Original Article

Serum Procalcitonin and CRP Level as Severity Marker of Dengue Fever : An Observational Study in Medical College, Kolkata

Sumit Kumar Ghosh[1], Manjari Saha[2], Souren Pal[3], Somnath Maji[4], Soumya Sarathi Mondal[5], Udas Chandra Ghosh[5]

Background : Among different markers of inflammation and sepsis, Procalcitonin (PCT) and C-reactive Protein (CRP) are being studied to investigate their accuracy for the diagnosis of bacterial infections. However, their role in viral diseases like Dengue is less explored.

Aims and Objectives : To find relationship between serum Procalcitonin and CRP with severity of Dengue Fever.

Materials and Methods : An Observational study conducted among 100 Dengue patients (IgM Positive) and were subjected to Tests for Serum Procalcitonin and CRP along with other routine blood tests, results were compared between three groups Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).

Results : We found that mean CRP in DF, DHF, DSS are respectively 16.52, 42.59 and 77.20 and mean Procalcitonin in DF, DHF, DSS are respectively 0.0519, 0.2574 and 0.7800.

Conclusion : We found that Abnormal CRP was more significant with DHF and DSS patients and Procalcitonin is more elevated in DSS, though abnormal Procalcitonin in DHF also statistically significant.

[*J Indian Med Assoc* 2025; **123(1):** 39-43]

Key words **: Dengue Fever, CRP, Procalcitonin.**

Editor's Comment :

- Elevated level of C-reactive Protein (CRP) is significantly associated in patient with Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) and Procalcitonin is more elevated in DSS.
- Procalcitonin and C-reactive Protein along with clinical judgement and hemodynamic parameters can be used as cost-effective severity marker of Dengue Fever. Though till more study and discovery of other parameters to determine or assess severity of Dengue is needed.

Dengue Is a Vector Borne Disease caused by four dengue virus serotypes (DENV 1-4), is the most important arboviral infection worldwide. The virus is transmitted to humans by the bites of infected female *Aedes aegypti* mosquitoes. Following an incubation period of 4-10 days within the mosquito, an infected mosquito is capable of transmitting the virus for the rest of its life. Dengue virus causes Dengue Fever (DF) and its more severe form, Dengue Hemorrhagic Fever (DHF) & Dengue Shock Syndrome (DSS). The major symptoms of Dengue are high grade fever, headache, retro-orbital pain, myalgia, arthralgia and rash. Most of the symptomatic infections will result in a benign disease course recover within 1 week of onset fever. The prevalence of Dengue Shock Syndrome (DSS) among adults is approximately 18%, it is the most common cause of death from Dengue. The occurrence and progression of DHF are similar to those of DF in the acute phase, eventually become more severe and may lead to vascular leakage and shock. To identify patients who are at high risk for detoriation, likely to be benefitted from early intervention with supportive therapy, has now become the focus of intense research in recent years[1,2]. CRP is an acute-phase reactant, used to aid in the diagnosis of bacterial infections, is synthesized by the liver, primary in response to IL-6, which is produce during infection and also in many types of inflammation. Studies have shown higher levels of C-reactive Protein (CRP) in Severe Dengue *versus* Non-severe Dengue, with a CRP cutoff level of 30.1 mg/L (AUC, 0.938; 100% sensitivity, 76.3% specificity)[3]. In a study on adult patients in Indonesia on the third day of fever, CRP was higher in those who developed plasma leakage, 10.1 (IQR 4.3-36.5) *versus* 6.3 (IQR 3.0-21.6) mg/L (p = 0.014)[4]. Though other studies using highly sensitive (hs) CRP did not find a difference between the severity grades[5]. Procalcitonin is the pre-hormone of calcitonin,

[1]MD, Assistant Professor, Department of Medicine, IPGME&R and SSKM Hospital, Kolkata 700020

[2]MD, Associate Professor, Department of Medicine, Medical College & Hospital, Kolkata 700073

[3]MD, Assistant Professor, Department of Medicine, Nil Ratan Sarkar Medical College and Hospital, Kolkata 700014

[4]MD, Senior Resident, Department of Medicine, Medical College & Hospital, Kolkata 700073 and Corresponding Author

[5]MD, Professor, Department of Medicine, Medical College & Hospital, Kolkata 700073

Received on : 14/04/2023

Accepted on : 09/07/2023

normally secreted by the C cells of the thyroid in response to hypercalcemia. It is also produced by the Hepatocytes and peripheral blood mononuclear cells[6], modulated by lipopolysaccharides and sepsis-associated cytokines mechanism of its production after inflammation still not completely understood. Study shows, In the patients with Dengue, 72% had a PCT level ≥0.1 ng/mL and 25% had a PCT level ≥0.5 ng/mL, which was higher than that of patients with influenza (34% at a PCT level ≥0.1 ng/mL and 16% at a PCT level ≥0.5 ng/mL[7-9].

