Determining the severity of *Plasmodium falciparum* malaria in Ethiopia

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**KEYWORDS**  
Severe anemia; Cerebral malaria; Circulatory collapse; Ethiopia

**Summary**

**Background:** In the majority of health centers in Ethiopia, the severity of *falciparum* malaria has been determined by parasitemia alone. However, it has been suggested that the use of peripheral infected RBC counts as an indicator of disease severity by itself is insufficient. Therefore, this study was performed to assess the severity of *falciparum* malaria infection in three Ethiopian localities with epidemic malaria and to compare the usual severe malaria determination technique (parasitemia) used in Ethiopia with other malaria severity determination parameters: circulatory collapse, cerebral malaria and severe anemia.

**Methods:** Blood samples were collected from 400 individuals to examine the presence of *falciparum* malaria in the Awash, Metehara and Ziway areas of Ethiopia. Data on cerebral malaria, circulatory collapse and severe anemia were collected from 210 *falciparum* malaria patients.

**Results:** Of the 400 individuals examined, 210 were positive for *falciparum* malaria, and 190 were negative and served as healthy controls (HC). Severe anemia (18 patients, 8.57%) and circulatory collapse (25 patients, 11.90%) were the common features associated with severe *falciparum* malaria. Additionally, the detection of severe malaria was comparable using parasitemia, circulatory collapse or anemia.

**Conclusion:** The findings of this study demonstrated comparable capacity for detecting severe *falciparum* malaria using circulatory collapse, severe anemia or parasitemia. Therefore, in addition to parasitemia, assessing severity of *falciparum* malaria using circulatory collapse and severe anemia will facilitate the diagnosis and management of malaria in Ethiopia.

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Introduction

Malaria is perhaps the most important eukaryotic parasitic disease, threatening the livelihood of over 2.2 billion people [1]. Four main species of malaria infect in humans: Plasmodium falciparum (P. falciparum), P. malariae, P. ovale and P. vivax. P. falciparum is the most highly virulent species and is responsible for almost all of the 1.7—2.5 million deaths worldwide caused by malaria [2—4].

In Ethiopia, malaria is the leading cause of mortality and morbidity, where an estimated 68% of the population lives in malarious areas and 75% of the total land mass is malarious [5]. The main malaria control strategies in Ethiopia include selective vector control, epidemic management and control, environmental management and personal protection through the use of insecticide-treated bed nets [6,7]. Despite recent efforts to control the disease, malaria remains the leading cause of mortality and morbidity in the country [5—7].

Although there are several factors that increase mortality due to falciparum malaria in Ethiopia, the absence of reliable diagnosis and management of severe malaria is the most important [8,9]. In almost all of the health centers in Ethiopia, severe malaria has been diagnosed by counting the number of Plasmodium parasites found in peripheral blood of the patients [10]. However, the use of peripheral counts (parasitemia) alone as an indicator of disease severity is clearly insufficient for two reasons. First, after initial infection, the peripheral parasitaemia increases exponentially, achieving a transient steady state that oscillates over 2 days [11]. Thus, the total parasite burden cannot be estimated with precision from the peripheral density at any single time-point. Furthermore, it has been reported that, in severe falciparum malaria infection, parasitized erythrocytes at the schizont stage are known to be sequestered in tissue capillaries and may result in a deceptively low parasite count in the peripheral blood [12]. As such, using appropriate determination and management of severe malaria may aid in decreasing mortality due to malaria in Ethiopia. Therefore, the aim of this study is to assess the severity of falciparum malaria infection and to compare the usual severe malaria determination technique (parasitemia) used in Ethiopia with other malaria severity determination techniques.

Materials and methods

Study site

This study was performed in three Ethiopian malaria endemic localities (Awash, Metehara and Ziway areas). Malaria is seasonal within the study areas, with frequent epidemics most often from September to December, following the main rainfall season. Each region has one malaria center where people with symptoms suggestive of malaria obtain free services for malaria diagnosis and treatment [13,14].

Study population

A total of 400 individuals were included in the study. Malaria patients who had received anti-malarial drugs prior to confirmation of malaria, patients critically ill and unable to give blood, patients who have other serious chronic infections and patients co-infected with P. falciparum or P. vivax parasites were excluded from the study.

Examination of blood for malaria parasite

Blood samples from patients’ fingers were taken, and thick and thin blood film slides were prepared using a 10% Giemsa solution. The stained slides were examined under a light microscope using 100× oil immersion by an experienced laboratory technician. Parasitemia was calculated per 200 white blood cells (WBC), assuming 8000 WBC/μl of blood [15]. Patients with 5% parasitized RBCs, as outlined by WHO [16], were considered severe parasitemia cases.

