

A Prospective Study of Serum Ferritin Level in Vector Born Disease.

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ABSTRACT:

Introduction: Present work was conducted to study serum ferritin level in vector born disease and find out the change from day 1 to day 5 and to assess changes in serum ferritin level or the course of illness of vector born disease at day 1 and day 5 to establish its utility as a prognostic marker. **Methodology:** A hospital based prospective observational study was conducted in Department of Medicine, S R.N.T. Medical College and M.B.G.H. Udaipur. A sample size of 140 was taken with inclusion criteria: suspected vector born disease with history of fever and age more than 18 year. Exclusion criteria: Patients with underlying malignancy, septicemia, Chronic kidney disease, liver disease, any autoimmune disorder, IBD, obesity (BMI >30 kg/m²), hyperthyroidism, extreme physical activity, respiratory infection etc and did not giving consent. **Results:** The mean (SD) age of study participants was 38.6 (16.8) years with 75 were female and 65 were male participants. Maximum (62 patients) were in age group of 20-40 years followed by 43 patients in 41-60 years. We found that mean ferritin level in malaria patients was significantly decrease on day 5 compare to day 1. Similarly, Ferritin level was decreased from day 1 to day 5 but it was statistically insignificant. And, also in scrub typhus Ferritin level was decreased from day 1 to day 5 but it was statistically insignificant. We also found that patients that were serious ill serum ferritin level was significantly high on day 1 and day 5 compare to rest of the patients. **Conclusion:** Our study concluded that serum ferritin level can be used as an inflammatory marker in vector borne diseases and it also predicts the severity of vector borne diseases.

INTRODUCTION:

Vector-borne diseases (VBDs) are among the most complex of all infectious disease to predict, prevent or control. Mosquitoes and ticks are notoriously difficult to reach and often develop resistance to insecticides.¹ Many VBDs are classified as neglected tropical diseases (NTDs), e.g., arboviral diseases like dengue and chikungunya, Chagas disease, human African trypanosomiasis (HAT), leishmaniasis, LF, and onchocerciasis.² VBDs contribute significantly to the global burden of disease, accounting for 17% of the global estimated burden of all infectious diseases. At the beginning of the 20th century, epidemic vector-borne diseases were among the most important global public health problems. Every year there are more than one billion cases and over one million deaths from VBDs globally.² Physical examination and serologic tests have been used to narrow down the range of diseases and differentially diagnose or exclude possible causes.³ "Serum ferritin" presents a paradox, as the iron storage protein ferritin is not synthesized in serum yet is to be found there. Serum ferritin is also a well-known

inflammatory marker, but it is unclear whether serum ferritin reflects or causes inflammation, or whether it is involved in an inflammatory cycle in mammals (in contrast, for instance, to some functions in insects, ferritin is supposed to be a cellular means of storing iron, not of transporting it, yet serum ferritin levels are widely measured as indicators of iron status. However, the soluble transferrin receptor (sTfR): log ferritin ratio (sTfR Index) probably provides a better estimate of body iron over a wide range of normal and depleted iron stores. This is because serum ferritin levels can be raised significantly in response to inflammation and/or a variety of diseases (see later). "Serum ferritin" thus presents something of a paradox. Taking a systems approach, we develop and summarize the view that "serum ferritin" actually originates from damaged cells (and thus reflects cellular damage), that it contains some iron but has lost or liberated most of its normal content, and that since the protein part of ferritin is assumed to be benign, that it is this (initially) free iron that correlates with and is causative of disease. The rest of this analytical and synthetic review summarizes the wide-ranging evidence for this.⁴

