Section: Miscellaneous

Original Research Article

TO STUDY THE UTILITY OF SERUM C-REACTIVE PROTEIN LEVELS FOR EARLY DETECTION OF SEVERITY OF DENGUE AMONG ADULTS

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ABSTRACT

Background: Dengue fever is an infectious disease that is difficult to distinguish from other viruses but can evolve with serious consequences and even be fatal. CRP (C-reactive protein) could be a useful biochemical marker in differentiating milder and severe forms at the earliest. **Materials and Methods:** Patients diagnosed with dengue infections were included and demographics, clinical symptoms and signs, test results, and therapy specifics were collected in performa. Within 24 to 48 hours of being admitted to the hospital, the CRP levels of the patients were assessed. CRP levels were correlated with laboratory indicators such as hemoglobin, hemoglobocrit, platelet count, white blood cell count, total bilirubin, AST, ALT, serum albumin, creatinine, etc. **Result:** The mean age of the patients was 38 years (Standard Deviation=13.9). Fever (n=221,100%) was the most common symptom. And 94 (42.5%) patients had hepatitis as the predominant complication, followed by acute kidney injury (14.9%). Median CRP level was very high in patients who developed acute kidney injury (43 mg/L), myocarditis (94.5 mg/L), pancreatitis (56 mg/L), and acute respiratory distress syndrome (88 mg/dl). Patients with severe dengue had significantly higher CRP levels, when compared to non-severe dengue ($p < 0.001$). **Conclusion:** Current study detected high levels of CRP in severe dengue patients compared to dengue without warning signs and dengue with warning signs. Patients with increased CRP levels are at higher risk of developing complications.

INTRODUCTION

In tropical and sub-tropical nations, dengue is one of the most prevalent vector-borne virus diseases with public health implications.[1] It has become a persistent global danger and a leading source of illness and mortality globally in recent years.[1,2]

Dengue has a wide range of clinical manifestations, and its course and results are unpredictable.[3] Patients with dengue were classified as either non-severe (with or without warning signs) or severe in the 2009 WHO revision. In the early stages of the infection, it can be challenging to distinguish between mild and severe forms of dengue. The 2009 WHO criteria's warning indicators are thought to be potentially important components for the early diagnosis of severe dengue.[4] However, it was observed that each warning sign's sensitivity for predicting severe dengue was incredibly low when utilized alone. Numerous studies have assessed a range of variables, such as laboratory data, to forecast dengue severity. However, no single parameter has been found to predict dengue severity accurately.[5]

The acute-phase reactant C-reactive protein (CRP), which is produced by the liver six hours after inflammation begins, has demonstrated potential as a trustworthy laboratory indicator. A crucial factor in infection and inflammation is CRP, an acute inflammatory marker.[6] It is mostly produced by the liver, although it is also produced by endothelial cells, smooth muscle cells, adipocytes, macrophages, and lymphocytes.[7] After a major infection, CRP levels in the blood increase within a few hours. Although they do not rise as much as they would with a bacterial illness, CRP levels can also rise during a viral infection.[8]

Only a small number of studies have found that dengue patients have higher CRP levels, suggesting that the sickness may be more severe.[9] There is, however, no information on how well CRP levels can differentiate between mild and severe dengue in the early stages of the illness. Given this context, the purpose of this study was to assess the predictive value of blood CRP levels for dengue severity in the early stages of the disease.[10]

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Objectives: To evaluate the usefulness of serum C-reactive protein levels for early prediction of the severity of dengue and to correlate other biochemical parameters with serum CRP levels in determining the severity of dengue.

MATERIALS AND METHODS

All adult patients admitted to Kasturba Hospital in Manipal with dengue virus infection were included in the cross-sectional study as cases.

The study comprised patients ≥ 18 years old who were admitted to medical wards and had positive serology results for dengue infection, as determined by the non-structural protein 1 (NS1) antigen test or dengue IgM ELISA. The study excluded patients with autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, cancer, concurrent culture-proven bacterial infections, leptospirosis, enteric fever, malaria, scrub typhus, and other infections in addition to dengue. Every patient who was included gave their informed consent.

Before the start of data collection, the institutional ethics committee IEC 790/2017 granted ethics approval.

A data proforma contained the following information: demographics, clinical symptoms and signs, test results, and therapy specifics.

Within 24 to 48 hours of being admitted to the hospital, the CRP levels of the patients were assessed. The hospital used Roche/Hitachi Cobas c systems and an incredibly sensitive assay called the immunoturbidimetric assay to determine the CRP levels of the patients. Every participant had a DENV infection test. By measuring dengue-specific immunoglobulin M (IgM) antibodies using a kit from the National Institute of Virology, Pune, dengue positive was confirmed.