Materials and Methods

This is a Hospital based Observational Study conducted at Medical College, Kolkata from January, 2020 to July, 2021, Purposive sampling done with study population 100. Fever for 5 days or more with Dengue IgM positive patient are included in the study while age less than 12 and more than 60 years, pregnant female patient of any age group and patients suffering from any Chronic Inflammatory Diseases are excluded from the study. The study was commence after obtaining permission from Institutional Ethics Committee was followed standard ethical guidelines. Permission was also taken from concerned HODs and Sister in Charge of the respective wards. Consent form to participate in a research study (in Bengali or English or Hindi) was used to take consent from the patients or their relatives (if patient cannot communicate). Dengue IgM antibody, Serum CRP, Serum Procalcitonin, Complete Hemogram (Includes platelet count, PCV), SGOT, SGPT, Creatinine and other relevant investigations are taken as Laboratory parameters. Serum CRP and Procalcitonin are main variables of the study and Socio-demographic parameters (Level of education, occupation, family income, marital status, Residence, BMI) and Severity of Dengue illness in terms of Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome act as co-variables.

Statistical Analysis :

For statistical analysis data were entered into a Microsoft Excel and analyzed by SPSS (version 27.0; SPSS Inc, Chicago, IL, USA) and Graph Pad Prism version-5. Paired t-tests and Chi-square test, one-way ANOVA analysis done as appropriate. Once a 't' value is determined, a p-value can be found using a table of values from Student's t-distribution. If the calculated p-value is below the threshold chosen for statistical significance then the null hypothesis is rejected in favor of the alternative hypothesis. p-value ≤0.05 was considered for statistically significant.

Results

In our study 42(42.0%) patients were Female and 58(58.0%) patients were Male with mean age 35.65±14 and 22 (22.0%) patients were from Rural area and 78(78.0%) patients were from Urban area. Among them 58(58.0%) patients had DF, 27(27.0%) patients had DHF and 15(15.0%) patients had DSS. In 49% patient complaints of retro- orbital pain, and 95% of Bodyache, while 59% patients developed rash. Respiratory complications in form of ARDS and Plural effusion seen in 3% and 12 % patients respectively. 13 patients develops Heart Failure, ACS seen in 6 patients and Arrthymia in form of Atrial fibrillation in 2 patients. Transaminitis observed in 54% of patients and 2(2%) patients develops encephalopathy. In our study 78(78.0%) patients had Abnormal CRP and 22(22.0%) patients had normal, with mean valve 32.66±27.29, and 8(8.0%) patients had abnormal Procalcitonin and 92(92.0%) patients had normal Procalcitonin, while mean value was 0.216±0.578.

On analysis we found that In DF Group, 18(31.0%) patients had Rash, In DHF Group 27(100.0%) patients had Rash, In DSS Group, 14(93.3%) patients had Rash, Association of Rash *versus* Severity Grade was statistically significant (p<0.0001). In DF Group, 36(62.1%) patients had Abnormal CRP and 22(37.9%) patients had Normal CRP, In DHF Group 27(100.0%) patients had Abnormal CRP, In DSS Group, 15(100.0%) patients had Abnormal CRP. Association of CRP group vs Severity Grade was statistically significant (p<0.0001). In DF Group, 58(100.0%) patients had normal Procalcitonin, In DHF Group 4(14.8%) patients had Abnormal Procalcitonin and 23(85.2%) patients had normal Procalcitonin, In DSS Group, 4(26.7%) patients had Abnormal Procalcitonin and 11(73.3%) patients had normal Procalcitonin. Association of Procalcitonin *versus* Severity Grade was statistically significant (p=0.0010). In DF Group, 51(87.9%) patients had PCV <45 and 7(12.1%) patients had PCV 45 to 50. In DHF Group 2(7.4%) patients had PCV <45, 23(85.2%) patients had PCV 45 to 50 and 2(7.4%) patients had PCV >50. In DSS Group, 14(93.3%) patients had PCV 45 to 50 and 1(6.7%) patients had PCV>50. Association of PCV *versus* Severity Grade was statistically significant (p<0.0001). In Normal CRP Group, 8(36.4%) patients had normal Transaminitis, In Abnormal CRP Group, 8(36.4%) patients had abnormal Transaminitis, Association of Transaminitis *versus* CRP was not statistically significant (p=0.0602). In Transaminitis, 8 (14.8%) patients had Abnormal Procalcitonin and 46(85.2%) patients had

Normal Procalcitonin. Association of Procalcitonin *versus* Transaminitis was statistically significant (p=0.0064).

