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Association Of Liver Enzymes And Severity Of Dengue Fever In Patients Presenting To A Tertiary Care Centre In Mangaluru.

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Abstract
Background: *Dengue, a viral disease transmitted by mosquitoes, holds significant global importance. It is vital to promptly identify the disease and provide appropriate care in order to minimize the associated illness and death. Early prediction of the disease's progression and timely interventions could potentially prevent these fatalities. In addition to using diagnostic tests to detect dengue fever, one noteworthy finding is that individuals with dengue fever tend to exhibit elevated levels of serum ferritin. Hyperferritinemia, characterized by increased ferritin in the blood, is linked to immune activation and disturbances in blood clotting. A direct correlation has been observed between the severity of dengue fever and the rise in serum ferritin levels. This study aims to find the association between the association between liver enzymes and severity of dengue.*
Materials and methods: *This prospective observational study was conducted in patients who were hospitalized with Dengue fever at Yenepoya Medical College, Mangalore. Patients with underlying liver disease and inflammatory conditions like bacterial infections, COVID 19 infection were omitted from the study. A total of 38 patients were admitted and their liver enzymes were sent. All the subjects detected with NS1 antigen or IgM for dengue fever confirmed by ELISA who are in acute febrile phase were included in the study. Their serum ferritin values and liver enzymes were checked. The data was analyzed using IBM SPSS version 23 operating on windows 10.*
Results: *Total of 38 dengue cases were studied out of them, 18 had mild dengue, 14 had Dengue with warning signs and 6 were severe dengue. Mean serum ferritin value in the study was 718.5+/-355.8 and with range of 36 to1000 ng/ml. The other parameters like SAST/ALT/ALP also showed association but are statistically insignificant.*
Conclusion: *Study showed liver parameters shows association with the severity of dengue illness, hence can be used to prognosticate the illness.*
Keyword: *Dengue fever, Liver enzymes, Ferritin*

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I. Introduction

Dengue fever is an acute febrile illness characterized by sudden onset of symptoms such as fever, severe headache, muscle pain, retro orbital discomfort, loss of appetite, gastrointestinal issues, and a rash. It is caused by flaviviruses, specifically four serotypes, and is transmitted to humans through the bite of infected Aedes aegypti mosquitoes. The incubation period ranges from 4 to 7 days [1]. Dengue Hemorrhagic Fever (DHF) is a more severe form of the disease, characterized by increased vascular permeability, hypovolemia, and abnormal blood clotting. Dengue fever, including DHF and Dengue Shock Syndrome (DSS), has become a major global public health concern. The geographical range of dengue has expanded due to factors such as population growth, urban development, and water storage practices. Dengue is now considered the most significant mosquito-borne viral disease worldwide. Approximately 112 countries are endemic, and about 40% of the global population (2.5-3 billion people) is at risk in tropical and subtropical regions. Each year, there are around 100 million cases of dengue fever and half a million cases of DHF worldwide. Early identification and prompt care are crucial to reduce disease-related complications and mortality. Early prediction of disease progression and timely interventions can help prevent deaths associated with dengue **[2]**.In addition to diagnostic testing, high levels of serum ferritin, an acute phase reactant released by reticuloendothelial cells, have been observed in dengue fever [3]. Hyperferritinemia is linked to immune activation and coagulation abnormalities [4]. An increase in serum ferritin levels has been found to correlate with the severity of dengue fever **[5]**.

II. Material & method

This prospective observational study was carried out on patients of Department of General Medicine at Yenepoya Medical College Hospital, Mangalore for a period of two years 2019 to 2021. A total of 38 subjects were included in this study.

Study setting and population: Patients of dengue fever admitted in wards and ICU of YMCH.

Study period: 2 years.

