

Evaluation of Serum Ferritin and CRP Level in Dengue Fever & its Correlation with Thrombocytopenia in Southren Odisha

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Abstract

Introduction: Dengue is one of the major re-emerging viral infections. In recent years, dengue has become a major global public health concern. In small subset of patients, there is life threatening condition with severe cytopenias and significant systemic response. The presence of macropage activation in dengue fever is well reported and could be one possible reason for mortality and morbidity. Dengue being an infective condition, a modest rise in ferritin levels and CRP are expected in dengue fever as well. In dengue fever sr. ferritin is disproportionately raised compared to any bacterial or viral infection.

Material and Methods: It was a prospective observational study conducted at MKCGMCH Berhampur over a period of 2 years from 2019 to 2021. The study population consisted of adults admitted to department of general medicine with diagnosis of dengue fever. 100 dengue patients admitted in dengue ward/to different wards of medicine department of MKCG Medical College, Berhampur were observed. Only who were seropositive for dengue fever NS1 antigen or IgM ELISA were recruited for the study. Their serum ferritin and CRP levels on the day of admission and on the fifth day were measured. The relationship between serum ferritin, CRP, platelets and severity of dengue fever was observed.

Results: Total number of uncomplicated dengue fever is 78 and that of severe dengue (DHF/DSS) is 22. The mean serum ferritin and CRP are high on day one as compared to day five, but the mean TPC on day five is high as compared to day one. Serum Ferritin and CRP are Negatively Correlated with the TPC in Linear Pattern in day one, which is statistically Significant. Serum Ferritin and CRP are Negatively Correlated with the TPC in Linear Pattern in Day Five, which is statistically significant. The mean TPC level on day one of hospitalization among DF, DHF, DSS are 79766.7, 1006.3 and 19100 respectively. The mean TPC level on day five of hospitalization among DF, DHF, DSS are 79766.7, 1006.3 and 19100 respectively. The above figures show that, the mean ferritin and CRP level on day five are significantly high among DHF/DSS as compared to DF.

CONCLUSION: This study shows that serum ferritin and CRP may help in identifying an uncomplicated dengue illness, from that of patients who may require inpatient admission/intensive critical care with or without tell-tale signs upon the time of presentation to the hospital or to the outpatient department itself.

Keywords: Serum Ferritin, CRP Level, Dengue Fever, Thrombocytopenia.

Introduction

Dengue is an acute febrile disease of viral etiology, the evolution of which is, benign in its classic form and dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Dengue virus is a small, 50 nm diameter, positive stranded encapsulated RNA virus with a genome size of approximately 11 kilo bases.¹ It encodes a single open reading frame of 10,170 nucleotides corresponding to 3390 amino acid residues. It encodes for 3 structural protein genes, which encode the nucleocapsid or core protein (C), a membrane associated protein (M), an envelope glycoprotein (E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). The size of the virion is approximately 50 nm in diameter.²

Dengue is one of the major re-emerging viral infections. In recent years, dengue has become a major global public health concern. Approximately 2.5 billion people (40% of the world's population), living mainly in urban areas of tropical and subtropical regions, are estimated to be at risk of acquiring dengue infection. The WHO estimates that 50100 million infections occur yearly including 5 lakhs DHF cases and 22,000 deaths, mostly among children. While dengue is endemic in more than 100 countries, most cases are reported from South-East Asia and the western Pacific regions.³

In small subset of patients, there is life threatening condition with severe cytopenias and significant systemic response. The presence of macrophage activation in dengue fever is well reported and could be one possible reason for mortality and morbidity.⁴ Macrophage activation syndrome (MAS) is a life threatening haematological syndrome that is associated with cytopenias and fever. MAS is result from inappropriate activation of tissue macrophages leading to histiocyte proliferation hypercytokinemia and T cell immunosuppression.⁵

