A Study Of Relation Of C- Reactive Protein With Hemoglobin, Platelet Count, Creatinine And Bilirubin Levels In Patients Of Malaria

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Abstract: Background: The burden of malaria warrants need of predicting severity of malaria early. CRP is a known acute phase reactant. Objectives: To find out if there is any correlation between CRP at the time of presentation with later complications in malaria. Material And Methods: This was an observational study. All patients ≥ 18 years with confirmed diagnosis of malaria were included. The data was analysed correlation of CRP at presentation with hemoglobin, platelet count, liver enzymes or creatinine levels. Result: Total 80 patients were included. There was positive correlation of CRP with T. bilirubin, SGPT, s.creatinine and blood urea (r = 0.21, 0.26, 0.51 and 0.44 respectively) while there was negative correlation of CRP with Hb and platelet count (r = -0.26, -0.56). A statistically significant difference was observed in values of haemoglobin, platelet count and serum creatinine between the two groups with CRP > 6 mg/l and CRP < 6mg/l. Conclusion: CRP at presentation in cases of malaria is positively correlated with s. bilirubin, liver enzymes and s creatinine and negatively correlated with hemoglobin and platelet counts. CRP should be tested in all malaria patients to identify patients requiring aggressive treatment to prevent serious complications of malaria and improve prognosis. [Kanojiya S Natl J Integr Res Med, 2020; 11(4):42-46]

Key Words: C reactive protein, Malaria, severity.

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Introduction: Malaria is a mosquito-borne disease[1] with complications like respiratory distress, hemolytic jaundice, cerebral malaria, renal failure, coagulopathy and shock[2]. According to the World Malaria Report, in 2016 more than half population was at risk of malaria[3]. Africa had the largest burden of malaria morbidity (200 million cases) in 2017, followed by South-East Asia Region[4,5].

This huge burden warrants need of predicting severity of malaria early. CRP (C reactive protein) is a known acute phase reactant[6]. Hence, we did this study to find out if there is any correlation between CRP at the time of presentation with later complications in malaria.

Material & Methods: This was an observational study done in a tertiary care hospital on western coast of India started after getting approval from Institutional Ethics Committee. All patients of age ≥ 18 years with confirmed diagnosis of malaria either on peripheral smear or malaria rapid diagnostic test (MDRT) (using antibodies against Plasmodium falciparum (Pf) histidine-rich protein 2 and Plasmodium vivax (Pv) lactate dehydrogenase-Nano sign) were included. According to current WHO report, if there is no other diagnostic support, it is appropriate to use MRDTS[7]. Only those who gave informed written consent for the study were included. Patients with history of chronic diseases like diabetes mellitus, tuberculosis, cirrhosis of liver, chronic kidney disease or connective tissue disease and who did not give written informed consent for participation were excluded from the study.

A detailed history was taken from all enrolled patients to identify the ones who met the inclusion criteria. All the participants included in the study were subjected to peripheral smear for malarial parasite (MP), MP Antigen, CRP (by Nephelometry) and routine investigations like complete blood count (coulter method), peripheral smear for malarial parasite, renal function test and liver function test. Other special investigations like serum electrolytes, chest X ray, random blood sugar, ECG, urine routine microscopy, USG abdomen, 2D echo, CT/MRI and ABG were done according to the requirement.

Malaria was diagnosed with Giemsa-stained peripheral blood smears or/and the MRDT. Nephelometry was used to measure CRP. Normal value of CRP was taken as 0 – 6 mg/L. Sysmese and Coulter methods were used for complete blood count. Normal value of hemoglobin was taken as 13-17 gm% and of platelets as 1.5-4.5 lacs/cumm. Enzymatic (Erba Em200) method was used to measure serum creatinine. Normal value of serum creatinine was taken to be 0.6-1.2 mg%.

Diazo method was used to measure serum bilirubin. Normal value of total bilirubin was taken to be 0.2-1.0 mg%, direct bilirubin 0.1-0.4 mg% and indirect bilirubin 0.2-0.8 mg%.

Clinical Presentation of Malaria was classified as severe on the basis of the WHO's 2010 severe falciparum malaria criteria[8]. (Table 1) The participant population was divided in two groups (CRP > 6 and CRP < 6) based on CRP level at presentation to find out if there was any difference in mean values of laboratory parameters of the two groups. Pearson's correlation coefficient was calculated to assess if there was any correlation between CRP levels at presentation with complications like anemia, jaundice and renal failure in patients of malaria.

