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Research Article

The Association between CRP Levels with Comorbidities, Species, and Complications of Severe Malaria

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ABSTRACT

Background: Malaria remains a leading cause of mortality in sub-Saharan Africa (including Sudan). C-reactive protein (CRP) is useful as a marker of severity in malaria. African studies have shown that serum CRP levels correlate with parasite burden and complications in malaria, especially falciparum. However, there are no data on CRP levels in Sudanese malaria patients.

This study aims to evaluate the association between CRP levels with comorbidities, species, and complications of severe malaria

Subjects and Methods: A cross-sectional study enrolled 65 severe malaria patients at Khartoum state hospitals during the period from April to June2021. Manifestations of severe malaria were defined according to WHO criteria. Data regarding demographics, presenting symptoms & signs, laboratory investigations, complications, length of hospital stay and outcomes were collected. CRP was classified as elevated when the measured level was >10 mg/l.

Results: Among 65 patients, 33(50.8%) were females and 32(49.2%) were males, and mean age was 48±21 years. The main manifestation of severe malaria diagnosis criteria was anemia in 26(40%) patients. Most of the patients had density 1+ (n=53; 81.5%) and were infected by P. falciparum (n=61; 93.8%). The overall case fatality rate for malaria was 8% (n=15 patients). The mean of CRP was 72±57 mg/L and 84% (n=55) of patients had elevated levels above 10 mg/L (ranged from 10-100 mg/L in 52%, and above 100 mg/L in 32%). The elevated CRP levels were significantly DM (P= 0.048), high malaria parasite density in blood film (P= 0.001), P. falciparum (P= 0.33), presence of complications (P= 0.001) and death (P= 0.003)

Conclusion: Elevated CRP levels were found in a considerable proportion of severe malaria patients. CRP is an effective biomarker in assessing malaria severity and poor prognosis in term of complications development and mortality.

Introduction

Anopheles mosquito bites from females carry the intracellular parasite that causes malaria. P. falciparum produces the bulk of infections and fatalities among the five Plasmodium species known to infect humans (P. vivax, P. ovale, P. malariae, and P. knowlesi). (1). In Sudan, malaria is a significant public health issue. Malaria poses a risk to over 75% of the population (2). The reported malaria cases represent 8.7% and 12.2% of total outpatient attendance and of hospital admissions respectively (2). Sudan is on track to achieve a 20–40% drop in incidence by 2020, according to the WHO's 2018 malaria report, despite a rise over the previous three years (3). There can be a wide range of symptoms associated with malaria parasite infection, from none at all or very minor to severe illness and even death. There are two types of malaria disease: mild (uncomplicated) and severe (complicated) (4). Clinical characteristics that are linked to a bad poorgnosis, such as prostration, decreased consciousness, convulsions, respiratory distress, anemia, jaundice, and shock, are used to define severe malaria (SM). This criteria identifies individuals who need hospitalization and parenteral treatment and captures the majority of patients who are at risk of dying; but, in situations with severe resource constraints, a definition with higher specificity may be required (5). Acute phase reactants include CRP. In response to pro-inflammatory reactions brought on by infection, stress, and tissue injury, the liver produces it. However, it is also thought to play a pathogenic function in malaria. According to some reports, CRP binds to diseased erythrocytes and aids in their removal. Numerous harmful indications are also brought on by this immunological activity in response to contaminated RBCs. Additionally, CRP triggers the complement pathway and platelet activation, which has a number of negative effects. Therefore, CRP testing can be helpful in figuring out how serious malaria develops (6). (CRP) as a biomarker in malaria patients is being researched. It is particularly crucial in areas with a high parasite burden, where patients may not exhibit typical illness symptoms like fever. CRP levels were found to substantially correspond with parasite density in patients' blood in a Tanzanian investigation, regardless of whether those patients experienced clinical symptoms or not (7). Additionally, a different study from Gambia discovered that CRP levels were useful for analyzing malaria in a community (8). CRP levels were employed in this investigation as a stand-in measure for malaria infection and sequelae. In a Tanzanian study, Hurt et al. discovered a correlation between CRP levels and morbidity in children with malaria, particularly in cases where falciparum infection was present (9). The goal of the current investigation was to evaluate the association between CRP levels with comorbidities, species, and complications of severe malaria.