Ferritin is a protein that take part in iron storage in body. Both ferritin and CRP are acute phase reactants. ferritin levels are important in MAS because it can be diagnostic for the disease as ferritin level >10,000 μ CG/L is 90% sensitive and 96% specific for MAS.⁶ Dengue being an infective condition, a modest rise in ferritin levels and CRP are expected in dengue fever as well. In dengue fever sr. ferritin is disproportionately raised compared to any bacterial or viral infection. Several studies, have shown that hyperferritinemia (ferritin>500ng/ml) and CRP emerged strong predictors of severe dengue (DHH/DSS) and worsening thrombocytopenia and with increased risk of developing complications.⁷

Material and Methods

It was a prospective observational study conducted at MKCGMCH Berhampur over a period of 2 years from 2019 to 2021. The study population consisted of adults admitted to department of general medicine with diagnosis of dengue fever. 100 dengue patients admitted in dengue ward/to different wards of medicine department of MKCG Medical College, Berhampur were observed.

INCLUSION CRITERIA:

1. Confirmed cases of dengue NS1 and IgM positive.
2. Age >14 years.

EXCLUSION CRITERIA:

1. Pregnancy
2. Other febrile illness
3. Patients on heparin
4. Mixed infections
5. Patients on chemotherapy and radiotherapy
6. Immunocompromised patients like Diabetes, Chronic Alcoholic, HIV etc
7. Known patients with qualitative &/or quantitative platelet disorder.
8. Patients on antiplatelets.

METHODS:

Only who were seropositive for dengue fever NS1 antigen or IgM ELISA were recruited for the study. During the study period 100 patients admitted with dengue fever were found to satisfy both the inclusion and Exclusion criteria. Their serum ferritin and CRP levels on the day of admission and on the fifth day were measured. The relationship between serum ferritin, CRP, platelets and severity of dengue fever was observed. Statistics were calculated for age, gender.

Statistical Analysis:

Data was obtained as per prescribed proforma and using standard statistical methods the various necessities were observed as per their p value. Observational views with insignificant p value were not considered for opinion.

Results

Table-1: AGE WISE DISTRIBUTION

Age(year)	Male	Female	Total
15-25	22	18	40
26-40	12	11	23
41-55	14	11	25
56-70	3	2	5
71-85	4	3	7

This table shows maximum number of patients are in the age group 15 to 25 and minimum number of patients are in the age group 56 to 70.

Table – 2: SEX WISE DISTRIBUTION

Sex	Frequency	Percentage
Male	55	55.0
Female	45	45.0
Total	100	100.0

This table shows out of 100 patients 55 are male and 45 female patients.

Table – 3: DISTRIBUTION OF SYMPTOMS

	Frequency	Percentage
Fever	99	99.0
Myalgia	90	90.0
Joint Pain	74	74.0
Rash	30	30.0
Bleeding abnormalities	18	18.0

This table shows 99 patients are having fever. This table shows total number of patients having myalgia is 90. This table shows total number of patients having joint pain is 74. This table shows total number of patients having joint rash is 30. This table shows total number of patients with bleeding abnormality is 18.

Table – 4: SEX WISE DISTRIBUTION OF SHOCK

Shock	Sex		Total	Test Statistics
	Male	Female		
Present	3	3	6	Chi Square = 1.207, p=0.272
Absent	52	42	94	
Total	55	45	100.0	

This table shows out of 6 DSS patients, 3 are male and 3 are female.

Table – 5: DISTRIBUTION OF CASES OF DENGUE AMONG VARIOUS SEX

Bleeding abnormalities	Sex		Total	Test Statistics
	Male	Female		
DF	41	37	78	Chi Square = 1.470, p=0.480
DHF	11	5	16	
DSS	3	3	6	
Total	55	45	100	

This table shows total number of uncomplicated dengue fever is 78 and that of severe dengue (DHF/DSS) is 22.