Studies revealed that in dengue fever, serum ferritin is disproportionately raised compared to any bacterial or viral infection and this elevated level corroborates with an increased risk of developing complications. Some studies showed a very strong correlation between serum ferritin level and severity of dengue infection.⁵ Again serum ferritin measured on 4th or 5th day roughly evaluates the prediction of dengue infection.⁶ Increased serum ferritin has been associated with severe dengue in children. Hyper-ferritinemia in dengue infected subjects is associated with intense immune activation and coagulation disturbances as noted in Aruba Dengue outbreak.⁷ An Indian study had shown that serum ferritin levels are significantly elevated in dengue infected cases compared to the controls; On group analysis, cases with severe dengue had higher ferritin levels than milder forms which was noted both during the febrile and defervescence stages of the illness.⁸

Results from the previous studies had shown that hyperferritinemia is associated with severe disease which is noted throughout the disease course. In a Malaysian study, a large proportion of patients developed severe dengue early during febrile stage.⁹ It is very crucial to predict the risk of progression to severe dengue at the earliest, by simple measurable tests to initiate appropriate intensive, supportive therapy. In the present study, we analyzed whether serum ferritin measured during early disease course can be used as a marker to indicate the severity which helps to triage and manage them appropriately.

MATERIALS AND METHODS:

A hospital based prospective observational study was conducted in Department of Medicine, S R.N.T. Medical College and M.B.G.H. Udaipur. A sample size of 140 was calculated while considering the prevalence of fever by vector born disease is about 10 % of total fever patients admitted in our medicine ward

with 95% of confidence interval with allowable error 5%.

Patients diagnosed with community acquired pneumonia admitted to medicine ward of R.N.T. Medical College and M.B.G.H. Udaipur were taken into the study with inclusion criteria: suspected vector born disease with history of fever and age more than 18 year. Exclusion criteria: Patients with underlying malignancy, septicemia, Chronic kidney disease, liver disease, any autoimmune disorder, IBD, obesity (BMI >30 kg/m²), hyperthyroidism, extreme physical activity, respiratory infection etc and did not giving consent.

In patients admitted at MB hospital with history of fever were asked for details sociodemographic history. All fever patients were sent for ferritin level at D1 and send all investigation CBC, PBF examination, LFT, RFT, MPQBC, Dengue NS1, IgM and IgG, scrub typhus IgM & IgG, chickengunya IgM & IgG. All patients were asked for again repeat sample of ferritin at D5

Data analysis was done using licensed SPSS software version 21.0 (Chicago, Illinois). A p-value <0.05 was considered as statistically significant.

OBSERVATIONS:

The mean (SD) age of study participants was 38.6 (16.8) years with 75 were female and 65 were male participants. Maximum (62 patients) were in age group of 20-40 years followed by 43 patients in 41-60 years. On general examination we found that most common symptoms were fever (140 patients) followed by giddiness present in 106 participants. Pallor was present in 50 patients, icterus was present in 23 patients, planter mute in 9 patients and B/L planter extension and neck rigidity was present in 8 patients, splenomegaly was present in 43 patients and hepatomegaly was found in 20 patients and crepitation was present in 16 patients (Table:1).

Table: 1 General Examination

		Frequency	Percent
Symptoms	Fever	140	100
	Nausea	59	42.1
	Vomiting	76	54.3
	Giddiness	106	65.7
	SOB	20	14.3
	Loos stool	11	7.9
	Pain abdomen	16	11.4
	Body ache	50	35.7
	Headache	34	24.3
	Decreased urine output	15	10.7
	Bleeding manifestation	3	2.1
	Rashes	13	9.3
	Eschar	6	4.3
Others	25	19.3	
GPE	Pallor	53	37.9

	Icterus	23	16.4
	Oedema	2	1.4
	Lymphadenopathy	2	1.4
	Cyanosis	4	2.8
CNS	Planter mute	9	6.4
	Altered sensorium	1	.7
	B/L planter extensor	8	5.7
	Cerebellar sign	1	.7
	GTCS	3	2.1
	Neck rigidity	8	5.7
P/A	Hepatomegaly	20	14.3
	Splenomegaly	43	30.7
	Ascites	4	2.9
RS	Crepitation	16	11.4
	Rhonchi	2	1.4
	Pleural effusion	1	0.7

Here, mean ferritin level on day 1 and day 5 was found to be 972.28 and 852.5 respectively with 64 (45.7%) participants had ferritin level < 500µg on day-1 and 86 (61.4%) participants on day-5 (Table:2).