The Pan Bio ELISA kit was used to detect the presence of dengue non-structural glycoprotein-1 (NS1) antigen. CRP levels were correlated with laboratory indicators such hemoglobin, hemoglobocrit, platelet count, white blood cell count, total bilirubin, AST, ALT, serum albumin, creatinine, etc. All laboratory results obtained at the time of admission or within 24 to 48 hours of admission were taken into account.

The patients were divided into three categories based on the WHO 2009 classification: severe dengue, dengue with warning signals, and dengue without warning signs. The scientists of this study did not administer any treatment interventions; it was purely observational. Either death or recovery was noted as the end result.

Statistical Analysis: Continuous data were summarized using mean ± SD or median (IQR), whilst categorical variables were summarized using frequency and percentage. To ascertain if two categorical variables were related, the chi-square test was employed. The cut-off value of CRP in predicting dengue severity and determining its sensitivity and specificity was determined by calculating the area under the Receiver Operating Characteristic (ROC) curve (univariate and multivariate analysis by Le Borgne F. et al., 2017). The ability of a parameter to differentiate between two diagnostic groups is indicated by the area under the ROC curve (AUC).

We classified failing, bad, fair, good, and outstanding as the area under the curve (AUC) between 0.50-0.60, 0.60-0.70, 0.70-0.80, 0.80-0.90, and 0.90-1, respectively. Multivariable logistic regression was utilized to determine the combined influence of significant variables from the univariate study in predicting the severity of dengue. If the P-value was less than 0.05, it was deemed statistically significant. The SPSS 20 program (IBM SPSS Statistics, USA) was used to calculate the appropriate descriptive and inferential statistics.

RESULTS

A total of 221 patients who were either dengue NS 1 antigen and/or IgM positive were enrolled as cases. Using 2009 WHO classification, 196 of 221 (88.6%) cases were classified as non-severe dengue and 25 (11.3%) as severe dengue. The majority of cases in the study were in the age group of 18-30 years (41.1%), followed by the age group 30-39 years (24.4%). The mean age of the patients was 38 years (SD=13.9). Males (n=166, 75.1%) outnumbered females (n=55, 24.9%) in the current study. [Table 1]

Table 1: Demographic characteristics of patients

Parameters	Percentage (%)
Age distribution	
• 18-30 years	41.1
• 31-40 years	24.4
• 41-50 years	15.3
• 51-60 years	11.7
• >60 years	7.2
Gender distribution	
• Male	75.1
• Female	24.9
Grading of dengue fever	
• Dengue without warning signs	56
• Dengue with warning signs	33
• Sever dengue	11

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Table 2 shows the clinical features of dengue patients. Fever (n=221,100%) was the most common symptom which was seen in almost all (100%) of the patients, followed by headache (57.9%), vomiting (35.7%), abdominal pain (27.6%) and skin rash (27.6%). Hypotension was present in 8 (3.6%) patients at the time of admission. Hepatomegaly (28.1%) and splenomegaly (22.2%) were common findings on systemic examination Male to female ratio was 3:1. [Table 2]

Table 2: Clinical features among severe and non-severe dengue patients

Clinical features	Non-severe Dengue n=196 (%)	Severe Dengue n=25 (%)
Fever	196(100)	25(100)
Headache	117(59.6)	11(44)
Skin rash	59(30.1)	2(8)
Vomiting	69(35.2)	10(40)
Abdominal pain	56(28.5)	13(52)
Bleeding	12(6.12)	5(20)
Jaundice	8(4.08)	5(20)
Hypotension	0(0)	8(32)
Hepatomegaly	51(26)	11(44)
Splenomegaly	41(20.91)	8(32)
Altered sensorium	0(0)	4(16)

Among the laboratory parameters, mean haemoglobin and haematocrit remained the same between the two groups, non-severe and severe dengue. Low platelet count was significant in severe dengue compared to non-severe dengue. Median AST, ALT and CRP levels were significantly high in severe dengue patients as observed in Table no 3.
Out of 221 cases, 23.9 % were NS1Ag positive, 41.1 % were IgM ELISA positive and 34.8 % were positive for both NS1Ag and IgM ELISA. [Table 3]

