Yemeni Journal of Medical and Health Research

C-Reactive Protein in Patients with *Plasmodium Falciparum* Malaria in Aden

Waiel M. A. Alkahiry

DOI: https://doi.org/10.47372/yjmhr.2025(14).1.2

Abstract

Introduction: Malaria is a major public health challenge causing a high morbidity and mortality worldwide. In *plasmodium falciparum* infection, determination of C-reactive protein (CRP) levels may enable quicker assessment of the overall burden of malaria severity. This study was conducted to investigate the relationship between CRP level and severity of *plasmodium falciparum* malaria in patients admitted at Al-Gamhouria Modern General Hospital in Aden, Yemen.

Methods: This is a cross-sectional study included 60 patients diagnosed with *plasmodium falciparum* malaria for the period from June 1st to Oct. 31st, 2024; and 30 healthy individuals as a control group for C-reactive protein level. Baseline and laboratory data were collected and analyzed statistically, then related to the severity of malaria.

Results: Fifty five percent of the included patients with *plasmodium falciparum* malaria were males, with a mean age of 34.1± 11.1 years, and mean body mass index of 22.7±2.6 kg/m^2. The median erythrocytes sedimentation rate (ESR) was 41.0 mm/hr, the median parasite density was 6660 parasites/µL, and the median percentage of parasitemia was 8%. The median CRP was significantly higher among malaria patients than in the control group (50.7 vs. 2.1 mg/L) (*p*: 0.001). According to the World Health Organization (WHO) criteria for severe malaria, 23.3% had severe *plasmodium falciparum* malaria. Severity of *plasmodium falciparum* malaria was significantly related to lower median hemoglobin concentration, higher median total white blood cells (WBCs) count, and higher median CRP ($p<0.05$). The percentage of parasitemia showed significant negative correlation to hemoglobin concentration (r: -0.299), red blood cells (RBCs) count (r: -0.302), and the percentage of eosinophils (r: -0.267), in addition to significant positive correlations to the red cell distribution width (RDW) (r: 0.279), total WBCs (r: 0.607), parasites density (r: 0.779), and CRP level (r: 0.583).

Conclusion: This study concluded that CRP level can be used to assess the severity of malaria. Elevated CRP level could be helpful in early prediction of the disease severity in patients infected with *Plasmodium falciparum* malaria.

Keywords: *Plasmodium falciparum*, Malaria, CRP, Parasitemia, Severity.

Department of Paraclinic, Faculty of Medicine and Health Sciences, University of Aden.
Corresponding Author: Waiel Mohmed Abdo Alkahiry **Email:** kahiry13@gmail.com

البروتين التفاعلي (ج) لدى المرضى المصابين بملاريا المتصورة المنجلية في عدن

وائل محمد عبده القاهري

ملخص الدراسة

المقدمة: تعتبر الملاريا من التحديات الصحية العامة الكبرى التي تتسبب في إرتفاع معدلات المضاعفات والوفيات في جميع أنحاء العالم. في حالة الإصابة بالملاريا المنجلية، قد يساعد تحديد مستويات البروتين التفاعلي (ج) في تقييم العبء الإجمالي لشدة الملاريا بشكل أسرع. تم إحراء هذا العمل لدراسة العلاقة بين مستوى البروتين التفاعلي (ج) وشدة الملاريا المتصورة المنجلية لدى المرضى الذين تم إدخالهم إلى هيئة مستشفى الجمهورية العام في عدن، اليمن.

المنهجية: تم إجراء دراسة مقطعية شملت 60 مريضًا تم تشخيصهم بمرض ملاريا المتصورة المنجلية خلال الفترة من 1 يونيو إلى 31 أكتوبر 2024م. بالإضافة إلى 30 فردًا مطابقين من حيث الجنس والعمر كمجموعة تحكم لقياس البروتين التفاعلي (ج). تم جمع البيانات الأساسية والمخبرية وتحليلها إحصائيًا ومن ثم ربطها بشدة الملاريا.