Subjects and Methods

This is a descriptive cross-sectional hospital-based study conducted in Khartoum state hospitals (governmental and private) in the period from April to June 2021. All patients admitted at Khartoum state hospitals with severe malaria diagnosed based on malaria tests (positive BFFM thick and thin blood film or positive ICT) with clinical or laboratory criteria or both of them. Total coverage of all severe malaria patients those fulfill the inclusion criteria, enrolled 65 patients during the study period.

Inclusion and exclusion criteria: Adult patients and both sexes were included. Adult patients admitted with severe malaria with sepsis either (bacterial or viral) on same presentation like (viral or bacterial chest infections, urosepsis, meningitis, etc.) or obvious focus of sepsis like (Infected bed sores or infected DSF) because sepsis causes high CRP. All patients with severe malaria with active inflammatory bowel diseases (ulcerative colitis and Crohn's disease) or active rheumatoid arthritis were excluded.

Data collection tools: Data collection carried out by the principal investigator. Data was collected through structured questionnaires used to collect data consisting of: demographics, presenting symptoms & signs, laboratory investigations, complications, length of hospital stay and outcomes. Manifestations of severe malaria were defined according to WHO criteria.

Data analysis: Data were analyzed by using Statistical Package for Social Studies Program (SPSS, V. 21.0. IBM; Chicago). The analyzed data presented in tables and figures designed by Excel Microsoft 2010. ANOVA test was used as significance test for continuous variables and Chi-Square for categorical variable. P. value is significant at level 0.05.

Ethical considerations: An ethical approval was obtained from Sudan medical specialization board (SMSB). Approval of acceptance to the hospital authority was given. Data used anonymously by using identity numbers instead of names is order to protect patient identity and kept securely and in a separated file. No reference to any individual participant made in study reports. Subject identities were being known only by study staff

Results:

The main manifestations of severe malaria diagnosis criteria were; anemia in 26(40%) patients, AKI in 25(38.5%): and cerebral malaria in 19(29.2%) patients .Concerning to the malaria microscopic features, most of the patients had density 1+ (n=53; 81.5%) and infected by P. falciparum (n=61; 93.8%) .15(32.1%) patients developed complications (with mean duration 4±1 days) as gram –ve sepsis in 10(15.4%) patients, anemic heart failure in 3(4.6%), ARDS in one (1.5%) and bleeding tendency in one (1.5%) patients. In outcomes, 60(92%) patients were normally discharged and 15(8%) were dead. Revealed that, CRP levels were not significantly affected by the age (P= 0.766) and gender (P= 0.111) of the patients. The association between CRP levels and comorbidities. Diabetes mellitus was significantly correlated with elevated CRP levels (P= 0.048). However, hypertension (P= 0.336), history of CVD (P= 0.564), HIV (P= 0.645), liver diseases (P= 0.771), CKD (P= 0.300) and other comorbidities (P= 0.151) were not significantly associated with CRP levels .In the association between CRP levels and malaria density, elevated CRP >100 mg/L was found in all patients (100%) with density 3+ (CRP average= 155), 75% of patients with density 2+ (CRP average= 119) and in 20.8% of those with density 1+ (CRP average= 58), the difference was statistically significant (p = 0.001) .In the association between CRP levels and malaria species, elevated CRP was frequent among patients infected by P. falciparum (CRP average= 75) more than those infected by P. falciparum and P. vivax (CRP average= 13), and the difference was statistically significant (P= 0.033) . The CRP levels were not significantly correlated with length of hospital stay (P= 0.612).CRP levels above 100 mg/L were presented in all non-survived patients