Study type: prospective observational study

Inclusion criteria: All the subjects detected with NS1 antigen or IgM for dengue fever confirmed by ELISA who are in acute febrile phase (1-3 days of fever)

Exclusion criteria:

- Patients with pre existing liver disease.
- Patients with active covid-19 infection
- Patients with iron deficiency anemia and iron over load state
- Bacterial infections
- All other acute febrile illness other than dengue.
- Patients on anti platelets and anticoagulants
- Vitamin B12 deficiency.
- Other causes of increased ferritin levels like hyperthyroidism, leukemia, rheumatoid arthritis, frequent blood transfusions.
- Patients with alcohol abuse**.**

Study procedure: All the patients meeting the inclusion criteria and exclusion criteria were explained about the study. Informed consent was taken from all the participants. •Serum ferritin levels was measured on the day of admission. Patients were followed up throughout the hospital stay and severity of dengue was assessed basing on WHO criteria. A 3ml of blood sample was drawn from included patients under all aseptic precautions and subjected to centrifuge the sample after 15mins at the RPM of 3000 for 5-7mins of time. The serum ferritin was measured using the standardized method on fully automated analyzer

Sample size: Sensitivity of Serum ferritin was estimated to be 85.7% by the article published on Role of serum ferritin and serum amino transferase in predicting the severity in dengue fever with thrombocytopenia by Diwakar(Tamil Nadu). Sample size: Total of 38 patients with dengue fever were included in present study. •Patients were classified in to

1. Classical (without warning signs) dengue that is dengue fever without complications.
2. Dengue with warning signs
3. Severe dengue : dengue fever with complications

Statistical analysis

All the data was entered in excel spreadsheet and the data was analyzed using IBM SPSS version 23 operating on windows 10. The continuous data were summarized as mean and standard deviation and categorical variables using frequency and percentage. The pie chart and bar charts were used to demonstrate the result graphically. The mean difference between the continuous data was analyzed using the student t-test and the correlation was assessed using Pearson's correlation. The diagnostic characteristics of the serum ferritin were calculated by ROC curve to derive the sensitivity, specificity and the accuracy of ferritin cutoff. A p-value <0.05 was considered statistically significant.

III. Results

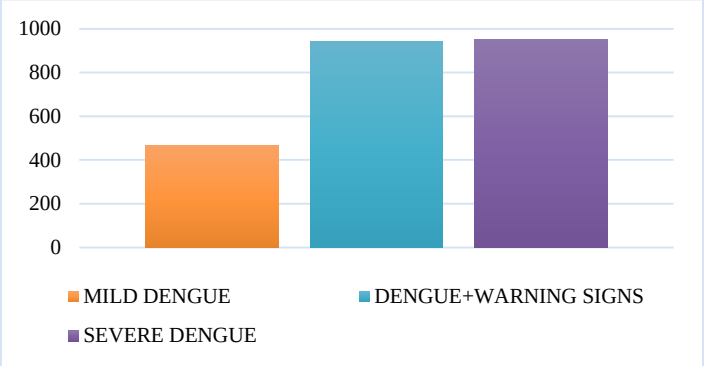
Table 1: MEAN age group of our study population

AGE	
Mean	34.57895
Standard Error	2.329119
Median	30
Mode	40
Standard Deviation	14.35765
Sample Variance	206.1422
Kurtosis	0.018849
Skewness	0.721506
Range	59
Minimum	16
Maximum	75
Count	38
Confidence Level(95.0%)	4.719244