Table: 2 Distribution of study participants according serum ferritin level on day 1 and day-5

Serum ferritin	Day-1		Day-5	
	Frequency	Percent	Frequency	Percent
< 500µg	64	45.7	86	61.4
500-1000 µg	17	12.1	20	14.3
>1000 µg	59	42.1	34	24.3
Mean±SD	972.286±695.5020		852.52±637.949	

In the present study, no statistically significant difference (p-0.622) was found between serum ferritin level on day 1 and Hb. But out of total 53 anaemic patients 28 patients had Hb <9g,m% and serum ferritin level >500 µg. Similarly, on day-5 also no statistically significant difference (p-0.852) was found between serum ferritin level and Hb. But out of total 53 anaemic patients 20 patients had Hb <9g,m% on day 5 and serum ferritin level >500 µg (Table:3).

Table: 3 Correlation between Serum Ferritin

		< 9 gm%		9-14 gm%		>14 gm%	
		Count	%	Count	%	Count	%
Day-1	< 500µg	25	39.06	37	57.81	2	3.13
	500-1000 µg	6	35.29	10	58.82	1	5.88
	>1000 µg	22	37.29	31	52.54	6	10.17
Day-5	< 500µg	33	38.37	49	56.98	4	4.65
	500-1000 µg	8	40.00	10	50.00	2	10.00
	>1000 µg	12	35.29	19	55.88	3	8.82

Among all VBD most common was found to be dengue and it was present in 83 participants, malaria was present in 18 patients and scrub typhus was found in 39 patients. Here, we also found that mean ferritin level in malaria patients was significantly decrease on day 5 compare to day 1. Similarly, Ferritin level was decreased from day 1 to day 5 but it was statistically insignificant. And, also in scrub typhus Ferritin level was decreased from day 1 to day 5 but it was statistically insignificant (Fig: 1). We also found that patients that were serious ill serum ferritin level was significantly high on day 1 and day 5 compare to rest of the patients (Fig:2).

