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C - REACTIVE PROTEIN LEVELS AS A POTENTIAL DIAGNOSTIC MARKER DURING MALARIAL INFECTIONS

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ABSTRACT

C-reactive protein is a plasma protein known to play an important role in the immune response to malaria. In this study, we measured the C - reactive protein levels during uncomplicated and severe malaria patients seeking medical attention at the district Wenlock hospital in Mangaluru. The study population consisted of 627 malaria infected patients; among which 554 had uncomplicated malaria and 73 suffered from severe malaria. We measured various hematological and biochemical parameters including C-reactive protein as well as inflammatory cytokines to correlate the changes during *P.falciparum*, *P.vivax* mono and mixed (Pv and Pf) infections. The C-reactive protein levels were found to be significantly high in patients suffering from both uncomplicated and severe malarial infections. (*P*=<0.0001).Increased C-reactive protein levels showed a positive correlation with increase in percentage parasitemia and a negative correlation with hemoglobin, RBCs, and platelets. While bilirubin showed a positive correlation in patients with *P.falciparum* and *P. vivax*, blood urea levels had a positive relationship only in *P.vivax* infections. Inflammatory cytokines, TNF α and IL-6, showed a positive correlation across various infecting species. The results indicate that C-reactive protein levels showed excellent sensitivity, specificity and odds ratio during malarial infections. In this study, the results i) confirm markedly elevated C-reactive protein levels in patients with severe malaria as compared to uncomplicated malaria, ii) support the idea of its possible significant role in malarial anemia and thrombocytopenia iii) provide the basis for the use of this acute phase protein as a cost effective biomarker.

KEYWORDS: Biomarker, C-reactive protein, *Plasmodium vivax* and *P. falciparum*, Mangaluru, Dakshina Kannada, severe malaria.

INTRODUCTION

Malaria still remains as a major health problem in the modern world. Malaria is transmitted by the bite of female Anopheles mosquito and is caused by protozoan parasites of the genus Plasmodium. Humans suffer from malaria caused majorly by four plasmodial species namely *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Earlier, *P.falciparum* has been traditionally credited with severe manifestations of malaria and the other remaining species were considered to be benign. However, recent worldwide studies have also identified *P.vivax* to cause similar clinical manifestations which may lead to mortality. As per WHO report of 2016, 91 countries reported a total of 216 million cases of malaria, an increase of 5 million cases over the previous year with 445 000 deaths reported worldwide. About 93% of Indians live in low to high transmission zones of malaria. In 2016 alone, 1,090,724 Indians suffered from malarial infections which resulted in 331deaths.[1]

Mangaluru, with a population of 4, 99,000 (2011 Census), is a southwestern coastal city in Dakshina Kannada district of Karnataka state. Until 1990, the National Malaria Control Programme in this region was a tremendous success with only few sporadic cases and Mangaloreans were not aware of malaria in this region. From this period onwards, increased urbanization and vigorous construction activities resulted in migrant population from other endemic regions of India resulting in the spread for this deadly disease.[2,3]

C-reactive protein is an acute phase protein primarily synthesized in the liver.[4] In response to an inflammatory stimulus, the CRP levels rise up to 50,000 times above normal, typically within 6 hrs and peak at 48 hrs.[5] CRP

is known to activate the classical complement cascade, stimulates phagocytic cells for phagocytosis.[6] In malaria, CRP secretion is induced by pro-inflammatory cytokines that are secreted by host mononuclear cells.[7] Though the primary function of CRP is conjugating pathogens and inducing their destruction by host complement system[8], its sustained release can also have adverse effects.[9,11] It is postulated that prolonged increased CRP levels could contribute to an imbalance in inflammatory response leading to a reduced control of parasitemia.[12,13] CRP has been valuable in assessing the severity of malaria, to assess asymptomatic carriers and in follow up treatments.[9] There are reports of severe malarial patients with increased CRP levels than the patients with milder forms. In this study, we set out to determine i) the C-reactive protein (CRP) levels in patients suffering from uncomplicated and severe *P.falciparum*, *P.vivax* mono and mixed (PV and Pf) infections ii) the relationship between CRP and the hematological, biochemical and inflammatory cytokine levels and iii) the usefulness of CRP as a prognostic marker during malarial infections.