النتائج: كان 55.0% من مرضى الملاريا بالمتصورة المنجلية من الذكور، بمتوسط عمر 34.1 ± 11.1سنة، ومتوسط مؤشر كتلة الجسم 22.7±2.6 كجم/م2. بلغ الوسيط لمعدل ترسيب كريات الدم الحمراء 41.0 مم/ساعة، والوسيط لكثافة الطفيليات 6660 طفيلي/ميكرولتر، والوسيط للنسبة المئوية للطفيليات في الدم 8%. كان الوسيط للبروتين التفاعلي (ج) أعلى بشكل ملحوظ بين مرضى ملاريا المتصورة المنجلية مقارنة بالمجموعة الضابطة (50.7 مقابل 2.1 مجم/لتر) (قيمة الأرجحية: 0.001). وفقًا لمعايير منظمة الصحة العالمية للملاريا الشديدة، كان 23.3% من المرضى الذين أجريت عليهم الدراسة مصابين بملاريا شديدة بالمتصورة المنجلية. كانت شدة الملاريا المنجلية مرتبطة بشكل إحصائي هام بانخفاض الوسيط لتركيز خضاب الدم، وارتفاع الوسط لإجمالي عدد كريات الدم البيضاء، وارتفاع الوسط للبروتين التفاعلي (ج). أظهرت نسبة الطفيليات في الدم ارتباطًا سلبيًا كبيرًا بتركيز الهيموجلوبين (معامل الارتباط: -0.299)، وعدد كريات الدم الحمراء (معامل الارتباط: -0.302)، ونسبة الخلايا حمضية الصبغة (معامل الارتباط: -0.267)، بالإضافة إلى ارتباطات إيجابية هامة إحصائياً بعرض توزيع خلايا الدم الحمراء (معامل الارتباط: 0.279)، وإجمالي كريات الدم البيضاء (معامل الارتباط: 0.607)، وكثافة الطفيليات (معامل الارتباط: 0.779)، ومستوى البروتين التفاعلي (ج) (معامل الارتباط: 0.583).

الخلاصة: خَلُصَت هذه الدراسة إلى أنه يمكن استخدام مستوى البروتين التفاعلي (ج) للتمييز بين الملاريا الشديدة والملاريا غير المعقدة كما يمكن أن يكون مستوى البروتين التفاعلي (ج) المرتفع مفيدًا في التنبؤ المبكر بشدة المرض لدى المرضى المصابين بالملاريا المتصورة المنجلية.

كلمات مفتاحية: المتصورة المنجلية، الملاريا، البروتين التفاعلي (ج)، نسبة الطفيليات في الدم، الشدة.

قسم الباراكلينيك، كلية الطب والعلوم الصحية، جامعة عدن.

Introduction

Malaria is one of the most common vector-borne parasitic infections which still cause significant morbidity and mortality worldwide as it causes more than 400,000 deaths every year globally [1]. It is endemic in Yemen, accounting for the second highest number of projected malaria cases after the leading contributor Sudan, in the World Health Organization (WHO) Eastern Mediterranean Region, and nearly all malaria cases in Yemen in recent years are due to *Plasmodium falciparum* [2].

The number of microscopic confirmed malaria cases progressively declined from 78,269 in 2010 to 42,052 in 2015, while it increased progressively after 2015 to reach 64,233 cases in 2018. Even the number of malaria deaths also increased from 1309 in 2015 to 2138 in 2018 [1,2].

In any malaria-endemic area, the presence of fever is a classical symptom of malaria; however, fever is also caused by other infections including bacterial or viral infection [3]. Therefore, the WHO recommends that microscopy or rapid diagnostic test (RDT) is a requirement for malaria diagnosis before treatment in all febrile individuals [4].

Some blood biomarkers have been well-described as candidates for malaria infection, including decreased leukocytes or platelet count [5,6]. Other markers related to the immune response to malaria infection have also been assessed, including acute-phase proteins, which are non-specific proteins released during infection, tissue damage, tissue injury, and inflammation process [7].

C-reactive protein (CRP) is one of the acute-phase proteins, considered as a classic marker for inflammation, synthesized by the hepatocytes, and modulated mainly by interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), all of these proteins were released during malaria infection [8-11].

Studies found that CRP activates the complement pathway in the infected erythrocytes, leading to hemolysis, which is the cause of anemia (one of the severe manifestations of malaria) [12]. In addition, it was found that CRP binds to phosphocholine and phospho-ethanolamine on the surface of dying or dead cells, which initiate phagocytosis of these cells [13].

Various studies were conducted in Yemen for malaria, but no study investigated CRP in malaria patients[14-16]. This study will be the first in Aden to assess the level of CRP, hematological parameters, parasites density and the severity of *Plasmodium falciparum* malaria in admitted patients at Al-Gamhouria Modern General Hospital in Aden, Yemen. Furthermore, the study aimed to investigate the relationship between CRP level and severity of *Plasmodium falciparum* malaria in patients admitted at Al-Gamhouria Modern General Hospital in Aden.