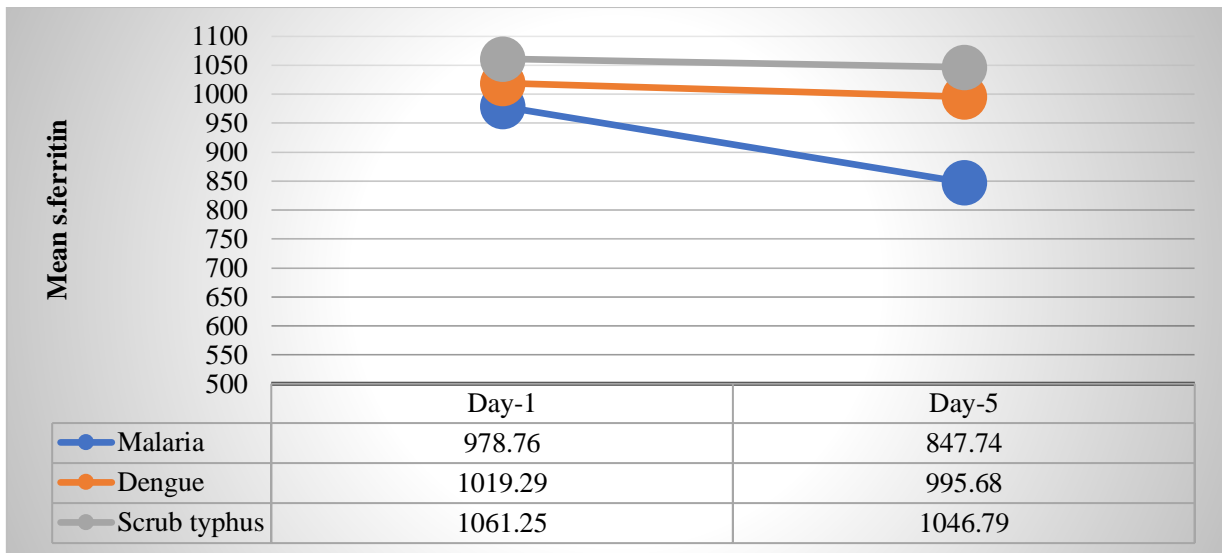


Fig: 1

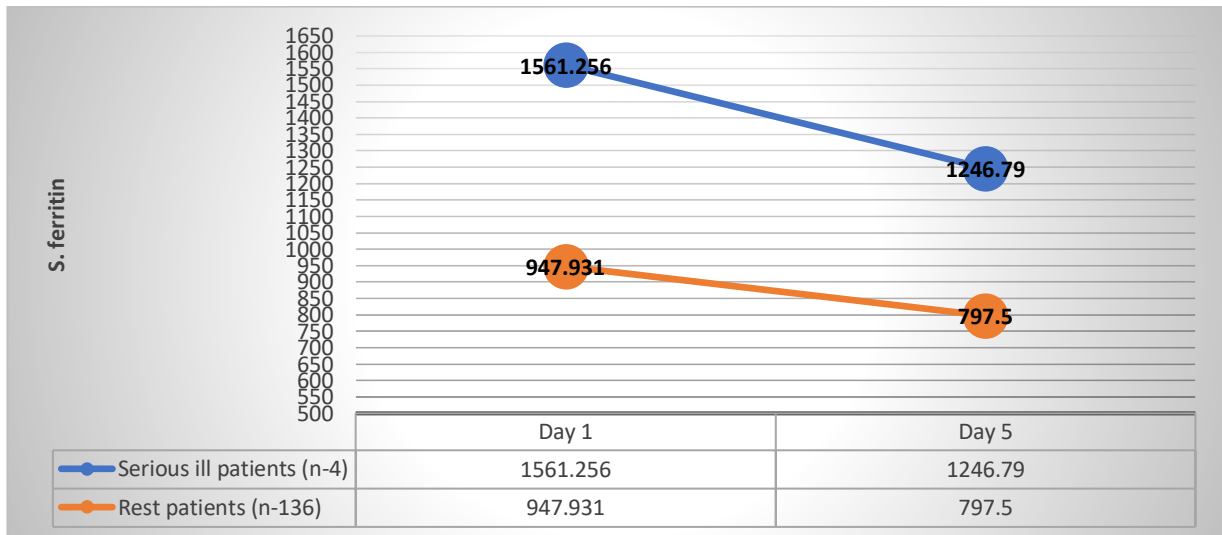


Fig:2

DISCUSSION:

Vectors are organism that transmits pathogen from one infected individual to another causing serious disease in human population. Mosquitoes are the best-known disease vectors. Rising deforestation and urbanization along with poor irrigation and water system, poor waste disposal and water storage are contributing to rise in VBDs.

Serum ferritin is disproportionately raised compared to any bacterial or viral infection and this elevated level corroborates with an increased risk of developing complications. Some studies showed a very strong correlation between serum ferritin level and severity of dengue infection. Again, serum ferritin measured on 4th or 5th day roughly evaluates the prediction of dengue infection.¹⁰

The mean (SD) age of study participants was 38.6 (16.8) years with 62 patients were in age group of 20-40 years followed by 43 patients in 41-60 years. As compared with study done by Prakash GM et al.¹¹ which showed Dengue fever had a higher incidence in individuals younger than 30 years of age. An another study by Kularatne SA et al¹² (2005) which showed mean age of 30 years.

There were 75 were female and 65 were male participants. Comparable to our results Afsar et al. on dengue fever showed a higher incidence of males than females (34 male and 11 female out of 45) and Prakash GM et al¹¹ study showed 55% were males and 45% were females. In Tak et al¹³ study there were 21 male and 19 females.