METHODS

During the period of November 2013 to October 2015, a prospective cross-sectional study in adults aged between 15-65 years was carried out at district Wenlock hospital, Mangaluru. Before enrollment into the study, a written informed consent was obtained from the study participants. The study protocol was approved by the ethical committees of Kuvempu University, Shivamogga, Karnataka state, the central ethics committee of NITTE University, Mangaluru, and the Institutional Review Board of the Penn State University, College of Medicine, USA. Individuals tested positive for HIV, HCV, Hepatitis B, pregnant women, use of any prophylactics prior to diagnosis were excluded from the study. A structured clinical questionnaire was used to record information regarding the study participant's socio-demographic profile, recent travel history, history of previous infections, clinical features and complications.

Diagnosis and treatment

The plasmodial infections were confirmed by the Geimsa stained conventional thick and thin blood smears. From each study participant, upon finger prick, two (thick and thin) blood slides were prepared, fixed, and stained with 4% Geimsa stain. Independent microscopic evaluation was performed by experienced microscopists for the presence or absence of plasmodial parasites, the species type and the number of asexual parasites. Percentage parasitemia were determined as (number of parasites per µL of blood/number of RBCs per µL of blood) x 100. The outpatients were treated by attending physicians at the hospital as per the as per National Vector Borne Disease Control Programme [NVBDCP] recommendations.[14] Severe malaria cases were treated by the attending physicians as required.

Grouping of study participants

Uncomplicated malaria (UM) was defined as febrile individuals managed on an outpatient basis with a positive blood smear for malaria parasite. Severe malaria (SM) was defined as patients with peripheral malaria parasitemia, severe clinical symptoms and with life threatening complications, thus admitted into the inpatient wards of the hospital. These features include any of the following: High intermittent fever, persistent vomiting (>5 episodes/day), weakness, hypotension (SBP 70–80mm Hg), hematuria, hepatomegaly, splenomegaly, severe anemia (hemoglobin < 5g/dl), severe thrombocytopenia (platelets <0.5x103/ul), metabolic acidosis (plasma bicarbonate level < 15 mmol/l), hypoglycemia (plasma glucose < 2.2mmol/l), renal failure (creatinine > 3mg/dL), jaundice (Total bilirubin >3mg/dl) creatinine > 3mg/dL), respiratory distress, hyperparasitaemia (parasitemia >5%).

Sample collection, preparation and quantification of hematological, biochemical and inflammatory cytokines

About 5 ml of venous blood was collected into sterile vacutainers (clot activator and heparin coated tubes) and stored at 4^{o}C. The serum and plasma were prepared by centrifugation, aliquoted and stored at -70^{o}C. The hematological and biochemical parameters such as, hemoglobin (g/dl), RBC(x10^{3}/µl) and platelets (x10^{3}/µl) were analyzed by automated hematology analyzer (Mind Ray-Biomedical, Shenzhen, China). The liver and renal function parameters such as Blood Urea (mg/dl), Serum Creatinine (mg/dl), CRP (mg/L), Bilirubin (mg/dl), Aspartate transaminases - AST (IU/L), Alanine transaminases- ALT(IU/L) were quantified using commercially available kits (kit by Agappe, India). The levels of serum CRP (kit by Eagle Biosciences, USA) and plasma inflammatory cytokines such as TNF-α, IL-6 and IL-10 were assayed in duplicate by ELISA using commercially available kits (R&D biotech, USA).

Statistical Analysis

Data analysis was performed by using Microsoft excel spreadsheet, graph pad prism (Graph pad prism software, Inc., San Diego California, USA), Quantitative variables are presented as mean values with standard deviations. Non-parametric data between various groups was analyzed by Kruskal-Wallis test and significance between two groups was determined by Mann-Whitney U test with a 95% confidence interval. A *p*-value less than 0.05 was considered to be significant. Correlations between two continuous data were determined by Pearson correlation and spearman's rank correlation. ROC curve was used to measure the diagnostic accuracy by calculating specificity, predictive values, odds ratios, likelihood ratio and 95% confidence intervals.

