Study of C-Reactive Protien as a Prognostic Marker in Malaria

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Abstract: Background: India is a hyper-endemic zone for malaria. We need tests which can be done easily and are cost effective to assess the severity of the disease and to help in prognostication. CRP is one such investigation which can be used. **Aims And Objectives:** We carried out this prospective study to find the correlation between the level of CRP and the complications in patients of P.vivax and P. falciparum malaria. **Material and Methods:** Level of C- reactive protein, was measured in 227 patients of P.vivax and P. falciparum malaria, admitted in GMERS medical college Gotri, Vadodara. It was then compared with single and multiple complications as well as with the duration of hospital stay in both vivax and falciparum patients.Statistical analysis was done using Chi-Square test, unpaired T-test and ROC curve. **Results:** Out of 227 patients,105(46.2%) had P.vivax and 122(53.7%) had P. falciparum malaria. CRP level was high in all patients. In vivax and falciparum patients with single complications, the mean CRP level was 24+11.6 mg/L and 24.1+6.2 mg/L respectively. Both types of malaria with multiple complications showed very high levels, 69.6 + 14.1mg/L in P.Falciparum and 71.6 + 6.5mg/L in P.vivax patients. Elevated CRP level (41.5 mg/L) also predicted a prolonged hospital stay. **Conclusion:** Our study corroborates the observation that high CRP level has a strong prognostic value for predicting the complications in malaria. [Surname + name char.NJIRM 2015; 6(1):52-56]

Key Words: malaria,C-reactive protein, mortality

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Introduction: Malaria is one of the important causes of morbidity and mortality in the world, particularly in tropical countries like India. According to the World Malaria Report 2012,India is the second most affected region in the world, having 24 million cases with approximately 20,000 deaths occurring per year.[1]

Thus, there is an increasing need to identify the subset of patients who may develop complications. Multiple markers either clinical or laboratory, have been used for prognostication. Clinical signs such as hypotension, fever , icterus and investigations like liver function tests, se. creatinine etc have been routinely used in the past, but are not very reliable to predict the severity.

Recently, biomarkers like angiopoietin-2, vwf and soluble intercellular adhesion molecule (ICAM-1) have been studied to predict the severity of malaria.[2] However; they are very expensive and can't be carried out in public hospitals.

CRP is one such inflammatory marker which is found to be useful for assessing the prognosis.

Paul et al have shown strong correlation between CRP levels and the multiple complications in malaria.[3] V. Agrawal et al too have used CRP levels to assess the severity and response to treatment in malaria patients.[4]

We undertook this study in a tertiary care teaching hospital to objectively predict the severity of malaria using CRP levels.

Material and Methods: A total of 227 adult patients of Malaria(P.vivax and P. Falciparum), admitted in the department of medicine, at GMERS, medical college and hospital, Gotri, Vadodara, Gujarat, between May 2013 to October 2013 were included in the study. All were above 18 years of age.

Patients with any concurrent medical disorders, chronic inflammatory diseases or malignancies,or patients on medications, which could alter CRP levels were excluded from the study. An ethical clearance of the institution was obtained, and individual patient/next of kin consent was also taken.

A detailed clinical evaluation and physical examination was done in all patients. Investigations including CBC with platelet count, urinalysis, thick and thin blood smear for

identification and quantification of malarial parasites, RDT for malarial antigen, liver function tests, serum creatinine, coagulation tests, blood sugars, serum electrolytes and X ray chest were done in all patients. CRP levels were done by turbidimetry method(microlab-Rx-5). The normal range was taken as 0 to 5mg/L.

The level was then compared in both P.vivax and P.falciparum malaria patients with single and multiple complications. It was also compared with the duration of hospital stay.

The data was arranged in Microsoft Excel worksheet and SPSS version 17 programme was used for statistical calculation. Continuous variables like CRP were expressed as mean ± S.D. Discreet variables were expressed as numbers/percentages. To compare discreet variables, 2*2 contingency tables were analyzed using Chi-Square test. To compare continuous variables, unpaired T-test for independent samples was used. P value < 0.05 was considered significant. ROC curve was used for different CRP values in hospital stay of more than 5 days.