Methods

This is a cross-sectional, center based study, conducted in the Medical Department of Al-Gamhouria Modern General Hospital, in Aden governorate, Yemen, during the period from June 1st to Oct. 31st, 2024. It included 60 patients diagnosed with *Plasmodium falciparum* malaria, and 30 healthy individuals, age and sex matched, used as a control for CRP level.

Inclusion criteria:

1. Patient with proved diagnosis of *Plasmodium falciparum* malaria by microscopy or rapid diagnostic test.
2. Adult patients (≥ 18 years) of any sex.
3. Patients who gave verbal consent.

Exclusion criteria:

1. Patients with proved diagnosis of malaria other than *Plasmodium falciparum* species.
2. Patient with comorbidities that increase the CRP, examples are: respiratory tract infection, renal failure, rheumatoid arthritis, inflammatory bowel diseases, polymyalgia rheumatic, recent surgical intervention or trauma, malignant disease, hereditary hemolytic anemia as sickle cell disease, and pregnancy.
3. Patients with *Plasmodium falciparum* malaria with >20% parasitemia (to exclude the role of bacterial infections in elevation of CRP).

Sample size

Sample size was calculated by the following formula for a known population, with the 95% confidence level and **p**=0.5:[17]

- **p** is the population proportion = 0.5 (for unsure population proportion, it is advised to use 50%, which is conservative and gives the largest sample size).

$$n = N / [1 + N (e)^2]$$

Where:

(n) is the calculated sample size.

(N) is the population size [number of malaria patients admitted in the hospital last year; 2023] = 193.

(e) is the level of precision or the margin of error = 12%.

The final calculated sample size was 51 and the quality control group was 25 in a ratio of 2:1.

$$n = 193 / [1 + 193 (0.12)^2] = 51$$

Data collection

Data were collected directly from patients and the quality control group in a questionnaire, previously designed for the purpose of the study, included demographic, clinical and laboratory data. Samples were taken at the same time as follows:

- Preparation of thin and thick blood films at bedside from capillary puncture.
- Venous blood of 3.0 ml in Ethylene Diamine Tetra-acetic acid (EDTA) tube for the complete blood count (CBC), and for erythrocytes sedimentation rate (ESR), and 2.5 ml in plain tube for CRP measurement.
- *Plasmodium falciparum* species were diagnosed by RDT, and confirmed by Giemsa stained thick and thin blood smears in conventional light microscopy.
- Parasite densities were counted as the number of asexual parasite/µl and calculated

according to the following formulae:
In thick film: Parasites/µl= (parasites counted / WBCs counted) × WBC count/µl.
In thin blood film: % Parasitemia= (parasitized red blood cells (RBCs) / total of RBCs) × 100.

- For the quality control group, after clinical examination, only CRP measurement done.
The CBC was performed by the Coulter HMX Hematology Analyzer with 5-Part Differential (The Celltac G MEK-9100; Nihon Kohden, Tokyo, Japan). The ESR done by the modified Westergreen method. The CRP done by immunoturbidimetric assay for the in vitro quantitative determination of CRP in human serum and plasma on Cobas integra 400 plus systems, by a commercially available compatible TURBILYTE® CRP kit in a Coralyzer integra 400 plus instrument (Tulip Diagnostics Pvt. Ltd, Goa, India).

Statistical analysis

Data analysis was performed by the Statistical Package for Social Science (SPSS v.24). Qualitative variables were presented as absolute and relative frequencies. Quantitative variables were tested for normality by the Kolmogorov-Smirnov test. Variables with non-parametric distribution were presented as medians with ranges, and tested by the Mann Whitney-U test for 2 medians. Correlation tests between quantitative variables were conducted by the Spearman correlation coefficient (r) for non-parametric data. Significance test results were quoted as two-tailed probabilities and judged at the 5% level. Thus, *p*-values of ≤ 0.05 were considered statistically significant.

Ethical considerations

This study was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, University of Aden. A formal approval was also obtained from hospital authority. Prior to enrollment into the study, the aims and methods of the research were explained to each participant in their best understood language. Concerns and clarifications which arose were addressed after which they were freely allowed to make their decisions to opt in or opt out of the study. During data collection, participants' names were coded to keep confidentiality of participants.

Results

Among the studied *Plasmodium falciparum* malaria infected patients, 55.0% were males, with a mean age of 34.1± 11.1 years, and a mean body mass index of 22.7±2.6 kg/m^2. The parasite density was estimated in the studied patients with a range from 1722 to 76000 parasites/µL, and a median of 6660 parasites/µL. The percentage of parasitemia was estimated in the studied patients with a range from 1.0 to 20.0%, and a median of 8.0%. CRP was ranging from 11.9 to 180 mg/L with a median of 50.7 mg/L as shown in Table 1.

