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Role of Serum Ferritin and Thrombocytopenia in Febrile Illness-Dengue: A Hospital Based Cross Sectional Study

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Abstract

The Dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) and the rare macrophage activation syndrome (MAS) are major causes of morbidity and mortality in many endemic Asian and South American countries. Increased serum ferritin levels have been proven to be helpful in predicting disease severity with a high sensitivity and specificity. Since the 1990s, epidemics of dengue have become more frequent in numerous parts of India.

Ferritin is a positive acute phase reactant, synthesized and secreted in hepatocytes, macrophages and cancer cells. Hyperferritinemia and platelet indices can be used to fulfill this criteria, and estimate severity of the disease in it's clinical course.

70 cases of serology positive dengue patients from the Sree Balaji medical college hospital were selected for this study. Venous blood was collected with minimal stasis using dry and disposable syringe and needle.

Calculations were done using SPSS21 and Microsoft excel. One way analysis of variance (ANOVA) with post-hoc test. Turkey's honest significance difference tests, Spearman's Rho Correlation, Chi-square test of independence were used to compare more than two independent samples. T-test for single samples was done. P 0.05(a=0.05) were considered to be statistically significant.

Keywords: Dengue, ferritin, biomarkers, morbidity and mortality

Introduction

Dengue: The dengue virus is an arthropod-borne (arbovirus), single stranded RNA virus that belongs to the family genus flavivirus, family flaviviridae, and has four different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Dengue is perhaps arguably the most significant arthropod-borne viral disease in the world, infecting with predictable, periodic and seasonal intervals. Dengue is a complicated illness with a variety of clinical manifestations. Studies on human volunteers and various epidemics show that the intrinsic virulence of various dengue virus strains varies significantly among these genotypes. DF is a severe influenza-like infection that affects people of any age (infants, young and older children and adults). The WHO revised classification categorizes and groups dengue into 4 subtypes with their complications [1, 2, 3].

Vector: The mosquitoes-female Aedes [Stegomyia] aegypti and Aedes [Stegomyia] albopictus are responsible for virus transmission to humans, which predominantly happen during the rainy season. Mosquitoes (Aedes aegypti sp. and Aedes albopictus sp.) are the most common and important vectors for dengue. The common domesticated, passive feeder is Aedes aegypti. The active feeder is Aedes albopictus. The Aedes mosquito transmits its disease by feeding on a human in the first five days of the course of the disease. The transmission is contagious and able to spread the infection after an incubation time of 3-10 days. Viremia generally lasts for 4 to 5 days, and the disappearance of viremia correlates with defervescence.

Ferritin in Dengue: Ferritin is a positive acute phase reactant, synthesized and secreted by hepatocytes, macrophages and cancer cells, among many others, with a positive role in various scenarios of inflammation. The subunit composition of ferritin like H, L units differentiate the various isoforms that ultimately determine the functional characteristics of ferritin. Iron storage during immune activation is essential for the protective function against infectious agents, oxidative damage, inflammatory conditions and neoplasms.

Ferritin molecule consists of a 3-D outer protein shell, with H and L subunits capable of converting and storing up to 4500 iron atoms in the harmless, insoluble oxidized form (Fe3+). Iron storage involves 3 steps: oxidation (by ferroxidase center in H subunit) and hydrolysis and iron core growth by nucleation (managed by L subunit) [6, 7].

Ferritin can function in both intracellular and extracellular capacity and some quantity is present in the serum. Intracellular ferritin is mainly concerned with iron metabolism and extracellular ferritin is part of iron delivery system. Therefore 'serum' ferritin is somewhat of a misplaced entity, in which case has been found to be released from

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damaged cells during inflammation. In case of cell damage by inflammation in the course of many systemic diseases or any pathology the cytokines take over as the major factor for initiation of ferritin synthesis [8, 9].

Ferritin is degraded by proteasomal or lysosomal pathways or in case of inflammatory diseases wherein ferritin is converted to its metabolite hemosiderin. Some examples of diseases where serum ferritin is used as an inflammatory marker are acute respiratory distress syndrome, amyotrophic lateral sclerosis (Lou Gehrig's disease), atherosclerosis, cancer, liver cirrhosis, CAD, CKD, type II diabetes mellitus, hypertension, metabolic syndrome, multiple sclerosis, myocardial infarction, NAFLD, preeclampsia, rheumatoid arthritis, SLE, stroke, sepsis and so on. Increased ferritin can be due to genetic factors as well which is associated with the hereditary hemochromatosis and neuroferritinopathy. Other common causes for increased ferritin include ineffective erythropoiesis (sideroblastic anemia, the congenital dyserythropoietic anemias, beta-thalassemia major), and chronic blood transfusion (in beta-thalassemia major, sickle cell disease). Uncommon causes include chronic liver diseases, and other autoimmune disorders, including the hereditary hyperferritinemia-cataract syndrome [10, 11, 12, 13, 14, 15, 16, 17].