RESULTS

Study site

This cross sectional study was conducted at District wenlock hospitals in Mangaluru (a southwestern coastal

city in Dakshina Kannada) of Karnataka state, India. Malaria is considered to be endemic in this region with an annual parasite incidence [API] in the range of 10-12.[2] Malaria in Mangaluru city is due to recently increased urbanization and migration of population from the various malaria endemic regions. The high rainfall, humid climatic conditions favor harboring of high vector density thus contributing to high prevalence of malaria in this region.[3]

During the study period, 795 study participants aged between (16-65 years) were invited to participate in the study, upon obtaining written informed consent. A total of 512(64.4%) males and 283(35.6%) females participated in the study. Among 795 study participants, 168(21.1%) were healthy controls (HC) and the remaining 627 (78.9%) study participants were diagnosed to have malarial infections. The number of *Plasmodium vivax* infections (384, 48.3%) was predominant, as compared to *P.falciparum* (172, 21.6%) and mixed (Pv and Pf) infections (71, 8.9%) (Table1). Among the infected, 554(88.64%) patients were managed on an outpatient basis and were grouped into uncomplicated malaria, whereas 73(11.36%) required hospitalization due to severe malaria.

The patients primarily complained of intermittent fever (100%) with a low to moderate level in uncomplicated malaria and high grade in severe malaria. Apart from being febrile, the patients also complained of symptoms such as chills 513(81.8), weakness 264(42.1%), nausea 285(45.5%), vomiting 148(23.6%).The patients suffering from *P. falciparum* had significantly high percentage parasitemia of 0.8±1.15in comparison to mixed (0.8±0.75) and *P. vivax* infections (0.3±0.49) (Table 2).

Hematological and biochemical changes

Decreased hemoglobin and RBC levels are commonly observed in malarial infections. In our study, in comparison to HC, we observed decreased RBC and Hb levels across *P.vivax*, *P.falciparum* and mixed (Pv and Pf) infections. Within the infecting species, the hemoglobin levels showed a significant decrease in patients with *P.falciparum* infections (Table2). The platelet levels were also found to be decreased in patients with malaria infection in comparison to HC. Upon comparison among the various infecting species, the platelet levels were found to be decreased significantly in patients with *P.falciparum* infections (Table2).

Among the biochemical parameters analyzed, the blood urea levels were found to be increased upon malarial infections and were found to be significantly high in mixed (Pv and Pf) infections. In comparison to HC, the mean bilirubin levels were increased in patients; however, there were no significant changes in bilirubin observed within the various infecting species(Table 2). The AST and ALT levels were found to be significantly increased during all malarial infections. Upon comparison within various infecting species, the levels were found to increase significantly in *P.vivax* infections. The levels of inflammatory cytokines such as TNF-α, IL-6 and IL-10 were found to be increased in malarial patients. Upon comparison within the various infecting groups, the levels of TNF-α, IL-10 remained similar, the IL-6 levels were found to be significantly increased in patients with *P.falciparum* infections (Table 2).

The CRP levels were found to be significantly increased upon malarial infection in comparison to HC; the levels were found to be significantly increased in *P.vivax* across various infecting species (Table 2). In comparison to the UM group, the levels of CRP were found to be increased in patients with SM*; P.vivax* (48.5±15.5 vs 63.8±16.2,*p*= 0.0001), *P.falciparum* (57.5±20.6 vs 84.3±19.2, *p*= 0.0001) and in mixed infections (42.6±15.5 vs 68.4±14.2, *p*= 0.0001). In comparison, within the UM and SM groups across various infecting species, the patients with severe *P. falciparum* had significantly higher CRP levels (Fig 1).