Table 1: Baseline Findings among the Studied Patients (n= 60)

Item	Value
Male gender [№., %]	33 55.0
Mean age ± SD (years)	34.1 ± 11.1 (18 – 59)
Mean body mass index (kg/m^2)	22.7 ± 2.6 (17.8 – 29.4)
Median Erythrocytes sedimentation rate (mm/hr)	41.0 (9.0 – 104)
Median parasite density (parasites/µL)	6660 (1722 – 76000)
Median percentage of parasitemia (%)	8.0 (1.0 – 20.0)
Median C-reactive protein (mg/L)	50.7 (11.9 – 180)

SD: standard deviation

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The median CRP for patients (50.7 mg/L) was significantly higher than the median reported among the 30 healthy individuals 2.1 mg/L (p: 0.001) [Fig. 1].

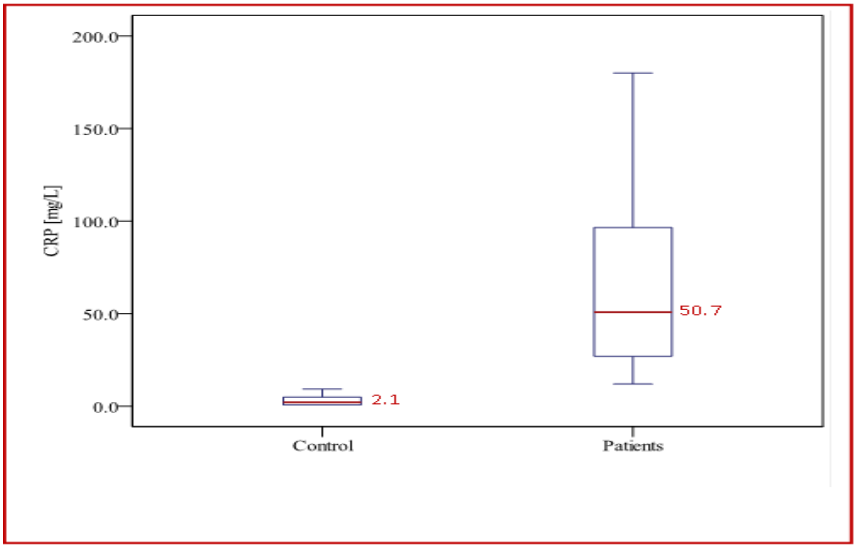

Figure 1: The Median CRP in Patients Versus the Quality Control Group

According to the WHO criteria for severe malaria, it was found that 14(23.3%) of patients had severe malaria (percentage of parasitemia of >10%), and 46(76.7%) had non-severe malaria (percentage of parasitemia of ≤10%) [Fig. 2].

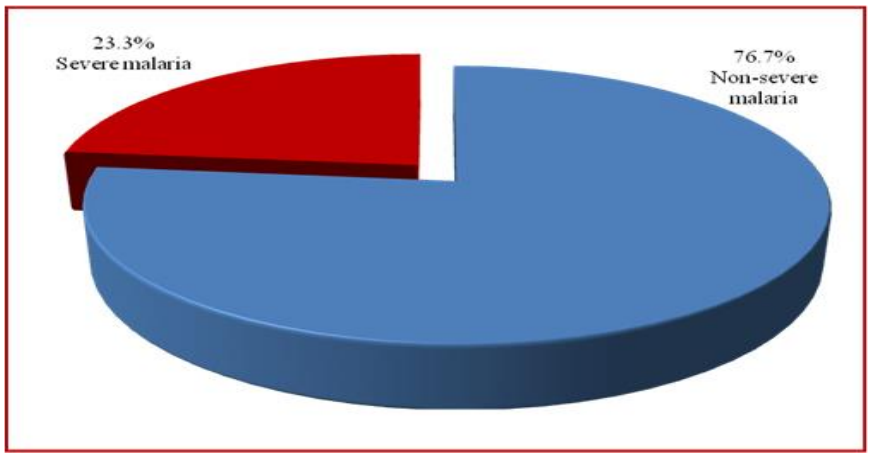

Figure 2: The Percentage of Severe Malaria in the Studied Patients

In relation to the severity of *Plasmodium falciparum* malaria, the CBC parameters that showed significant relationship to severity of malaria were the hemoglobin concentration and the total WBCs count. Severe malaria was significantly associated with lower median hemoglobin concentration and higher median total WBCs count. The median parasite density was significantly higher among severe malaria than in non-severe malaria (14300 vs. 5700 parasites/µL, respectively). The median CRP was significantly higher among patients with severe *Plasmodium falciparum* malaria (126.0 mg/L) when compared to patients with non-severe *Plasmodium falciparum* malaria (35.7 mg/L) [Table 2].