Table 2: Table with respect to age and gender

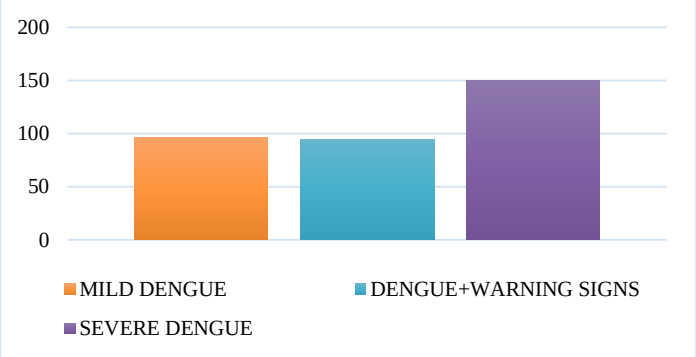
AGE	Female		Male		Total	
0-19	1	2.63%	5	13.16%	6	15.79%
20-39	7	18.42%	9	23.68%	16	42.11%
40-59	5	13.16%	10	26.32%	15	39.47%
60-80		0.00%	1	2.63%	1	2.63%
Grand Total	13	34.21%	25	65.79%	38	100.00%

Graph 1: Graph showing the serum ferritin in dengue groups



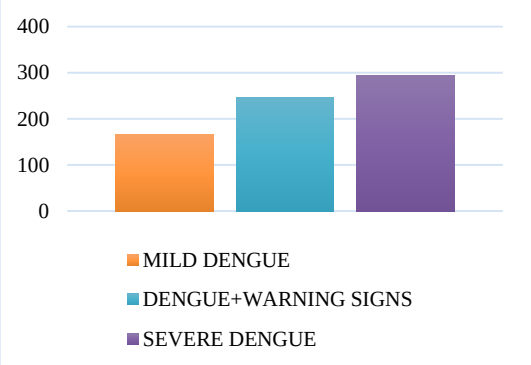
The present study showed mean values of serum ferritin least being the mild dengue with 466.1,dengue with warning signs and sever dengue had higher serum ferritin values with 942.9and 952.3 respectively.

Graph 2: Graph showing serum ALP with severity of dengue fever .

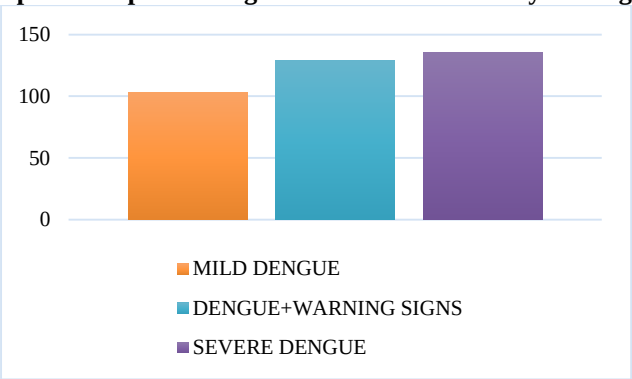


The study showed mean ALP of 104.1/-81,with a range of 52-345.with the increases in sevierity of dengue there is rise in ALP level but it was statistically insignificant with p>0.05.

Graph 3: Graph showing AST and severity of dengue



Graph 4: Graph showing serum ALT and severity of dengue



Objective-wise Table

Table 1: Serum ferritin in different dengue groups

ANOVA: Single Factor					
SUMMARY					
Groups	Count	Sum	Average		Variance
MILD DENGUE	18	8388.9	466.05		122476.1
DENGUE+WARNING SIGNS	14	13200	942.8571		27252.75
SEVERE DENGUE	6	5714	952.3333		13632.67

ANOVA						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	2179932	2	1089966	15.23185	0.0000174	3.267424
Within Groups	2504543	35	71558.37			
Total	4684475	37				

F-Test Two-Sample for Variances		
	Variable 1	Variable 2
Mean	674.6531	952.3333
Variance	136345.9	13632.67
Observations	32	6
Df	31	5
F	10.00141	
P(F<=f) one-tail	0.008607	
F Critical one-tail	4.491621	

t-Test: Two-Sample Assuming Unequal Variances		
	Dengue+/-warning sign	Sever dengue
Mean	664.1581	942.8
Variance	137248.6	16359.2
Observations	31	5
Hypothesized Mean Difference	0	
Df	18	
t Stat	-3.17558	
P(T<=t) one-tail	0.002618	
t Critical one-tail	1.734064	
P(T<=t) two-tail	0.005236	
t Critical two-tail	2.100922	