In DF Group, the mean CRP (Mean±SD) of patients was 16.52±14.24, In DHF Group, the mean CRP (Mean±SD) of patients was 42.59±13.04, In DSS Group, the mean CRP (Mean±SD) of patients was 77.20± 27.02. Difference of mean CRP with both Group was statistically significant (p<0.0001). In DF Group, the mean Procalcitonin (Mean±SD) of patients was 0.0519±0.0547, In DHF Group, the mean Procalcitonin (Mean±SD) of patients was 0.257± 0.208. In DSS Group, the mean Procalcitonin (Mean±SD) of patients was 0.780±1.346. Difference of mean Procalcitonin with both Group was statistically significant (p<0.0001). In DF Group, the mean Platelet count (Mean±SD) of patients was 59268.9655± 25772.5422, In DHF Group, the mean Platelet count (Mean±SD) of patients was 15092.5926± 11157.9887, In DSS Group, the mean Platelet count (Mean±SD) of patients was 28733.3333±26053.4250. Difference of mean Platelet count with both Group was statistically significant (p<0.0001). In DF Group, the mean PCV (Mean±SD) of patients was 41.98±2.25, In DHF Group, the mean PCV (Mean±SD) of patients was 47.89±2.12. In DSS Group, the mean PCV (Mean±SD) of patients was 47.91±1.43. Difference of mean PCV with both Group was statistically significant (p<0.0001). In DF Group, the mean Creatinine (Mean±SD) of patients was 0.86±0.30, In DHF Group, the mean Creatinine (Mean±SD) of patients was 1.09±0.30. In DSS Group, the mean Creatinine (Mean±SD) of patients was 1.49±0.84. Difference of mean Creatinine with both Group was statistically significant (p<0.0001). In DF Group, the mean SGOT (Mean±SD) of patients was 48.79± 104.37, In DHF Group, the mean SGOT (Mean±SD) of patients was 113.81±88.68. In DSS Group, the mean SGOT (Mean±SD) of patients was 147.06±78.75. Difference of mean SGOT with both Group was statistically significant (p=0.0005). In DF Group, the mean SGPT (Mean±SD) of patients was 32.34±48.29. In DHF Group, the mean SGPT (Mean±SD) of patients was 87.48±57.23. In DSS Group, the mean SGPT (Mean±SD) of patients was 112.86±61.15.Difference of mean SGPT with both Group was statistically significant (p<0.0001)(Tables 1-3).

Discussion

In our study among total 100 study population 58(58.0%) patients had DF, 27(27.0%) patients had DHF and 15(15.0%) patients had DSS. Among them 42(42.0%) patients were Female and 58(58.0%) patients were Male with mean age 35.65±14 and 22 (22.0%) patients were from Rural area and 78(78.0%) patients were from Urban area. Similar to study by Pan ST, *et al*[10](2014), Retro-orbital pain observed in 49(49%), rash in 59(59%) patients, 3(3.0%) patients had ARDS and 12(12.0%) patients had Plural effusion. 6(6.0%) patients had ACS, 2(2.0%) patients had Arrhythmia, 13(13.0%) patients had Heart failure, 2(2.0%) patients had Encephalopathy, 40(40.0%) patients had Nausea/Vomiting. And 15(15.0%) patients had diarrhea also 15(15.0%) patients had Pain abdomen.

In our study 78(78.0%) patients had Abnormal CRP and 22(22.0%) patients had Normal CRP, 8(8.0%) patients had abnormal Procalcitonin and 92(92.0%) patients had normal Procalcitonin. It was