Relationship between CRP and Hematological, biochemical parameters and inflammatory cytokines

A highly significant positive correlation was found between increase in parasitemia and C-reactive protein levels in *P.falciparum* and *P.vivax* patients (Table 3).While a significant positive correlation was observed between the increased parasitemia (%) and CRP levels, a significant negative correlation was observed between CRP and decreased hemoglobin, RBC, platelets and across various infecting species. Among the biochemical parameters analyzed, while the CRP levels had a significant positive relationship with increased blood urea in *P.vivax* groups, the bilirubin levels showed no such relationship. The AST and ALT levels showed a significant positive correlation across various infecting species. Among the inflammatory cytokines analyzed, a highly significant positive correlation was found between increasing CRP and TNF-alpha levels in various infecting groups (Table 3).

Among the various parameters studied, most had a good specificity, but lacked sensitivity. Thrombocytopenia (platelets $<1.5x10^3/\mu l$) had a fairly good sensitivity and specificity with better odds ratio (OR). Decreased hemoglobin though had fairly good specificity and odds ratio, but lacked sensitivity to accurately diagnose malarial infections. However, among all the parameters studied, the C-reactive protein emerged to have an excellent diagnostic potential, as it had excellent sensitivity, specificity and OR across all the infecting species (Table 4).

There were no statistically significant changes on the influence of age and gender on various hematological, biochemical and inflammatory cytokines analyzed during malaria across various infecting species(*P*-value = >0.05). There was no significant association between status of malarial infection and cut off values of hemoglobin (males – 14 - 18; females – 12 - 16 g/dl),

RBC (4.0 - 6.0 x$10^{3/}$µl), Platelets (1.0 - 4.0 x$10^{3/}$µl), Blood urea (10 – 45 mg/dl), Serum Creatinine (0.5 - 1.4 mg/dl), Bilirubin (0.0 - 1.0 mg/dl), AST (males - Up to 38 IU/L; females- Up to 31 IU/L), and ALT(males - Up to 40 IU/L; females- Up to 32 IU/L) (*P*-value = >0.05).

Table 1: Classification of study participants by various infecting species.

	Healthy controls	***P.vivax***	***P.falciparum***	**Mixed (Pv and Pf)**
Number of study participants, n (%)	168(21.1)	384(48.3)	172(21.6)	71(8.9)
UM, n (%)	0	351(44.2)	149(18.7)	54(6.8)
SM, n (%)	0	33(4.2)	23(2.9)	17(2.1)
Gender				
Males, n (%)	110 (65.5)	246(64.1)	111(64.5)	45(63.4)
Females, n (%)	58 (34.5)	138(35.9)	61(35.5)	26(36.6)
Age (in years, Mean, Range)	30.1(16-58)	30.5(16-65)	32.7(16-65)	31.7(16-65)
15-25, n (%)	79(47.0)	175(45.6)	57(33.1)	29(40.8)
26-35, n (%)	45(26.8)	100(26.0)	53(30.8)	18(25.4)
36-45, n (%)	27(16.1)	69(18.0)	41(23.8)	15(21.1)
>45, n (%)	17(10.1)	40(10.4)	21(12.2)	9(12.7)

Table 2: Changes in hematological, biochemical and inflammatory cytokines during malarial infections.