Table 2: Serum ALP median in the different dengue groups

Anova: Single Factor						
SUMMARY						
Groups		Count	Sum	Average	Variance	
MILD DENGUE		18	1726	95.88889	1070.928	
DENGUE+WARNING SIGNS		14	1329	94.92857	1191.918	
SEVERE DENGUE		6	902	150.3333	10144.27	
ANOVA						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	15216.30242	2	7608.151	3.154215	0.055019	3.267424
Within Groups	84422.03968	35	2412.058			
Total	99638.34211	37				

F-Test Two-Sample for Variances		
	Variable 1	Variable 2
Mean	95.46875	150.3333
Variance	1087.353831	10144.27
Observations	32	6
Df	31	5
F	0.107189003	
P(F<=f) one-tail	1.68058E-05	
F Critical one-tail	0.396426167	

t-Test: Two-Sample Assuming Unequal Variances		
	MILD DENGUE+/-WARNING SIGNS	SEVERE DENGUE
Mean	95.46875	150.3333
Variance	1087.353831	10144.27
Observations	32	6
Hypothesized Mean Difference	0	
df	5	
t Stat	-1.3211023	
P(T<=t) one-tail	0.121847006	
t Critical one-tail	2.015048373	
P(T<=t) two-tail	0.243694012	
t Critical two-tail	2.570581836	

Table 3: Serum AST in different dengue groups

Anova: Single Factor						
SUMMARY						
Groups		Count	Sum	Average	Variance	
MILD DENGUE		18	1854	103	6453.176	
DENGUE+WARNING SIGNS		14	1800	128.5714	4415.187	
SEVERE DENGUE		6	811	135.1667	14163.37	
ANOVA						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	7373.238	2	3686.619	0.542336	0.586195	3.267424
Within Groups	237918.3	35	6797.665			
Total	245291.5	37				

t-Test: Two-Sample Assuming Unequal Variances		
	MILD DENGUE+/-WARNING SIGNS	SEVERE DENGUE
Mean	201.0938	293.3333
Variance	19838.35	88391.07
Observations	32	6
Hypothesized Mean Difference	0	
df	5	
t Stat	-0.74445	
P(T<=t) one-tail	0.245045	
t Critical one-tail	2.015048	
P(T<=t) two-tail	0.490089	
t Critical two-tail	2.570582	

F-Test Two-Sample for Variances		
	Variable 1	Variable 2
Mean	114.1875	135.1667
Variance	5556.48	14163.37
Observations	32	6
Df	31	5
F	0.392313	
P(F<=f) one-tail	0.048139	
F Critical one-tail	0.396426	

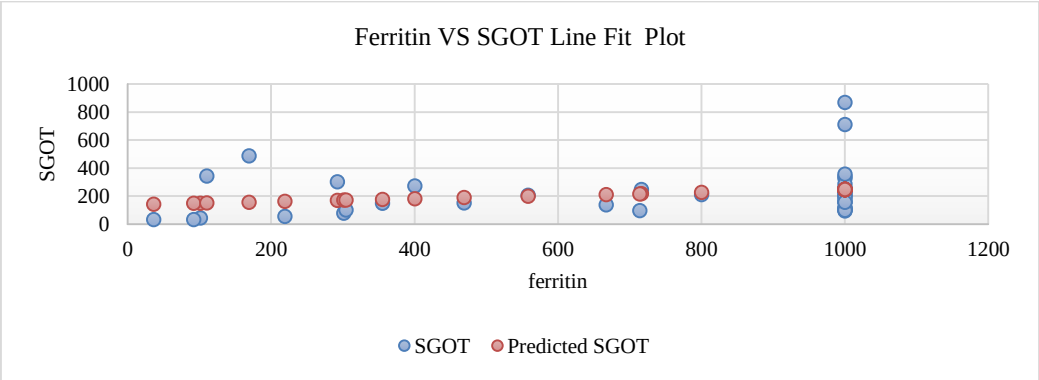
t-Test: Two-Sample Assuming Unequal Variances		
	MILD DENGUE+/-WARNING SIGNS	SEVERE DENGUE
Mean	114.1875	135.1667
Variance	5556.48	14163.37
Observations	32	6
Hypothesized Mean Difference	0	
Df	6	
t Stat	-0.41674	
P(T<=t) one-tail	0.345683	
t Critical one-tail	1.94318	
P(T<=t) two-tail	0.691365	
t Critical two-tail	2.446912	