An excess of serum ferritin is termed hyperferritinemia (greater than 500ng/ml). A value above 500 ng/ml is significant in inflammatory diseases, while in some diseases (Macrophage activation syndrome and HLH) as much as greater than 10000 ng/ml is considered significant. Ferritin values >1000ng/ml are considered non-specific markers of inflammatory activity [18, 19, 20].

Ferritin has been exhaustively researched and many new utilities and functions unearthed, such as, and in addition to those mentioned above-the function of an immune modulation system, regulation of myelopoiesis and angiogenesis, regulation of levels of inflammatory mediators such as prostaglandins and bradykinin, as a theranostic and diagnostic marker in certain types of cancer (pancreatic cancer, lung cancer, Hodgkin's lymphoma), and other new functions being revealed. In a study, ferritin is detected at higher levels in blood of oncology cases and higher levels were found to be consistent with poor prognosis [21, 22, 23, 24, 25].

Serum ferritin is now being evaluated as a more sensitive biomarker that has shown more significant elevations in inflammatory conditions than in iron overload or iron deficiency states (for example in iron deficiency anemia). The sensitivity and specificity of it's utility as a prognostic and diagnostic marker can be experimented in the clinical milieu.

Materials and Methods

Seventy fever cases from outpatient centers of departments of Medicine, Surgery, Obstetrics and Gynecology, Hematology and Biochemistry labs of Sree Balaji Medical College, Chennai during 2021 to 2022 Observational, Analytical cross sectional study was done by the approval of the institutional ethical committee.

Inclusion Criteria: Seventy (29 Male and 41 Female) serologically confirmed dengue patients were selected for the study Out of 70 patients 11 patients were additional symptoms of joint pain, cough, constipation and abnormal CBC counts (as per 2012WHO criteria) remaining patients with fever, weakness and rashes. Both male and female were above the eighteen years. Serum ferritin and platelet were used as a variable. Severity of dengue fever was evaluated by these markers.

Exclusion Criteria: Dengue cases not confirmed by the laboratory were not included. Hematological neoplasm was not considered. The critical and recovery phase Dengue patients were eliminated. Less than eighteen years of male and female Dengue patients were excluded.

Methodology

Patients from selected population who presented to the outpatient service center were inquired about demographic details, duration of fever, and other history specific to natural history of other causes. History regarding bleeding and complications of dengue fever (e.g., petechiae, vomiting, abdominal pain, joint pain, maculopapular rashes and shock) was elicited. DHF and DSS were diagnosed based on the WHO revised criteria for dengue. NS1 serology was done and seropositive dengue cases identified. Laboratory tests for serum ferritin, complete blood count (CBC) was done.

Sample Collection

- Under aseptic precautions, venous blood was collected with minimal stasis using dry and sterile disposable syringe and needle.
- Venous samples for complete blood count (CBC), serum Ferritin were collected in EDTA tubes. Samples were labeled with patients name, age, sex, identification number and stored at room temperature.
- Samples were tested as soon as possible or within one hour of collection to reduce variations caused by sample changes associated with time.
- Samples were run in Mindray BC-6800 analyzer and values collected.

Laboratory Analysis

Complete blood count (CBC) was done using MINDRAY, a 5 part analyzer. Platelet count and values of platelet indices were isolated from the CBC of each case. Serum ferritin was done separately. Standardization and calibration of the instrument and sample processing was done as per as instructions of manufacturers and lab quality control protocol. The analyzer followed the sheath fluid impedance principle to calculate Total RBC counts and platelet count. The laser flow cytometry principle was used to calculate the total WBC count. Serum ferritin was calculated by an automated Beckman-Coulter analyzer. Clinical history was collected from medical records department. After baseline investigations and review of clinical history, patients were classified into different categories of dengue according to the WHO classification of dengue: Undifferentiated fever/viral syndrome, Dengue fever (with or without hemorrhage, Dengue hemorrhagic fever, Dengue shock syndrome and isolated organopathy.

