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# Clinical Update Regarding Fever with Thrombocytopenia

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**KEYWORDS**

thrombocytopenia, fever, prevalence, disease, HIV

**ABSTRACT:**

**Introduction:** Fever with Thrombocytopenia generally refers to the symptom of the extremely low count of platelets occurring in the blood of a patient bearing fever. Generally parasitic diseases like Malaria and Viral diseases like Dengue act as the reasons for such health adversities.

**Objective:** The study has mainly focused on evaluating the concept of Fever with thrombocytopenia along with the prevalence of the disease discussion. The regularised treatment processes that are gradually enhancing for preventing fever with thrombocytopenia are discussed.

**Methodology:** A prospective study design is used by excluding patients aged 17 and younger and having diseases like Cirrhosis of the liver and HIV. The simple random sampling method is used for choosing the 100 participants who have been admitted to the Medicine OPD of MMCH&RI during 2021 and 2022.

**Results:** The results noted 35 females and 65 males present in the study group. the results for positive diagnosis cases included dengue fever (50%), malaria (28%), leptospirosis (14%), enteric fever (8%) and scrub typhus (4%). The mean difference of platelet between gender illustrated to be not statistically significant. This was also the same case for diagnosis cases for dengue, malaria, and leptospirosis.

**Conclusion:** The following study noted hematological and demographic changes to be connected with thrombocytopenia onset development. The study concluded to deliver a contribution towards disease awareness along with aiding policymakers to note the causes and integrate appropriate policies for strengthening prevention programs.

## 1. Introduction

Fever generally refers to the temporary increment of body temperature of an individual due to an illness. The process of increment of the body temperature occurs naturally and acts as an automatic response of the physical system to the infection and inflammation. Fever gets triggered by the immune system of the body to resist the attacks of pathogens including different types of Bacteria, viruses and various foreign invading objects. Normal body temperature, in case of getting increased by two degrees, can be considered as a fever condition.

### Background

Fever with Thrombocytopenia refers to the prevalence of fever in the body of an individual along with the abnormal lowering in the number of platelets in the blood. Platelets bear the scientific name Thrombocytes and act as the main cells for making the blood clot. Thrombocytopenia makes a person disabled in getting their blood clot and fever with thrombocytopenia show symptoms of some adverse physical conditions and indicate the prevalence of important systemic diseases[1]. Starting from various viral infective diseases including Dengue, Chikungunya, and COVID 19 along with parasitic diseases like Malaria act as important reasons behind the occurrence of Thrombocytopenia within a person. The holistic physical disorder creates two simultaneous problematic indications including Fever, acting as the natural reaction against the potential infection and malignancy[2]. Moreover, Thrombocytopenia increases the destruction rate of platelets and decreases the production rate of bone marrow. These processes impact the normal and well-maintained distribution of platelets in the body of an individual. Infections lead to direct destruction of

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platelets and sometimes the immune mechanism of the body attacks the platelets.

**Rationale**

Clinical update generation on fever with thrombocytopenia generally targets identifying various causes and managing the symptomatic combinations. A range of serious conditional disorders indicates the prevalence of the simultaneous occurrence of two diseases in the body of an individual. The infections occurring on the body of the individual include the prevalence of various viral, parasitic and autoimmune diseases like Dengue, Malaria and Systemic Lupus Erythematosus[3]. Some typical advancements have been found in the current treatment processes, found in the field of diagnosing and curing the thrombocytopenia condition from the body. Rapid diagnostic tools including PCR for detecting viral and bacterial infections along with parasitic infection are being used[4]. Earlier pathogenic identification becomes possible due to advancements that enhance the fever and thrombocytopenia. Another identified process is Flow Cytometry development and Autoantibody testing development which include the identification of antiplatelet antibodies that evolve the diagnostic advancements.

## 2. Aim and Objectives

**Aim of the study**

The Study aims to develop an idea about the challenges of Fever with Thrombocytopenia and evaluate the feasibility of the treatment processes conducted against different symptomatic causes for the occurrence of these diseases.

