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Original Research Paper

Role of Serum Ferritin as a prognosticating tool in the course of Dengue fever

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ABSTRACT:
BACKGROUND: Dengue is the most significant mosquito-borne viral disease in the world. Identification of the disease along with initiation of care is crucial if disease-related morbidity and mortality are to be reduced. These deaths could be prevented by early prediction of the course of the disease and early interventions. Apart from diagnostic testing for the detection of dengue fever, serum ferritin level found to be high in dengue fever. Hyperferritinemia is associated with immune activation and coagulation disturbances. A rise in serum ferritin level has been observed to have a linear correlation with severity of dengue fever. **MATERIALS AND METHODS:** A total of 38 patients admitted under general medicine in Yenepoya Medical College and hospital, Mangalore, Karnataka, and who has been diagnosed with dengue fever, confirmed by Dengue IgM ELISA were taken and their serum levels of ferritin were measured. **RESULTS AND OBSERVATIONS:** 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 to1000ng/ml. As the severity of dengue increased there was increase in the serum ferritin level (P value < 0.05). Serum ferritin of 714 was considered as the cut off value for differentiation of the severe dengue from mild dengue and dengue with warning signs. **CONCLUSION**: In this study, the ROC curve was used to calculate the cut of value with highest sensitivity. Serum ferritin of 714 was considered as the cut off value for differentiation of the severe dengue from mild dengue and dengue with warning signs. There was statistically significant association of ferritin with severity of dengue, as the severity increases there is increase in serum ferritin. Thus we conclude that Serum ferritin is a reliable predictor of the dengue fever with a sensitivity of 100% and Specificity of 43.75%. Thus the study results suggest that serum ferritin can be used as a prognosticating tool in the course of dengue fever.

INTRODUCTION:

Dengue fever is an acute febrile condition characterised by a sudden onset of 3-5 days of fever, extreme headache, myalgia, retroorbital discomfort, anorexia, gastrointestinal disturbance and rash. Dengue viruses are flaviviruses, including four serotypes 1,2,3 and 4. These same viruses are responsible for Dengue Hemorraghic Fever (DHF). Viruses are spread to humans by bite of infectious mosquitoes, primarily Aedes aegypti. The incubation period is 4-7 days, but varies from 3 to 14 days.[(1)] The disease is currently endemic in most tropical and subtropical countries. DHF is characterised by increased vascular permeability, hypovolemia and irregular processes of blood clotting. Dengue fever (DF) with its extreme manifestations such as DHF and DSS has emerged as a major public health issue of international concern. The geographical range has increased considerably over the last 30 years due to the increased potential for breeding Aedes aegypti. This has been triggered by the population boom, the rapid development of urban centres with a strain on public services, such as drinking water, and the rise in rainwater collection in different types of containers, resulting in a multiple storage practices. Dengue is now ranked as the most significant mosquito-borne viral disease in the world. Latest figures suggest that at least 112 countries are endemic to Dengue and that about 40 % of the world 's population (2.5-3 billion people) is at risk in the tropics and subtropics. Every year, 100 million cases of dengue fever and half a million cases of DHF occur worldwide. Early identification and early initiation of care are crucial if disease-related morbidity and mortality are to be reduced[(2)] . Apart from diagnostic testing for the detection of dengue fever, serum ferritin level found to be high in dengue fever.[(3)] Ferritin is an

acute phase reactant released by the reticuloendothelial cells. Hyperferritinemia is associated with immune activation and coagulation disturbances.[4] A rise in serum ferritin level has been observed to have a linear correlation with severity of dengue fever.[5]

AIMS AND OBJECTIVES:

1. To measure the serum ferritin levels in dengue fever and establish the role of ferritin in determining the course of the disease early.
2. To compare its levels in dengue fever with complications and dengue fever without complications.

MATERIALS AND METHODS:

Study type : prospective observational study
Study period : 2 years.
Study place : Patients of dengue fever admitted in wards and ICU of Yenepoya Medical College and Hospital .