Table 1: WHO's 2010 Severe Falciparum Malaria Criteria

Jaundice	S.Billirubin>3 mg %
Renal failure	S. Creatinine >3 mg%
Severe anaemia	Hemoglobin <5 gm %
Thrombocytopenia	Platelets <1,00,000
Cerebral Malaria	Glassgow coma scale ≤ 9/14
Shock	Systolic BP< 80 mm of Hg
Hypoglycemia	< 40 mg%
Multi Organ Dysfunction Syndrome	≥ 2 complications

Results: Total 80 patients were included. Out of these, 71(88.75%) were males and 9 (11.25%) were females. Most of them 20 (25.00%) were between 31 to 40 years age group, followed by 17 (21.25%) between 21 to 30 years, 16 (21%) between 41 to 50 years, 11 (13.75%) between 51 to 60 years, 9 (11.25%) between 61 to 70 years, 6 (7.50%) in the age group of below 20 years and 1 (1.25%) above 70 years.

Most common presenting complaint was chills seen in 66 (82.50%), followed by sweating in 53 (66.25%) and headache in 27 (33.75%). Other complaints were vomiting in 11(13.75%), rigors in six (7.50%), cough in four (5.00%) and breathlessness in one patient (1.25%). Most common signs were pallor and icterus. Twelve patients (15.00%) had pallor and four patients (5.00%) had icterus. Only two patients (2.50%) had oedema. None of the study participants had cyanosis, clubbing or lymphadenopathy.

Mean haemoglobin in study population was 10.16 ± 3.63 gm%, mean total count was 5455.00 ± 2273.62 cells/cu.mm, mean platelet count was 49350.00 ±21040.71 cu.mm, mean CRP was 69.89 ± 52.03 mg/l, mean SGPT was 74.00 ± 98.86 IU/l, mean SGOT was 74.64 ± 104.11 IU/l, mean total bilirubin was 3.14 ± 1.70 mg%, mean blood urea was 43.25 ± 21.67 mg%, mean serum creatinine was 1.67 ± 1.12 mg% and mean RBS was 121.03 ± 16.71mg/dl. Maximum number of patients that is 44 (55.00%) had severe anemia. Twenty two patients (27.50%) had mild anemia and 14 patients (17.50%) had moderate anemia. Forty three patients (53.75%) had serum creatinine more than 1.2 mg% and 27 patients (33.75%) had serum creatinine less than 1.2 mg%.

On correlation analysis, it was found that there was positive correlation of CRP with T. bilirubin, SGPT and blood urea (r = 0.21, 0.26 and 0.44 respectively) while there was negative correlation of CRP with Hb (r = -0.26). We also found a positive correlation of CRP with s.creatinine (r = 0.51) and negative correlation with platelet counts (r = -0.56). (Table 2)

Table 2: Correlation Of CRP With Various Lab Parameters

	Hb	**TLC**	**Platelet count**	**CRP**	**SGPT**	**SGOT**	**T.Bili¶**	**B. Urea****	**S.cr‡‡**
Hb*	1								
TLC†	-0.056	1							
Platelet count	0.089	-0.008	1						
CRP‡	-0.262	0.017	-0.565	1					
SGPT§	-0.278	-0.224	-0.184	0.218	1				
SGOT‖	-0.306	-0.203	-0.110	0.196	0.976	1			
T.Bilirubin	-0.367	-0.153	0.047	0.263	0.584	0.594	1		
B. Urea	-0.515	-0.121	-0.260	0.446	0.066	0.081	0.111	1	
S. Creatinine	-0.700	-0.011	-0.243	0.519	0.173	0.193	0.370	0.800	1

*Hemoglobin, † Total Leucocyte count, ‡ C reactive protein, § Serum glutamic pyruvic transaminase, ‖ Serum glutamic oxaloacetic transaminase, ¶ Total bilirubin , **, †† Blood Urea, ‡‡ Serum creatinine

There was a significant difference in mean value of haemoglobin in patients with CRP > 6 mg/l (9.98 ± 3.62 gm%) as compared to the other group with CRP < 6 mg/l (13.68 ± 1.14 gm%); p=0.001. Similarly mean value of platelet count was 48131.58 ± 20734.09 cu.mm in patients with CRP > 6 mg/l as compared to 72500.00 ± 12583.06 cu.mm in group with CRP < 6 mg/l; p=0.023. The mean value of total bilirubin was 3.16 ± 1.73 mg% in patients with CRP > 6 mg/l as compared to 2.73 ± 1.14 mg% in those with CRP < 6 mg/l; p=0.515. The mean value of serum creatinine was 1.17 ± 1.13 mg% in patients with CRP > 6 mg/l as compared to 0.85 ± 0.10 mg% in those with CRP < 6 mg/l; p=0.001. Thus, a statistically significant difference was observed in values of haemoglobin, platelet count and serum creatinine between the two groups with CRP >6 mg/l and CRP <6mg/l. (Table 3)

Table 3: Comparison Of Hemoglobin, Platelet Count, Bilirubin And Serum Creatinine Level In Patients With CRP >6 And <6

Lab reports	CRP* > 6		CRP < 6		p value
	Mean	SD	Mean	SD	
Hemoglobin [gm%]	9.98	3.62	13.68	1.14	0.001
Platelet count [cu.mm]	48131.58	20734.09	72500.00	12583.06	0.023
Total bilirubin [mg%]	3.16	1.73	2.73	1.14	0.515
S.Creatinine [mg%]	1.71	1.13	0.85	0.10	0.001

Discussion: More than 200 million clinical cases of malaria are seen per year all over the world (Deroost et al, 2014). It was estimated to cause 584,000 deaths in 2013 (WHO, 2014)[9]. In humans, plasma levels of CRP may rise rapidly and markedly, as much as 1000-fold or more, after an acute inflammatory stimulus. Recent data have raised the possibility that it may participate in the pathogenesis of disease.