Table 1 — *Association between CRP and Procalcitonin versus Severity Grade*

	SEVERITY GRADE								
CRP gr	DF	DHF	DSS	TOTAL	Procalcitonin gr	DF	DHF	DSS	TOTAL
Abnormal	36	27	15	78	Abnormal	0.0	4	4	8
Row %	46.2	34.6	19.2	100.0	Row %	0.0	50.0	50.0	100.0
Col %	62.1	100.0	100.0	78.0	Col %	0.0	14.8	26.7	8.0
Normal	22	0.0	0.0	22	Normal	58	23	11	92
Row %	100.0	0.0	0.0	100.0	Row %	63.0	25.0	12.0	100.0
Col %	37.9	0.0	0.0	22.0		100.0	85.2	73.3	92.0
TOTAL	58	27	15	100	TOTAL	58	27	15	100
Row %	58.0	27.0	15.0	100.0	Row %	58.0	27.0	15.0	100.0
Col %	100.0	100.0	100.0	100.0	Col %	100.0	100.0	100.0	100.0
Chi-square value=20.4244; p-value = <0.0001					Chi-square value = 13.8486; p-value = 0.0010;				

Table 2 — *Distribution of mean CRP : Severity Grade*

		Number	Mean	SD	Minimum	Maximum	Median	P-value
CRP	DF	58	16.5224	14.2457	1.0000	98.2000	15.0000	<0.0001
	DHF	27	42.5926	13.0414	22.0000	75.0000	38.0000	
	DSS	15	77.2000	27.0283	27.2000	122.0000	88.0000	

Table 3 — *Distribution of mean Procalcitonin : Severity Grade*

		Number	Mean	SD	Minimum	Maximum	Median	P-value
Procalcitonin	DF	58	0.0519	0.0547	0.0100	0.3000	0.0300	<0.0001
	DHF	27	0.2574	0.2087	0.0300	0.9000	0.2000	
	DSS	15	0.7800	1.3467	0.0200	4.5000	0.3000	

found that 28(28.0%) patients had platelet count under <20,000, 35(35.0%) patients had 20,000 to 50,000 Platelet count, 33(33.0%) patients had 50,000 to 1,00,000 Platelet count and 28(28.0%) patients were >1,00,000 Platelet count.

It was found that in DF Group, 18(31.0%) patients had Rash, In DHF Group 27(100.0%) patients had Rash and in DSS Group, 14(93.3%) patients had Rash which was statistically significant (p<0.0001).

Present study showed that in DF Group, 8(13.8%) patients had Pain abdomen, in DHF Group 5(18.5%) patients had Pain abdomen and in DSS Group, 2(13.3%) patients had Pain abdomen which was not statistically significant (p=0.8348).

Simon L, *et al*[11] (2004) found that Procalcitonin (PCT) level was more sensitive and more specific than CRP level for differentiating bacterial from non-infective causes of inflammation. We found that in DF Group, 36(62.1%) patients had Abnormal CRP and 22(37.9%) patients had Normal CRP. In DHF Group 27(100.0%) patients had Abnormal CRP. In DSS Group, 15(100.0%) patients had Abnormal CRP. This was statistically significant (p<0.0001). It was found that in DF Group, 58(100.0%) patients had normal Procalcitonin, in DHF Group 4(14.8%) patients had Abnormal Procalcitonin and 23(85.2%) patients had normal Procalcitonin and In DSS Group, 4(26.7%) patients had Abnormal Procalcitonin and 11(73.3%) patients had normal Procalcitonin. This was statistically significant (p=0.0010).

It was found that in DF Group, the mean CRP (Mean±SD) of patients was 16.5224±14.2457, in DHF Group, the mean CRP (Mean±SD) of patients was 42.5926± 13.0414 and in DSS Group, the mean CRP (Mean±SD) of patients was 77.2000±27.0283 which was statistically significant (p<0.0001).

Thanachartwet V, *et al*[9] (2016) found that Procalcitonin ≥0.7 ng/mL and Pereipheral Venous Lactate (PVL) ≥2.5 mmol/L were independently associated with dengue shock and/or organ failure. A combination of Procalcitonin ≥0.7 ng/mL and PVL ≥2.5 mmol/L provided good prognostic value for predicting dengue shock and/or organ failure . Our study showed that in DF Group, the mean Procalcitonin (Mean±SD) of patients was 0.0519± 0.0547, In DHF Group, the mean Procalcitonin (Mean±SD) of patients was 0.2574±0.2087 and in DSS Group, the mean Procalcitonin (Mean±SD) of patients was 0.7800±1.3467 which was statistically significant (p<0.0001).

Present study showed that in DF Group, the mean Platelet count (Mean±SD) of patients was 59268.9655±25772.5422, in DHF Group, the mean Platelet count (Mean±SD) of patients was 15092.5926±11157.9887 and in DSS Group, the mean Platelet count (Mean±SD) of patients was 28733.3333±26053.4250 which was statistically significant (p<0.0001).