Selection Criteria:

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:

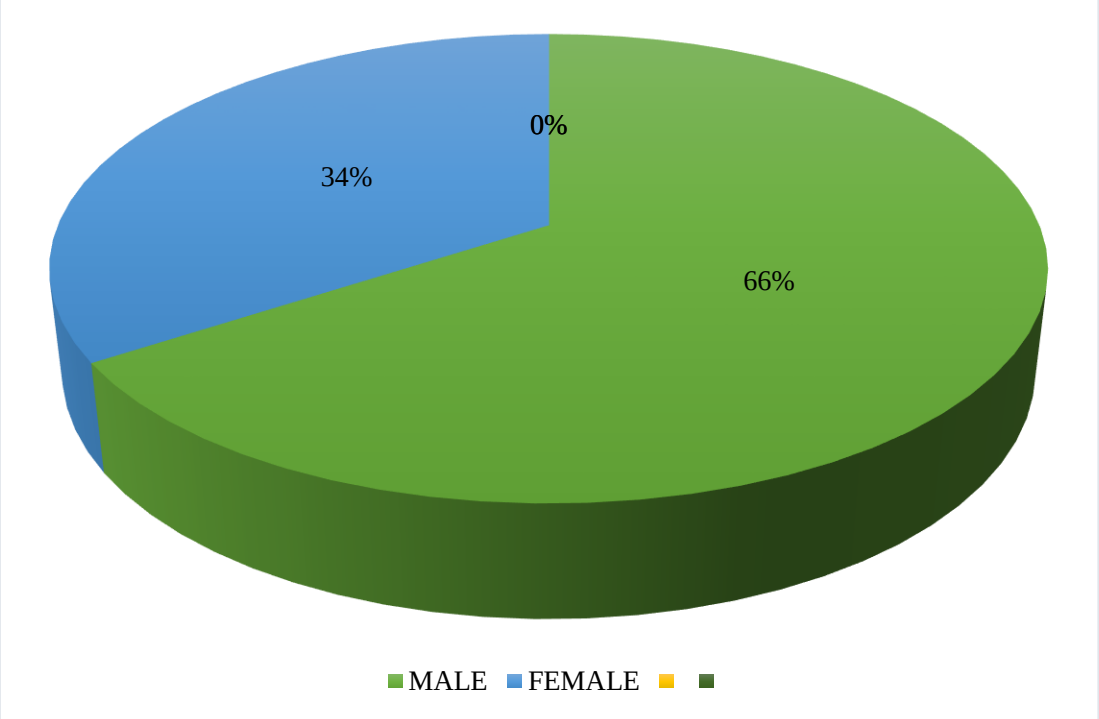
• Patients with pre existing liver disease.
• Patients with active covid-19 infection
• Patients with iron deficiency anemia and iron over load state
• Bacterial infections
• All other acute febrile illness other than dengue.
• Patients on anti platelets and anticoagulants
• Vitamin B12 deficiency.
•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

Statistical Analysis:

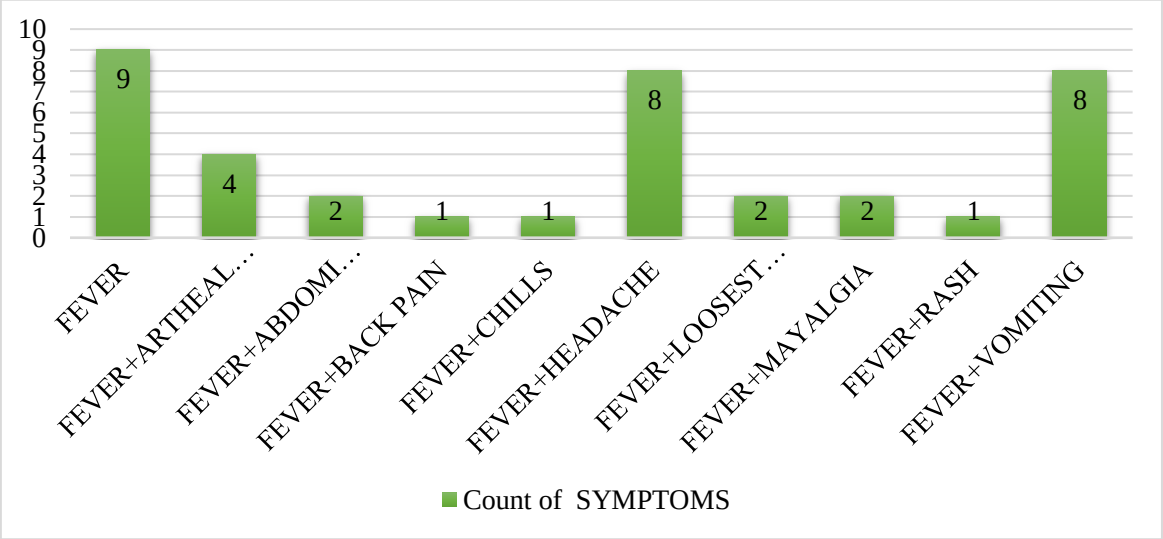
All the data was entered in excel spreadsheet and the data was analysed using IBM SPSS version 23 operating on windows 10. The continuous data were summarized as mean and standard deviation and categorical variables using frequency and percentage. The pie chart and bar charts were used to demonstrate the result graphically. The mean difference between the continuous data was analysed 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 < 0.005 was considered statistically significant.