Table – 6: DESCRIPTIVES

Item	N	Minimum	Maximum	Mean	Std. Deviation
Age	100	15.0	85.0	35.450	18.3426
Hb	100	7.6	15.8	12.028	2.1509
PCV	100	32.0	72.0	45.129	9.0112
TPCD1	100	5000.0	280000.0	64965.000	47940.2098
FerritinD1	100	160.00	1480.00	778.3035	318.39221
CRPD1	100	1.3	20.1	9.880	4.2406
FerritinD5	100	106.0	1232.0	519.650	280.3021
CRPD5	100	1.2	17.2	7.308	2.9179

This table shows the mean serum ferritin and CRP are high on day one as compared to day five, but the mean TPC on day five is high as compared to day one.

Table – 7: CORRELATION BETWEEN TPC AND SERUM FERRITIN AND CRP DAY ONE

Item	TPC d1	Ferritin d1	Crp d1
TPCD1	1	-0.822	-0.730
Pearson’s correlation			
Significance	-	<0.001	<0.001

Figure-1

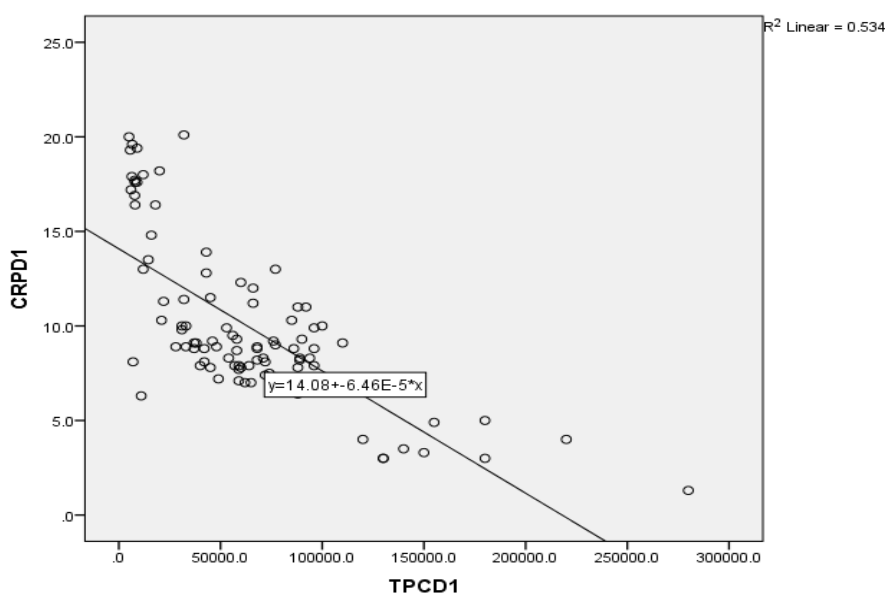
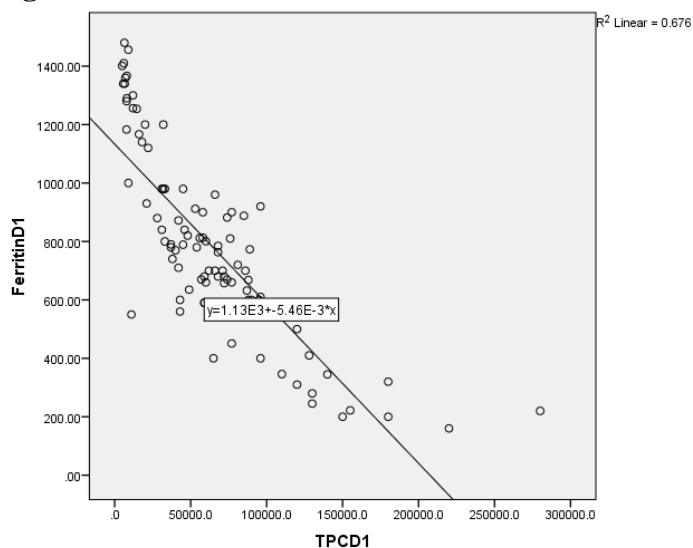


Figure-2



Serum Ferritin and CRP are Negatively Correlated with the TPC in Linear Pattern in Day One, Which Is Statistically Significant

