



RESEARCH ARTICLE

A STUDY OF HS-CRP AS A MARKER OF CLINICAL SEVERITY AND OUTCOME IN COMPLICATED AND UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA

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Manuscript Info

Manuscript History

Received: 05 April 2020

Final Accepted: 07 May 2020

Published: June 2020

Key words:-

Plasmodium Falciparum Malaria, Hs-CRP, C3 Complement

Abstract

Background: Malaria is the most important of the parasitic disease of humans, with transmission in 106 countries containing three billion people and causing one million deaths each year. Recently some acute phase reactants have emerged as biomarkers in malaria infection in addition to chemokines and cytokines. In particular high Sensitive C-reactive protein (hs-CRP) has been identified as important inflammatory biomarkers.

Methods: The present study included 100 untreated falciparum malaria patients attending Department of Medicine at M.B.G.H, Udaipur (Raj.), with symptoms of fever, rigor, and vomiting who tested positive for falciparum malaria by slide microscopy and/or MP QBC test was enrolled in this study. Venous blood sampling from eligible candidates was taken and their hs-CRP was analyzed with the help of immunoturbidimetric assay.

Results: Mean age of patients was 54.35 years, while male to female ratio for uncomplicated, complicated and healthy controls were 2.1:1, 1.2:1 and 1.5:1 respectively. Results showed significantly higher level of hs-CRP in patients who had complications and also in patients who died, compared to uncomplicated patients and patients who discharged. [P value < 0.001 (HS)].

Conclusions: In this prospective case control study, we found that hs-CRP at presentation correlate significantly with morbidity and mortality in falciparum malaria. Thus hs-CRP can be considered a new, cost-effective, and reliable tool in assessment of prognosis in falciparum malaria.

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Introduction:-

Malaria is the most important of the parasitic disease of humans, with transmission in 106 countries containing three billion people and causing one million deaths each year.¹ Malaria occurs mostly in the tropics. India harbours both *P. vivax* (50% to 55%) and *P. falciparum* (45% to 50%) and contributes 70% of malarial cases in the South East Asian region. *P. falciparum* predominates in Africa, New Guineas, and Haiti; The true burden of malaria in India is difficult to ascertain. There are an estimated 70 to 100 million cases each year, but only 1.6 to 1.8 million cases are reported by the National Vector Borne Disease Control Programme (NVBDCP).²

It is transmitted by the bite of female *Anopheles* mosquito and caused by protozoan parasites of the genus *Plasmodium*. Six species of the genus *Plasmodium* cause nearly all malarial infections in humans. These are *P.*

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Falciparum, P. Vivax, two morphologically identical sympatric species of P. ovale, P. malariae and – in Southeast Asia – the monkey malaria parasite P. knowlesi can infect humans. Most serious forms of the disease are caused by P. Falciparum.³

Plasmodium causes biological disorders which are not totally elucidated. When malaria occurs there is destruction of infected erythrocyte, opsonisation of red cells and dyserythropoiesis.⁴

When schizontes rupture, host monocytes and macrophages secrete pro-inflammatory cytokines stimulating the production of acute phase protein. An acute-phase protein is defined as one of which plasma concentration increases (positive acute phase proteins) or decreases (negative acute-phase proteins) by at least 25 percent during inflammatory disorders.⁵ Recently some acute phase reactants have emerged as biomarkers in malaria infection in addition to chemokines and cytokines. In particular high Sensitive C-reactive protein (hs-CRP) and nitric oxide (NO) have been identified as important inflammatory biomarkers.^{6,7}

hs-CRP is an acute phase protein that is involved in the activation of complement, acceleration of phagocytosis and detoxification of substances released from the damaged tissue. Measurement of serum hs-CRP is most frequently used for the evaluation of injury in the body tissue or for the detection of inflammatory event somewhere in the body. In malaria hs-CRP secretion is induced by pro – inflammatory cytokines that are secreted by host mononuclear cells and strong correlations have been found between hs-CRP levels and parasitemia.⁸

In malaria, hs-CRP is said to have a pathogenic role. hs-CRP is said to bind to infected erythrocytes and help in their clearance. This immune activation towards infected RBCs also results in various deleterious manifestations. Also, hs-CRP activates complement pathway and platelet activation, and results in various untoward effects. Thus, measurement of CRP can be useful in understanding the pathogenesis of severe malaria⁹.