On general examination we found that most common symptoms were fever (140 patients) followed by

giddiness present in 106 participants. Pallor was present in 50 patients, icterus was present in 23 patients, planter mite in 9 patients and B/L planter extension and neck rigidity was present in 8 patients, splenomegaly was present in 43 patients and hepatomegaly was found in 20 patients and crepitation was present in 16 patients. Comparable to our results Williams et al¹⁴ also revealed similar kind of symptoms and stated that fever was present in all patients, Hepatomegaly was seen in 66 (91.7%) and splenomegaly in 43 (59.7%) children. Eschar, a pathognomonic clue to trombiculid bite, was seen only in 14 (19.4%) children. A rash was noted in 11% patients which varied from macular, blanching erythematous rash to petechial purpuric lesions.

In our study, most common VBD was found to be dengue and it was present in 83 (59.3%) participants, malaria was present in 18 (12.9%) patients and scrub typhus was found in 39 (27.9%) patients. According to National vector borne disease control program, Ministry of government of India, there are various types of vector borne diseases like Malaria, Dengue, Japanese encephalitis, Kala-Azar, Lymphatic filariasis and Chikunguniya, etc.

In our study, mean ferritin level on day 1 and day 5 was found to be 972.28 and 852.5 respectively. So current study found high serum ferritin level in VBDs and its decrease from day 1 to day 5.

Dengue fever is a dynamic febrile illness that can range from a mild self-limiting form to the other end of the spectrum which ranges from plasma leakage, haemorrhage, or severe multiorgan dysfunction leading to severe life-threatening situation.

In our study, a statistically significant high ferritin level was found among patients affected by dengue compare to others on day 5. Ferritin level was decreased from day 1 to day 5 but it was statistically insignificant. Chaudhary SR et al¹⁵ found similar results that Mean ferritin level in the dengue subgroup was 3492.56 and median was 2745 with IQR (interquartile range) 1574–3452 whereas. Bharti et al¹⁶ did a study to find out the serum ferritin level in dengue fever and its correlation with severity of dengue fever. Their serum ferritin levels on the day of admission was measured. The relationship between serum ferritin levels and platelets and severity of dengue fever was observed. Hence high ferritin levels can be used as a indicator for assessing disease severity and prognosis of dengue fever patients. Nadeem M et al¹⁷ found that in 70% serum ferritin level was found >100 µg/dl, whereas 30% had ferritin level ≤ 100µg/dl. Out of 31 with normal ferritin level only 2 (6.45%) developed severe dengue, whereas 35 (47.94%) out of 73 developed severe dengue with ferritin level >100 µg/dl(p Value <0.05). It was concluded that Serum ferritin levels on the day of admission may serve as biomarker for an early prediction of disease severity in dengue virus infection.

Current study found that mean ferritin level in malaria patients was significantly decrease on day 5 as compared to day 1. They found that the destruction of red blood cells during malaria and suppression of erythropoiesis resulting in profound anaemia, would shift iron out of heme towards storage form; and as long as heme is effectively recycled, the total body stores of iron would not be altered, although iron status indicators like serum ferritin will certainly be altered.

In our study, a statistically significant high ferritin level was found among scrub typhus patients compare to others on day 5. Ferritin level was decreased from day 1 to day 5 but it was statistically insignificant. William V et al¹⁴ found that hyperferritinemia is common in scrub typhus and about a third (30.7%) had ferritin values more than 2000 µg/L. Severe hyperferritinemia (> 10,000 µg/L) was seen in 10%. The limitation in our study is that due to inflammation, serum ferritin levels were even higher on day 5, and we were unable to follow the patients until serum ferritin levels returned to normal, most likely due to the brief stay of VBD patients in the hospital.

Our study concluded that serum ferritin level can be used as an inflammatory marker in vector borne diseases and it also predicts the severity of vector borne diseases.

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