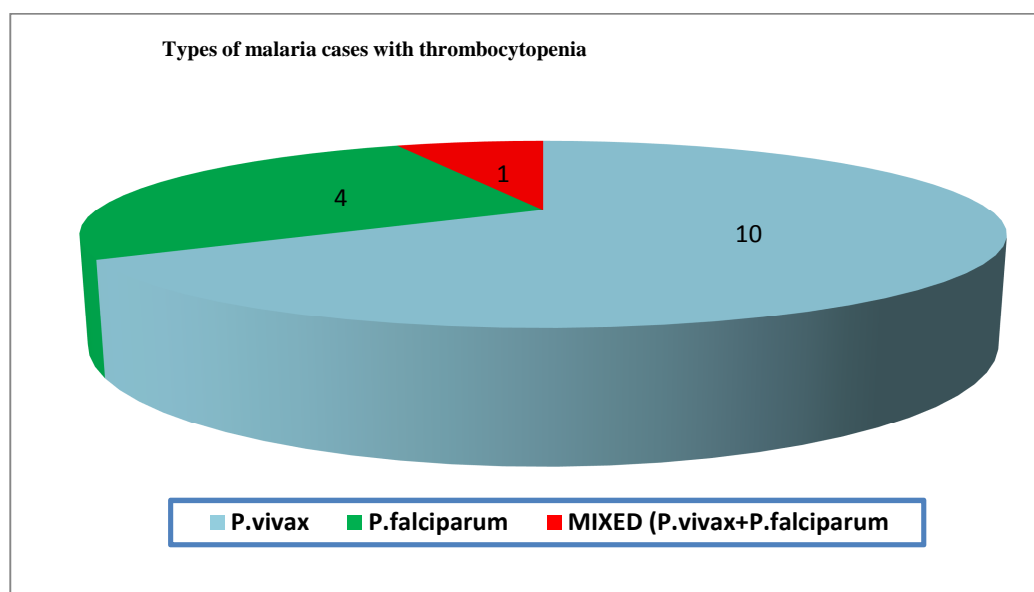
2. Etiological Distribution

In the 100 cases fever with thrombocytopenia, all of them had a definite diagnosis with dengue fever 56 (56%) followed by septicaemia 17 (17%), malaria 15 (15%), HIV 5 (5%), Viral Hepatitis 4 (4%), Typhoid 3 (3%).



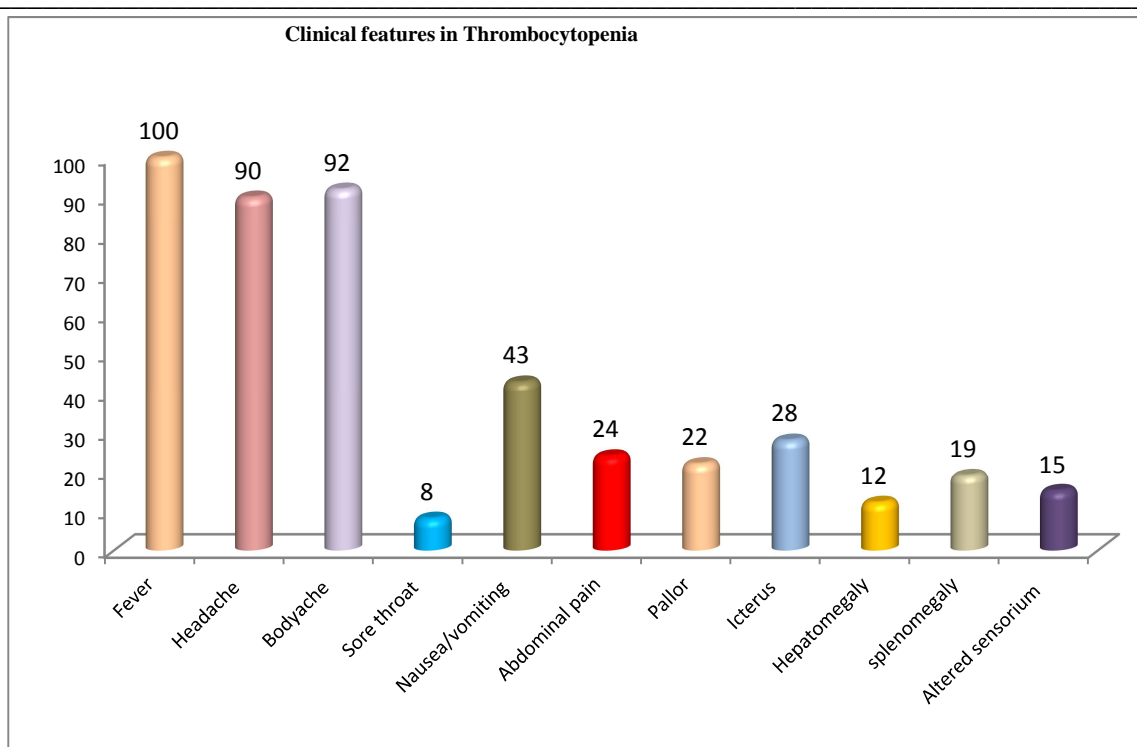
Malaria

In 15 cases of Malaria, *P.vivax* was the commonest Plasmodium species with 10, followed by *P.falciparum* 4, and mix type (*P.vivax* and *P.falciparum*) 1.