**Objectives**

- To develop an overview of various types of physiological agents regarding the health conditions of admitted patients with fever with thrombocytopenia
- To evaluate the demographic and clinical data regarding thrombocytopenia
- To create an analysis regarding the clinical investigation done on the patients suffering from fever with Thrombocytopenia
- To generate an idea about the complications regarding the investigative treatment process against the disease

## 3. Review of Literature

**Fever as a sign of physical adversity**

Since the beginning of ancient medical studies, the then medical practitioners came to understand that fever is an indication of underlying physical adversities present within the health of an individual. The ancient medicos used to consider fever as a manifestation of adverse diseases and physical imbalance occurring within the body[5]. Early descriptions and interpretations of fever have been found in different scriptures regarding the medical traditions of ancient times. Egyptian medical texts, including the Ebers Papyrus, show that fever was considered a depiction of an illness by the body in the ancient Egyptian medical tradition. Similarly, from the writings of Hippocrates and Galen, the evidences are found that Fever was considered a clinical symptom of illness in the ancient Greek and Roman civilisations[6]. In the Ayurvedic references of Indian ancient medical traditions, Fever was named “Jvara” and Charaka was the one medical practitioner that termed fever as an indication of different types of diseases.

The renowned medico of ancient India depicted Fever as an imbalanced conditional depiction of three doshas, namely “Vayu”, “Pitta” and “kapha”, referring to gas, bile and mucus movement in the body. During the medieval era, fever was scientifically interpreted and described by the Humoral Theory which showed that fever was generally made up of four humours including blood, phlegm, yellow and black biles[7]. Along with these medical interpretations, fever was often considered a purification process of the soul.

**Agents that can cause a fever**

Different types of infectious agents remain present in the environment acting as the main factors causing severe levels of fever within the body of a human being. Among these agents, one significantly important agent is bacteria like Streptococcus pneumoniae, E.Coli and Mycobacterium tuberculosis[8]. These generally act as the main agents causing diseases like Pneumonia, Urinary Tract infection and Tuberculosis. Along with these, influenza viruses and SARS-COV-2 remain responsible for influenza occurrence and COVID-19 prevalence in

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patients. Moreover, Plasmodium is a parasite that causes Malaria by getting spread through the body of mosquitoes. The malaria infection creates an episodic cycle of fever condition and chilling within the patient with the gradual loss of platelets from the blood of the individual. These external pyrogens generate a part in Leukocytes called Endogenous pyrogen. These Endotoxins act as the main ingredients in leveraging complex Lipopolysaccharides for forming cell walls of gram-negative bacteria[9]. The lipid-based pyrogens use beta 1-6 linked Diglucosamine backbone that acts as ester-linked and amide-linked groups to generate the fatty acids. Moreover, the generation of 2-keto 3-deoxycholate and the pyrophosphate groups the mainly dependent upon the endotoxin bacterium that can be diagnosed by intravenous concentrated injection of biphasic fevers.

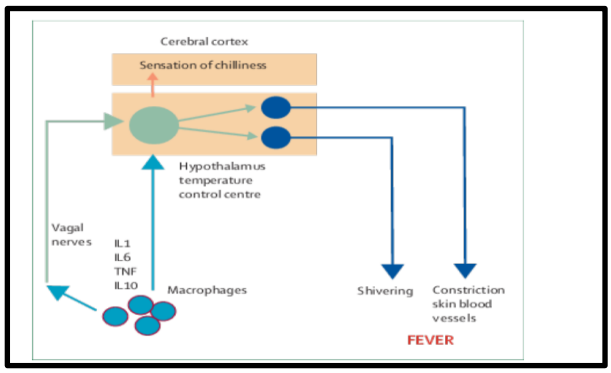


**Figure 1.** Agents that can cause fever[8]

**Endogenous pyrogen**

"Endogenous Pyrogen" are a form of protein, released from "Lyphocytosis", now termed as "Cytokines." One of the most important "pyrogleukocytesines" is "IL-1" which is formerly known as the factor, affecting the lymphocyte. This cytokine stimulates the proliferation of T-lymphocytes during the presence of indigenous substances enhancing the immunity system of human beings. The mediator between the Hypothalamus and the pyrogen acts as the regulatory body to increase the level of calcium in the body. "Interleukin-1" increases fever by influencing the synthesis of "prostaglandins- E2" within the function of the hypothalamus[10]. This increasing level of temperature induces heat production and conservation of temperature within the body. Endogenous Pyrogen occurs through the instigation of the "arachidonic acid" that causes the synthesis of "prostaglandins." Arachidonic acid regulatory products modulate the "hypothalamic thermoregulatory mechanism."