Table – 8: CORRELATION BETWEEN TPC AND SERUM FERRITIN AND CRP DAY FIVE

Item	TPC d5	Ferritin d5	Crp d5
TPCD5	1	-0.859	-0.762
Pearson's correlation			
Significance	-	<0.001	<0.001

Figure-3

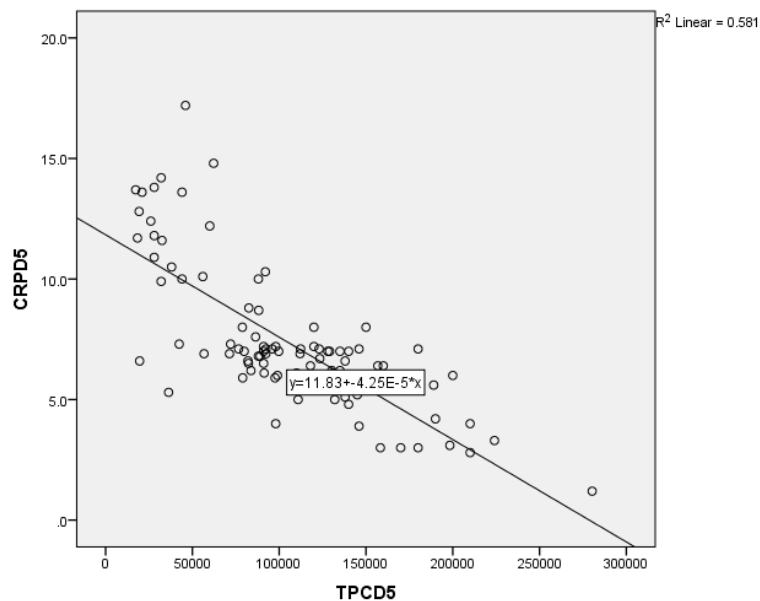
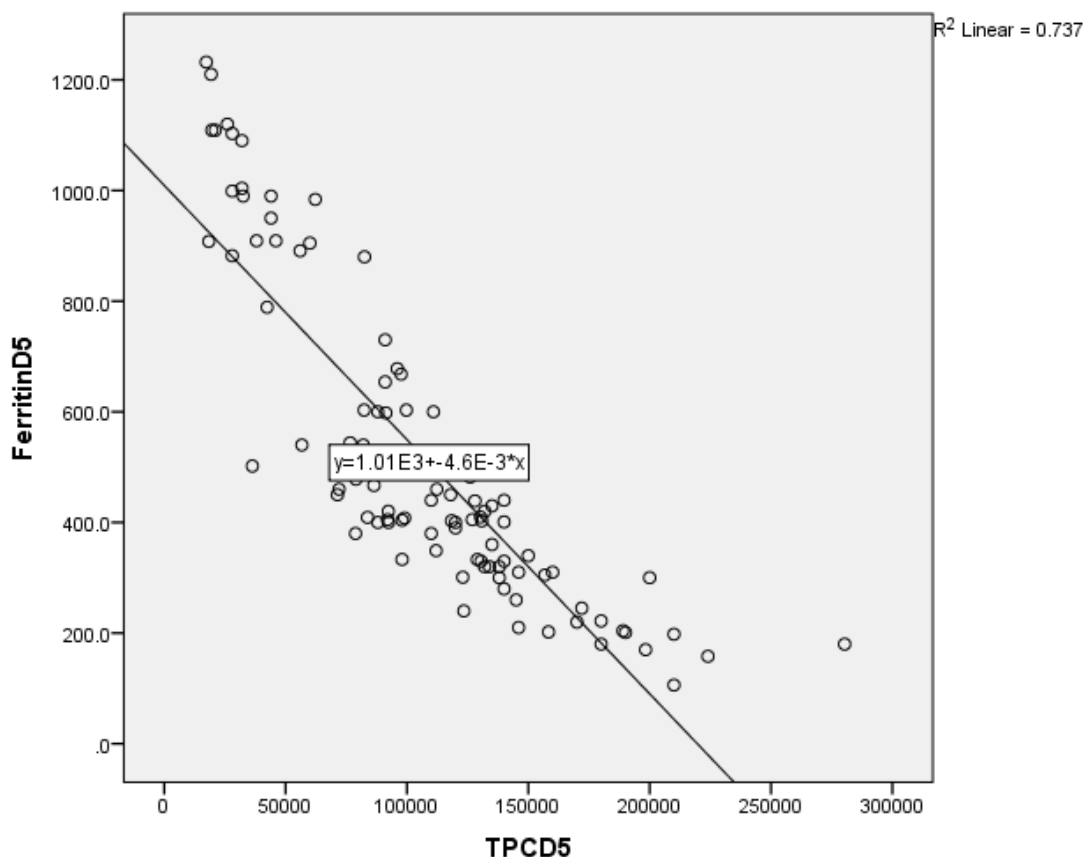