Determination of hemoglobin concentration

Peripheral blood was collected from a finger prick using a sterile blood lancet, and hemoglobin was measured by Hemocue™ (hemoglobinometer, Angelholm, Sweden).

Clinical data

Data were collected by medical practitioners as outlined by WHO [16]: cerebral malaria, characterized by unarousable coma not attributable to any other cause, with a Glasgow Coma Scale score ≤9; circulatory collapse, characterized by systolic blood pressure <70 mmHg in patients >5 years of age and <50 mmHg in children aged 1—5 years; and severe anemia, characterized by hemoglobin concentration <6 g/dl.

Statistical analysis

The collected data were input into Microsoft Excel, exported and analyzed using SPSS (version 13.0, Chicago, IL, USA) and SISA software. Chi-square was used to determine association between age, gender
Table 1  Characteristics of the study participants from Awash, Metehara and Ziway, Ethiopia, November 2007 to January 2008.

<table>
<thead>
<tr>
<th>Category</th>
<th>Malaria</th>
<th>Severe malaria N (%)</th>
<th>Health control N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107 (50.95)</td>
<td>37 (53)</td>
<td>86 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>103 (49.05)</td>
<td>33 (47)</td>
<td>104 (55)</td>
</tr>
<tr>
<td>( \chi^2 ), P-value</td>
<td>0.076, 0.78</td>
<td>0.22, 0.63</td>
<td>1.71, 0.19</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>95 (45.24)</td>
<td>35 (50.0)</td>
<td>60 (31.58)</td>
</tr>
<tr>
<td>5–15</td>
<td>68 (32.38)</td>
<td>19 (27.14)</td>
<td>66 (34.73)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>47 (22.38)</td>
<td>16 (22.86)</td>
<td>64 (33.69)</td>
</tr>
<tr>
<td>( \chi^2 ), P-value</td>
<td>16.54, 0.0003</td>
<td>8.94, 0.011</td>
<td>4.45, 0.108</td>
</tr>
</tbody>
</table>

and prevalence of malaria. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). Values were considered to be statistically significant when P-values were less than 0.05.

Results

Description of the study participants

During the study period, a total of 400 blood samples were collected from individuals living in the Awash, Metehara and Ziway areas. Of these, 210 (52.5%) were found to be positive for falciparum malaria; the remaining 190 individuals were not infected by falciparum malaria and/or P. vivax and were thus considered healthy control (HC) cases (Table 1). There were 107 (50.95%) males and 103 (49.05%) females infected with falciparum malaria. Out of the 190 healthy controls, there were 86 (45%) males and 104 (55%) females (Table 1).

Of note, the age groups of <5 years old (45.24%) and 5–15 years old (32.38%) were highly affected by P. falciparum infection. Furthermore, while the severity of P. falciparum infection was statistically associated with individuals’ ages, individuals’ genders had no statistically significant association with P. falciparum severity (Table 1).

The clinical and parasitological characteristics of 70 severe falciparum malaria patients at admission are shown in Fig. 1. Severe anemia and circulatory collapse were the dominant features of severe malaria present in 18 (8.57%) and 25 (11.90%) of the patients, respectively. Parasitemia and cerebral malaria occurred in 17 (8.09%) and 6 (2.86%) of the patients, respectively. There were 6 (2.86%) cases of severe anemia and parasitemia, 5 (1.40%) cases of severe anemia and circulatory collapse, 4 (1.90%) cases of cerebral malaria and circulatory collapse, 4 (1.90%) cases of circulatory collapse and parasitemia and 2 (0.90%) cases of severe anemia, circulatory collapse and cerebral malaria (Fig. 1).

The odds ratios and P-values for the probability of being parasitemic or non-parasitemic in the study participants

The probability of patients with falciparum malaria having parasitemia was comparable with the chance of having either circulatory collapse or severe anemia (Table 2). In contrast, individuals with severe falciparum malaria were about three-fold less likely to have cerebral malaria as they were to have parasitemia (odds ratio of 0.33, 95% confidence interval = 0.12–0.86).

Discussion

In this study, it has been shown that 11.90%, 8.57% and 2.86% of patients had circulatory collapse, severe anemia and cerebral malaria, respectively, despite low parasite density in their circulatory blood. Other studies have also reported the presence of single or several severe malaria indicators in patients with low parasitemia [17–19]. Furthermore, the likelihood of having circulatory collapse and severe anemia is comparable with the chance of presenting with parasitemia. However, this parasitemia data in the patients may not be accurate because in falciparum malaria infection, parasitized erythrocytes at the schizont stage are known to be sequestered in tissue capillaries, which can

Table 2  The odds ratios and P values for the chance of being parasitemic and non-parasitemic in patients with falciparum malaria from Awash, Metehara and Ziway, Ethiopia, November 2007 to January 2008.