Table 4: Serum ALT in different dengue groups

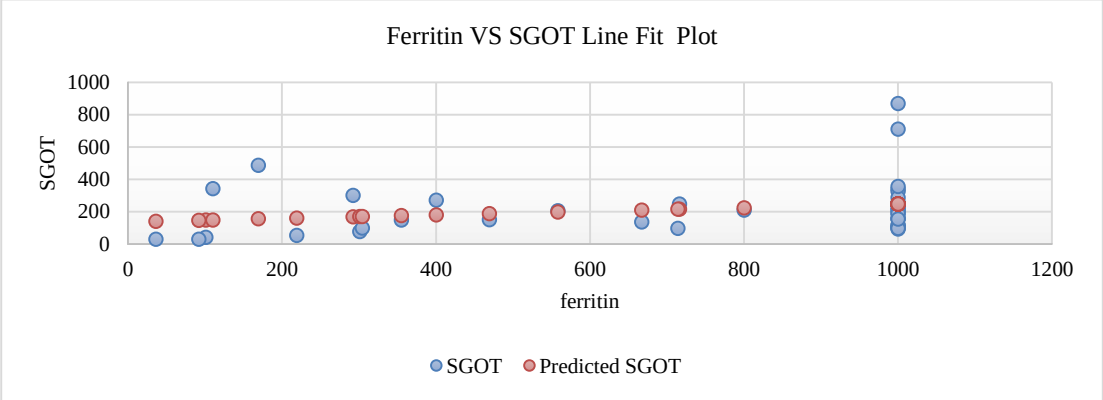
F-Test Two-Sample for Variances		
	Variable 1	Variable 2
Mean	201.0938	293.3333
Variance	19838.35	88391.07
Observations	32	6
df	31	5
F	0.224438	
P(F<=f) one-tail	0.003569	
F Critical one-tail	0.396426	

Ferritin vs AST								
Regression Statistics								
Multiple R	0.225474							
R Square	0.050838							
Adjusted R Square	0.024473							
Standard Error	170.294979							
Observations	38.000000							
ANOVA								
	df	SS	MS	F	Significance F			

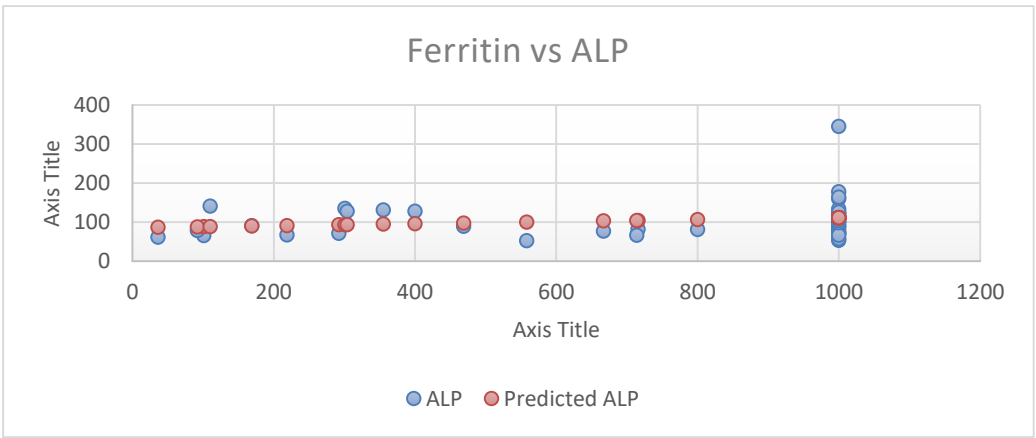
Regression	1.000000	55918.876225	55918.876225	1.928212	0.173487			
Residual	36.000000	1044013.676407	29000.379900					
Total	37.000000	1099932.552632						
	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Uper 95%	Lower 95.0%	Upper 95.0%
Intercept	137.157120	62.921122	2.179826	0.035891	9.547169	264.767070	9.547169	264.767070
ferritin	0.109257	0.078681	1.388601	0.173487	-0.050316	0.268830	-0.050316	0.268830