Results: As seen from Table 1, out of 227 patients, 152 were males and 75 were females. The range of age in P.falciparum group was 18years to 78years and in P. Vivax group was 18years to 80years. One hundred and five (105) patients had P.vivax (46.26%) and 122(53.74%) had P.falciparum malaria.

Table 1: Clinico-Demographic Profile of Patients.

	P.falciparum	P.vivax	Total
Males	83	69	152
Females	39	36	75
Complications			
Hematological	122	105	227
Renal	12	4	16
Hepatic	8	5	13
Metabolic	1	0	1
Cerebral	1	0	1

The haematological complications in the form of anaemia, thrombocytopenia or leucopenia were found in all 227 patients. Sixteen patients had ARF while 13 patients showed altered liver function test. Metabolic and cerebral complications were seen in 1 patient each.

Table 2: Comparison Between P.Vivax And P.Falciparum Malaria Patients As Regards The Number Of Complications And The Duration Of Stay In The Hospital.

	P.VIVAX (N= 105)	P.FALCIPARUM (N=122)	TOTAL N= 227	Chi ^{2} test	P value
No of complication					
Single	96	104	200	3.93	0.14
Multiple	9	18	27		
Duration of hospital stay					
3 days	82	9	91		
4 days	10	1	11		
5 days	10	96	106		
6 days	3	16	19		

Table 2 shows the comparison between P.vivax and P.falciparum malaria patients as regards the number of complications and the duration of stay in the hospital.

Single complications were found in 200(88.1%) patients while 27((11.89%) patients had multiple ones.

As seen from Table 3, the mean CRP level in patients with P.falciparum was 30.8±18mg/L.Patients with single complications had mean level of 24.1±6.2mg/L while those with multiple complications had mean level of 69.6±14.1mg/L.

Mean CRP level in patients with P.vivax was 28±17.5mg/L.Patients with single and multiple complications had the mean level of 24±11.6mg/L and 71.6±6.5mg/L respectively.

There wasn't much difference between the level of CRP in P.vivax and P. falciparum patients when compared for the number of complications (for single complications p value was 0.87 and for multiple complications p value was 0.25).

Table 3: Comparison between Level of CRP (Mg/L) In P.Vivax and P.Falciparum Patients with Single and Multiple Complications.

	Single complications	Multiple complications	Total	Unpaired t test	P value
P.falciparum	24.1+6.2	69.6+14.1	30.8+18	22.791	<0.0001
P.vivax	24+11.6	71.6+6.5	28+17.5	12.098	<0.0001
Total	24.1+9.2	70.3+11.9	33.6+15.5	23.592	<0.0001
Unpaired t test	0.159	1.144			
P value	0.873	0.25			

However, multiple complications in both types of malaria showed very high levels viz.69.6 ± 14.1mg/L(P.falciparum)and 71.6 ± 6.5mg/L (P.vivax).The mean CRP levels in both P.vivax and P.falciparum were high which was statistically significant (p<0.0001).

Figure 1: Correlation between the duration of hospital stay and the level of CRP among malaria patients.

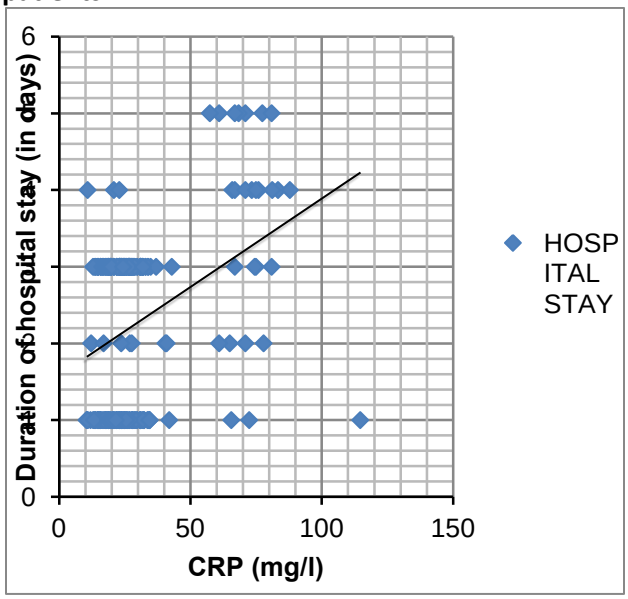
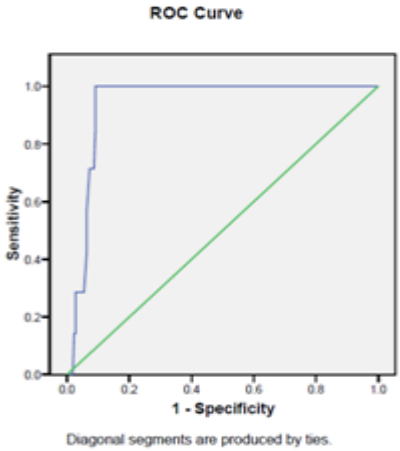


