Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi:

Indicators of fatal outcome in severe *Plasmodium falciparum* malaria: a study in a tertiary-care hospital in Thailand

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ARTICLE INFO

Article history:
Received 19 August 2010
Received in revised from 18 September 2010
Accepted 29 September 2010
Available online 20 November 2010

Keywords:
Plasmodium falciparum
Severe malaria
Fatal indicator
Tertiary care
Thailand

ABSTRACT

Objective: To illustrate the clinical features and investigate the indicators associated with a fatal outcome in adult patients with severe *Plasmodium falciparum* malaria admitted to the Hospital for Tropical Diseases, Bangkok, Thailand. **Methods:** We studied 202 adult malaria patients admitted to the Intensive Care Unit. A total of 43 clinical variables were identified by univariate and logistic regression analyses, to eliminate confounding factors. **Results:** Regarding the statistical methods, only 6 variables-jaundice, cerebral malaria, metabolic acidosis, body mass index, initial respiratory rate, and white blood cell count-were significant indicators of death, with adjusted odds ratios (95% *CI*) of 15.2 (2.1-32.3), 4.3 (2.3-12.6), 3.3 (2.3-5.7), 2.4 (1.9-3.5), 2.2 (1.5-2.6), and 1.7 (1.2-3.1), respectively. **Conclusions:** Our study found that jaundice, cerebral malaria, metabolic acidosis, body mass index, initial respiratory rate and white blood cell count were indicators of fatal outcome in severe *Plasmodium falciparum* malaria. Further studies on the fatal indicators in severe malaria need to be compared with data from different geographical areas, to construct practical measures to address potentially fatal indicators in different settings.

1. Introduction

Malaria is an infectious disease that continues to be a major health problem in tropical and subtropical countries. According to WHO report, about 3.3 billion people - half of the world's population - are at risk of malaria. This leads to about 250 million malaria cases occurring annually and estimates of one million deaths per year[1]. Among all species of malaria that are able to infect humans, *Plasmodium falciparum (P. falciparum)* causes most of severe malaria and deaths worldwide[1]. In some areas, mortality rates among malaria patients remain high, for a number of reasons, including limited access to healthcare services and increased drug resistance. The clinical manifestations of *P. falciparum* malaria patients are highly diverse and complex. Clinical outcome may range from a mild headache and fever, to a life-threatening condition; this variability results from a complex interplay among parasite, host, and environmental factors[2]. Improved classification of severe malaria could help clinicians who care for malaria patients avoid diagnostic delays, identify severe malaria patients who are most likely to die, and thus improve management, by targeting resources to the sickest patients.

In previous reports, several factors of life-threatening malaria were investigated[2-5]. However, mostly, the indicators of life-threatening malaria were studied in endemic areas and included children, in Africa. Few studies have reported on areas of unstable malaria transmission, in Southeast Asia. Here, we report the results of a malaria study in the Hospital for Tropical Diseases, a tertiary-care setting, in Thailand. The main objective of this study was to investigate indicators associated with lethal outcomes among adult patients with severe *P. falciparum* malaria, using WHO criteria, 2000[6].

