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STUDY OF SERUM FERRITIN LEVEL AS PREDICTOR OF SEVERITY OF DENGUE FEVER AT A TERTIARY HOSPITAL

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Abstract

Background: Dengue fever is one of commonest viral hemorrhagic fevers, clinical spectrum of dengue infection is variable from mild fever to severe forms of dengue such as dengue hemorrhagic fever and dengue shock syndrome. Present study was aimed to study serum ferritin level as predictor of severity of dengue fever at a tertiary hospital. **Material and Methods:** Present study was Hospital based descriptive cross sectional study, conducted in patients of age above 18 years, diagnosed case of Dengue, willing to participate in present study. **Results:** In present study, mean age of the patients was 35.5 ± 14.8 years. Majority of the patients (58 %) were males, while 42 % patients were females with male-female ratio of 1.4:1. In study, three-fifth of the patients (60%) suffering from dengue without warning signs, followed by 32 % patients who has dengue with warning signs, while 8 % patients has severe dengue. Mean levels of serum ferritin was 1363.1 ± 1505.3 ng/ml with minimum levels of 17 ng/ml and maximum levels of 6129 ng/ml. More than three-fourth of the patients (78%) had serum ferritin levels above normal level (>350 ng/ml), while 20% patients had normal range ferritin level (30 –350 ng/ml) and 2 % patients had ferritin level below normal level (<30 ng/ml). Serum ferritin level has significantly positive correlation with serum creatinine (r= -0.353), SGOT (r= 0.554; p<0.05) and SGPT level (r =0.610; p<0.05), while significantly negative correlation with platelet count (r= -0.344; p<0.05). However, serum ferritin has non-significant correlation with age of patients, durations of hospitalization, and hematocrit level (p>0.05). **Conclusion:** However, statistically significant relationship of SGOT and SGPT levels with severity of dengue. Serum ferritin level has significantly positive correlation with serum creatinine, SGOT and SGPT level, while significantly negative correlation with platelet count.

Keywords: dengue, serum ferritin, severity of dengue, platelet count

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Introduction

Dengue fever is one of commonest viral hemorrhagic fevers, most geographically widespread of the arthropod-borne viral illnesses, caused by Arbovirus of Flavivirus genus with four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4).[1] The clinical spectrum of dengue infection is variable from mild fever to severe forms of dengue such as dengue hemorrhagic fever and dengue shock syndrome. Severe dengue is considered by severe thrombocytopenia

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with bleeding, plasma leakage causing fluid accumulation, respiratory distress and multi-organ dysfunction.[2]

The clinical manifestations of dengue fever could be explained by the raised capillary permeability and endothelial damage. Like other viral infections, the treatment was typically supportive management with intravenous fluids and blood product transfusions as necessary. However, for a small subsection of patients, this infection was life threatening with severe cytopenias and significant systemic response.[3]

Past study had shown that cases with severe dengue had higher serum ferritin levels compared milder forms that was noted both during the febrile and defervescence stages of the disease.[4] Dengue being an infective condition, a modest rise in ferritin levels was predictable in dengue fever as well. Ferritin could be used as a marker to distinguish between dengue and other febrile diseases. The presence of hyperferritinaemia (ferritin levels $\geq$ 500 µg/L) was related with markers of immune activation and coagulation disorders and clinical disease severity, proposing that it could serve as a marker of activity of disease.[5] Present study was aimed to study serum ferritin level as predictor of severity of dengue fever at a tertiary hospital.