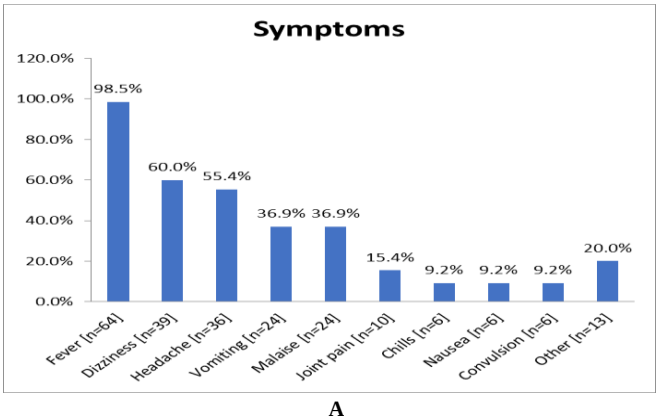
(100%; CRP average= 155) comparing to 26.7% (CRP average= 65) of survived patients (P= 0.003). In total, this study enrolled 65 severe malaria patents, 33(50.8%) were females and 32(49.2%) were males, their mean age was 48±21 year, and most of them 25(38.5%) belonged to the age group from 40-59 year and also, the majority of the patients were workers (n=31; 47.7%) and resided in Khartoum state (n=52; 80%) (Table 1). More than one-half (n=36; 55.4%) of the patients had comorbidities and mainly as diabetes mellitus (n=17; 26.2%) (Table 2).Regarding to symptoms, almost all the cases had fever (n=64; 98.5%); in addition, dizziness (n=39; 60%) and headache (n=36; 55.4%) were the major symptoms in more than 50% of the patients. Tachycardia (n=43; 66.2%) was the predominant sign among our study group (Table 2).In hematological parameters, the mean of ESR was 38±19 mm/hr, hemoglobin 9.5±3 g/dl, MCV 85±9, leucocyte count 8±3 x 10^3 cell/Cumm, PMN differential 55±16%, lymphocyte differential 45±16% and platelets count was 220±140 x 10^3 cell/Cumm. In biochemical parameters, the mean of blood glucose was 140±106 mg/dl, creatinine 2.3±2 mg/dl, urea 74±70 mg/dl, sodium 136±7 mmol/L and potassium was 3.7±0.6 mmol/L (Table 3). Regarding to symptoms, almost all the cases had fever (n=64; 98.5%) and more than 50% had headache (n=36; 55.4%), dizziness (39; 60%), and Tachycardia (n= 43; 66.2%). (Figure 1) .The mean of CRP was 72±57 mg/L, also 10(16%) patients had CRP levels below 10 mg/L, 34(52%) from 10-100 mg/L and 21(32%) patients above 100 mg/L (Figure 2).The Pearson's correlation illustrated that, CRP levels showed significant direct correlation with ESR levels (r= 0.231; P= 0.04) and blood glucose levels (r= 0.262; P= 0.039) (Table 8). The presence of complications was significantly associated with elevated CRP levels above 100 mg/L comparing to those without complications (73.3% vs 20%; P= 0.001; complication CRP average= 130.4 and non-complication CRP average= 54). Also, patients those developed anemic heart failure (66.7%) were more tended to had CRP levels ranged from 10-100 mg/L, while patients those developed ARDS (100%), bleeding tendency (100%) and gram –ve sepsis (80%) were more tended to had CRP above 100 mg/L (P= 0.015) (Table 4).

Table 1: The demographic characteristics of severe malaria patients

	N	%
Age (yrs.)	**48±21**	
<20	6	9.2
20-39	16	24.6
40-59	25	38.5
60+	18	27.7
Gender		
Female	33	50.8
Male	32	49.2
Residence		
Khartoum	52	80.0
Central	9	13.8
West	4	6.2
Occupation		
Worker	31	47.7
Housewife	24	36.9
Student	7	10.8
Employee	1	1.5
None	2	3.1

Table 2: The co morbidities among severe malaria patients

	N	%
Comorbidities (Yes)	36	55.4
DM	17	26.2
Hypertension	9	13.8
History of CVD	9	13.8
HIV	3	4.6
Liver disease	2	3.1
CKD	2	3.1
Other	10	15.4



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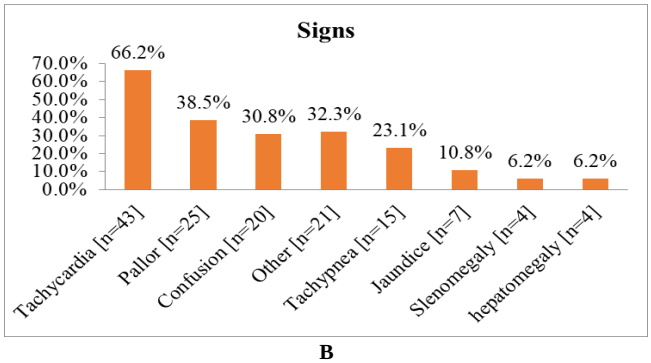