Statistical Analysis

Calculations were done using SPSS 21 and Microsoft excels data analysis Tool Pak. Data are presented as mean along with SD. One way analysis of variance (ANOVA) with post-hoc Tukey's Honest Significant Difference test, Spearman's Rho correlation, Chi square test of independence were used to compare more than two independent samples for correlation and significance. T test for single samples were done. $P < 0.05$ ($\alpha = 0.05$) was considered to be statistically significant.

Results and Discussion

70 cases of fever of various causes were studied. The study of age distribution, gender distribution and serum ferritin was

done. Serum ferritin derived parameters such as MPV, PDW were studied in: a) Seropositive dengue cases b) Cases clinically diagnosed and confirmed as dengue fever, dengue hemorrhagic fever c) For identifying, if any, the relation and correlation between individual variable and multiple variables (of independent means) in the study sample.

Table 1: Age Distribution

Age (in years)	Number	Percentage
<30	30	43%
30-44	15	21%
45-60	12	17%
>60	13	19%

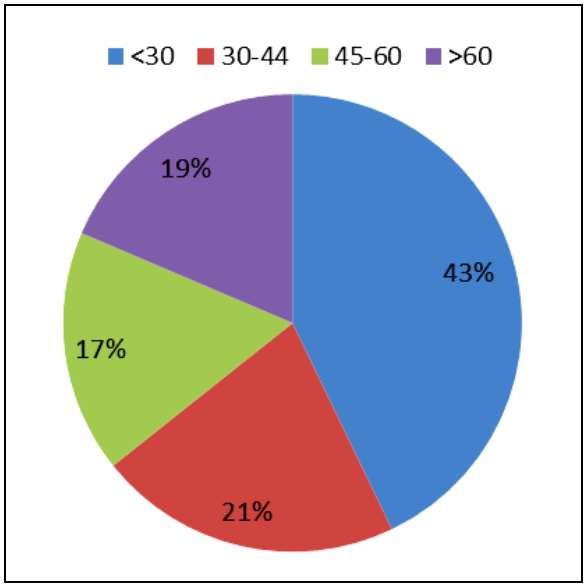

Chart 1: Age Distribution

Most common ages affected is between 18-30 years (43%). 21% of cases were between 30-44 years of age. 17% of cases were between 45-60 years of age. 19% of cases were above 60 years of age. Mean age in years of population affected in the study is 18-30 years.

Table 2: Sex Distribution

Sex	Number	Percentage
F	41	59%
M	29	41%

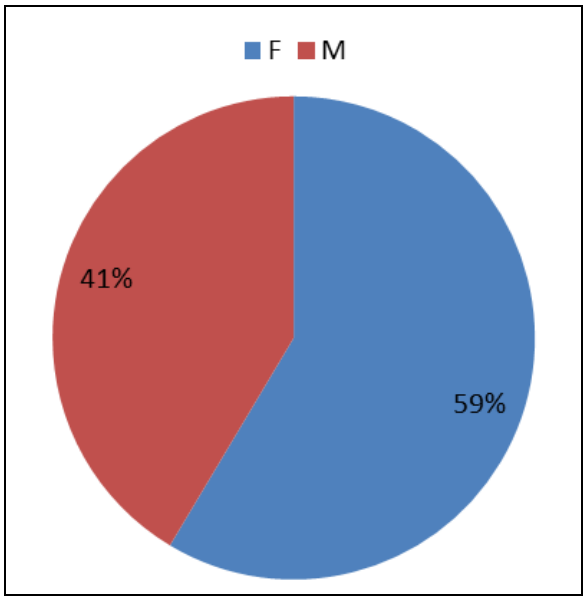

Chart 2: Sex Distribution

Female patients (59%) are more commonly affected than male patients (41%). The ratio is 1.44:1 (male: female).