Material And Methods

Present study was Hospital based descriptive cross sectional study, conducted in department of Medicine, at Venus hospital, Surat, Gujarat, India. Study duration was of 1 years (July 2018 – July 2019). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients of age above 18 years, diagnosed case of Dengue, willing to participate in present study

Exclusion criteria

- Those who were not willing to participate
- Age less than 18 years
- Severely ill patients

Study was explained to patients in local language & written consent was taken for participation & study. All the patients were enrolled after their written informed consent. Relevant history noted to study Performa. The routine investigation was done as required. Semi structured questionnaire and laboratory test like Serum Ferritin levels, Complete blood count including platelet counts and hematocrit, Renal and Liver function test. 10 ml of blood sample was collected for various blood investigation such as Complete blood count, Renal function test, Liver function test, Serum Ferritin level, and other required investigation.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

In present study, mean age of the patients was 35.5 ± 14.8 years with minimum age 19 years and maximum age 72 years. Half of the patients (50%) were 18 – 30 years old, followed by 31 – 40 years (24 %), 41–50 years (10 %), > 60 years (10 %) and 51–60 years (6 %). Majority of the patients (58 %) were males, while 42 % patients were females with male-female ratio of 1.4:1. By applying chi square test, the relationship of age and gender was

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statistically non-significant (p>0.05).

Table 1: Age and gender wise distribution of all patients

Age group (Years)	Gender		
	Male (%)	Female (%)	Total (%)
18 – 30	17 (58.6)	8 (38.1)	25 (50.0)
31 – 40	4 (13.8)	8 (38.1)	12 (24.0)
41 – 50	4 (13.8)	1 (4.8)	5 (10.0)
51 – 60	1 (3.4)	2 (9.5)	3 (6.0)
>60	3 (10.3)	2 (9.5)	5 (10.0)
Total	29 (100.0)	21(100.0)	50(100.0)
Chi square test =5.774,df=4, p =0.217			

Comorbidities were noted in 18 % patients, such as hypertension (10 %), epilepsy (2 %), COPD (6 %), diabetes mellitus (4 %), IHD (2 %), chronic kidney disease (2%), pulmonary hypertension (2 %) and solitary kidney (2 %). More than two-thirds of the patients (70 %) were hospitalized for 4–6 days, while 18 % patients hospitalized for 0–3 days and 12 % patients require 7 – 9 days hospitalization. In current study, three-fifth of the patients (60%) suffering from dengue without warning signs, followed by 32 % patients who has dengue with warning signs, while 8 % patients has severe dengue.

Table 2: Distribution of patients based on presence of other comorbidities

	No. of patients	Percentage
Comorbidity Present	09	18.0
Duration of hospitalization (days)		
0 – 3	9	18.0
4 – 6	35	70.0
7 – 9	6	12.0
Dengue severity		
Dengue without warning sign	30	60.0
Dengue with warning sign	16	32.0
Severe dengue	4	8.0

Mean levels of serum ferritin was 1363.1 ± 1505.3 ng/ml with minimum levels of 17 ng/ml and maximum levels of 6129 ng/ml. More than three-fourth of the patients (78%) had serum ferritin levels above normal level (>350 ng/ml), while 20% patients had normal range ferritin level (30 –350 ng/ml) and 2 % patients had ferritin level below normal level (<30 ng/ml).

Table 3: Distribution of patients based on levels of Serum ferritin

Serum Ferritin (ng/ml)	No. of patients	Percentage
Below Normal (<30)	1	2.0
Normal range (30 –350)	10	20.0
Above Normal (>350)	39	78.0
Mean ± SD: 1363.1 ± 1505.3 ng/ml, minimum 17 ng/ml & maximum 6129 ng/ml		

Mean values of Platelet count was lowest among dengue patients with warning signs (0.76 ± 0.41 Lakhs /mm^3), while mean platelet count was increasing in severe dengue patients (0.98 ± 0.56 Lakhs/mm^3) and dengue patients without warning signs (1.29 ± 0.79 Lakhs/mm^3). By applying one-way ANOVA test, platelet count had statistically significant

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relationship with severity of dengue ($p<0.05$).

Mean values of serum ferritin level was lowest among dengue patients without warning signs(670.5 ± 598.5 ng/ml), while mean ferritin level was increasing in dengue patients with warning signs(1972.7 ± 1500.5 ng/ml) and severe dengue patients (4119.8 ± 2319.7 ng/ml). By applying one-way ANOVA test, serum ferritin level was found to be significantly increasing with increasing the severity of dengue ($p<0.05$).