B

Figure 1: The distribution of symptoms and signs among severe malaria patients

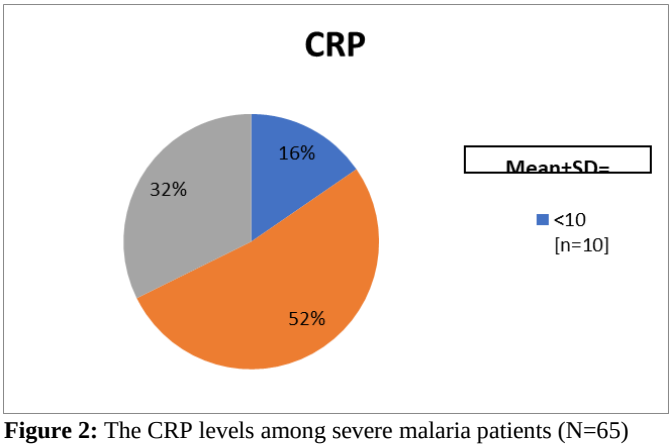

Figure 2: The CRP levels among severe malaria patients (N=65)

Table 3: The laboratory investigations of severe malaria patients (N=65)

	Mean	SD
Hematology		
ESR (mm/hr)	38	19
Hemoglobin (g/dl)	9.5	3
MCV	85	9
TWBC (*10^3 cell/Cumm)	8	3
PMN diff (%)	55	16
Lymph diff (%)	45	16
Platelets (*10^3 cell/Cumm)	220	140
Biochemistry		
RBG (mg/dl)	140	106
Creatinine (mg/dl)	2.3	2
Urea (mg/dl)	74	70
Na+ (mmol/L)	136	7
K+ (mmol/L)	3.7	0.6

Table 4: The Pearson's correlation between CRP levels and laboratory investigations

	Correlation coefficient (r)	P
Hematology		
ESR (mm/hr)	0.231	0.040*
Hemoglobin (g/dl)	-0.183	0.879
MCV	-0.055	0.687
TWBC (*103 cell/Cumm)	0.139	0.272
PMN diff (%)	0.015	0.912
Lymph diff (%)	-0.014	0.914
Platelets (*103 cell/Cumm)	0.009	0.942
Biochemistry		
RBG (mg/dl)	0.262	0.039*
Creatinine (mg/dl)	-0.158	0.210
Urea (mg/dl)	0.044	0.731
Na+ (mmol/L)	0.028	0.825
K+ (mmol/L)	0.139	0.269