<table>
<thead>
<tr>
<th>Criteria compared</th>
<th>Odds ratio, [95% CI], (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P vs. CC</td>
<td>1.53, [0.80–2.93], (0.19)</td>
</tr>
<tr>
<td>P vs. SA</td>
<td>1.06, [0.53–2.12], (0.85)</td>
</tr>
<tr>
<td>P vs. CM</td>
<td>0.33, [0.12–0.86], (0.02)*</td>
</tr>
</tbody>
</table>

* Significant difference; CM, cerebral malaria; CC, circulatory collapse; SA, severe anemia; P, parasitemia.
result in deceptively low parasite counts in the peripheral blood [12]. Therefore, patients with high parasitemia may be missed if the count is determined from peripheral blood alone.

Although this study’s findings indicated a comparable probability of detecting severe malaria using circulatory collapse and severe anemia, severity of infection is still determined in most health centers of Ethiopia only by counting the number of parasites found in the peripheral blood. However, complications of malaria may occur when the number of parasites has decreased from baseline or even when parasites have disappeared from the peripheral blood. Therefore, assessing the severity of malaria using other severe malaria indicators, such as circulatory collapse and severe anemia, will facilitate the diagnosis and management of severe malaria in Ethiopia.

This study also noted that there was a relatively higher percentage of circulatory collapse cases compared to the other severe malaria indicators. In contrast, other studies conducted in Ethiopia and other countries reported a lower percentage of circulatory collapse cases compared to other severe malaria indicators [19–21]. For instance, Mockenhaupt et al. [20] assessed the symptoms of severe malaria and their contribution to mortality in 290 Ghanaian children and reported a lower percentage of circulatory collapse cases than did this study. Furthermore, a relatively low percentage of circulatory collapse cases was also reported from a retrospective study conducted in northwest regions of Ethiopia [19]. The pathogenic mechanisms underlying circulatory collapse are not fully understood, but a logical explanation is the capacity of malaria-infected RBCs to aggregate on either one or more receptors expressed on the surface of vascular endothelium, resulting in the blockage of blood vessels [22–24]. Therefore, the presence of high levels of aggregation in patients in this study may have been the reason for the differing reports of circulatory collapse percentages between the studies.

In this study, there was a low percentage of cerebral malaria cases compared to other severe malaria indicators. This is inconsistent with two studies conducted in different regions of Ethiopia [17,18], in which there were relatively high percentages of cerebral malaria cases. There are a number of possible explanations for this difference. First, because the areas included in this study have endemic malaria, a higher level of anti-disease immunity may exist in the community and thus may reduce the chance of developing cerebral malaria. Second, previous studies suggested that the prevalence of cerebral malaria depends on the number of cerebral malaria strains of *P. falciparum* in a certain community [25,26]. Therefore, a small number of ‘‘cerebral malaria strains’’ of *P. falciparum* in this community may have led to the low frequency of cerebral malaria cases in this area. Furthermore, although deposition of immune complexes in brain capillaries, reduced humoral or cell-mediated immune responses and actions of endotoxin and TNF [27] all play roles in development of cerebral malaria, the accumulation of large numbers of parasites in specific sites, such as the brain or placenta, is the major cause [28,2,29,30]. Therefore, unlike some other severe malaria indicators that can occur due to the accumulation of parasites at various sites, organ-specific accumulation of parasites may have been the reason for the low percentage of cerebral malaria cases in the study participants.

![Figure 1](image_url)  
*Figure 1*  Frequency of severe malaria in the study participants from Awash, Metehara and Ziway, Ethiopia, November 2007 to January 2008.

**Conclusion**

The findings of this study indicated comparable capacities for detecting severe *falciparum* malaria
using circulatory collapse, severe anemia and parasitemia. Therefore, in addition to parasitemia, assessing the severity of *falciparum* malaria using circulatory collapse and severe anemia will facilitate the diagnosis and management of malaria in Ethiopia.

**Authors’ contributions**

ZT was involved in all aspects of the project; data collection, analysis, interpretation, determining hemoglobin concentrations and writing the manuscript. BP contributed to the design, data interpretation, work supervision and critical revision of the manuscript. MW participated in the revision of the manuscript.

**Competing interests**

The authors declare that they have no competing interests.

**Ethical approval**

Ethical clearance was obtained from the Ethical Review Committee of the Department of Biology, Addis Ababa University. Written informed consent was obtained from all study participants and from mothers/caretakers of children under 18 who participated in the study after explaining the purpose and objective of the study.

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**References**