Figure-4



Serum Ferritin and CRP are Negatively Correlated with the TPC in Linear Pattern in Day Five, Which is Statistically Significant.

Table-9: ASSOCIATION BETWEEN PROFILE OF THE PATIENT WITH TPC, FERRITIN AND CRP AT DAY 1

	DF		DHF		DSS		TEST STATISTICS
	Mean	SD	Mean	SD	Mean	SD	
TPCD1	79766.7	43926.6	10006.3	4018.7	19100.0	11599.1	<0.001
FerritinD1	653.54	216.36	1243.31	219.93	1160.15	177.33	<0.001
CRPD1	8.3	2.7	15.7	3.8	14.8	4.5	<0.001

This figure shows mean TPC level on day one of hospitalization among DF, DHF, DSS are 79766.7, 1006.3 and 19100 respectively. The above figures shows that, the mean ferritin and CRP level on day one are significantly high among DHF/DSS as compared to DF.

Table – 10: ASSOCIATION BETWEEN PROFILE OF THE PATIENT WITH TPC, FERRITIN AND CRP AT DAY 5

	DF		DHF		DSS		TEST STATISTICS
	Mean	SD	Mean	SD	Mean	SD	
TPCD5	125013	42610	32615	13305	61500	29836	<0.001
FerritinD5	398.1	152.1	983.1	173.2	863.8	222.2	<0.001
CRPD5	6.2	1.8	11.4	2.9	10.3	3.1	<0.001

This figure shows mean TPC level on day five of hospitalization among DF, DHF, DSS are 79766.7, 1006.3 and 19100 respectively. The above figures show that, the mean ferritin and CRP level on day five are significantly high among DHF/DSS as compared to DF.

Discussion

Out of 100 hospitalized patients 55 patients are male and rest 45 are female. Maximum number of patients are in the age group 15-25 and minimum number of patients are in the age group 56-70 that is 40 and 5 respectively.

The study showed that 99% cases had fever and 90% cases had myalgia. Joint pain was seen in 74% cases and rash in 30% cases. Bleeding abnormalities seen in 18 % and shock like feature in 6% cases. It also showed that DF affected 52.56% male and 47.43% female. Likewise 68.75 % male and 31.25 % female were affected by DHF. 50 % male and female were affected by DSS.

The mean serum ferritin level was found to be 653.54 +/-216.36 in DF, 1243.31 +/- 219.93 in DHF, 1160.00 +/- 177.33 in DSS on day 1. It shows serum ferritin was elevated more in DSS (five times of upper limit) and DHF (more than 6 times of upper limit) than DF (more than two times of upper limit). The mean serum ferritin level on day 5 was 398.1 +/- 152.1 in DF, 983.1 +/- 173.2 in DHF, 863.8 +/- 222.2 in DSS. It shows a decrease in ferritin level during next 5 days. This type of serum ferritin elevation has been reported in several other studies.