Parameter	**H.C**	***P.vivax***	***P.falciparum***	**Mixed**	***P*-value (between groups)**		
					P.vivax* Vs *P.falciparum	***P.vivax* Vs Mixed**	***P.falciparum Vs Mixed***
Parasitemia (%)	0	0.3±0.49	**0.8±1.15**	0.8±0.75	< 0.0001	< 0.0001	0.5957
Hemoglobin (g/dl)	12.5±1.26	11.5±2.86	**10.4±2.93**	10.7±3.22	**0.0003**	0.0699	0.5383
RBC (x10^3µl)	5.0±0.73	4.7±0.92	4.6±0.91	4.8±1.98	0.0611	0.5994	0.5285
Platelets (x10^3µl)	2.1±0.57	1.1±0.55	**0.92±0.45**	1.1±0.75	**0.0095**	0.7869	0.1506
Blood Urea (mg/dl)	22.2±6.87	24.9±13.67	27.2±15.28	**32.7±20.21**	0.0854	< 0.0001	**0.0063**
Bilirubin (mg/dl)	0.9±0.48	1.5±1.09	1.9±1.78	2.9±4.06	0.0315	0.0858	0.6832
AST (IU/L)	56.0±25.83	**71.4±39.04**	62.5±30.14	58.4±33.71	0.0097	0.1507	0.0415
ALT (IU/L)	52.8±30.73	**69.1±35.08**	59.5±44.10	59.2±68.97	0.0189	0.3192	0.994
CRP (mg/l)	2.8±2.62	49.0±22.21	**53.6**±17.06	48.7±18.75	0.002	0.0044	0.7727
TNF-α (pg/ml)	66.7±29.3	251.8±184.2	248.8±233.8	236.7±190.2	0.0513	0.2536	0.6804
IL-6 (pg/ml)	87.5±54.3	230.8±174.2	**288.7**±191.0	292.9±194.2	0.0005	0.0062	0.9908
IL-10 (pg/ml)	134.1±103.7	634.9±430.1	619.5±454.7	637.3±399.1	0.4208	0.6862	0.4012

Significant data are highlighted in bold.

Table 3: Correlation of CRP levels with hematological, biochemical and inflammatory cytokines across various infecting species.

Parameter	***P.vivax***		***P.falciparum***		**Mixed**	
	r-Value	***P-value***	**r-Value**	***P-value***	**r-Value**	***P-value***
Parasitemia (%)	**0.2162**	0.0000	**0.3600**	0.0000	**0.1608**	0.0119
Hemoglobin (g/dl)	**-0.1834**	0.0003	**-0.2182**	0.0040	**-0.3480**	0.0029
RBC (x10^3µl)	**-0.1042**	0.0412	**-0.1522**	0.0429	**-0.2249**	0.0494
Platelets (x10^3µl)	**-0.2816**	0.0000	**-0.2064**	0.0066	-0.1508	0.2095
Blood Urea (mg/dl)	**0.2100**	0.0000	0.0062	0.9363	0.0393	0.7446
Bilirubin (mg/dl)	**0.1110**	0.0296	**0.1689**	0.0272	0.0201	0.8679
AST (IU/L)	**0.1602**	0.0395	**0.1513**	0.0051	**0.1450**	0.0252
ALT(IU/L)	**0.0055**	0.0369	**0.0057**	0.0412	**0.0091**	0.0403
TNF-α (pg/ml)	**0.2068**	0.0000	**0.2362**	0.0018	**0.4702**	0.0000
IL-6 (pg/ml)	**0.0820**	0.0091	**0.1161**	0.0294	**0.0079**	0.0480
IL-10 (pg/ml)	0.0807	0.1148	0.0626	0.4147	-0.0259	0.8317

Significant data are highlighted in bold

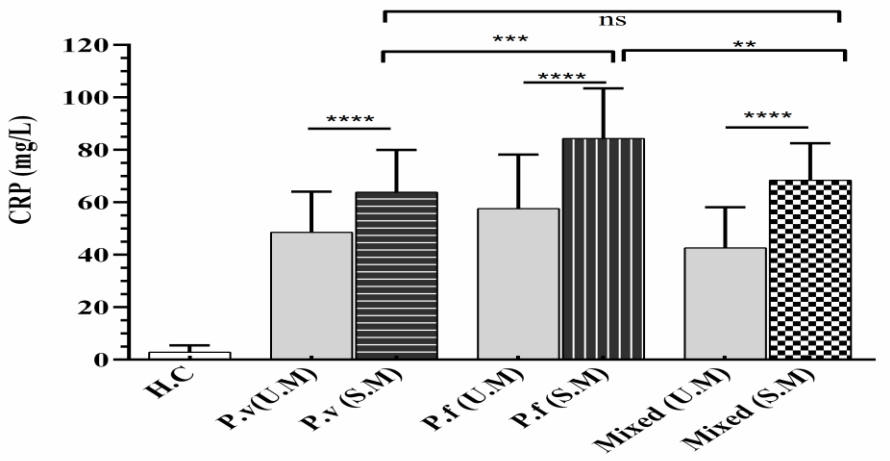

Fig. 1: The C - reactive protein levels in patients with uncomplicated and severe malaria across various infecting species.