Table 3: Serum Ferritin

Serum Ferritin (µg/L)	Number	Percentage
0-500	55	79%
500-1000	6	9%
1000-1500	2	3%
1500-2000	6	9%
2000-2500	1	1%

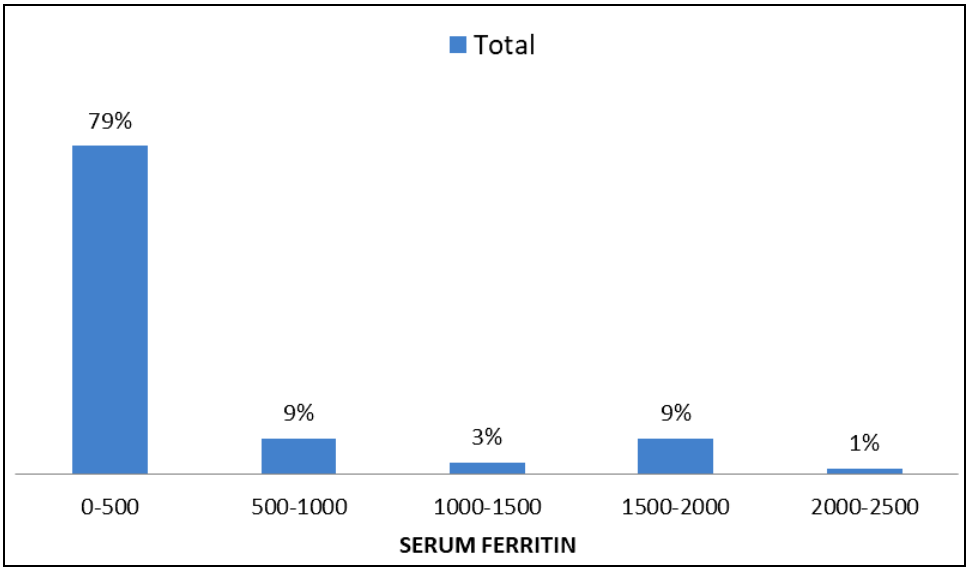

Chart 3: Serum Ferritin Distribution

Most of the cases (79%) had serum ferritin values less than 500µg/L, which was not statistically significant. 21% percent of cases, had serum ferritin values above 500µg/L.

Table 4: Age Distribution of Serum Ferritin

Age (In Years)	Serum Ferritin (µG/L)				
	0-500	500-1000	1000-1500	1500-2000	2000-2500
<30	30	0	0	0	0
30-44	12	0	0	2	1
45-60	10	1	0	1	0
>60	3	5	2	3	0

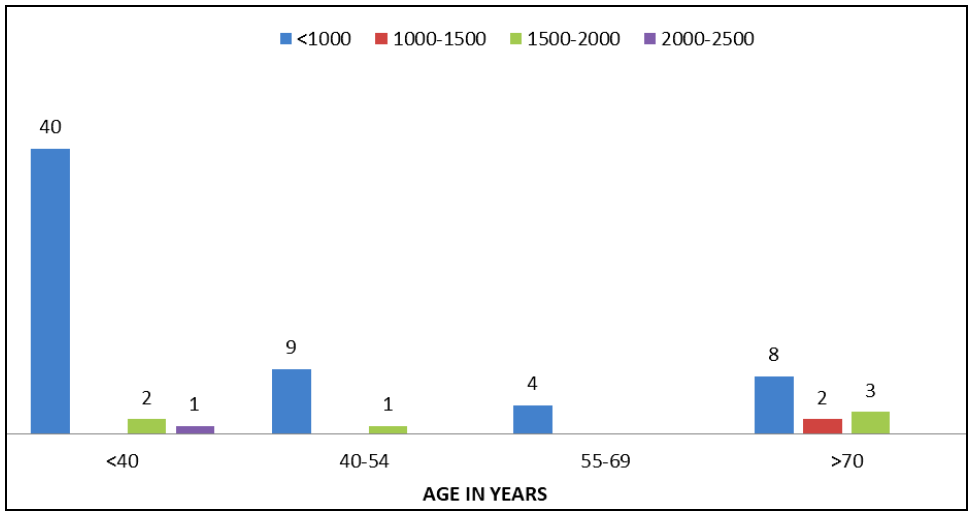

Chart 4: Age Distribution of Serum Ferritin

Serum ferritin values were mostly between 0-500 µg/L for age group less than 30 years. Patients of that age group did not present with a high serum ferritin value. Higher serum ferritin values (>500µg/L) were seen in cases more than 30 years of age.