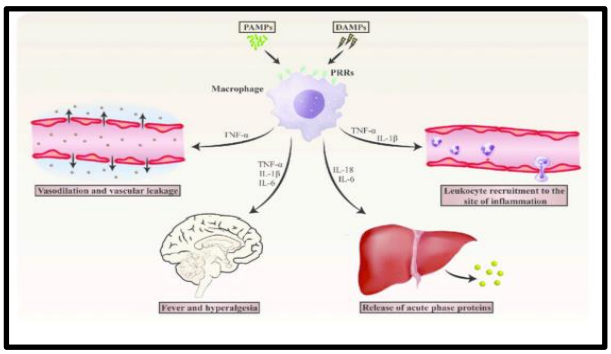


**Figure 2.** Endogenous Pyrogen[11]

The "physiologic mechanism" increases the fever in the human body, synthesised by the previous explosion of pyrogenic substances. This bacterial reaction within the human body is exerted on the portion of a thermoregulatory portion of hypothalamus tissues to raise the temperature of the body[11]. Vasodilation, flaccidity of muscles, and sweating are the effects of the initial level of the reduction of plasma level in the body. The total plasma count and the rate of plasmas within the human body are part of this disease in human bodies.

**Activation, production and release of leukocytes**

Activation of Leukocytes is generally referred to as the process of Leukopoiesis indicates the formation of Leukocytes. The process generally takes place in the bone marrow that involves the process of differentiation of the stem cells bearing Hematopoiesis. These result in the generation of different types of Leukocytes including Hematopoietic stem cells that are generally multipotent and get raised within the bone marrow and give rise to different types of blood cells. Another important type is granulocyte-based myeloid lineage creation that gradually gets formed in differentiated macrophages[12]. Another important type of Leukocytes belongs to the Lymphoid lineage and acts as the main forming backbone of Lymphocytes including B cells, T cells and different Natural Killer cells. The next process of the Leukocytic life cycle after the activation and the production phases are completed, is the process of release of mature leukocyte cells[13]. The process focuses on the mixing of Leukocytes from the bone marrow to

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the blood vessel cells. The leukocytes get transmitted from

The bone marrow to the blood vessels is based on the needs of the body depending on various triggering incidents. Granulocytes are generally released during different infections and inflammations based on the fight against different pathogens. On the other hand, the monocytes get migrated to tissues as needed.

**Thrombocytopenia is caused by Malaria, Dengue and HIV**

Thrombocytopenia can occur through Malaria with various types of mechanisms. The parasite malaria can affect the red blood corpuscles of the human body which effect the destruction of platelets. The deficit in the immunity system can contribute to the destruction of platelets and Malaria leads to "splenomegaly" that reduces the circulation of platelets and their numbers in the count. Thrombocytopenia causes different types of infections in the human body that cause a lower rate of counts of platelets[14]. The Dengue virus affects the bone marrow and restrains the production of platelets in the human body. The Dengue Virus diminishes the coagulation process of blood and causes "hemorrhagic fever." Monitoring counts of platelets during Dengue fever is significantly low and that causes the issues in abrupt bleeding of different parts of the body[15]. Chronic infection with the HIV Virus affects the immune system of human bodies and platelets. The co-infections of HIV within the baffectfect the malignancies and thrombocytopenia address the difficulties in the counts of platelets in the blood.

## 4. Materials and Methods

A prospective study design is a common research design principle applied in observational studies that are generally conducted through an observational study method. The researcher has focused on using a prospective study design in conducting these studies based on the creation of a sample of suitable participants that can be considered as the sample elements present within the study. For selecting the participants, a cohort group of individuals that are initially free of interest. The minimum age of the participants has been bounded within the age group of eighteen years. Based on different risk factors and comorbidity factors, the researcher has focused on excluding them from the sample. The exclusion criteria that act as prevalent factors in classifying the sample elements are based on patients getting admitted to hospital emergency departments with high fever and other symptoms that can considerably act as the main reasons behind the generation of Thrombocytopenia[16]. These exclusion criteria include inherited causes bearing severe tendencies for occurring thrombocytopenia. Moreover, those patients are under such types of medications that can cause thrombocytopenia and the autoimmune causes that act as agents in thrombocytopenia prevalence occurrence.