Table 4: Sensitivity, specificity, predictive values and odds ratio of the CRP, hematological and liver function parameters.

Variable	Infecting Species	Sensitivity* (95%CI)	Specificity* (95%CI)	PPV(95%CI)	OR**	PLR	*p*-value
CRP (>6 mg/L)	P.v	98.18(96.28-99.26)	94.05(89.33-97.11)	97.42(95.3-98.75)	850.90	16.49	< 0.0001
	P.f	96.55(92.65-98.72)	94.05(89.33-97.11)	94.38(89.91-97.27)	442.40	16.22	< 0.0001
	Mixed	92.21(83.81-97.09)	94.05(89.33-97.11)	87.65(78.47-93.92)	187.00	15.49	< 0.0001
Hb <11g/dL	P.v	34.11(29.38-39.1)	89.88(84.29-93.99)	88.51(82.25-93.16)	4.60	3.37	< 0.0001
	P.f	42.44(34.95-50.2)	89.88(84.29-93.99)	81.11(71.49-88.59)	6.55	4.19	< 0.0001
	Mixed	46.48(34.55-58.71)	89.88(84.29-93.99)	66.00(51.23-78.79)	7.71	4.59	< 0.0001
RBC <4*10^3/µL	P.v	18.23(14.49-22.46)	96.43(92.39-98.68)	92.11(83.6-97.05)	6.02	5.10	< 0.0001
	P.f	22.09(16.13-29.04)	96.43(92.39-98.68)	86.36(72.65-94.83)	7.66	6.19	< 0.0001
	Mixed	27.14(17.2-39.1)	96.43(92.39-98.68)	76.00(54.87-90.64)	10.06	7.60	< 0.0001
Platelets <1.5 x10^3 /µL	P.v	77.58(73.16-81.59)	91.76(86.57-95.42)	95.65(92.81-97.6)	38.56	9.42	< 0.0001
	P.f	75.56(68.61-81.64)	91.76(86.57-95.42)	90.67(84.84-94.8)	34.44	9.17	< 0.0001
	Mixed	64.86(52.89-75.61)	91.76(86.57-95.42)	77.42(65.03-87.07)	20.57	7.88	< 0.0001
Blood Urea (> 45mg/dl)	P.v	3.65(2.007-6.041)	96.43(92.52-98.7)	70.00(45.72-88.11)	1.04	1.02	< 0.0001
	P.f	8.19(4.548-13.36)	96.43(92.39-98.68)	70.00(45.72-88.11)	2.41	2.29	< 0.0001
	Mixed	14.08(6.966-24.38)	96.43(92.39-98.68)	62.50(35.43-84.8)	4.43	3.94	1.000
Bilirubin (>1mg/dl)	P.v	67.65(62.65-72.37)	72.96(65.35-79.69)	85.47(80.94-89.28)	5.64	2.50	< 0.0001
	P.f	74.25(66.92-80.7)	72.96(65.35-79.69)	74.25(66.92-80.7)	7.78	2.75	< 0.0001
	Mixed	69.01(56.92-79.46)	72.96(65.35-79.69)	53.26(42.56-63.74)	6.01	2.55	< 0.0001
AST (>38 IU/L)	P.v	84.86(80.87-88.3)	31.90(24.83-39.65)	74.54(70.18-78.57)	2.63	1.25	< 0.0001
	P.f	78.11(71.11-84.09)	31.90(24.83-39.65)	54.32(47.83-60.7)	1.67	1.15	0.047
	Mixed	69.01(56.92-79.46)	31.90(24.83-39.65)	30.63(23.59-38.39)	1.04	1.01	1.000
ALT (>40 IU/L)	P.v	66.58(61.61-71.29)	42.86(35.26-50.71)	72.65(67.66-77.25)	1.49	1.17	< 0.0001
	P.f	60.59(52.82-67.98)	42.86(35.26-50.71)	51.76(44.58-58.88)	1.15	1.06	0.581
	Mixed	54.93(42.66-66.77)	42.86(35.26-50.71)	28.89(21.42-37.31)	0.91	0.96	0.777

PPV, positive predictive value; PLR, Positive likelihood ratio; value; **OR, odds ratio,*expressed in percentage; PLR, positive likelihood ratio.