Discussion

In the present study, we aimed to determine the significance of CRP levels among 65 severe malaria patients in Khartoum state . Severe malaria was approximately affected males (49.2%) and females (50.2%) equally, and was common among middle-aged patients aged from 40-59 year (38.5%) a mean age 48±21 years. This is in accordance with Sudanese studies (10, 11) those reported severe malaria affected male and female equally. Also, another study in India reported severe malaria affected male and female equally with mean age 42 years (12). Fever was the common symptom in all cases, in addition to dizziness, and headache. Also, in the study of Hasan et al in Khartoum state, fever was presented in all severe malaria patients (81 patients) and vomiting combined with diarrhea . Our study similar to another study reported that fever and vomiting were the main symptoms (14). P. falciparum was the causative agent of severe malaria in 93.8% of the patients, and this confirmed that P. falciparum is the commonest malaria species in Sudan as reported by other studies (2, 13 and 10). Our results showed the frequency of P. vivax infection was 6.2% and this rate was comparable to the study in Eastern Sudan (6). This may be due to an influx of people from Ethiopia where : P. vivax infection is increasing (15). Severe malaria anemia (SMA) was reported in patients with severe disease, which is a result from intravascular hemolysis caused by malaria species. These findings were higher than the studies in Sudan (13) and in Ethiopia (16) those reporting severe malaria anemia (SMA) were presenting in 14.2% and 15.9% of severe malaria patients, respectively. And lower than that reported by Zeidan A et al in Sudan (44), Achidi EA et al in Cameroon (17) and Oduro et al in Ghana (18) those reported severe malaria anemia in 62%, 87.9%, and 81%, respectively. This variation may be due to the multifactorial etiology of SMA that could also be influenced by the nutritional status and severity of malaria as well as late presentation. The current study demonstrated that, cerebral malaria (CM) was present in 19(29.2%) of patients. These findings were similar to the studies in Sudan (13) and in Cameroon (17): In the present study, we recorded acute kidney injury in 25(38.5%) patients with severe disease. And this disagree with the result the results of several studies in Sudan (13,19,20) those reported acute renal failure in 17.4%, 15.4% and 18.3% of patients, respectively. The current study illustrated that, the overall case fatality rate of malaria was 8% (n=15 patients). Other studies (24,25,26), had different results where the percentages of mortality were (17.2, 23, 24, 24)%, respectively. These disparities in fatality rates might be attributed to differences in geographical areas, causative malaria species and management protocols and guidelines used. This study showed that, 15(32.1%) patients developed complications (with mean duration 4±1 days) and gram –ve sepsis was the major complication in 10(15.4%) patients. Recent studies in sub-Saharan Africa showed that 4–23% of patients with severe malaria had concomitant sepsis (27, 28). Bacterial sepsis is less common but still considerable, with a reported incidence of 13% in Asians population (29). C-reactive protein (CRP), an acute phase reactant, whose plasma concentration increases during inflammatory disorders, has gained considerable attention as a biomarker in malaria. Our findings were comparable with tothe study that found 92% o SM patients had elevated CRP levels above 10 mg/L (30). Also, our finding is consistent with results from studies conducted in The Gambia, Mozambique and Malawi (8, 9,31) where malaria was also found to be associated with elevated CRP levels. In contrast, our CRP mean was higher than that reported (31.29 ± 20.4 mg/L) (6). The association between CRP levels and co morbidities showed that, DM was significantly correlated with elevated CRP levels (P= 0.048). Additionally, CRP levels showed significant direct correlation with blood glucose levels. These findings were confirmed by the study of Tabassum R et al who found that the mean CRP level was significantly higher in diabetic patients -diabetics . Also, they concluded and supported a possible role of inflammatory markers in diabetogenesis (32). Similar study showed a significant association between C-reactive protein levels and hyperglycemia concluding that hyperglycemia is a related factor to the increase of serum CRP levels (33). Our study demonstrated that, elevated CRP levels were significantly increased with malaria parasite density in blood film .These observations are indicating that, the levels of CRP are directly correlated with the severity of malaria. Correspondingly, researchers in Nigeria reported the predictors of the C-reactive protein response in malaria (CRP ≥ 10mg/l) were malaria parasite count (34). Also, study in Ghana reported that the median CRP level was significantly higher in high malaria parasitaemia compared to moderate and low malaria parasitaemia(35). In a study from Tanzania, CRP levels were found to correlate strongly with parasite density in the blood of patients, whether they had clinical features or not (7). Other researcher found

that, patients with increased CRP levels had more than an eight-fold likelihood for parasitemia (30). In this study we noticed that elevated CRP was frequent among patients infected by P. falciparum (CRP average= 75) more than those infected by P. falciparum and P. vivax (CRP average= 13); the difference was statistically significant (P= 0.033). However, in India, reported that average CRP levels did not significantly affected by malaria species either P.f or P.v (6). Considerably, our study illustrated that the levels of CRP were significantly greater in patients with complicationsthan those without complications (P< 0.05). Consistently, several studies (6,9,36) mentioned that patients with complications had significantly elevated CRP levels compared to those without complication (P< 0.05). Although, found CRP levels at presentation showed positive correlation with duration of hospital stay (r = 0.59; P < 0.05) (6), we showed that CRP levels were not significantly correlated with length of hospital stay . Interestingly, the present study revealed that, elevated CRP levels were significantly associated with mortality among our study participants . These findings should emerge the use the CRP s monitor and prognostic marker for all patients with malaria. Our results were confirmed where patients who died had higher CRP levels compared to survivors (6). We recommended that use of CRP levels as a surrogate marker for malaria infection and complications. CRP should be used as tool in assessment of prognosis in malaria. Further prospective studies with larger sample size are needed.

Conclusion:

The present study concluded that, elevated CRP levels were found in a considerable proportion of severe malaria patients. Also, elevated CRP levels were significantly correlated with DM in comorbidities, high malaria parasite density in blood film, P. falciparum infection, complications, and mortality.

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Conflict of Interest

The authors declared no conflict of interests

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