Table 2: The Median Hematological Parameters, Parasites Density, and CRP in Relation to Malaria Severity (n=60)

Parameter	Severe malaria (n=14) Median (Min. - Max.)	Non-severe malaria (n=46) Median (Min. - Max.)	Mann-Whitney-U test *p*-value
Hemoglobin concentration (g/dl)	11.2(5.6-12.7)	12.2(8.1-14.9)	**0.006***
Red blood cells count (x 10^{12}/L)	3.9(1.8-5.4)	4.4(3.0-5.9)	0.080
Hematocrit (%)	32.3(18.1-44.3)	37.3(13.2-46.2)	0.144
Mean corpuscular volume (fl)	86.7(66.2-96.3)	84.0(66.0-95.0)	0.499
Mean corpuscular hemoglobin (pg)	28.6(21.0-30.2)	28.0(19.0-31.1)	0.497
Mean corpuscular hemoglobin concentration (g/dl)	33.2(28.6-35.8)	32.9(28.6-36.1)	0.892
Red cells distribution width (%)	15.2(5.8-18.2)	13.6(5.8-17.8)	0.120
White blood cells count (x 10^9/L)	7.4(4.7-15.6)	5.7(2.8-8.5)	**0.001***
Neutrophils (%)	51.7(26.0-82.1)	58(37.0-87.3)	0.789
Eosinophils (%)	1.1(0.3-10.2)	2.4(0.1-12.3)	0.149
Basophils (%)	0.2(0.1-0.9)	0.3(0.1-5.8)	0.197
Lymphocytes (%)	25.7(7.3-47.3)	23(0.9-47.3)	0.386

Monocytes (%)	8.8(2.9-15.7)	9.9(1.3-22.0)	0.555
Platelets count (x 10^9/L)	141.5(51-240)	133(34.5-512)	0.849
Platelets distribution width (%)	18.3(8.2-19.6)	15.8(7.6-18.3)	0.150
Mean platelets volume (fl)	9.4(7.2-18.4)	8.9(5.2-18.3)	0.554
ESR (mm/hr)	46.0(20 – 70)	40.0(9.0 – 104)	0.285
Parasite density (parasites/µL)	14300 (10300– 76000)	5700 (1722 – 10300)	**0.001***
C-reactive protein (mg/L)	126(18.9 – 180)	35.7(11.9 –172)	**0.001***

g/dl: gram per deciliter fl: femtoliter pg: picogram
*Statistically significant ESR: Erythrocytes sedimentation rate

The Spearman correlation test for the percentage of parasitemia in the studied patients with *Plasmodium falciparum* malaria showed significant negative correlation to hemoglobin concentration (r: -0.299), RBCs count (r: -0.302), and the percentage of eosinophils (r: -0.267). The percentage of parasitemia showed significant positive correlations to the red cell distribution width (RDW) (r: 0.279), total WBCs (r: 0.607), parasites density (r: 0.779), and CRP level (r: 0.583) [Table 3].

Table 3: Correlation of the Percentage of Parasitemia to the Studied Parameter in Patients with *Plasmodium Falciparum* Malaria (n=60)

Parameter	Spearman Correlation	
	r	*p*-value
Age (years)	-0.220	0.091
Body mass index (kg/m^2)	-0.084	0.525
Hemoglobin concentration (g/dl)	-0.299*	**0.020**
Red blood cells count (x 10^{12}/L)	-0.302*	**0.019**
Hematocrit (%)	-0.194	0.137
Mean corpuscular volume (fl)	0.137	0.296
Mean corpuscular hemoglobin (pg)	0.108	0.412
Mean corpuscular hemoglobin concentration (g/dl)	-0.014	0.913
Red cells distribution width (%)	0.279*	**0.031**
White blood cells count (x 10^9/L)	0.607*	**0.001**
Neutrophils (%)	-0.028	0.831
Eosinophils (%)	-0.267*	**0.039**
Basophils (%)	-0.100	0.446
Lymphocytes (%)	0.096	0.467
Monocytes (%)	0.008	0.949
Platelets count (x 10^9/L)	0.034	0.796
Platelets distribution width (%)	0.219	0.093
Mean platelets volume (fl)	0.065	0.622
Erythrocytes sedimentation rate (mm/hr)	0.164	0.211

Parasites density (Parasitemia) (parasites/µl)	0.779*	**0.001**
C-reactive protein (mg/L)	0.583*	**0.001**

r: Correlation Coefficient for Spearman correlation test. *Correlation is significant at the 0.05 level (2-tailed).