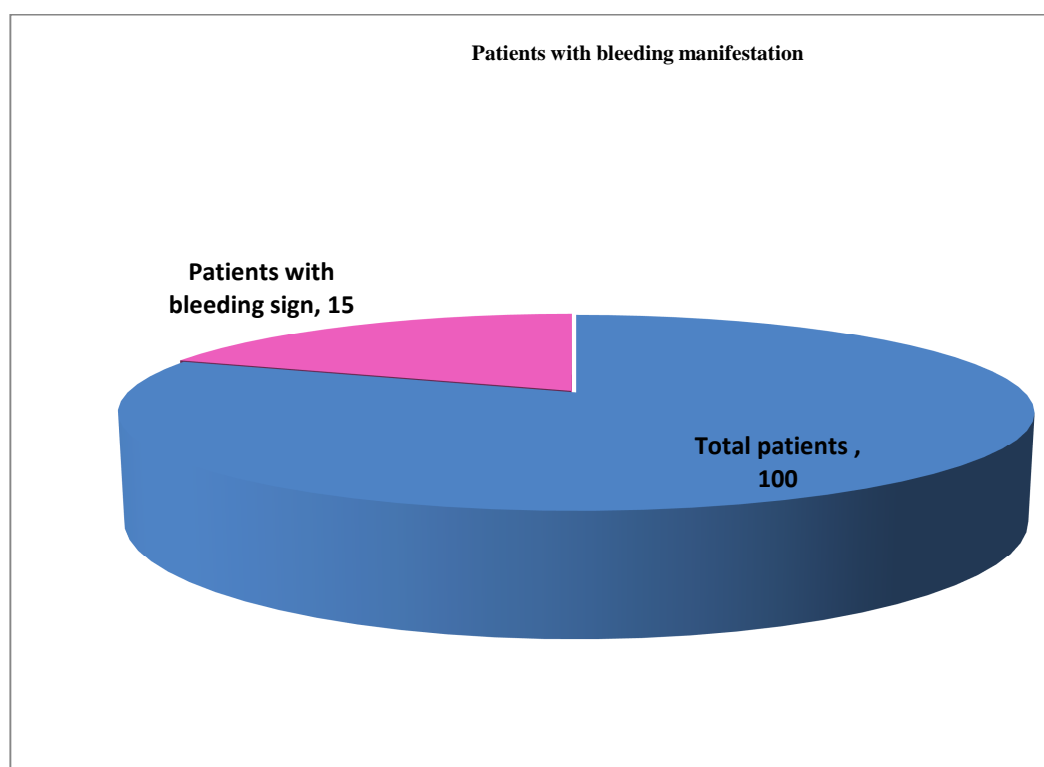
3. Distribution on basis of symptomatic manifestations.

Amongst 100 cases in the study, all of them presented with fever, 90 complained of headache, 92 of bodyache, 8 of sore throat, 43 of nausea, 24 of abdominal pain, 15 had altered sensorium. In general physical findings, 22 cases had pallor, 28 had icterus, 12 had hepatomegaly, 19 had splenomegaly.



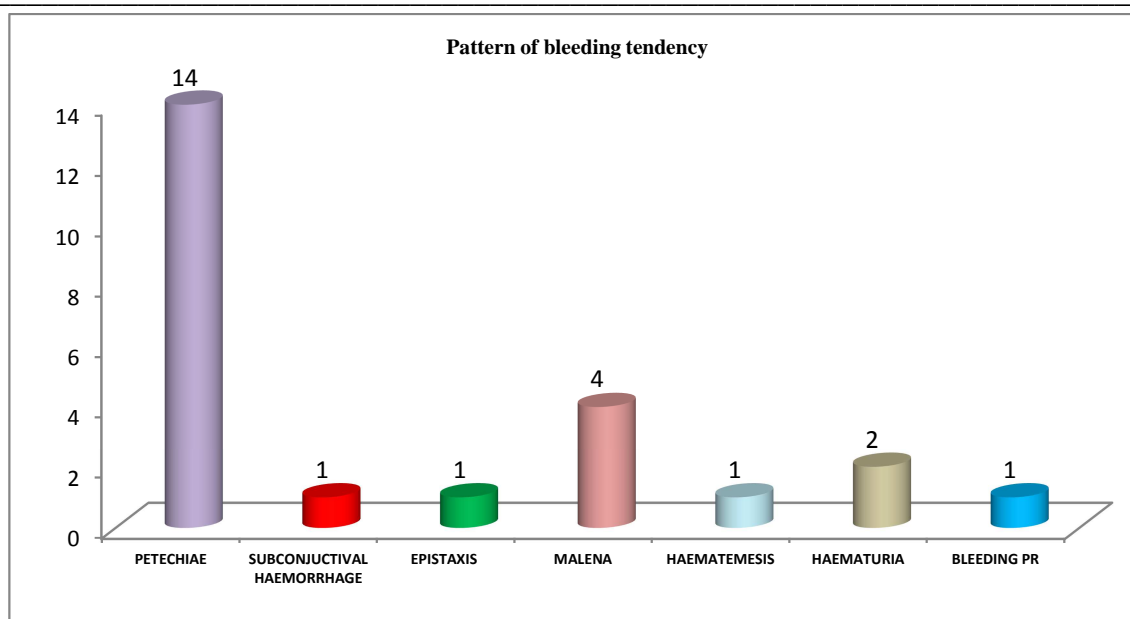
4. Distribution on the basis of Bleeding manifestations

Out of 100 cases of febrile thrombocytopenia 15% patient had signs of bleeding manifestation and the rest 85% did not have any bleeding manifestation.



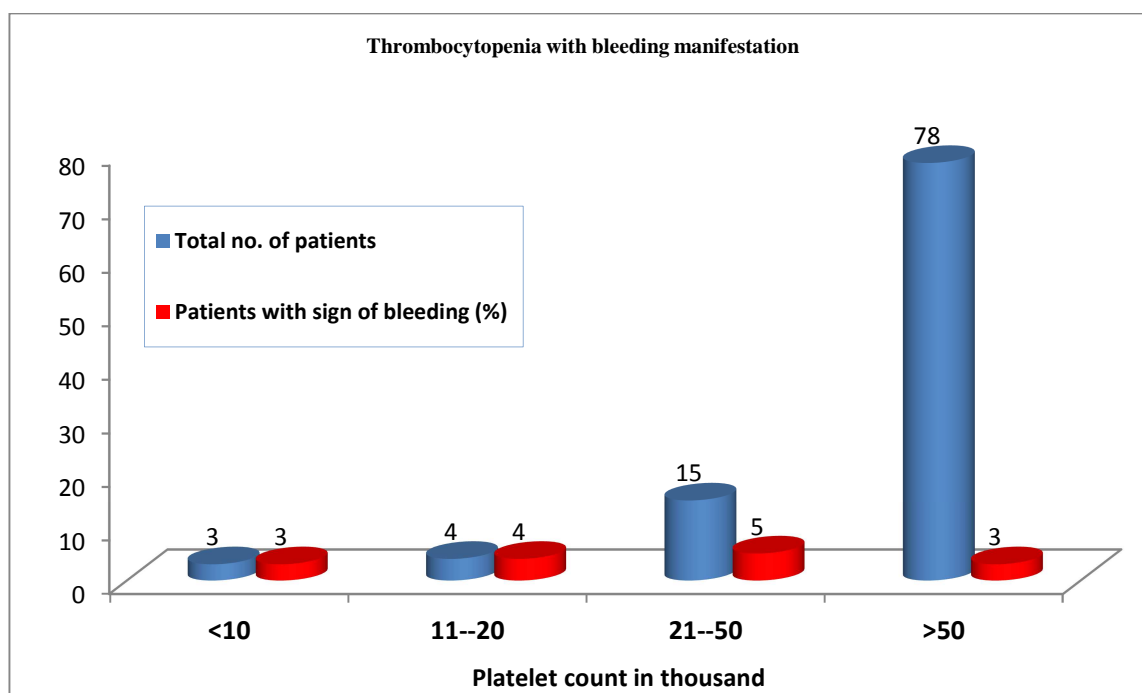
5. Distribution on basis of pattern of Bleeding Tendency

Among the cases which had a bleeding manifestations, petechiae/ purpura, was the most common presentation with 14 (14%) followed by malena 4 (4%), 2 (2%) had haematuria, 1 (1%) had subconjunctival haemorrhage, 1 (1%) had epistaxis, 1(1%) had haematemesiis, 1 (1%) had bleeding Per Rectum.