Ferritin vs ALT								
Regression Statistics								
Multiple R	0.123969							
R Square	0.015368							
Adjusted R Square	-0.01198							
Standard Error	81.90811							
Observations	38							
ANOVA								
	df	SS	MS	F	Significance F			
Regression	1	3769.73	3769.73	0.561897	0.458368			
Residual	36	241521.8	6708.938					
Total	37	245291.5						
	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	97.11786	30.26366	3.209058	0.002798	35.7403	158.4954	35.7403	158.4954
ferritin	0.028368	0.037844	0.749598	0.458368	-0.04838	0.105119	-0.04838	0.105119



Ferritin vs ALP								
Regression	Statistics							
Multiple R	0.180232							
R Square	0.032483							
Adjusted R Square	0.005608							
Standard Error	51.74772							
Observations	38							
ANOVA								
	df	SS	MS	F	Significance F			
Regression	1	3236.598	3236.598	1.208666	0.278894			
Residual	36	96401.74	2677.826					
Total	37	99638.34						
	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	85.24562	19.11991	4.458474	7.75E-05	46.46864	124.0226	46.46864	124.0226
ferritin	0.026285	0.023909	1.099394	0.278894	-0.0222	0.074775	-0.0222	0.074775



IV. Discussion

The dengue virus affects over 50 million people annually, making it a significant healthcare issue, particularly in developing countries like India where proper water storage and handling techniques are lacking, leading to mosquito breeding and the spread of dengue and malaria. Dengue infection can manifest as dengue without warning signs, dengue with warning signs, or severe dengue. Elevated ferritin levels are observed in

immune activation and have recently been identified as an important marker of disease activity [6]. In our study, we found that the mean values of serum AST were 215.7+/-172.4, with a range of 30 to 868, and the mean values of serum ALT were 117.5+/-81.4, with a range of 14 to 371. The mean ALP levels were 104.1+/-81, ranging from 52 to 345. Other studies reported higher AST and ALT values, such as 1126.4 IU/L and 395.7 IU/L, respectively. The severity of dengue appeared to increase with higher levels of serum AST, ALT, and ALP, although statistical significance was not observed (P value > 0.05). In our study, we found that increased ferritin concentrations were associated with severe dengue. Hyperferritinemia in dengue was also linked to thrombocytopenia and increased levels of liver enzymes (AST, ALT, ALP). However, the Pearson correlation test and line fit plot did not reveal a significant correlation between Hyperferritinemia and elevated liver enzymes. In contrast, a study by van de Weg et al. did find a significant correlation between Hyperferritinemia, severe dengue, and elevated liver enzymes [7].

V. Limitations of study

There are several limitations to consider in this study.

- The study was conducted at a single center, which may limit the generalizability of the findings to a broader population.
- The sample size was relatively small, primarily due to factors such as the seasonal nature of the disease and the impact of the COVID-19 pandemic.

These limitations should be taken into account when interpreting the results and further research with larger and more diverse samples would be beneficial.

VI. Conclusion

Study showed liver parameters shows association with the severity of dengue illness, hence can be used to prognosticate the illness.

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