Table 3: Laboratory parameters among severe and non-severe dengue

Laboratory parameters	Non-severe Dengue Mean ± SD/ Median (Q1, Q3)	Severe Dengue Mean ± SD/ Median (Q1, Q3)	p-value
Hemoglobin	14.8 ± 2.19	13.11 ± 2.4	<0.001
Hematocrit	43.3 ± 6.3	42.8 ± 6.5	0.002
Serum albumin	3.98 ± 0.5	3.88 ± 0.57	<0.001
Total leucocyte count	4000(3000,6075)	9300(6650,14850)	<0.001
Platelet count	63500 (22250,115250)	38000 (17000,103000)	0.1
Total bilirubin	0.62(0.42,0.86)	1.61 (0.77,2.4)	<0.001
Aspartate transaminase	104(58.75,108.2)	224 (89,1529)	0.001
Alanine transaminase	73.5(39,136.7)	142 (53,632)	0.013
C- Reactive protein	4.9(1.87,12.8)	96 (18.6,173.5)	<0.001

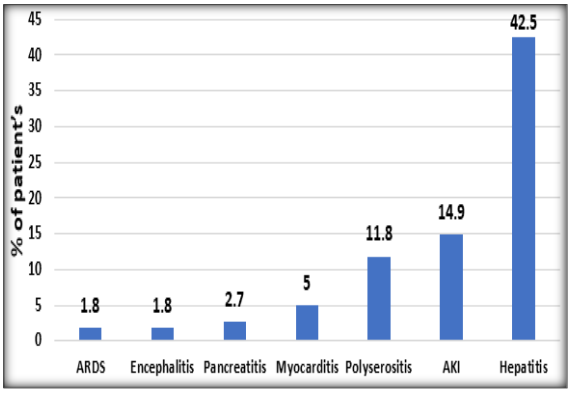

Figure 1: Complications among dengue patients

Figure 1 shows the complications seen in dengue fever. Out of 221 patients, 94 (42.5%) patients had hepatitis as the predominant complication followed by acute kidney injury (AKI) (14.9%), polyserositis (11.8%), myocarditis (5%), pancreatitis (2.7%), encephalitis (1.8%) and acute respiratory distress syndrome (ARDS) (1.8%). [Figure 1]
Median CRP level was very high in patients who developed acute kidney injury (43 mg/L), myocarditis (94.5 mg/L), pancreatitis (56 mg/L), and acute respiratory distress syndrome (88 mg/dl). Median CRP in severe and non-severe dengue were 4.9 and 96 respectively. Patients with severe dengue had significantly higher CRP levels, when compared to non-severe dengue (p <0.001). [Table 4]

Table 4: CRP level distribution

	Total no of dengue patients n=221	Non severe dengue n=196	Severe dengue n=25	P-value
Median CRP	6.24	4.9	96	<0.001

Univariate receiver operating characteristic (ROC) analysis of CRP showed cutoff value of 16.2mg/dl with AUC of 0.88 for non-severe dengue versus severe dengue had good sensitivity of 80% and a specificity of 79% highlighting the usefulness of CRP

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level in differentiating non severe dengue and severe dengue, which is statistically significant.

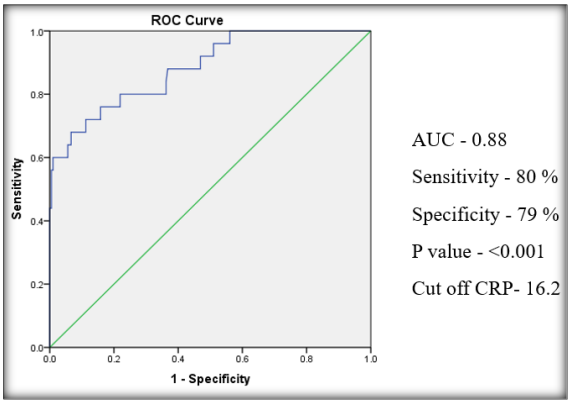

Figure 2: C-reactive protein ROC curve for non-severe and severe dengue

CRP has better predictive ability in determining the severity of dengue with good sensitivity and specificity when correlated with other laboratory parameters like hemoglobin, hematocrit, AST, AST, albumin, TLC and platelets which was statistically significant.

Univariate ROC curve analysis of different parameters showed AUC of <0.5 for hemoglobin, hematocrit and TLC so they don't have role in differentiating non severe and severe dengue.

DISCUSSION

In our study, the mean age of presentation was 38 + 13.9 years, with non-severe dengue patients being 37.4 years old and severe dengue patients being 37 years old. Studies by Tahir Z et al and Hafeez et al showed similar outcomes.[11,12] We found that the age group most frequently impacted was 18 to 30 years old (41.1%). This is comparable to the research done by Damodar et al. and Mallhi et al.[13,14] However, a study by Von Gorp et al, revealed that the pediatric age group was more prevalent.[15] These findings demonstrate that dengue affects people of all ages and has no age preference.