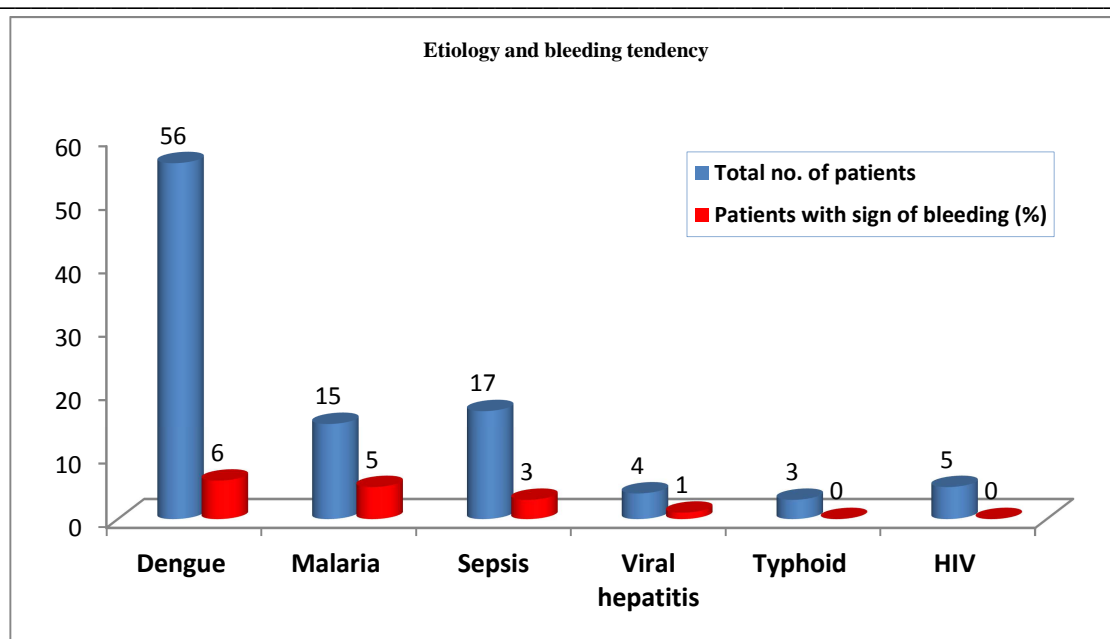
6. Distribution on the basis of platelet count and bleeding manifestations

Out of the 15 cases who had bleeding manifestations, 3 patients had platelet count below 10000/ μ L, 4 patients had platelet count between 11000 to 20000/ μ L, 5 had between 21000/ μ L to 50000 / μ L, 3 had platelet count above 50000/ μ L.



7. Distribution according to Etiology and Bleeding Tendency

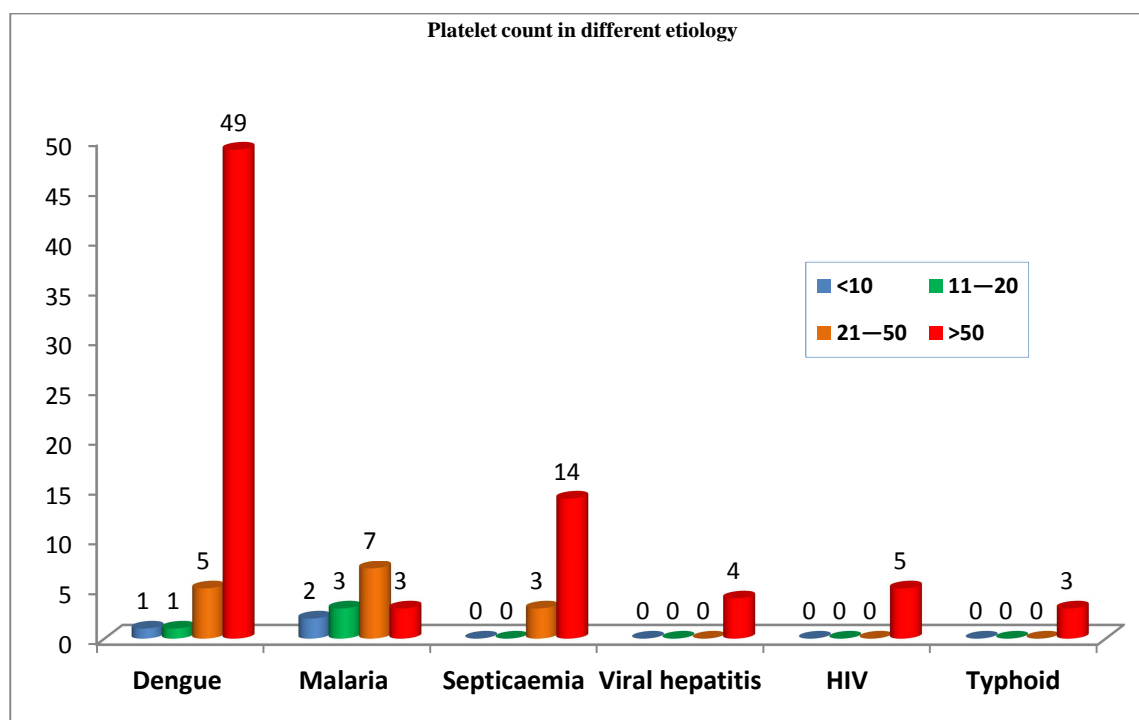
Out of the 56 cases of dengue, 6 (10.71%) had bleeding manifestations. Out of the 15 cases of malaria 5 (33.33%) had bleeding manifestations. Out of the 17 cases of septicaemia 3 (17.64%) had bleeding manifestations and in viral hepatitis 4 (25%) had bleeding manifestations.