Table 5: Age Vs Serum Ferritin

Age (In years)	Serum Ferritin (µg/L)					Total
	0-500	500-1000	1000-1500	1500-2000	2000-2500	
<30	30	0	0	0	0	30
30-44	12	0	0	2	1	15
45-60	10	1	0	1	0	12
>60	3	5	2	3	0	13
Total	55	6	2	6	1	70

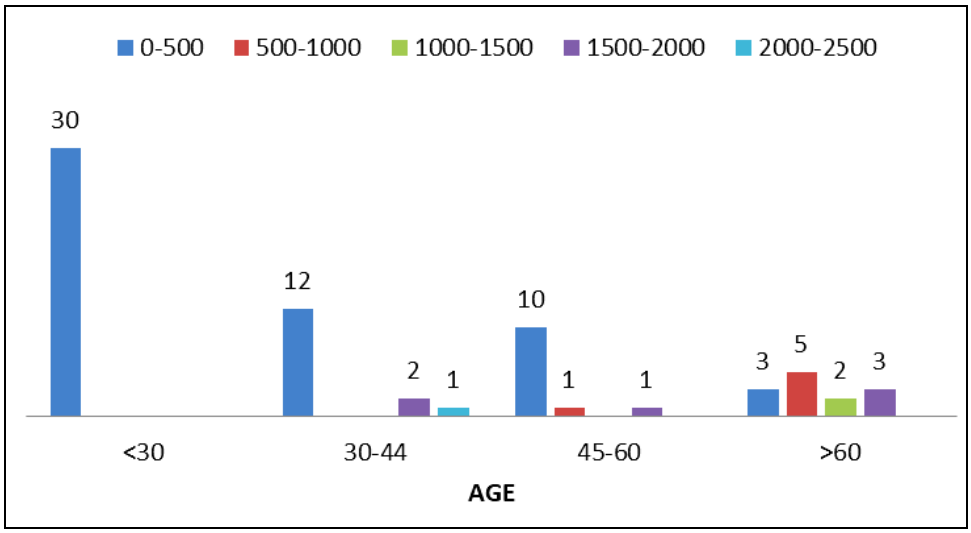

Chart 5: Age Vs Serum Ferritin

Patients less than 30 years commonly presented with lower serum ferritin values (0-500µg/L). Patients older than 30 years commonly presented with higher serum ferritin values (>500µg/L).

Table 6: Diagnosis Vs Serum Ferritin

Diagnosis	Serum Ferritin (µg/L)					Total
	0-500	500-1000	1000-1500	1500-2000	2000-2500	
DF	55	3	0	1	0	59
DHF	0	3	2	5	1	11
Total	55	6	2	6	1	70

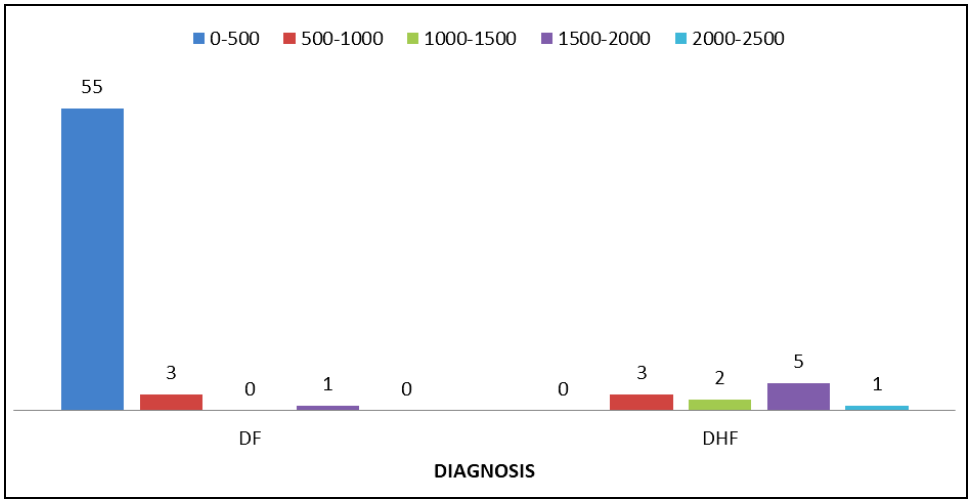

Chart 6: Diagnosis Vs Serum Ferritin

Most cases presenting with DF had lower serum ferritin values (0-500µg/L). Most cases presenting with DHF had higher serum ferritin values (>500µg/L).