Along with these, patients suffering from diseases like HIV and Cirrhosis of the Liver show significant issues with the formation of blood. The researcher has categorically focused on excluding the patients bearing an age less than 17 years and having syndrome like Leukemia. The patients bearing an age of a minimum of 18 years and having a body temperature of "am minimum temperature" of greater than 37.2 degrees Celsius and "pm minimum temperature" of greater than 37.7 degrees Celsius. Along with these, while including the patients in the sample, the researcher has focused on determining whether the patient has a platelet count of less than 1.5 lakh or not. The data collected from the patients by diagnosing them and conducting tests like Malaria Parasite, Dengue test and others, are gathered in an Excel sheet and entered into the SPSS 22[17]. There has not been any conflict of interest that has been prevalent for the researcher in selecting the 100 participants. A simple random sampling method is used for choosing the sample elements from the General Medicine Department OPD-based Casualty wards present in the MMCH&RI. The patients who are admitted to the wards from May 2021 to August 2022 are considered as the sample elements by the researcher.

## 5. Results and Statistical Methods

**Table 1:** Demographic statistics for age group in study population (N=100)

| Age | Frequency | Percentages |
|---|---|---|
| 18 to 30 years | 56 | 56% |
| 31 to 60 years | 42 | 42% |
| >60 years | 2 | 2% |

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The study's sample study population included 100 participants. It was observed that 56% of the sample population were within the 18-30 years age group, 42% were 31 to 60 years age group and 2% over 60 years.

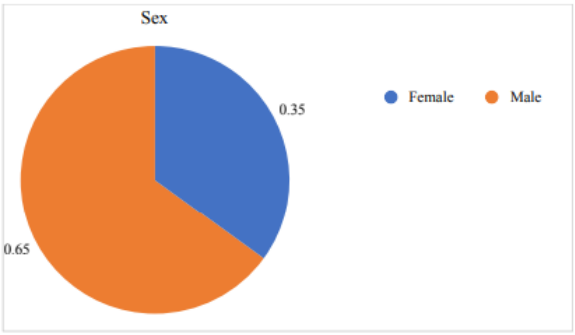


**Figure 3.** Demographic statistics of sex within study population

The study identified constituting sex demographics of the study population included 35 females and 65 males.

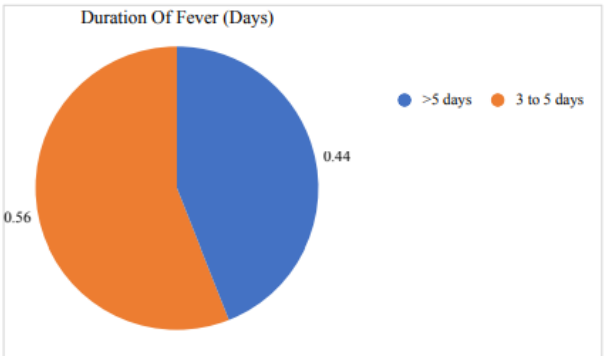


**Figure 4.** Duration of fever (days) in study population (N=100)

The duration of fever for different days are identified in the following graph. The present evaluation identified that 44 people had reported to have fever for more than 5 days while 56 people reported to have fever for 3 to 5 days.