Figure1 A strong correlation was found between the duration of hospital stay and the level of CRP (Figure 2). Patients with high CRP level had prolonged hospital stay.

Figure 2: ROC for different CRP values for hospital stay of more than 5 days.



In figure 2 , ROC analysis shows that CRP level >41.5 mg/L has 100% sensitivity and 90% specificity to predict the hospital stay for more than 5 days (Area under Curve = 0.940), with highly significant AUC (p<0.0001).

Discussion: CRP is an acute phase reactant which rises rapidly in response to any inflammation. It binds to the damaged cells in case of malaria, to the RBCs infected with malarial parasites, to activate the complement system. CRP is used as a marker of inflammation. However, in malaria a strong correlation has been observed between the level of CRP and the severity of the disease.

In any infection, levels of CRP rises within 6 hours and reaches the peak at approximately 48 hours. The increase in level depends on its rate of production and so indirectly upon the severity of the precipitating cause.

A recent study showed that binding of CRP to infected red blood cells (RBCs) increased the removal of damaged RBCs from the circulation [7], which could lead to a more pronounced anaemia. Further, the control of P. falciparum parasitaemia is dependent on a pro-inflammatory response, and an uncontrolled inflammation is suggested to cause severe symptoms [8]. Higher levels of

circulating CRP could influence the IL-10 levels and thereby affect the delicate balance between pro- and anti-inflammatory responses, leading to a reduced control of parasitaemia.

Support for this notion comes from previous studies showing high circulating CRP levels in individuals with high parasitaemia [9], indicating an effect of CRP on parasite clearance.

IL-10 is also involved in the generation of peripheral regulatory T cells [10]. The up-regulation of peripheral regulatory T cells in a malaria infection has been shown to increase the parasite growth [11]. Moreover, CRP may show direct effects on dendritic cell differentiation, maturation and function [12], and neutrophil chemotaxis and signalling [13]. Since dendritic cells are important in initiating and regulating immune responses, and neutrophils have shown a protective effect against malaria in vitro [14,15], such influences may seriously hamper an effective immune response.\

Serial measurement of CRP is also important to see response to treatment. A study done by S H Gillespie showed that mean CRP level increases till second day of treatment and then it fall slowly till next 5 days. It is parallel with disappearance of parasitemia and clinical recovery.

P.Naik and A.Voller developed a microplate ELISA to measure CRP and studied the association between CRP and malaria in African patients. They found highest levels with high parasitemia.[5] A study done by N Hurt et al in Tanzanian children also demonstrated high levels of CRP in P.falciparum malaria with high parasitemia.[6]

The presence of high levels of pro-inflammatory mediators such as TNF-α, IL-1β,IL-10,amyloid 10,ferritin and IFN-γ is correlated with severe malaria [16]. Furthermore, there is a marked increase in plasma concentrations of adhesion receptors such as ICAM-1 and E-selectin . In addition to cytokines, others biomarkers have been used to discriminate cerebral malaria from uncomplicated malaria, such as serum angiopoietin-1 and -2 (ANG-1 and ANG-2). The levels of ANG-1 significantly decrease while ANG-2 increases in cerebral malaria patients. But all this marker are difficult to measure and they are costly. The results of our study are in accordance with the other studies which have also shown a strong correlation between levels of CRP and malaria specific morbidity or complications.

Conclusion: In our study we found that CRP levels were high in all admitted patients of malaria. There was no statistical difference in the levels, in patients with P.vivax or P.falciparum malaria. Patients with multiple complications had higher CRP levels than those with single ones. High CRP also predicted a prolonged hospital stay. Thus CRP is a cheaper alternative to evaluate the severity of malaria. This is especially useful in a resource crunched country like ours.

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