Table 7: Serum Ferritin Vs PDW

PDW (fl)	Serum Ferritin (µg/L)					Total
	0-500	500-1000	1000-1500	1500-2000	2000-2500	
<14	13	2	0	0	0	15
14-15	21	2	1	0	1	25
>15	21	2	1	6	0	30
Total	55	6	2	6	1	70

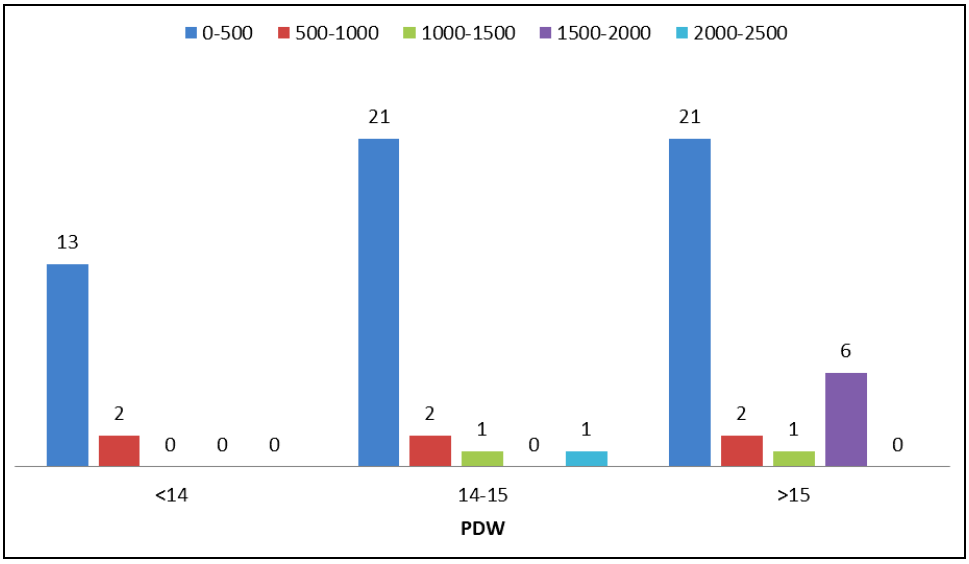

Chart 7: Serum Ferritin vs PDW

Patients presenting with high PDW values (>14 fl) more commonly had higher serum ferritin values (>500µg/L) when compared to those with lower PDW values (<14 fl) who had lower serum ferritin values (0-500µg/L).

Table 8: Age Vs Serum Ferritin\

Serum Ferritin (µg/L)	Age (in years)	
	Mean	SD
0-500	13.75	11.50
500-1000	1.5	2.38
1000-1500	0.5	1.00
1500-2000	1.5	1.29
2000-2500	0.25	0.50
P value = <.001 (0.00095)		
SPEARMAN's RHO Correlation		

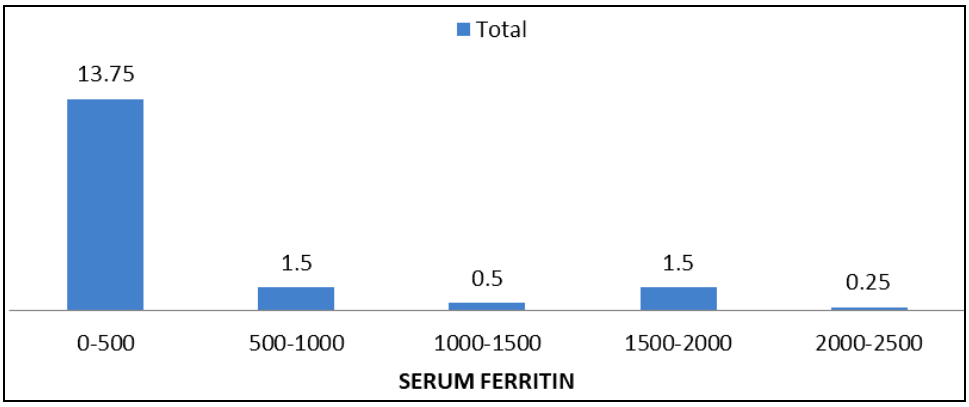

Chart 8: Age

In this study, age (in years) and serum ferritin values were mildly correlated (r(138) = 0.39, p value = <.001).

Table 9: Diagnosis VS age

Diagnosis	Age (in years)	
	Mean	SD
DF	14.75	10.37
DHF	2.75	2.5
P value = .007		
CHI Square Test of Independence		