Mean values of hematocrit was lowest among severe dengue patients (37.1 ± 2.81 %), this mean value of hematocrit was increasing in dengue patients without warning signs (38.14 ± 4.28 %) and dengue patients with warning signs (38.23±2.53%). By applying one-way ANOVA test, hematocrit was found to be non-significantly related with severity of dengue($p>0.05$).

Mean values of serum creatinine level was lowest among dengue patients without warning signs (0.87 ± 0.37 mg/dl), while mean creatinine level was increasing in dengue patients with warning signs (1.0 ± 0.71 mg/dl) and severe dengue patients (2.4 ± 2.23 mg/dl). By applying one-way ANOVA test, serum creatinine level was found to be significantly increasing with increasing the severity of dengue ($p<0.05$).

Mean values of SGOT level was lowest among dengue patients with warning signs (117.9 ± 88.4 IU/L), while mean SGOT level was increasing in dengue patients without warning signs (117.9 ± 88.4 IU/L) and severe dengue patients (1275.5 ± 1539.5 IU/L). By applying one-way ANOVA test, SGOT level had statistically significant relationship with severity of dengue($p<0.05$).

Mean values of SGPT level was lowest among dengue patients with warning signs (87 ± 46.5IU/L), while mean SGPT level was increasing in dengue patients without warning signs (87.8 ± 96.6IU/L) and severe dengue patients (757 ± 780.6 IU/L). By applying one-way ANOVA test, SGPT level had statistically significant relationship with severity of dengue ($p<0.05$).

Mean duration of hospitalization was 4.57 ± 1.33 days in dengue patients without warning signs, 4.5 ± 0.97 days in dengue patients with warning signs, 5.5 ± 3.12 days in severe dengue patients. By applying one-way ANOVA test, the relationship of duration of hospitalization with severity of dengue was statistically non-significant ($p>0.05$).

Table 4: Dengue severity & other factors

Mean ± SD	**Dengue severity**			**One way ANOVA test**
	Without warning sign (%)	**With warning signs (%)**	**Severe dengue (%)**	
Platelet count (Lakhs/mm^3)	1.29 ± 0.79	0.76 ± 0.41	0.98 ± 0.56	F statistics = 3.344; P=0.044
Serum ferritin level (ng/ml)	670.5 ± 598.5	1972.7 ± 1500.5	4119.8 ± 2319.7	F statistics = 2.686; p<0.001
Hematocrit (%)	38.14 ± 4.28	38.23 ± 2.53	37.10 ± 2.81	F statistics = 0.155; P=0.857
Serum creatinine level (mg/dl)	0.87 ± 0.37	1.0 ± 0.71	2.40 ± 2.23	F statistics = 7.389; P=0.002
SGOT level (IU/L)	118.3 ± 171	117.9 ± 88.4	1275.5 ± 1539.5	F statistics = 14.344;

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				P<0.00
SGPT level (IU/L)	87.8 ± 96.6	87 ± 46.5	757 ± 780.6	F statistics = 18.189; P<0.00
Duration of hospitalization	4.57 ± 1.33	4.50 ± 0.97	5.50 ± 3.12	F statistics = 0.85, p=0.434

Serum ferritin level has significantly positive correlation with serum creatinine (r= -0.353), SGOT (r= 0.554; p<0.05) and SGPT level (r =0.610; p<0.05), while significantly negative correlation with platelet count (r= -0.344; p<0.05). However, serum ferritin has non-significant correlation with age of patients, durations of hospitalization, and hematocrit level (p>0.05).