RESULTS:

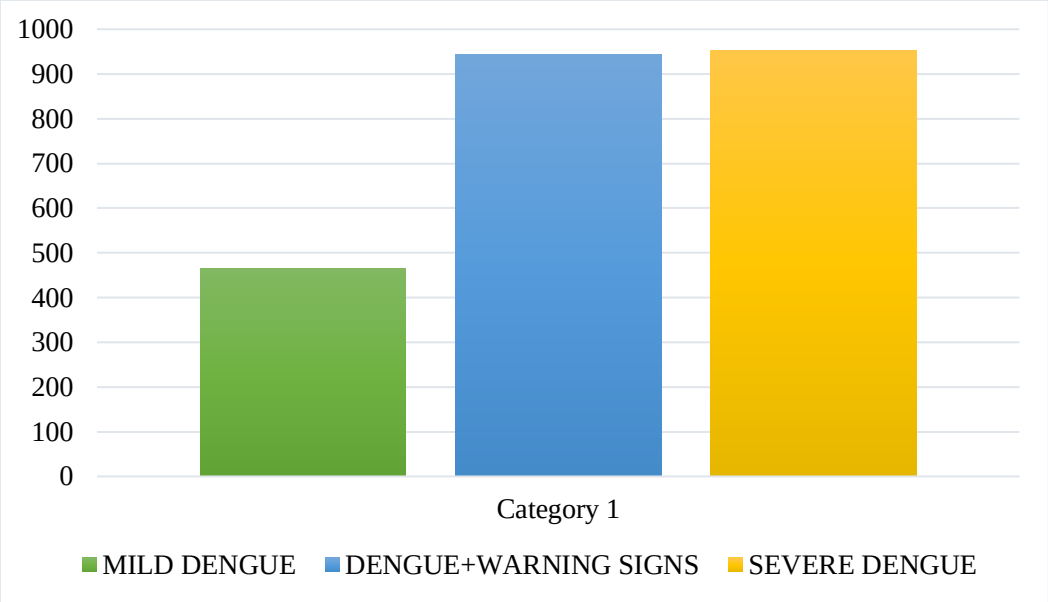
Graph 1: Graph showing the gender distribution



Graph 2: Distribution according to the symptoms



Graph 3: Graph showing the serum ferritin in dengue groups



This 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 942.9 and 952.3 respectively.

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				

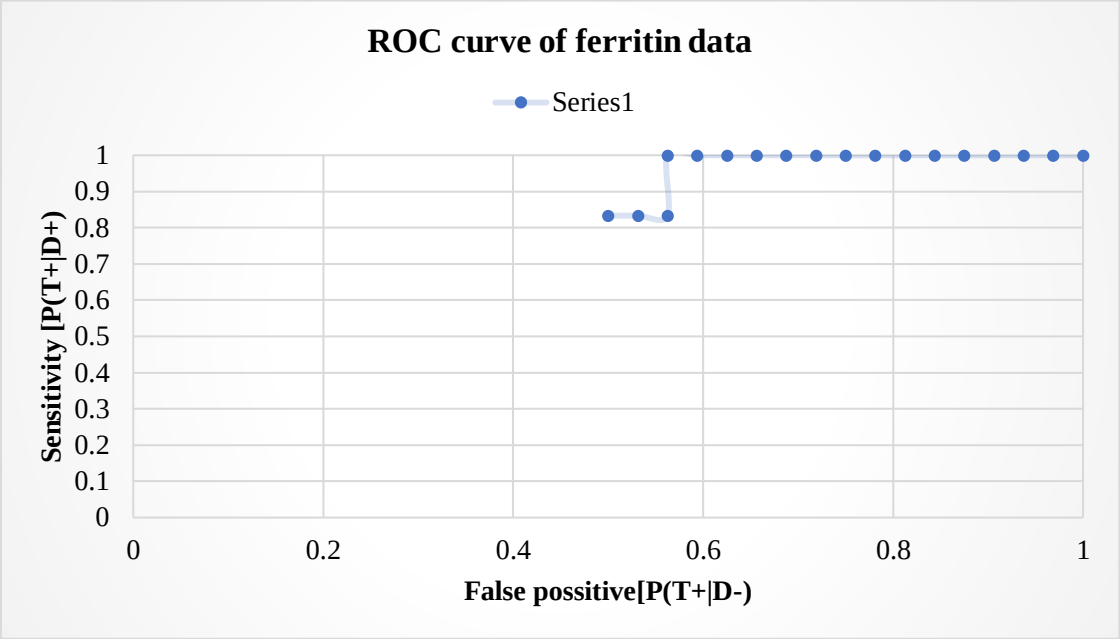
F-Test Two-Sample for Variances		
	Variable 1	*Variable 2*
Mean	674.6531	952.3333
Variance	136345.9	13632.67
Observations	32	6
df	31	5
F	10.00141	
P(F<=f) one-tail	0.008607	
F Critical one-tail	4.491621	