B] HEMATOLOGICAL FINDINGS

1. Distribution according Platelet Count and Etiology

In the present study, among the cases of dengue, about 49 had platelet counts above 50,000/ μ L followed by 5,1,1 cases had platelet counts in the range of 21-50000/ μ L, 11-20000/ μ L and <10000/ μ L respectively. Among the cases of malaria, 3 had platelets in the range of >50000/ μ L followed by 7,3,2 in the range of 21-50000/ μ L, 11-20000/ μ L and <1000/ μ L respectively. Among all the cases of viral hepatitis, HIV and typhoid had platelet count above the >50000/ μ L.



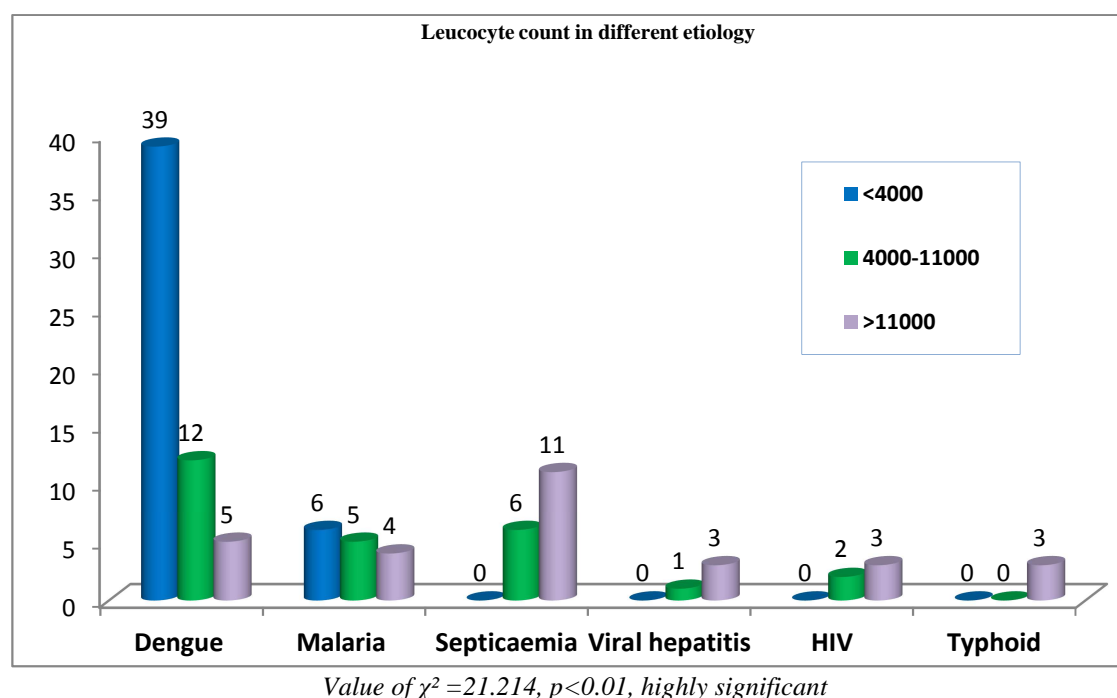
Value of $\chi^2 = 44.821$, $p < 0.01$, highly significant

By applying Chi-square test there is a significant association between platelet count and etiology ($p < 0.01$)

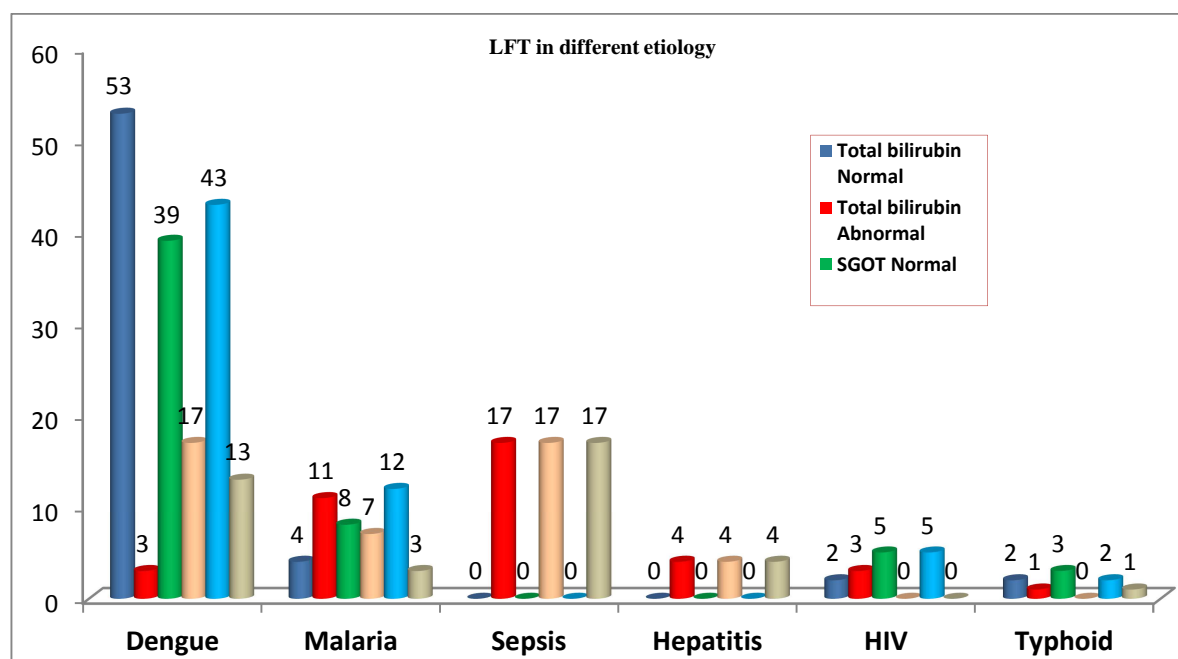
2. Distribution according to Total Leucocyte Count with Etiology

In present study 45 patients had leucopenia accounting to 45% cases. Out of those, 39 were dengue cases, followed by 6 malaria cases. No leucopenia was found in sepsis, viral hepatitis, HIV, and typhoid cases. Leucocytosis was seen in

29 cases (29%). Majority of leucocytosis was found in 17 septicaemia cases followed by 5, 4, 3, 3, and 3 in dengue, malaria, hepatitis, HIV and typhoid respectively.