Discussion

Malaria represents a medical emergency because it may rapidly progress to complications and death without prompt and appropriate treatment [6]. Severe malaria is almost exclusively caused by *Plasmodium falciparum*, and in Yemen it is the predominant type of malaria species detected [1,2].

The median CRP in the current study was 50.7 mg/L, which was significantly higher in comparison to the healthy individuals ($p<0.05$). This finding was proved by Bhardwaj *et al*. in India [18], who reported significant higher level of CRP among all malaria patients when compared to the healthy quality control group. Similarly, Paul *et al*.[19], in India, reported a median CRP of (47.11 mg/L) among malaria patients.

The increased CRP level is logic in any infection, since it is an acute phase reactant [20], however, in malaria; it is believed that it has a pathogenic role, where it binds to infected erythrocytes and helps in their clearance [12]. The mechanism of this clearance was explained by Ansar *et al*.[12], in their experimental study, where they found that CRP plays an important phagocytic functional interaction by triggering the CRP-complement pathway after binding of CRP with infected RBCs, and this pathway triggers hemolysis, that causes anemia, a common clinical manifestation in malaria.

According to the WHO criteria, severe malaria was defined by the presence of one of the clinical or laboratory evidence of vital organ dysfunction. In the current study, diagnosis of severe malaria was defined by the percentage of parasitemia which is considered more useful than the parasite density[21-23]. To decrease the effect of increasing CRP due to co-existing bacterial infection, this study excluded patients with >20% parasitemia [21-23]. According to the last modification by WHO criteria [23], the percentage of parasitemia of >10% was considered severe malaria [24], in this study (23.3%) were diagnosed with severe malaria.

In the current study, hemoglobin concentration, the total WBCs count, and CRP were significantly related to severity of *Plasmodium falciparum* malaria. The significant association of hemoglobin concentration to malaria severity was logic. According to the WHO criteria, severe malaria was characterized by hemoglobin level of less than 7 g/d1[21,22,24]. For the total WBCs count, the study of Ladhani *et al*.[25], in Kenya, showed similar association of WBCs to severity of *Plasmodium falciparum* malaria, where severe malaria cases had higher median WBCs count similar to the currently reported cases.

The higher median CRP in the studied patients with severe *Plasmodium falciparum* malaria is coinciding with the results of the meta-analysis conducted by Wilairatana *et al*,[26], who demonstrated higher mean CRP

levels in patients with severe malaria compared with non-severe malaria cases ($p < 0.001$). CRP plays an important phagocytic functional interaction by triggering the CRP-complement pathway after binding of CRP with infected RBCs, and this pathway triggers hemolysis, that causes anemia [12]. These effects may be a leading factor to the severity of malaria. Thus, measurement of CRP may be useful in understanding the pathogenesis of severe malaria.

The bivariate correlation tests used in this study showed that the severity of malaria when estimated by the percentage of parasitemia had significant negative correlation to hemoglobin concentration and RBCs count. These negative correlations are logic in regard to the severity of malaria, where increasing malaria severity as expressed by increased percentage of parasitemia was associated with decreasing hemoglobin concentration and RBCs count.

Severity of malaria in the current study had significant negative correlation to the percentage of eosinophils. The increased percentage of parasitemia in relation to decreased percentage of eosinophils was attributed that *Plasmodium falciparum* malaria infection induces eosinophils production, but the excess production in clinical malaria is out-balanced by increased sequestration or destruction due to inflammatory processes in the tissues [27].

The current study showed that severity of malaria had significant positive correlation to the RDW, total WBCs, parasites density, and CRP level. The RDW describes the population dispersion of red cell volume or the range of changes in size of red blood cells which mostly enlarged after malarial invasion [28]. Although the RDW has no role in the diagnosis of malaria, its significant positive correlation to the percentage of parasitemia as an indicator for malaria severity can put it as one of the markers for malaria severity. Similar findings were reported by the study of Jairajpuri *et al*.[29], who reported that RDW values were higher in severe malaria patients, and the study of Lathia *et al*.[30], who considered high RDW as a marker of poor outcome in *plasmodium falciparum* malaria patients.