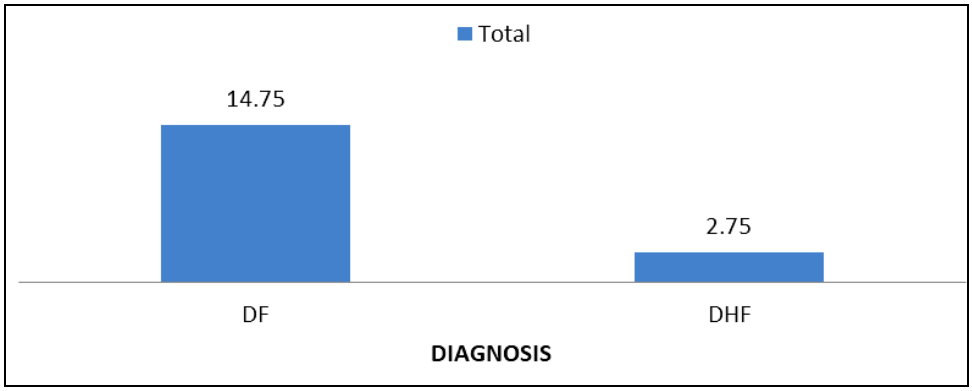

Chart 9: Diagnosis VS Age

In this study, the relation between diagnosis and age in years was significant ($\chi 2$ (3, n = 70) = 12.08, p value = .007). Most common diagnosis for the ages (18-60 years) was Dengue fever followed by Dengue hemorrhagic fever.

Table 10: Diagnosis Vs Serum Ferritin

Serum Ferritin (µg/L)	Diagnosis	
	Mean	SD
0-500	27.5	38.89
500-1000	3	0.00
1000-1500	1	1.41
1500-2000	3	2.83
2000-2500	0.5	0.71
P value = <.001		
CHI Square Test of Independence		

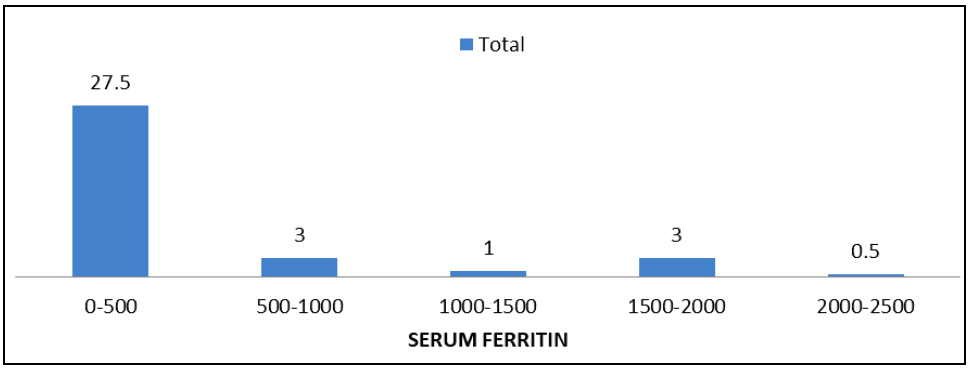

Chart 10: Diagnosis Vs Serum Ferritin

In the study sample, the relation between diagnosis and serum ferritin values were strongly correlated ($\chi 2$ (1, n = 70) = 41.75, p value = <.001). Seropositive dengue cases are more likely to present with increased serum ferritin values.

Table 11: Serum Ferritin VS PDW

Serum Ferritin (µg/L)	PDW (fl)	
	Mean	SD
0-500	18.33	4.62
500-1000	2	0.00
1000-1500	0.67	0.58
1500-2000	2	3.46
2000-2500	0.5	0.58
P value = .0032		
Spearman's RHO Correlation, ANOVA with Tukey's HSD Test		