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. ROC curve of ferritin data

Count of CATEGORY OF DISEASE	**CATEGORY OF DISEASE**			**sensitivity**	**FALSE POSSITIVE**
FERRITIN	**m**	**S**	**Grand Total**	**P(T+|D+)**	**P(T+|D-)**
36	1		1	1	1
91.9	1		1	1	0.96875
101	1		1	1	0.9375
110	1		1	1	0.90625
169	1		1	1	0.875
219	1		1	1	0.84375
292	1		1	1	0.8125
301	1		1	1	0.78125
304	1		1	1	0.75
355	1		1	1	0.71875
400	1		1	1	0.6875
469	1		1	1	0.65625
558	1		1	1	0.625
667	1		1	1	0.59375
714		1	1	1	0.5625
716	1		1	0.833333	0.5625
800	1		1	0.833333	0.53125
1000	16	5	21	0.833333	0.5
Grand Total	32	6	38		

Figure – ROC Curve



DISCUSSION:

- The World Health Organization has estimated that dengue viruses infect more than 50 million per year. Dengue fever is a major health care problem in recent time especially in developing countries like India as there is still lack of proper water storage and handling techniques, they have become breeding spots for mosquitoes causing spread of mosquito born infections like dengue and malaria. the dengue infection can either be any of the three
- Dengue without warning signs
- Dengue with warning signs
- Severe Dengue. [6-9]
- In Dengue fever monitoring of certain blood parameters become important part of diagnosis and management. Platelets and packed cell volume are monitored and are the important parameters in the care of dengue. In febrile phase they are measured to establish patients baseline. Any drastic decrease in platelet level and increase in PCV suggest that there is plasma leak and the patient is going to severe phase of dengue.[9,10]
- Elevated ferritin levels are seen in immune activation and has been recently found to be important marker of disease activity.[11]
- Most Dengue clinical studies were done in paediatric age group. Adult studies are quite limited, especially in India. Many studies have already established higher levels of ferritin in severe forms of dengue. But there is deficit in the areas like Karnataka which have higher number of cases in southern parts of India and also there is no established value above which severe forms of dengue can be anticipated.[10,11]
- This study was done on 38 patients of dengue, out of them males were 25 that is 66%, females were 13 that is 34%. The mean age group is 34.6+/-4.6 years and most of them 16 patients constituting 42.2% were in t 20-39 years age.
- In this study patients with mild dengue are 18, Dengue with warning signs are 14 and severe dengue are 6. This is close to the study done by Eregowda A and Valliappan S which was conducted on 57 cases, out of them 46 were mild dengue, 8 were with warning signs, and 3 were severe dengue.[12]
- Mean serum ferritin value in the present study was 718.5+/-355.8 and with a range of 36 to1000ng/ml. As the severity of dengue increased there was increase in the serum ferritin level. There was statistical significant deference between the three groups. There was also significant difference in the serum ferritin level to differentiate sever dengue from others two groups (P value < 0.05).Chaiyaratana W *et al*., Soundravally R *et al*., found high levels of serum ferritin levels in severe forms of dengue and can be used to establish that serum ferritin is a better marker of severe dengue with better sensitivity and specificity[8,13]
- Receiver Operating Characteristic curve was done by plotting different cut-offs of values of serum ferritin levels and found that serum ferritin levels was statistically significant in predictor of the sever dengue,with 0.734 as area under the curve, SE=0.0028 and 95% CI from 0.712 to 0.957 and p statistically significant.(P<0.05). Similarly in the study conducted by Roy Chaudhuri S et al ROC was plotted found that serum ferritin value of