In the current study, increasing percentage of parasitemia was significantly associated with increasing total WBCs count, similar to that reported by the study of Ladhani *et al*.[25], in Kenya, and the study of McKenzie *et al*.[31], in Thailand. The increased WBCs count may be attributed to the increase release of leukotrienes that act as chemotactic agent for WBCs.

An increasing percentage of parasitemia was significantly associated with increasing CRP level, which means that CRP at presentation of *Plasmodium falciparum* malaria patients can be used a predictor for severity of malaria. Consistent finding was reported by the study of Bhardwaj *et al*.[18], where CRP level was significantly associated with severity of *Plasmodium falciparum* malaria. As well, Agrawal *et al*.[32], found strong positive correlation between CRP and parasitemia in *Plasmodium falciparum* malaria patients, and they concluded that serum CRP levels can provide an effective measure of disease severity and efficacy of therapy.

The current study found strong link between CRP and severity of *Plasmodium falciparum* malaria. Sarfo *et al*.[33], in Sub Saharan Africa, found CRP in *Plasmodium falciparum* malaria have high negative predictive value, and that it could have a role in identifying those patients unlikely to be present with clinically severe malaria.

Conclusion

This study concluded that CRP level can be used to assess the severity of malaria. The finding of elevated CRP level could be helpful in early prediction of the disease severity in patients infected with *Plasmodium falciparum* malaria. It should be estimated at presentation of any patient with *Plasmodium falciparum* malaria for early detection of severe cases, with early intervention to avoid complications.

Acknowledgment
Great thanks to all laboratory technicians who helped in laboratory work including diagnosis of malaria, estimation of parasitemia level and measurement of CRP level. They are Waleed Bahelwan, Afnan Shabbir Hussain, Faeza Abdulraheem Qassem, Hager Raid Mustafa, Hanan Khaled Nasser, Homam Mohamed Mohsen, Lamia Salahaddin Ahmed, Mutahar Mohammed Obady, Rehab Omer Abubaker, Reham Adel Abdo, Safa Mohammed Morshed, Safwan Munasser, and Shatha Ibrahim Abdullah.

References

1. World Health Organization. World Malaria Report; WHO: Geneva, Switzerland, 2019. [cited 2024 March 16]. Available at: https://www.who.int/malaria/publications/world-malaria-report-2019/en/
2. World Health Organization. World Malaria Report; WHO: Geneva, Switzerland, 2020; [cited 2024 March 17]. Available at:https://www.who.int/publications/i/item/9789240015791
3. El-Radhi AS. Fever in Common Infectious Diseases. In: El-Radhi A. (eds) of Clinical Manual of Fever in Children. 2nd ed. Springer, Cham. Germany. 2018. P. 85-140.
4. World Health Organization. WHO Guidelines for Malaria 2021. [cited 2024 March 18]. Available at: https://www.who.int/publications/i/item/WHO-UCN-GMP-2021.01
5. Kotepui M, Kotepui KU, Milanez GD, Masangkay FR. Reduction in total leukocytes in malaria patients compared to febrile controls: A systematic review and meta-analysis. PLoS One. 2020;15(6): e0233913.
6. Kotepui M, Phunphuech B, Phiwklam N, Chupeerach C, Duangmano S. Effect of malarial infection on haematological parameters in population near Thailand-Myanmar border. Malaria J. 2014;13:1-7.
7. Idemudıa NL, Ogefere HO, Omoregie R. Use of some surrogate markers of inflammation as predictor of malaria severity. J Microbiol Infect Dis. 2021;11(04): 201-8.
8. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. New Eng J Med. 1999;340(6):448-54.
9. Mackintosh CL, Beeson JG, Marsh K. Clinical features and pathogenesis of severe malaria.