Table 5: Correlation of serum ferritin level with other factors

	Serum ferritin level		
	No of patients	**Pearson correlation (r)**	**P value**
Age	50	0.149	0.303
Durations of hospitalization	50	-0.009	0.950
Platelet count	50	*-0.344*	*0.014*
Hematocrit	50	0.143	0.323
S. Creatinine	50	*0.353*	*0.012*
SGOT	50	*0.554*	*<0.001*
SGPT	50	*0.610*	*<0.001*

Among dengue patients without warning signs (n=30), all patients (100%) discharged and none expired, while among dengue patients with warning signs (n=16), all patients (100%) discharged and none expired. However, among severe dengue patients (n=4), 75 % patients discharged and 25 % patients expired.

Table 6: Distribution of all patients based on dengue severity and final outcome

Final outcome	**Dengue severity**			**Total (%)**
	Without warning sign (%)	**With warning signs (%)**	**Severe dengue (%)**	
Discharged	30(100.0)	16(100.0)	3(75.0)	49(98.0)
Expired	0	0	1(25.0)	1(2.0)
Total	30(100.0)	16(100.0)	4(100.0)	50(100.0)

Discussion

Dengue fever is a dynamic febrile illness that could ranges from a mild self-limiting form to the other end of the spectrum that ranges from plasma leakage, hemorrhage, or severe multi-organ dysfunction leading to severe life threatening condition.[6] Presently there is no specific drug or preventive vaccine existing for dengue infection. The mainstay of treating of dengue positive patients is symptomatic treatment and close watching for the development of complications.[7]

Augmented expression of acute phase reactants is found among severe dengue infected patients compared to non-severe dengue patients. This aids to predict the dengue infected patients well before the presence of clinical warning signs. One such acute phase reactant is ferritin, which is manufactured by reticuloendothelial cells in reaction to infection and inflammation. Ferritin is highly raised in dengue infected patients compared to patients with other febrile illnesses.[5]

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In present study, among males, majority of patients were 18 – 30 years (58.6%) and 31 – 40 years (13.8%) old, while among females, majority of patients were 18 – 30 years (38.1%) and 31 – 40 years (38.1%) old. This relationship of age and gender was statistically non-significant (p>0.05). Similarly, Petchiappan *et al.*,[8] had found non-significant difference in the mean age between male and female (p>0.05). While a study by Selvamuthukumara[9] had found that majority of patients among males were 20 – 40 years old (31%) and among females were 20 – 40 years (28.3%) and <12 years (28.3%).

In current study, three-fifth of the patients (60%) suffering from dengue without warning signs, followed by 32% patients who has dengue with warning signs, while 8% patients has severe dengue. A study conducted by Petchiappan *et al.*,[8] had found that 4.2% patients had severe dengue. In Chauyaratana *et al.*,[10] study, 24.9% children were classified as having DF and 75.1% as having DHF (27.7% grade I, 35% grade II and 12.4% grades III and IV). 5.6% children were diagnosed with primary and 94.4%children with secondary dengue antibody response. Diwakar TN *et al.*,[11] had found that 28% patients had severe dengue.

Ferritin is an acute-phase reactant and produced by reticulo-endothelial cells in response to inflammation and infection. Hyper-ferritinemia was found in patients, which exhibit two opposite functions; initially in the phase of clinical illness, raised serum ferritin levels shows protective effect by chelating the toxic free iron radicals at the site of inflammation. However, in severe cases, higher ferritin levels might have a pathogenic role by activating immune cells resulting in cytokine storm.[5,12] Ferritin levels were raised in inflammatory conditions, but ferritin levels were much higher in dengue virus infected patients compared to patients with other febrile illnesses. This suggests that ferritin could be used as a marker to discriminate between dengue and other febrile diseases.[13]

In present study, mean serum ferritin levels was 1363.1 ± 1505.3 ng/ml (range 17 to 6129 ng/ml). Majority of the patients had serum ferritin levels >350 ng/ml (78%), while 20% patients had ferritin level between 30 – 350 ng/ml and 2% patients had ferritin level <30 ng/ml. A study done by Selvamuthukumara[9] had found that 20.4% patients serum ferritin between 200-300 ng/dl, 33.3% patients had serum ferritin between 300- 400 ng/dl, 46.2% patients had ferritin level >400 ng/dl. In Petchiappan *et al.*,[8] study, mean ferritin levels was 1399.53 ± 690.68 ng/ml.