We observed that in DF Group, the mean PCV (Mean±SD) of patients was 41.9845±2.2536, in DHF Group, the mean PCV (Mean±SD) of patients was 47.8963±2.1272 and in DSS Group, the mean PCV (Mean±SD) of patients was 47.9133±1.4337 which was statistically significant (p<0.0001).

In our study 54(54.0%) patients had Transaminitis. It was found that in Normal CRP Group, 8(36.4%) patients had Transaminitis and in Abnormal CRP Group, 8(36.4%) patients had Transaminitis which was not statistically significant (p=0.0602).

We found that among the patients having Transaminitis, 8 (14.8%) patients had Abnormal Procalcitonin and 46(85.2%) patients had Normal Procalcitonin which was statistically significant (p=0.0064).

We examined that in DF Group, the mean SGOT (Mean±SD) of patients was 48.79±104.37. In DHF Group, the mean SGOT (Mean±SD) of patients was 113.81±88.68 and in DSS Group, the mean SGOT (Mean±SD) of patients was 147.06± 78.75 which was statistically significant (p=0.0005). It was found that in DF Group, the mean SGPT (Mean±SD) of patients was 32.34± 48.29, In DHF Group, the mean SGPT (Mean±SD) of patients was 87.48±57.23 and in DSS Group, the mean SGPT (Mean±SD) of patients was 112.86±61.15 which was statistically significant (p<0.0001).

Conclusion

We concluded that both Procalcitonin and C-reactive Protein can be used as cost-effective severity marker of Dengue Fever. Diagnostic accuracy could be enhanced by combining these tests with bedside clinical judgment. The results improve their knowledge of the pathogenesis of DSS by identifying the association between the epidemiology, clinical signs and biomarkers involved in DSS.

References

1 Yacoub S, Wills B — Predicting outcome from Dengue. *BMC Med* 2014; **12:** 147. [PubMed] [Ref list]

2 Huy NT, Van Giang T, Thuy DH — Factors associated with dengue shock syndrome: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2013; **7(9):** e2412. Published 2013 Sep 26. doi:10.1371/journal.pntd.0002412

3 Chen CC, Lee IK, Liu JW, Huang SY, Wang L — Utility of C-reactive protein levels for early prediction of dengue severity in adults. *Biomed Res Int* 2015; 2015: 936062.

4 Eppy S, Nainggolan L, Rumende CM — The differences between interleukin-6 and c-reactive protein levels among adult patients of dengue infection with and without plasma leakage. *Acta Med Indones* 2016; **48(1):** 3-9.
5 Durán A, González A, Delgado L, Mosquera J, Valero N — Serum level of Creactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. *J Med Virol* 2016; **88(2):** 351-5. 8.
6 Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, *et al* — Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. *J Lab Clin Med* 1999; **134(1):** 49-55. doi: 10.1016/s0022-2143(99)90053-7. PMID: 10402059. Anonymous. Dengue hemorrhagic fever, diagnosis, treatment and control. Geneva, Switzerland: World Health Organization; 1986. [Google Scholar]
7 Lubell, Yoel & Blacksell, Stuart & Dunachie, Susanna & Tanganuchitcharnchai, Ampai & Althaus, Thomas & Watthanaworawit, Wanitda & Paris, Daniel & Mayxay, Mayfong & Peto, Thomas & Dondorp, Arjen & White, Nicholas & Day, Nicholas & Nosten, Francois & Newton, Paul & Turner, Paul. (2015). Performance of C-reactive protein and procalcitonin to distinguish viral from bacterial and malarial causes of fever in Southeast Asia. *BMC Infectious Diseases* 15. 10.1186/s12879-015-1272-6.
8 Ingram PR, Inglis T, Moxon D, Speers D — Procalcitonin and C-reactive protein in severe 2009 H1N1 influenza infection. *Intensive Care Med* 2010; **36(3):** 528-32. doi:10.1007/s00134-009-1746-3
9 Thanachartwet V, Desakorn V, Sahassananda D, Jittmittraphap A, Oer-Areemitr N, Osothsomboon S, *et al* — Serum procalcitonin and peripheral venous lactate for predicting dengue shock and/or organ failure: a prospective observational study. *PLoS Neglected Tropical Diseases* 2016; **10(8):** e0004961.
10 Pan ST, Su PA, Chen KT, Lin HJ, Lai WP — Comparison of the clinical manifestations exhibited by dengue and nondengue patients among children in a medical center in southern Taiwan. *Journal of Acute Medicine* 2014; **4(2):** 53-6.
11 Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J — Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clinical Infectious Diseases* 2004; **39(2):** 206-17.