Trends Parasitol. 2004;20(12): 597-603.
10. Moxon CA, Gibbins MP, McGuinness D, Milner Jr DA, Marti M. New insights into malaria pathogenesis. Ann Rev Pathol: Mechanisms of Dis. 2020;15(1): 315-43.
11. Punnath K, Dayanand KK, Chandrashekhar VN, Achur RN, Kakkilaya SB, Ghosh SK, *et al*. Association between inflammatory cytokine levels and anemia during *Plasmodium falciparum* and *Plasmodium vivax* infections in Mangaluru: A Southwestern Coastal Region of India. Tropical Parasitol. 2019;9(2):98-107.
12. Ansar W, Bandyopadhyay SMN, Chowdhury S, Habib SH, Mandal C. Role of C-reactive protein in complement-mediated hemolysis in Malaria. Glycoconjugate J. 2006;23:233-40.
13. Mattecka S, Bock C, Vogt B, Yapici G, Schrödl W, Janko C, *et al*. CRP and SAP from different species have different membrane ligand specificities. Autoimmunity. 2013;46(5):347-50.
14. Bamaga OA, Mahdy MA, Mahmud R, Lim YA. Malaria in Hadhramout, a southeast province of Yemen: prevalence, risk factors, knowledge, attitude and practices (KAPs). Parasit Vectors. 2014; 7: 351.
15. Bakhubaira S. Hematological parameters in severe complicated Plasmodium falciparum malaria among adults in Aden. Turkish Journal of Hematology. 2013; 30(4): 394.
16. Derwesh SA, Fareed AT, Muthanna FM, Mazen R, Abduaslam M, Abdulatef SA, et al. Impact of Malaria Severity on Selected Liver Function Markers in Aden, Yemen: A Pilot Study. Yemeni Journal for Medical Sciences. 2025; 19(4): 52-9.
17. Singh AS, Masuku MB. Sampling techniques and determination of sample size in applied statistics research: An overview. Intern J Economics, Commerce Manag. 2014;2(11):1-22.
18. Bhardwaj N, Ahmed MZ, Sharma S, Nayak A, Anvikar AR, Pande V. C-reactive protein as a prognostic marker of Plasmodium falciparum malaria severity. J Vector Borne Dis. 2019;56(2):122-6.
19. Paul R, Sinha PK, Bhattacharya R, Banerjee AK, Raychaudhuri P, Mondal J. Study of C reactive protein as a prognostic marker in malaria from Eastern India. Advanced Biomed Res. 2012;1:41.
20. Markanday A. Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. Open Forum Infect Dis. 2015;2(3):ofv098.
21. Severe falciparum malaria. World Health Organization Transactions of the Royal Society of Tropical Medicine and Hygiene. 2000;94: 1-90.
22. World Health Organization. Severe and complicated malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1990;84:1-65.
23. White NJ. Severe malaria. Malaria J. 2022; 21(1): 284.
24. Balerdi-Sarasola L, Muñoz J, Fleitas P, Rodriguez-Valero N, Almuedo-Riera A, Antequera A, *et al*. Not all severe malaria cases are severe: Is it time to redefine severity criteria for malaria in non-endemic regions? Travel Med Infect Dis. 2024;60:102740.
25. Ladhani S, Lowe B, Cole AO, Kowuondo K, Newton CR. Changes in white blood cells and

platelets in children with falciparum malaria: relationship to disease outcome. Bri J Haematol. 2002;119(3):839-47.
26. Wilairatana P, Mahannop P, Tussato T, Hayeedoloh IM, Boonhok R, Klangbud WK, *et al*. C-reactive protein as an early biomarker for malaria infection and monitoring of malaria severity: a meta-analysis. Sci Rep. 2021;11(1):22033.
27. Kurtzhals JA, Reimert CM, Tette E, Dunyo SK, Koram KA, Akanmori BD, et al. Increased eosinophil activity in acute Plasmodium falciparum infection--association with cerebral malaria. Clin Exp Immunol. 1998;112(2): 303-7.
28. Koltas IS, Demirhindi H, Hazar S, Ozcan K. Supportive presumptive diagnosis of Plasmodium vivax malaria. Saudi Med J. 2007;28(4): 535-9.
29. Jairajpuri ZS, Rana S, Hassan MJ, Nabi F, Jetley S. An analysis of hematological parameters as a diagnostic test for Malaria in patients with acute febrile illness: An institutional experience. Oman Med J. 2014;29(1):12-7.
30. Lathia T, Joshi R. Can hematological parameters discriminate malaria from nonmalarious acute febrile illness in the tropics? Indian J Med Sci. 2004;58(6):239-44.
31. McKenzie FE, Prudhomme WA, Magill AJ, Forney JR, Permpanich B, Lucas C, *et al*. White blood cell counts and malaria. J Infect Dis. 2005;192(2):323-30.
32. Agrawal V, Jain V, Biswas S. Evaluation of C-reactive protein as a biochemical marker for assessing disease severity in Malaria. Headache. 2013;8:10.
33. Sarfo BO, Hahn A, Schwarz NG, Jaeger A, Sarpong N, Marks F, *et al.* The usefulness of C-reactive protein in predicting Malaria parasitemia in a Sub-Saharan African region. PloS one. 2018; 13(8):e0201693.