By applying chi-square test there is a **significant association** between **Total Leucocyte Count and Etiology** ($p < 0.01$)



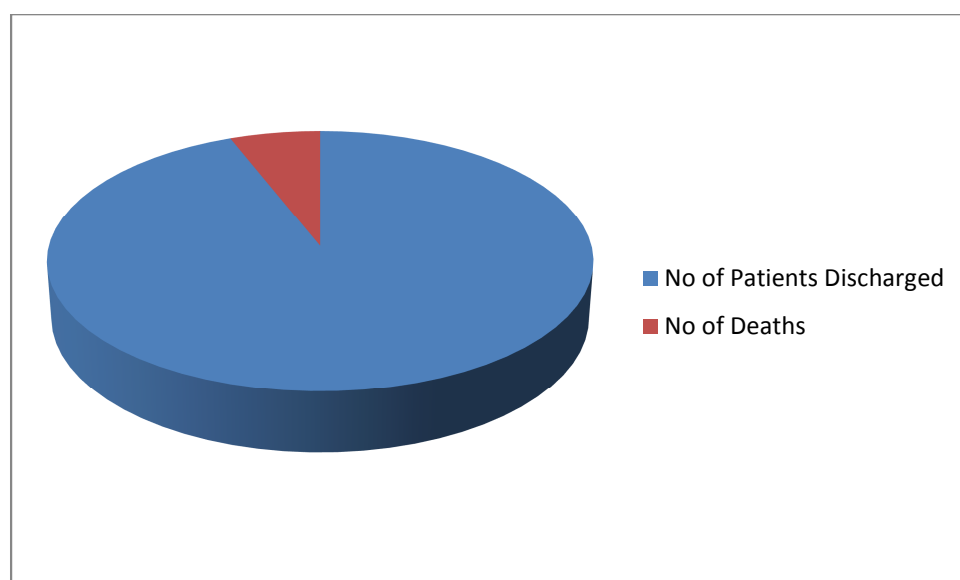
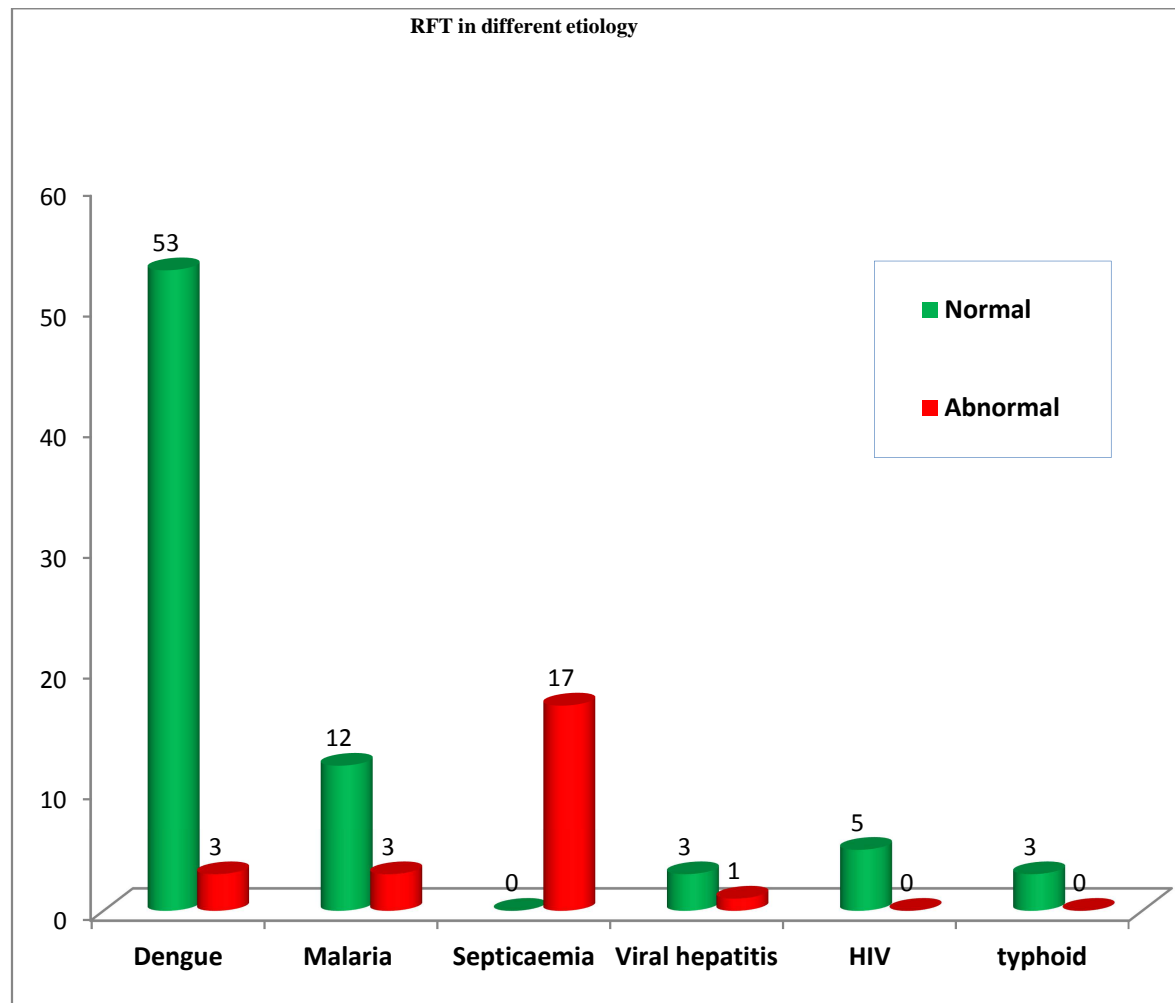
C] LABORATORY FINDINGS

1. Distribution of cases according to Etiology and Liver Function Tests

In present study in patients with dengue fever, out of 56 cases 3 cases had abnormal total bilirubin values, 17 cases had abnormal SGOT levels and 13 cases had abnormal SGPT levels. In patients with malaria out of 15 cases, 11 cases had abnormal total bilirubin values, 7 cases had abnormal SGOT levels and 3 cases had abnormal SGPT levels. In the present study there were 17 cases of septicaemia and all of them had abnormal levels of total bilirubin, SGOT and SGPT. All cases of viral hepatitis showed abnormal LFT. Out of 5 cases of HIV, 3 cases had abnormal total bilirubin values. Out of 3 cases of typhoid, 1 case had abnormal total bilirubin values, 0 cases had abnormal SGOT levels and 1 case had abnormal SGPT levels.