**Table 2:** Descriptive analysis of clinical variables in study population

| **Shortness Of Breath** | Frequency | Percentages |
|---|---|---|
| NO | 86 | 86% |
| YES | 14 | 14% |
| **Decreased Urine Output** | Frequency | Percentages |
| NO | 86 | 86% |
| YES | 14 | 14% |
| **Pallor** | Frequency | Percentages |
| NO | 88 | 88% |
| YES | 12 | 12% |
| **Cough** | Frequency | Percentages |
| Absent | 99 | 99% |
| Present | 1 | 1% |
| **Bleeding Manifestations** | Frequency | Percentages |
| Absent | 98 | 98% |
| Present | 2 | 2% |
| **Myalgia** | Frequency | Percentages |
| Absent | 80 | 80% |
| Present | 20 | 20% |
| **Arthralgia** | Frequency | Percentages |
| Absent | 72 | 72% |
| Present | 28 | 28% |
| **Fever** | Frequency | Percentages |
| Absent | 48 | 48% |
| Present | 52 | 52% |
| **Vomiting** | Frequency | Percentages |
| Absent | 85 | 85% |
| Present | 15 | 15% |
| **Loose stool** | Frequency | Percentages |
| Absent | 85 | 85% |
| Present | 15 | 15% |
| **Dehydration** | Frequency | Percentage |
| Absent | 87 | 87% |
| Present | 13 | 13% |

The above table noted the descriptive analysis of the clinical variables regarding the principal complaints that the people faced. This included 14% complaint of shortness of breath, decreased urine output (14%), pallor (12% complaints), manifestations of bleeding (2%), Myalgia (20%), Arthralgia (28% cases), 52% cases complaining of fever, 15% cases complained of vomiting, 15% mentioned loose stool, and 13% complained dehydration.

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**Table 3:** Lab parameter study population descriptive analysis

| Parameter | Mean ± SD | Median | Minimum | Maximum |
|---|---|---|---|---|
| Pulse Rate | 98.71 ± 6.21 | 98 | 90 | 110 |
| Hemoglobin | 9.65 ± 2.64 | 9.70 | 5.50 | 14.40 |
| Total Count | 7 7 7 8. 9 6 ± 1783.5 | 7942.50 | 4581 | 10989 |
| Platelet | 5 9 1 5 8. 3 3 ± 35123.98 | 52649 | 6521 | 119904 |
| Urea | 18.17 ± 6.97 | 19 | 6 | 30 |
| Creatinine | 0.7 ± 0.31 | 0.70 | 0.20 | 1.20 |
| Rbs | 100.44 ± 12.1 | 101.50 | 80 | 120 |
| Pt/Inr | 1 ± 0.08 | 1 | 0.90 | 1.10 |
| Aptt Seconds | 28.35 ± 4.3 | 28 | 21 | 35 |
| T. Protein | 7.13 ± 0.69 | 7.10 | 6 | 8.20 |
| S. Bilirubin | 1.12 ± 0.27 | 1.10 | 0.80 | 1.80 |
| Sr. Albumin G/Dl | 4.29 ± 0.72 | 4.30 | 3 | 5.50 |
| Sgot | 67.36 ± 88.49 | 35 | 15 | 360 |
| Sgpt | 64.4 ± 70.97 | 42 | 10 | 314 |
| Sr. Cholesterol | 127.2 ± 33.35 | 127 | 75 | 178 |
| Vldl | 17.38 ± 7.58 | 17 | 5 | 30 |
| Ldl | 79.02 ± 24.95 | 79.50 | 35 | 126 |
| S. Triglycerides | 151.07 ± 42.01 | 144 | 88 | 232 |
| Neutrophil % | 48.39 ± 6.38 | 47 | 40 | 60 |
| Lymphocytes % | 24.3 ± 8.45 | 23 | 10 | 40 |
| Pcv | 41.93 ± 3.58 | 42.55 | 35 | 48 |
| Hdl | 47.86 ± 20.61 | 43.50 | 18 | 86 |

Some of the laboratory parameters through mean differentiation included platelet with 59158.33 ± 35123.98, urea (18.17 ± 6.97), creatinine (0.7 ± 0.31), neutrophil (48.39 ± 6.38), lymphocyte (24.3 ± 8.45), albumin (4.29 ± 0.72), total protein (7.13 ± 0.69) and others.

**Table 4:** Descriptive analysis of study population diagnosis

| Diagnosis | Frequency | Percentage |
|---|---|---|
| DENGUE | 50 | 50% |
| LEPTOSPIROSIS | 14 | 14% |
| MALARIA | 28 | 28% |
| Enteric fever | 8 | 8% |
| Scrub Typhus | 4 | 4% |

The frequency of diagnoses are identified in the above table as discussed above in the descriptive analysis. Dengue fever was recognised as one of the most

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commonly diagnosed diseases in this case. The positive diagnoses cases included 50% of all cases. Malaria diagnosis included 28% of positive disease diagnosis. Leptospirosis included 14% of the total diagnosed disease cases. The frequency for diagnosis for enteric fever was identified as 8%. Scrub typhus were recognised to be the lowest diagnosed cases with only 4% of the cases as diagnosed.