Aims and Objectives:-

To evaluate the hs-CRP level as a marker of clinical severity and outcome in uncomplicated and complicated plasmodium falciparum malaria.

To evaluate the serum complement C3 level as a marker of clinical severity and outcome in uncomplicated and complicated plasmodium falciparum malaria.

Material and Method:-

After approval from the institutional ethical committee and written and well informed consent from patient, the present study was performed in Department of medicine at R.N.T Medical College and Associated group of Hospitals Udaipur(Raj.).

Source of Data:

The present study included 100 untreated falciparum malaria patients attending Department of Medicine at M.B. Govt. Hospital, Udaipur (Raj.), with symptoms of fever, rigor, headache and vomiting. Patients who tested positive for falciparum malaria by slide microscopy and/or MP QBC test was enrolled in this study. In all the patients' falciparum malaria infection was the only diagnosis.

A finger prick blood sample was taken to prepare thick and thin blood films and stained with Geimsa stain to determine the presence of falciparum malaria parasites. The following lab investigations were performed when the patient was admitted: - complete blood count, PBF, MPQBC, ESR, Dengue by card, widal test, ELISA test for scrub typhus and chickenguniya, BT, CT, PT-INR, Random Blood sugar, ABG, Liver function test, Renal function test, HIV, HbsAg, anti HCV, Urine routine and microscopy, hs-CRP, C3 complement, serum electrolyte, chest x-ray, ECG, Fundus examination, lumbar puncture, CT scan, MRI brain.

Inclusion Criteria:

Age > 18 years of both sexes.

Only plasmodium falciparum malaria

Exclusion Criteria:

1. Patients with other febrile illnesses (eg. scrub typhus, typhoid fever, dengue, p.vivax malaria and mixed p.vivax and p.falciparum etc.) that can alter the hs-CRP.
2. Patients with any auto immune disease.
3. Patients with malignancy.
4. Patients who are on steroids and on immunosuppressive drugs.

Study Design:

Our study is a prospective case control study. This Study included 50 uncomplicated and 50 complicated plasmodium falciparum malaria patients who were admitted in medical ward of our institute and these were taken as cases and 50 age and sex matched healthy persons among the hospital staff and attendants of the patients were taken as control in this study.

Venous blood sampling from eligible candidates was taken and their hs-CRP was analyzed with the help of immunoturbidimetric assay.

Results and Observation:-

In this prospective study, we categorized the patients into two category, uncomplicated and complicated (table 1). We have also taken a total of 50 volunteers as a healthy control. Among the 50 uncomplicated patients Male female ratio was 2.1:1 (table 2). Among the 50 complicated patients Male female ratio was 1.3 : 1. Among the 50 healthy controls Male female ratio was 1.5 : 1. Among the 50 uncomplicated cases, majority 23 (46%) of the patients were below 30 year age group, 7 (14%) patients were in the age group between 30-39 and 5(10%) patients were in the age group between 40-49, 50-59 and 60-69. Among the 50 complicated cases, majority 17 (34%) of the patients were below 30 year age group, 12 (24%) patients were in the age group between 40-49 and 9(18%) patients were in the age group between 30-39, 7 (14%) patients were in the age group between 60-69. Among the 50 healthy controls, majority 17 (34%) of the persons were below 30 year age group, 14 (28%) persons were in the age group between 30-39 and 10 (20%) persons were in the age group between 40-49, 5 (10%) persons were in the age group between 50-59. In our study out of the 50 patients who had complications, 12 (24%) died. No death occurred in patients with uncomplicated plasmodium falciparum malaria.

Table no.3 shows the hs- CRP levels in various patients as well as in healthy controls. Patients with complicated malaria (n=50) had significantly higher hs-CRP(49.07 ± 14.30) level as compare to patients with uncomplicated malaria(n=50). Patients with uncomplicated falciparum malaria (n=50) had significantly higher hs-CRP(10.17 ± 2.67) level compared to healthy controls (n = 50), whose hs-CRP level were in range of 2.65 ± 0.92 . (table 4) (P = 0.001 by Mann Whitney U Test;). The patients who died (n = 12) had hs- CRP levels significantly higher than survivors (P = 0.001 by Mann Whitney U Test;)(table 5). hs- CRP levels showed strong correlation with duration of hospital stay (P < 0.001).