2. Distribution of cases according to Etiology and Renal Function Tests

In present study 24 (24%) cases had abnormal RFT out of 100 cases. Majority of abnormal RFTs were seen in 17 septicaemia cases followed by 3, 3 and 1 cases of dengue, malaria and viral hepatitis, respectively. In HIV and typhoid cases RFT was within normal limit.

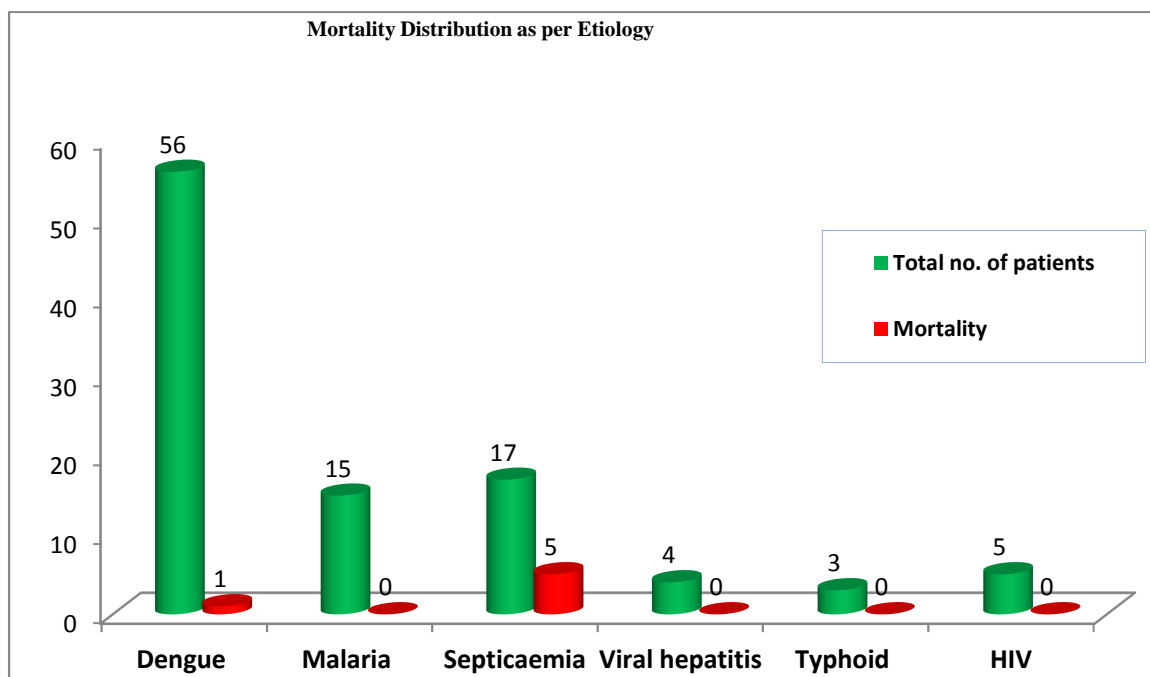


D] PROGNOSTIC FINDINGS**1. Mortality**

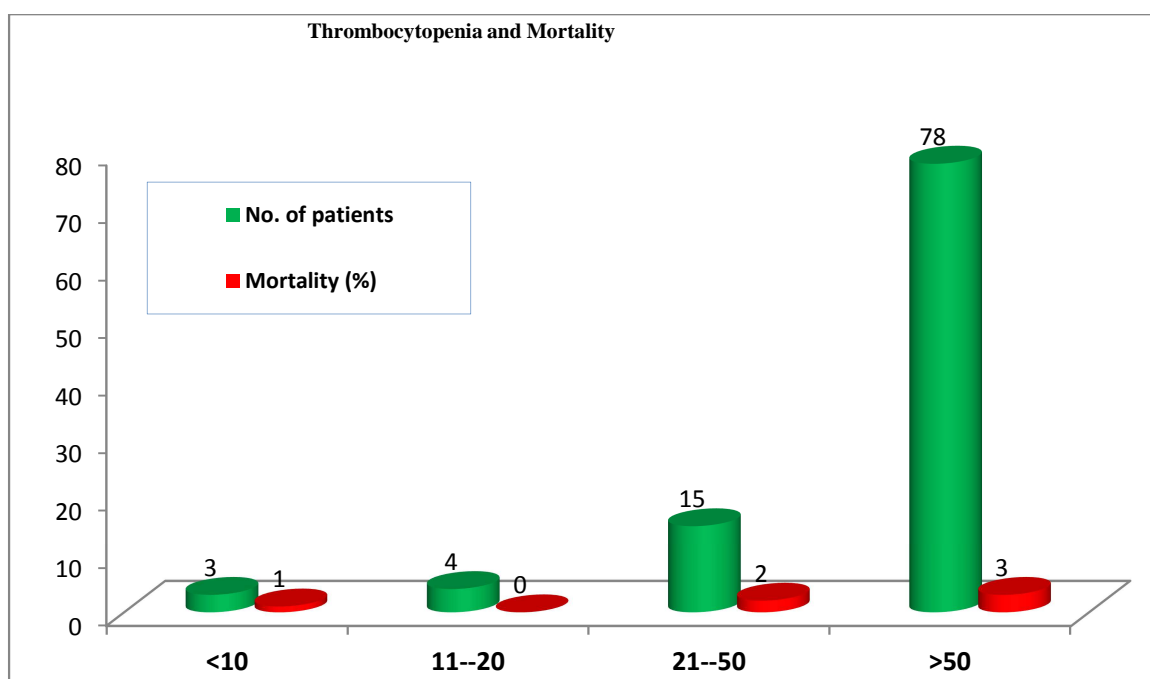
Out of the 100 cases, 94 cases had complete recovery and were discharged while 6 patients expired during their period of hospital stay.

2. Mortality as seen with Etiology

In the present study, in the cases of septicaemia, we had 5 (29.41%) mortalities out of 17 cases. In dengue cases we had 1 (1.79%) out of 56 cases.

**3. Mortality as seen with Thrombocytopenia**

Out of the 6 mortality cases, 1 case had platelet counts below 10000/ μ L, 2 cases in the 21000 to 50000/ μ L range and 3 cases more than 50000/ μ L group.