The present observational study was conducted on patients diagnosed with malaria with the aim to assess association of CRP with anemia, hemolysis and acute kidney injury. Various studies have shown increased levels of CRP in patients of malaria[10]. In one study done in southern part of Iran on one hundred and sixty-two patients suffering from malaria, 85·2% showed high CRP[11]. A study from Australia including 69 patients of p.vivax cases found elevated CRP levels in 85% cases[10]. In another study done on 17 patients with acute falciparum malaria, the mean value of CRP was 49.0 mg/l[11]. In the present study also, the mean CRP was 69.89 ±52.03 mg/l. which is much higher than the normal value of CRP [0-6].

A study done in Assam, India also found that patients with high CRP had protracted course of illness, hence implying greater severity[10]. In another study in India, CRP was studied as a prognostic marker in malaria. It was found that the CRP levels were 40.82 ± 18.63 mg/l in patients with one complication and 58.91 ± 14.56 mg/l in patients with multiple complications (haematological / hepatic/ renal/ cerebral/ metabolic). The patients who died had CRP levels significantly higher than survivors. CRP levels showed strong correlation with duration of hospital stay[10].

Thrombocytopenia is commonly seen in patients of malaria. Reduced platelet production and survival, and increased splenic uptake of platelets resulting in thrombocytopenia lead to bleeding diathesis in patients of malaria[12]. A study done in 66 patients found that 63% had platelet count <100000/mm3[12]. A study on paediatric population in Bikaner in northwest India reported thrombocytopenia in 61.5% children with malaria. A study from Venezuela reported thrombocytopenia in 58.9% children with P.vivax malaria, with 25.6% requiring platelet transfusions. Mean platelet count was 1,18,650/mm3 range being 8000/mm3–6,10,000/mm3[12]. In our study also mean platelet count was in place of 'of' of 49350.00 ±21040.71 per cu.mm.

Malarial hepatopathy is more common in adults than children and may present alone or along with other complications[9]. 134 malaria cases were studied by Anishka Jain et al and it was seen that hyperbilirubinemia occurred in 41.04%. Serum aspartate aminotransferase (AST) was raised >3-fold in 17.16% and serum alanine aminotransferase (ALT) was increased in 4.47% cases[9]. In another study 57.5% patients had

jaundice[13]. We also had similar result, mean value of total bilirubin in our study being 3.14 ± 1.70 mg%. Acute kidney injury (AKI) is one of the most dreaded complications of severe malaria[14].

It may be present as a component of multi-organ dysfunction or as a lone complication[13]. In a study, AKI was seen in 23 (38 %) of the 61 patients with severe malaria. Eight patients eventually needed renal replacement therapy (RRT)[15]. Some authors report AKI incidence rates as high as 52.5 % in patients with malaria[16]. Similarly, we observed that 53.75% of the patients in our study developed AKI.

Haematological abnormalities are considered a hallmark of malaria, and reported to be most pronounced in P. falciparum infection, probably as a result of the higher levels of parasitemia found in these patients. P.falciparum malaria is one of the most common causes of anemia. A total of 430 patients (59.2%) were anemic at presentation in the study done by Layla A.M. Bashawri et al[17]. In present study 44 (55.00%) had severe anemia. 22 patients (27.50%) had mild anemia and 14 patients (17.50%) had moderate anemia.

Thus, complications like anemia, thrombo-cytopenia, AKI and hyperbilirubinaemia are well known complications of malaria. This study reports a positive correlation of CRP at presentation in malaria with serum bilirubin, SGPT, blood urea and serum creatinine. It also shows a negative correlation of CRP with hemoglobin and platelet counts. It can be said that CRP level is indicative of development of complications like anemia, thrombocytopenia, jaundice and AKI in cases of malaria. Hence, measuring the CRP levels at presentation will help to manage the patients more vigilantly.

Conclusion: The CRP level at presentation in cases of malaria is positively correlated with values of s. bilirubin, liver enzymes and s creatinine and negatively correlated with hemoglobin and platelet counts. Hence, we recommend testing for CRP levels in patients of malaria to identify patients who should be treated more vigilantly to prevent serious complications of malaria and improve the prognosis. A multi centric randomized controlled study will help in understanding the effects of CRP levels in malaria patients better and also the overall impact on the clinical outcome in these patients.

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