Table 1:- Distribution of Patients According to Complications.

Complication	Outcome				Total
	Death		Discharge		
	No.	%	No.	%	
Uncomplicated	0	0.00%	50	100.00%	50
Complicated	12	24.00%	38	76.00%	50

Table 2:- Distribution of Patients According to Sex.

Gender	No. in uncomplicated	%	No. in complicated	%	No. in healthy control	%
Female	16	32%	22	44%	20	40%
Male	34	68%	28	56%	30	60%

Table 3:- Distribution of hs-CRP Levels According to Complications.

Complication	hs-CRP Levels
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	Mean	±SD
Uncomplicated	10.17	2.67
Complicated	49.07	14.30
Healthy control	2.65	0.92

Table 4:- Comparison of hs-CRP levels with Complications (p value).

	P value
Uncomplicated/ Complicated	<0.001 (HS)
Uncomplicated/ Healthy Controls	<0.001 (HS)
Complicated/ Healthy Controls	<0.001 (HS)

Table 5:- Distribution of hs-CRP Levels According to Outcome.

Outcome	hs-CRP Levels		P value
	Mean	±SD	
Death	67.25	3.32	<0.001 (HS)
Discharge	23.88	18.18	

Discussion:-

In this prospective case control study, we found significantly high hs-CRP levels in plasmodium falciparum malaria patients. hs- CRP levels were higher for patients who had complications and also hs-CRP levels were higher for patients who died, compared to uncomplicated patients and patients who discharged. hs-CRP levels were also higher in patients with MODS compared to patients with single complication. Also, hs-CRP levels were higher in patients with uncomplicated falciparum malaria, compared to healthy controls. High hs-CRP also predicted prolonged hospital stay.

Hs-CRP is known as a marker of morbidity and mortality in malaria. This acute phase reactant level correlates closely with other complications in malaria and can be used to predict severity.

A study by rudrajitpaul et al⁹ in 2010 from kolkatta, India also came to the same conclusion. They also found that patients who died had significantly higher CRP levels (49.47±14.46 mg/L) than patients who survived (28.31±19.75 mg/L). Also, found that CRP levels were significantly higher in patients with multiple complications (58.91±14.56 mg/L) compared to patients with single complications (40.82±18.65 mg/L). Also found that CRP levels rise in complicated malaria (47.11±19.13 mg/L), compared to uncomplicated (23.71±16.35 mg/L). In our study, we found significantly high hs-CRP levels in patients who died as a result of malaria. In this study, we have measured CRP only once, at first contact. However, serial CRP measurements in malaria patients can be even better at assessment of course of the disease.

A similar study done by MitulChhatriwala et al¹⁰ in 2013, they also found that patients who died had significantly higher CRP levels (48.22±13.56 mg/L) than patients who survived (27.47±14.76 mg/L). also found that CRP levels were significantly higher in patients with multiple complications (52.08±9.51 mg/L) compared to patients with single complications (40.21±12.34 mg/L). Also found that CRP levels rise in complicated malaria (47.80±12.73 mg/L), compared to uncomplicated (24.14±12.17 mg/L).

A similar study done by Vandana Agrawal et al⁸ in 2013. The study showed significant correlation between serum CRP concentrations and various laboratory markers of severity of malaria like serum bilirubin, serum concentrations of SGPT and SGOT in P. falciparum patients but not in P. Vivax.

Summary:

In this prospective study, we categorized the patients into two category, uncomplicated and complicated. Venous blood sampling from eligible candidates was taken and their hs-CRP was analyzed with the help of immunoturbidimetric assay. Patients with complicated malaria had significantly higher hs-CRP (49.07±14.30) level as compare to patients with uncomplicated malaria. hs- CRP levels showed strong correlation with duration of hospital stay (**P** < 0.001).

Conclusion:-

In this prospective case control study, we found that hs-CRP at presentation correlate significantly with morbidity and mortality in falciparum malaria. Thus hs- CRP can be considered a new, cost-effective, and reliable tool in assessment of prognosis in falciparum malaria.

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