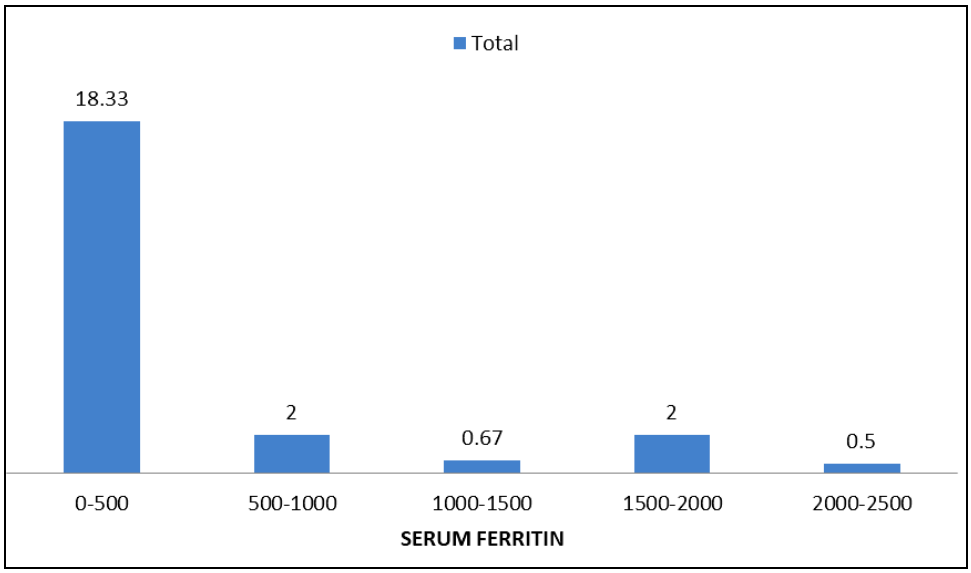

Chart 11: Serum Ferritin VS PDW

In the study sample, serum ferritin and PDW were positively correlated (r(138) = 0.35, p value = .003). A high serum ferritin is likely to present with high PDW values in seropositive dengue cases.

Discussion

In this study of 70 serologically confirmed dengue cases, the following can be concluded. Most of the cases in this study were between 18-30 years of age, followed by older adults and the elderly. Several previous studies also report similar findings. Egger *et al* note a high incidence of dengue in the age group of 20-40 years age group [26]. Barraquer *et al* also report similar findings [27]. Cavalcanti *et al* note their findings of DF/DHF cases most commonly presenting in the age range of 20-59 years [28].

Patients in this study predominantly presented with only fever, weakness, rashes, thus categorizing them as dengue fever (as per WHO 2012 criteria). Of the 70 cases that were studied, 11 cases presented with additional symptoms of joint pain, vomiting, abdominal pain, cough, constipation, petechiae and abnormal lab CBC counts. Such cases were clinically categorized as DHF (as per 2012 WHO criteria). Similar findings have been noted by Basawarajappa *et al* and Mohammed *et al*. [29, 30]. In this study, patients underwent clinical management and supportive therapy and did not develop shock due to plasma leakage. Younger people (<30 years) more commonly presented with DF and older age group (>30 years) presented with DHF (p = .007).

Hyperferritinemia is usually seen in inflammatory conditions as it is an acute phase reactant, due to infections, autoimmune conditions and other innumerable diseases. The value of serum ferritin in dengue as a diagnostic and prognostic indicator has been a topic of study among many researchers. Lee *et al* studied 1826 patients presenting with high serum ferritin levels, of which 15.8% presented with a non-HIV systemic infection. These cases had a serum ferritin value of above 1000 ng/ml. Valero *et al* note a correlation between serum ferritin and dengue cases. Kanitkar *et al* note that severe dengue cases present with a higher serum ferritin values (>600 ng/ml). Similar findings have been reported by Moras *et al*, Kiran *et al*, Suresh *et al* and Sethi *et al*.[31,32,33] Lodha *et al* report a positive correlation between serum ferritin and platelet count in their cohort.[32] In this study, most cases presented with serum ferritin values of less than 500/µL. Younger cases (<30 years) present with lower serum ferritin values (<500µg/L). Older adults and the elderly more commonly presented with higher serum ferritin values. In the cases diagnosed as DF, most serum ferritin values were less than 500 µg/L, while DHF cases predominantly had higher serum ferritin values (up to 2300 µg/L). Patients with high serum ferritin in a positive dengue case commonly presented with low platelet count (p = .036), high PDW value (p < .003) in the present study.

Conclusions

The relation between age, sex, diagnosis, serum ferritin and platelet derived parameters such as Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet count were studied in 70 cases of NS1 serology positive dengue. Some variables showed statistically significant correlations. It was found that:

i). Age (in years) and serum ferritin values were mildly correlated
ii). The relations between diagnosis and serum ferritin values were strongly correlated-Seropositive dengue cases are more likely to present with increased serum ferritin values.
iii). Serum ferritin and platelet count were found to be negatively correlated-A high serum ferritin is likely to present with low platelet count in seropositive dengue cases.
iv). Serum ferritin and PDW were positively correlated-A high serum ferritin is likely to present with high PDW values in seropositive dengue cases.
v). MPV and PDW were negatively correlated-Low MPV is likely to present with high PDW values in seropositive dengue cases.
vi). These markers can be used as an indicator for diagnosis of dengue and in predicting complications of dengue vasculopathy such as dengue hemorrhagic fever and dengue shock syndrome. At the minimal state, these parameters and trends can be used as preclinical indicators of development of complications and 'warning signs' of dengue.

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