A similar type of study among 96 patients conducted by *R Soundravally et al* shows elevated serum ferritin on day could predict the disease severity with highest sensitivity and specificity of 76.9% and 83.9% respectively.⁸ Another study conducted by *Ahmed et al* published in journal of infectious disease in 2020 shows that higher sr.⁹ Ferritin level during febrile phase is significantly associated with low platelet count and higher haemocrit level during critical period of dengue fever.

The mean serum CRP level was found to be 8.3 +/- 2.7 in DF, 15.7 +/- 3.8. In DHF, 14.8 +/- 4.5 in DSS on day 1. This shows there was increase in CRP level more in DHF and DSS than DF.

The mean of serum CRP on day 5 was 6.2 +/-1.8 in DF, 11.4 +/- 2.9 in DHF and 10.3 +/- 3.1 in DSS. The serum CRP level is gradually decreased on day 5. Similar results are also detected by *chien-chin chen et al* in the year 2015 showing the level of CRP is more raised among severe dengue patients as compared to dengue fever.¹⁰

The mean TPC level on day 1 was 79766.7 +/- 43926.6 in DF, 10006.3 +/- 219.93 in DHF, 19100 +/- 11594 in DSS. It was more decreased in DHF than DSS than DF. On day 5 the level was 125013 +/- 42610 in DF, 32615 +/- 13305 in DHF, 61500 +/- 29836 in DSS. This showed an increasing trend in following days.

The study also showed that there was a negative correlation between TPC and serum ferritin, serum CRP level in a linear pattern. As the serum ferritin level and CRP level increased the TPC level showed a decrease pattern on day 1. And on day 5 when there was decrease in level of serum ferritin and CRP, the TPC showed a increasing pattern which was significant.

CONCLUSION

This study shows that serum ferritin and CRP may help in identifying an uncomplicated dengue illness, from that of patients who may require inpatient admission/intensive critical care with or without tell-tale signs upon the time of presentation to the hospital or to the outpatient department itself.

References

1. Lindenbach BD, Rice CM. Molecular biology of flaviviruses. *Adv. Virus Res* 2003; 59:23-61.
2. Santos HWGD, Poloni TRRS, Souza KP, Muller VDM, Tremeschin FV, Nali LVC, Fantinatti LR, Amarilla AA, Castro HLA, Nunes MR, Casseb SM, Vasconcelos PF, Badra SJ, Figueiredo LTM, Aquino VH. A simple one-step Real-Time RT-PCR for diagnosis of dengue virus infection. *Journal of Medical Virology* 2008; 80: 1426-1433.
3. WHO. 1999. Prevention and control of Dengue and Dengue Haemorrhagic Fever-Comprehensive guidelines. World Health Organization, Regional Office for South-East AS NewDehli.173.Wang S et al. Antibody-enhanced binding of dengue-2 virus to human platelets. *Virology* 1995; 213: 254-257.
4. Twiddy SS, Farrar JJ, Chau NV, Wills B, Gould EA, Gritsun T, Lloyd G Holmes EC. Phylogenetic relationships and differential selection pressures among genotypes of Dengue-2 Virus. *Virology* 2002;298: 63-72.
5. McBride WJH, Bielefeldt-Ohmann H. Dengue viral infections;

- pathogenesis and epidemiology. *Microbes and infection* 2000;2: 1041-1050
6. Maroun SLC, Marliere RCC, Barcellus RC, Barbosa CN, Ramos JRM, Moreira MEL. Case report: vertical dengue infection. *Jornal de Pediatria* 2008; 84: 556-559.
 7. WHO. Global Alert and Response(GAR)-Impact of dengue. World Health Organisation, 2013
 8. R Soundravally et al. *Infection*. 2015 Feb. Department of Biochemistry, JIPMER, Pondicherry, 605006 PMID:25354733
 9. Ahmed et al. *journal of infectious Disease & Therapy* 2020,8:3
 10. Chen LH, Wilson ME. Dengue and chikungunya infections in travelers. *Curr Opin Infect Dis* 2010; 23