1291ng/ml can be used as cut off value to differentiate dengue from others.[14]

- The ROC curve was used to calculate the cut of value with highest sensitivity. Serum ferritin of 714 was considered as the cut off value for differentiation of the of the sever dengue from mild dengue and dengue with warning signs. The outcome of the study was calculated considering the cut off value of serum ferritin level as 714. Considering this new cut off value the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 100%, 43.75%, 25%, 100% and 42.8%.
- This study revealed, increased concentrations of ferritin were associated with a severe dengue. Moreover, hyperferritinemia in dengue had association with thrombocytopenia and increased levels of liver enzymes (SGOT, SGPT, ALP). However Pearson correlation test and line fit plot revealed no significant correlation between hyperferritnemia and elevated liver enzyme. Unlike our study van de Weg et al revealed significant correlation between hyperferritinemia and sever dengue/ elevated liver enzyme.[15]

CONCLUSION:

In this study, the ROC curve was used to calculate the cut of value with highest sensitivity. Serum ferritin of 714 was considered as the cut off value for differentiation of the severe dengue from mild dengue and dengue with warning signs. There was statistically significant association of ferritin with severity of dengue, as the severity increases there is increase in serum ferritin. Thus we conclude that Serum ferritin is a reliable predictor of the dengue fever and consists of: Sensitivity - 100%, Specificity - 43.75%.

Thus the study results suggest that serum ferritin can be used as a prognosticating the course of dengue fever with 714 value as cut off.

REFERENCES:

1. Dengue haemorrhagic fever: Diagnosis, treatment, prevention and control, [Internet]. Geneva; 1997. Available from: http://apps.who.int/iris/bitstream/10665/41988/1/9241545003_eng.pdf
2. World Health Organization. Dengue: Guidelines for diagnosis, treatment, prevention and control, [Internet]. Geneva; 2009. Available from: http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf?ua=1
3. Soundravally R, Agieshkumar B, Daisy M, Sherin J, Cleetus CC. Ferritin levels predict severe dengue. Infection. 2015;43(1):13–9.
4. Roy Chaudhuri S, Bhattacharya S, Chakraborty M, Bhattacharjee K. Serum Ferritin: A Backstage Weapon in Diagnosis of Dengue Fever. Lanzafame M, editor. Interdiscip Perspect Infect Dis. 2017;2017:7463489.
5. Wan S-W, Lin C-F, Yeh T-M, Liu C-C, Liu H-S, Wang S, et al. Autoimmunity in dengue pathogenesis. J Formos Med Assoc. 2013;112(1):3–11.
6. WHO Monograph on Dengue/Dengue Haemorrhagic Fever,. Compiled by PrasertThongchroen, Regional Publication, SEARO No.22. World Health Organization.1993.
7. WHO Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever, . In: SEAR. Roo, editor. World Health Organization 2011.
8. GOI. Annual Report 2011-2012, . In: DGHS MoHaFW, editor. New Delhi. Govt. of India.
9. K P. Concept of health and disease. Park's Textbook of Preventive and Social Medicine.23rd edition. Jabalpur : MS BanarasidasBhanot publishers 2016; p.31-32.2016. p. p.31-2.
10. Ho TS, Wang SM, Anderson R, Liu CC. Antibodies in dengue immunopathogenesis. J Formos Med Assoc. 2013;112(1):1-2.
11. Rigau-Perez JG. Severe dengue: the need for new case definitions. Lancet Infect Dis.2000
12. Eregowda, A., &Valliappan, S. (2015). Clinical

profile of dengue infection in a tertiary care hospital. Indian Journal of Child Health, 2(2), 68-71.
https://doi.org/10.32677/IJCH.2015.v02.i02.007

13. Chaiyaratana W, Chuansumrit A, Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children with dengue infection. Southeast Asian J Trop Med Public Health. 2008;39:832–6.
14. Roy Chaudhuri S, Bhattacharya S, Chakraborty M, Bhattacharjee K. Serum Ferritin: A Backstage Weapon in Diagnosis of Dengue Fever. Lanzafame M, editor. Interdiscip Perspect Infect Dis. 2017;2017:7463489.
15. van de Weg, Cornelia A M et al. "Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances." PLoS neglected tropical diseases vol. 8,10 e3214. 9 Oct. 2014, doi:10.1371/journal.pntd.0003214

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