A study conducted by Chaudhauri *et al.*,[14] had found that serum ferritin level in dengue patients was significantly higher compared toother febrile illness group (p<0.001). The best cut-off for ferritin level to differentiate dengue from other febrile illness was 1291 ng/ml. The sensitivity at this cut-off was 82.6% and the specificity at this cut-off was 100%. A study by In Bharathi *et al.*,[15] study, 60% dengue patients had high level of serum ferritin level and 40% patients had normal ferritin level.

In present study, Mean values of serum ferritin level was lowest among dengue patients without warning signs (670.5 ± 598.5 ng/ml), while mean ferritin level was increasing in dengue patients with warning signs (1972.7 ± 1500.5 ng/ml) and severe dengue patients (4119.8 ± 2319.7 ng/ml). By applying one-way ANOVA test, serum ferritin level was found to be significantly increasing with increasing the severity of dengue (p<0.05).

A study done by Selvamuthukumara[9] had found that 40% patients with ferritin levels 200- 300ng/dl had developed severe dengue, whereas 61.2% patients with ferritin levels 300–400ng/dl had developed severe dengue and 76.5% patients with ferritin levels >400 ng/dl had developed severe dengue. In Petchiappan *et al.*,[8] study, significantly higher levels of median serum ferritin levels among severe dengue patients (2000 ng/ml) compared to non-severe dengue patients (1593 ng/ml) (p<0.05).

A study conducted by Soundravally *et al.*,[4] had found steady increase in the level of

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serum ferritin throughout the course of illness. However, the elevated ferritin level could predict the disease severity with highest sensitivity and specificity of 76.9% and 83.3%, respectively, on the day of admission and the same was found to be 90% and 91.6 % around defervescence. In study of Chauyaratana *et al.*,[10] median serum ferritin levels (ng/ml) in children with DHF were higher than those with DF. A cutoff level of serum ferritin of 1,200 ng/ml was used to calculate sensitivity and specificity for DHF. The results reveal the sensitivities on Days 5, 6 and 7 of illness were 81.5%, 84.4% and 89.9%, respectively, and the specificities were 42.4%, 39% and 36.4%, respectively. High serum ferritin levels ≥1,200 ng/ml might be a predictor of dengue hemorrhagic fever.

Study conducted in Aruba and Brazil had shown higher levels of serum ferritin were significantly associated with disease severity indengue virus infection*(10)*. A study in Indonesia by Evalda *et al.*,[16] had found that mean serum ferritin concentration in children with dengue shock (3628.8 ± 1582.4) was significantly higher than in children without dengue shock (717.8 ± 695.8; $p<0.001$). Hence, there was a statistically significant association between serum ferritin concentration and dengue shock. The cutoff point of serum ferritin concentration that could be used to show dengue shock with high sensitivity (92%) and specificity (97%) was 2304.5.

Limitation of study were, study was done in a single hospital set up with small sample size so generalization of study findings will be doubtful. Further study require with larger sample size. Every dengue patient will have to be routinely screened for serum ferritin level. Based on higher Serum ferritin level, early diagnosis of Severe cases of dengue patients isdone, which will be helpful in preventing mortality from severe cases of dengue.

Conclusion

Most of the dengue patients had serum ferritin levels above normal range and platelet counts below normal range. With increasing the severity of dengue, serum ferritin level, Serum creatinine level was significantly increasing, while platelet count was significantly decreasing and hematocrit level non-significantly decreasing. However, statistically significant relationship of SGOT and SGPT levels with severity of dengue. Serum ferritin level has significantly positive correlation with serum creatinine, SGOT and SGPT level, while significantly negative correlation with platelet count.

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