DISCUSSION

Inflammatory mediators play a significant role in pathogenesis of malaria. The C-reactive protein (CRP) is a plasma protein, known to function through interaction of components of both humoral and cellular effector mechanisms of inflammation.[4] This acute phase protein binds to the damaged host cells including erythrocytes resulting in complement activation and aids in parasite clearance by both humoral and cellular immune mechanisms.[15]

In this cross sectional study, our aim was to evaluate the CRP levels in adults with uncomplicated and severe malaria. We found that the CRP levels were significantly increased in patients with malaria across various infecting species. The levels were significantly increased in admitted patients with severe malaria than the uncomplicated malaria patients, who were managed on

an outpatient basis. Similar observations of elevated CRP levels were made in children and adults in different endemic settings.[16,18] We also found that the patients with *P.falciparum* infections had higher CRP levels in comparison to *P.vivax* and mixed (Pv and Pf) infections during uncomplicated and severe malaria. Our observations are in line with the previously published reports of increased CRP levels during *P.falciparum* infections from researchers in Papua New Guinea and were in contrast from other studies which credit *P.vivax* with higher CRP levels.[5,19]

We observed significant correlations between the CRP levels and various hematological, biochemical and inflammatory cytokines such as parasitemia, hemoglobin, RBC levels, platelets, blood urea, bilirubin, AST, ALT and TNF-alpha and IL-6. A strong association between the increasing CRP levels and malaria parasite densities across various infecting species was observed. During parasite life cycle, the schizont rupture results in release of malarial parasites into the blood stream, leading to the synthesis and release of inflammatory cytokines by monocytes and macrophages, which in turn aids the release of CRP by liver.[4] In this study, a strong positive correlation was observed between CRP and parasitemia (%) as reported by earlier.[20] Several researchers have argued a possible involvement of CRP in malarial anemia. During malaria, the produced CRP is able to bind to the infected red blood cells and activate the classical pathway of the complement system, leading to complement-dependent hemolysis, ultimately leading to anemia.[21] In this study, we found a strong inverse relationship between increased CRP levels and decreased hemoglobin and RBC levels. Acute plasma proteins are synthesized by hepatocyte cells in the liver and it was also shown that liver as the site of CRP formation.[4] Among the biochemical parameters studied, AST and ALT levels resulted in significant positive relationship with CRP levels. While studies by some researcher's credited only *P.falciparum* with increased CRP levels in malaria, we found a highly significant positive correlation across various infecting species.[5,9,22] The CRP synthesis is stimulated by the cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF)-α from the macrophage and monocytes.[4] In our study, we also found a highly significant positive correlation between increased CRP levels and inflammatory cytokines such as TNF-α and IL-6.[23]

Worldwide studies have reported the usefulness of CRP in assessment of malarial severity.[9] In our study, we found that CRP had high sensitivity and specificity for malarial infections and can be used to suspect malarial infection. However, further studies are needed to be undertaken to evaluate the diagnostic potential of CRP in asymptomatic individuals.

CONCLUSIONS

The present work showed i) a significantly increased serum C-reactive protein levels in uncomplicated and severe malarial patients; the patients with severe *P.falciparum* infections had significantly elevated levels in comparison to other infecting species ii) that the CRP levels also showed a significant correlation with hemoglobin, RBCs and inflammatory cytokines such as TNF-α and IL-6 during malarial infections, and iii) the usefulness of CRP as an effective biomarker in malarial diagnosis.

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