**Table 5:** Comparison of mean of platelet

| **PLATELET (Parameter)** | | **(Mean± SD)** | **P value** |
|---|---|---|---|
| SEX | Male (N=65) | 60718.69 ± 36101.53 | 0.548 |
| | Female (N=35) | 56260.51 ± 33550.25 | |
| SMEAR FOR MP | Positive (N=28) | 61108.96 ± 33609.64 | 0.731 |
| | Negative (N=72) | 58399.75 ± 35896.63 | |
| IGM DENGUE | Positive (N=50) | 56307.02 ± 34356.27 | 0.420 |
| | Negative (N=50) | 62009.64 ± 35994.73 | |
| IGM LEPTO | Positive (N=14) | 62009.64 ± 35994.73 | 0.130 |
| | Negative (N=86) | 57008.78 ± 33774.08 | |
| Blood culture sensitivity | Positive (N=8) | 57008.78 ± 33774.08 | 0.908 |
| | Negative (N=92) | 57008.78 ± 33774.08 | |

The comparison of mean as per the following table included mean comparison for the sex demographic and the positive and negative diagnosis of dengue, leptospirosis, malaria, and enteric fever. The p value for all of the following parameters had been not statistically significant. This implied that the p value for the mean differentiation of the platelet between 65 males and 35 females was identified as 0.548, hence statistically non significant. This indicated that sex of the study population is not identifiable as a significant aspect. The platelet mean differentiation for malaria diagnosis showed p value as 0.731, dengue diagnosis included a p value of 0.420, the p value in the case of leptospirosis is 0.130, and p value in the case of enteric fever included 0.908. These values illustrate that the diagnoses and sex of the population are not significant to the mean difference of platelet count for thrombocytopenia and fever.

## 6. Discussion

The following study identified that the larger segment of age demographics that were seemingly affected by this disease were mostly within the age group of 18-60 years. However, there are certain exceptions to this as certain studies illustrate that there is a higher tendency of this disease's fatality rate to be occurring mostly among elderly[18]. The development of this epidemiological disease is often identified by studies as attributed to having close contact with saliva of infected dogs and cats, adding that infected animals could also be contributors to the disease. The following study's descriptive analysis for lab parameters suited similar to other studies.

One study identified lymphocyte count as 0.63(0.44–1.03), neutrophil count 1.58(0.93–3.86), total protein (61.91±6.69), albumin (34.90±4.40) and platelet count being 49.50(32.50–69.50) among survivors[19]. This

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indicates some similarity in terms of neutrophil count. Additionally, other studies also identified that thrombocytopenia fatality patients mostly include fever as a non-specific manifestation followed by others such as myalgia, gastrointestinal symptoms such as vomiting, and respiratory symptoms include cough[20]. Though studies identified demographics included older age and males more[21], though the study identified that age is not as much of a factor demographically. Studies suggested that hematological symptoms included hemorrhagic manifestations[22]. The study hence supported the note that hematological and demographic elements affect thrombocytopenia onset. This is due to the fact that the descriptive analysis further insisted on the findings as associated with the same.

## 7. Summary

The summary of this study would indicate the following statements in respect to the above conducted and discussed study. A study was conducted among 100 patients with thrombocytopenia and fever, while following the inclusion and exclusion scope of the study effectively for minimal bias of results.

## 8. Conclusion

Hematological and demographic changes are potentially related to thrombocytopenia onset. Symptoms apart from fever included arthralgia, myalgia and bleeding, dengue was the highest diagnosed case, with malaria coming second and leptospirosis, enteric fever, and scrub typhus coming afterwards. Platelet mean comparison is not statistically significant in the case of population sex and diagnosis. Serological and hematopoietic tests ensured in the above study. Difficult clinical presentations and other complications could lead to incorrect diagnosis and impact prognosis. The following study concerns the development of disease awareness policy formation and development of prevention programs through the utilization of findings.

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