DISCUSSION

For a clinical study of fever with thrombocytopenia, patients must satisfy the above mentioned criteria's; prospective case collection is necessary and careful follow up is warranted. These three conditions allow the delineation of a standard study population.

A study was conducted by **Nair PS et al** ^[76] (2003) at **St. Stephen's Hospital, New Delhi**, for period of one and half years. A total of 109 cases (76 male, 33 female patients) were studied with the same criteria as in our study. In present study 56 were males and 44 were female.

In the present study the maximum prevalence of fever with thrombocytopenia was in the age group of 21-30 years of about 32%.

In Nair study ^[22] septicaemia with 29 cases was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever 16 followed by dengue 15, Megaloblastic anaemia 13, malaria 10, Haematological malignancy with 4 cases respectively.

In Srinivas study ^[23] malaria with 41 cases was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever followed by septicaemia, dengue, leptospirosis with 24, 19, 2 cases respectively.

Table No.1: Comparison of Diseases above given profile with other studies.

Disease category	Nair et al. ²²		Srinivas Study ²³		Present study	
	No. of cases	Percentage	No. of Cases	Percentage	No. of cases	Percentage
Dengue fever	15	13.8	14	14	56	56
Enteric fever	16	14.7	24	24	3	3
Malaria	10	9.2	41	41	15	15
Haematological Conditions	17	15.6	0	0	0	0
Septicaemia	29	26.6	19	19	17	17
HIV	0	0	00	00	5	5
Hep B	0	0	00	00	4	4
Leptospira	0	0	2	2	0	0
Unknown	20	18.3	00	00	0	0

In the present study Dengue with 56 cases was leading cause of fever associated with thrombocytopenia. Second common cause was Septicaemia 17 followed by Malaria 15, HIV5, viral hepatitis 4, and enteric fever 3 cases. This might be due to seasonal, regional variations and other multi-factorial etiologies.

In the present study infections (100%) are the established diagnosis as compared to Nair study in which along with infection (68%), hematological conditions (15%), was also documented. In Srinivas study infections (100%) were the established diagnosis.

Table No.2: Comparison of distribution of malarial parasites

Plasmodium species	Nair et al ^[22]	Present study
P.vivax	20 (48%)	10 (66.67%)
P.falciparum	13 (32%)	04 (26.66%)
Mixed (P.vivax + P.falciparum)	08 (20%)	01 (6.67%)

In the present study there were 15 cases of malaria, out of which plasmodium falciparum are 4 cases, plasmodium vivax are 10 cases and mixed infections are 1 case compared to Nair study there were 41 cases of malaria, out of which plasmodium falciparum 13, plasmodium vivax 20 cases and mixed infection were 8 cases.

Table No.3: Platelet Count – Comparison with other studies.

Distribution of platelet count in thousands	Nair et al (2003) ^[22]		Present study	
	No. of cases	Percentage	No. of cases	Percentage
<10	19	17.5	3	3
11-20			3	3
21 – 50	28	25.7	15	15
>50	80	40	78	78

Clinical presentation of 100 cases in the present study, all of them 100 had fever 90 had headache, 92 had Body Ache, 8 had sore throat, 43 had Nausea, Vomiting, 24 had abdominal pain, 15 had Altered Sensorium. General physical finding 22 Cases had Pallor, 28 cases had Icterus, 12 cases had Hepatomegaly, 19 cases had Splenomegaly.

In our study distribution of platelet counts in the range of more than 50000/ μ L was seen in 78(78%) cases as compared to 62(56.8%) cases in study by Nair et al.

Platelet counts in the range of 21000-50000/ μ L was seen in 15 (15%) cases in our study as compared to 28(25.7%) in the studies by Nair et al respectively.

Platelet counts less than 10000/ μ L was seen in 3 (3%) cases in our study as compared to 19(17.5%) in the study by Nair et al

In conclusion, >50000/ μ L was the commonest range for the distribution of cases in our study of fever with thrombocytopenia.

Table No.4: Comparison of Thrombocytopenic Signs

Thrombocytopenic Signs (Bleeding diathesis)	Nair et al(2003) ^[22]		Srinivas Study ^[23]	Present study		
	No. of cases	Percentage	No.of Case	Percentage	No. of cases	Percentage
Present	45	41.3	49	49	15	15
Absent	65	58.7	51	51	85	85
Bleeding diathesis	Nair et al(2003) ^[22]		Srinivas Study ^[23]	Present study		
	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
Petechiae / purpura	10	22.22	31	63	14	14
SBP	31	68.00	18	37	10	10
Others	4	9.88	00	00	00	00

In Nair study group during the course of follow up platelet count showed increasing trends accounting for 63.3% and continuously falling counts in 7.3%. But in this present study it showed increasing trends in platelet count at the time of discharge in all cases who recovered. There was no decreasing trend of platelet count observed since in this study only infectious causes been considered.

In Nair study Out of 109 patients 45 patients had thrombocytopenic signs accounting for 41.3%. Out of 45 patients. In Srinivas study out of 100 patients 49 patients had thrombocytopenic signs accounting for 49 %. In present study out of 100 patients 15% had thrombocytopenic sign accounting for 15 %.

BLEEDING PATTERN

In Nair study spontaneous bleeding was the commonest bleeding manifestation with 31 cases(68%) followed by petechiae / purpura accounting for 10 cases (22.22%), others 4 cases (9.88%). In Srinivas study petechiae /purpura was the commonest bleeding manifestation with 31 cases(63%) followed by spontaneous bleeding accounting for 18 cases(37%). In present study petechiae / purpura was the commonest bleeding manifestation with 14 cases (14%) followed by spontaneous bleeding accounting for 10 cases(10%).

PLATELET COUNT

In present study 45 (45%) cases had leucopenia out of 100 cases. majority of leucopenia were found in 39 dengue cases out of 56 dengue cases followed by 6 malaria cases out of 15 malaria cases and no leucopenia found in sepsis, viral hepatitis, HIV, and typhoid cases. leucocytosis were seen in 29 cases(29%). majority of leucocytosis were found in 17 septicaemia cases out of 17 septicemia cases followed by 5, 4,3,3, and 3 dengue, malaria, hepatitis, HIV and typhoid subsequently.