In the current study, there were more males (n=166, 75%) than females (n=55, 25%). Deshkar et al. and Garg et al. observed similar results in the Indian population.[16,17] The male majority in all studies may be explained by either improved access to medical services or increased outdoor activity, which increases exposure to mosquito bites.

Hepatomegaly was the most prevalent clinical symptom in our sample (28.1%), followed by ascites (21.8%) and pleural effusions (20.5%), which are indicators of fluid retention. According to research by Mittal et al., the most prevalent clinical symptom in 23% of cases was fluid retention.[18] Similar to research by Damodar et al. which were all based on the Indian population, bleeding tendencies were observed in 7.7% of patients.[16]

This contrasts with a study by Fujimoto et al., which found that 35% of people had a bleeding tendency.[19] This may be partially explained by the fact that Fujimoto et al. only examined cases of Dengue hemorrhagic fever. Subconjunctival hemorrhage and mouth bleeding were the most frequent among 7.7% of patients with bleeding tendencies.

Both the severity of the disease and the age groups of the population afflicted may be responsible for the broad variances in the clinical symptoms of the patients seen.

In contrast to non-severe dengue, the median CRP levels in severe dengue were higher in our study. The median CRP for severe dengue, dengue with warning signs, and dengue without warning signs was 96 mg/L, 9.35 mg/L, and 3.73 mg/L, respectively. It was comparable to the Chen et al study, which indicated that the mean CRP level was considerably greater in severe dengue (median CRP>30 mg/L) and DSS (median CRP>100 mg/L) than in non-severe DF.[20] According to a 2014 study by Kutsuna S et al., patients with elevated CRP levels were more likely to experience fluid accumulation, thrombocytopenia, and bleeding symptoms.[21] However, because of the small sample size, the study's findings were not statistically significant.

Additionally, a study by Atakuri et al. discovered a favorable relationship between C-reactive protein levels and dengue severity.[22]

The study's cutoff CRP level was 16.2 mg/L, which was statistically significant (P <0.001) and showed strong sensitivity (80%) and specificity (79%) in predicting dengue severity. It suggests that individuals who have an initial CRP level higher than 16.2 mg/L are more likely to develop severe dengue; therefore, early detection and vigorous treatment, together with regular laboratory parameter monitoring, should be carried out. The CRP threshold value of 30.1 mg/L was 100% sensitive in predicting DSS, according to research by Chen et al.

On the other hand, Kutsuna et al. discovered that malaria had higher CRP and total bilirubin levels and non-severe dengue fever had lower values.[21] However, these investigations were unable to identify the CRP cut off level that might be connected to dengue severity.

Acute inflammatory response brought on by viremia causes elevated CRP levels during the feverish stage of dengue infection. Because CRP is an acute phase protein, tissue damage is indicated by elevated serum CRP because it rises rapidly and strongly in response to different inflammatory conditions. Actually, the majority of individuals with extremely high CRP frequently exhibit organ dysfunction, such as myocarditis, hepatitis, acute renal injury, and pancreatitis. In our investigation, the CRP was greater than 100 mg/dl in three of the four patients who died. All of them indicate severe tissue damage brought on by increased inflammation, which is linked to a bad prognosis. Together with the results of the current investigation, a small number of studies on CRP and dengue indicate that elevated CRP levels

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may be related to the severity of dengue and aid in early differentiation between milder and more severe forms. In nations with limited resources and a high illness burden, CRP may be a viable laboratory biomarker.

Limitations of the study: The study only included inpatients. Cases were not grouped according to the stage of the disease. The statistical power is extremely low because there aren't many severe dengue patients to compare with non-severe dengue. To improve generality, more prospective studies with a bigger sample size are required to validate our findings in other populations.

CONCLUSION

Current study detected high levels of CRP in severe dengue patients compared to dengue without warning signs and dengue with warning signs. Hepatitis was the most common complication followed by acute kidney injury, polyserositis and myocarditis. Patients with increased CRP levels are at higher risk of developing complications. Median CRP level was high in patients who developed complications than patients without complications. Our study highlights the use of CRP as single potential laboratory marker to identify patients who are at risk for developing severe dengue. CRP level is a better predictor of severity of dengue than haemoglobin, TLC, haematocrit, albumin, AST and ALT levels.

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Author Contribution: All the authors were involved in the study concept and design, literature search, data acquisition, analysis, interpretation of results, manuscript preparation, and manuscript editing, study concept and design, data acquisition, manuscript editing, and review.

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