ORGAN FUNCTION TESTS

In present study in patients with dengue fever, out of 56 cases 3 cases had abnormal total bilirubin values, 17 cases had abnormal SGOT levels and 13 cases had abnormal SGPT levels. In patients with malaria out of 15 cases, 11 cases had abnormal total bilirubin values, 7 cases had abnormal SGOT levels and 3 cases had abnormal SGPT levels. In the present study there were 17 cases of septicemia and all of them had abnormal levels of total bilirubin, SGOT and

SGPT. All cases of viral hepatitis showed abnormal LFT. Out of 5 cases of HIV, 3 cases had abnormal total bilirubin values. Out of 3 cases of typhoid, 1 case had abnormal total bilirubin values, 0 cases had abnormal SGOT levels and 1 case had abnormal SGPT levels.

In present study 24 (24%) cases had abnormal RFT out of 100 cases. Majority of abnormal RFT seen in 17 septicaemia cases followed by 3, 3 and 1 cases in dengue, malaria and viral hepatitis. In HIV and typhoid cases RFT within normal limit.

In the mortality group platelet count in 6 cases remained fluctuating between 10000 – 10,0000 cells/ μ L. However patient received platelet transfusion till the time death.

In conclusion present study of fever with thrombocytopenia reveals that among infectious diseases the commonest cause was Dengue, which is of higher incidence compared to the Nair study this might be because of seasonal, regional and ethnical variations. Definitive increase in platelet count was noted after the underlying cause was treated. Among the cases that died **Dengue shock syndrome** was seen in 1 case accounted for 1% of mortality in this study followed by 5 cases (5%) of septicemia.

CONCLUSION

Fever with thrombocytopenia is one of the most challenging problems in the field of medicine. Fever with thrombocytopenia consists of occult presentations of common diseases rather than rare disease. Infection is the commonest cause of fever with thrombocytopenia. Among infections, dengue was the commonest cause.

A prospective study of 100 patients, who had fever and thrombocytopenia was done in our hospital. The inclusion and exclusion criteria was followed according to the criteria mentioned in the material and methods of the study.

- 1) The Age Range of the patient was more than 12 years to 80 years with Male: Female ratio being 56%:44%.
- 2) A definitive diagnosis was made in all of them.
- 3) Among the diagnosed cases, Dengue **formed the largest group with 56(56%) cases.**
- 4) Septicaemia formed the second largest group with 17(17%) cases.
- 5) Malaria formed the third largest group 15(15%) cases with Vivax, Falciparum and mixed malaria 10(10%), 4(4%) and 1(1%) cases respectively.
- 6) Other cases diagnosed were HIV, viral hepatitis and Typhoid cases, constituting 5(5%), 4(4%) and 3(3%) respectively.
- 7) The common range of platelet count at the time of admission was above 50,000/ μ L in 78 cases, followed by 21-50,000/ μ L in 15 cases, 11-20,000/ μ L in 4 cases and less than 10,000/ μ L in 3 cases.
- 8) **The Clinical Manifestations of thrombocytopenia were present in 15 cases and was not present in 85 cases.**
- 9) Out of the 15 cases which had thrombocytopenic manifestations petechiae/ purpura was present in 14 cases accounting for 14% and spontaneous bleeding in 10 cases accounting for 10%.
- 10) In present study 45 patients had leucopenia accounting to 45% cases. Out of those, 39 were dengue cases, followed by 6 malaria cases. **No leucopenia** was found in septicaemia, viral hepatitis, HIV, and typhoid cases. **Leucocytosis** was seen in 29 cases(29%). Majority of leucocytosis was found in 17 septicaemia cases followed by 5, 4, 3, 3, and 3 in dengue, malaria, hepatitis, HIV and typhoid respectively.
- 11) In patients with dengue fever, out of 56 cases 3 cases had abnormal total bilirubin values, 17 cases had abnormal SGOT levels and 13 cases had abnormal SGPT levels. In patients with malaria out of 15 cases, 11 cases had abnormal Total Bilirubin values, 7 cases had abnormal SGOT levels and 3 cases had abnormal SGPT levels. In the present study there were 17 cases of septicaemia and all of them had abnormal levels of total bilirubin, SGOT and SGPT. All cases of viral hepatitis showed abnormal LFT. Out of 5 cases of HIV, 3 cases had abnormal total bilirubin values. Out of 3 cases of typhoid, 1 case had abnormal total bilirubin values, 0 cases had abnormal SGOT levels and 1 case had abnormal SGPT levels.
- 12) **In present study 24 (24%) cases had Abnormal RFT out of 100 cases.** Majority of abnormal RFTs were seen in 17 septicaemia cases followed by 3, 3 and 1 cases of dengue, malaria and viral hepatitis, respectively. In HIV and typhoid cases RFT was within normal limit.
- 13) In general, 94 cases had good recovery and 6 cases ended in mortality.
- 14) Out of the 6 mortality, 1 case was due to dengue accounting for 1% and 5 were due to septicemia accounting for 5% of the total mortality.
- 15) **The range of platelet count in the mortality cases was less than 10,000/ μ L in 1 case, followed by 21-50,000/ μ L in 3 cases, followed by >50,000/ μ L in 3 cases.**

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ANNEXURE**CONSENT FORM**

I voluntarily agree to take part in this study by signing below. My signature below indicates that I have read or it has been read to me this entire consent form, and have had all my questions answered.

Name of the participant or legally authorized representative-----

Signature/thumb print

PROFORMA

Age-

Sex-

Address-

Date of admission -

Date of discharge-

IPD NO / OPD NO:

Symptoms and signs:

1. Fever
2. Chills
3. Headache
4. Nausea
5. Vomiting
6. Giddiness
7. Body ache
8. Abdominal pain
9. Retro orbital pain
10. Loss of appetite
11. High coloured urine
12. Sore throat
13. Breathlessness
14. Bleeding signs

Personal History

Past History

Family History

GENERAL EXAMINATION:

- Pallor
- Icterus
- Lymphadenopathy
- Cyanosis
- Clubbing
- Edema
- Rash or any Bleeding Sign

SYSTEMIC EXAMINATION

1. CVS
2. RS
3. P/A
4. CNS

LABORATORY INVESTIGATIONS

- Complete blood count.
- Platelet count.
- Peripheral smear for morphology.
- Bleeding time and clotting time.
- Urine routine and microscopy.
- Blood culture.

- Urine culture.
- Renal function test
- Liver function test.
- HIV, HbSAg.
- PS FOR MP AND ICT MALARIA
- Widal Test
- Dengue(NS1 antigen, IgG, IgM)
- Chest x-ray (PA)
- Other specific investigations(if needed)

Diagnosis:

Treatment