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2. Materials and methods

2.1. Study site and recruitment procedures

The study was conducted at the Hospital for Tropical Diseases (HTD), a tertiary-care hospital for the management of tropical diseases, particularly severe malaria, located in Bangkok, Thailand. The hospital was well-equipped to provide intensive care for cases of severe malaria. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Thailand. Due to the limited number of death cases by severe malaria occurred in the study site, we made the enrollment ratio of fatal case per survival case to 1:5. An independent statistician generated a randomized list of surviving patients, before recruitment into the study. A total of 202 in-patients had positive asexual *P. falciparum* blood films, confirmed by microscopy, and classified as severe malaria according to the WHO criteria, 2000[6]. Of the 202 patients, 157 (77.8%) were male and 45 (22.2%) female, with an average age (±SD) of (29.16 ±12.10) years[range (15-74) years]. No significant concomitant disease was found in any of the patients. Among these, 170 were cured and discharged well on day 28 post-treatment; there were 32 deaths. All patients who fulfilled the inclusion criteria were included. The inclusion criteria were as follows: (1) either male or female, (2) admitted for treatment for severe *P. falciparum* malaria, (3) body weight $\geqslant$40 kg, (4) age $\geqslant$15 years, (5) on admission, pre-treatment, microscopically confirmed positive for asexual-stage *P. falciparum* parasites, (6) received artemisinin combination therapy (7) had no history of antimalarial therapy during 1 month prior admission, and (8) provided blood samples, before admission, for examination. Patients who survived had to remain in hospital for 4 weeks after admission. We excluded pregnant or lactating females, mixed malarial infection and patients with a history of significant systemic disease or disease requiring therapy, other than falciparum malaria, *e.g.*, malignancy, immunosuppressive disorders, cardiovascular, pulmonary, gastrointestinal, neurological, endocrine, and metabolic diseases.

2.2. Treatments

The patients were treated with artemisinin combination therapy (ACT) as part of the clinical protocol for severe *P. falciparum* malaria, *e.g.*, artesunate 2.4 mg/kg *i.v.* as loading dose, then 1.2 mg/kg artesunate *i.v.* 12-hourly. Once the patients were able to tolerate oral therapy, they would be switched to oral dose of artesunate until 5 days, with the addition of 2 doses of oral mefloquine (25 mg/kg in divided doses, 8 h apart) started 12 h after the last dose of artesunate.

Apart from specific treatment with antimalarial drugs, symptomatic and supportive cares were carried out to all patients according to standard practice of the hospital, *e.g.*, mechanical ventilation for respiratory failure, hemodialysis for renal failure, including fever reduction by tepid sponging or fanning. Clinical evaluation and parasite counts were conducted 12-hourly until negative, and then daily. While the clinical laboratory tests were performed on admission (pre-treatment), and post-dosing, as appropriate.

2.3. Data collection

Baseline clinical demographic and laboratory variables were recorded upon admission. These consisted of age, gender, body mass index, initial vital signs and duration of fever before admission, history of malaria, initial parasite counts, liver and spleen size, and clinical manifestations, *e.g.*, chill-rigor, abdominal pain and vomiting. The investigating team also examined and recorded clinical signs, *e.g.*, cerebral malaria (unrousable coma), severe anemia (pale at conjunctiva, tongue, lips and palms with hemoglobin<5 g/dL), respiratory distress (physically labored breathing), hypoglycemia (sweating and palpitation with blood glucose <40 mg/dL), circulatory collapse (clammy skin and weak peripheral pulse with systolic blood pressure <80 mmHg), acute renal failure (serum creatinine>3 mg/dL with urine output <400 mL/24 h), spontaneous bleeding (significant bleeding from gums, nose and gastrointestinal tract), multiple convulsions ($\geqslant$2 convulsions observed in 24 h), metabolic acidosis (plasma bicarbonate<15 mmol/L or arterial blood pH<7.35), hemoglobinuria (dark red or black urine), hyperparasitemia (parasitemia $\geqslant$5%), and jaundice (yellow discoloration of sclera with total bilirubin>3 mg/dL). The clinical qualitative variables were scored as follows: absent=0 and present=1. Baseline hematological data, *e.g.*, white-blood-cell count, red-blood-cell count, hemoglobin and platelet count, were determined by automated cell counter (Advia 120 Hematology System, Siemens Medical Solutions Diagnostics; commercial reagents by Roche Diagnostics, Berlin, Germany). The following biochemical parameters were measured, using a Cobas Integra 400 (Roche Diagnostics), with commercial reagents from the same supplier: glucose, blood urea nitrogen, creatinine, total bilirubin, direct bilirubin, aminotransferases, and electrolytes. Thick and thin blood films were prepared from fingerprick blood samples and stained with Giemsa. Malaria parasite counts per microliter were obtained by counting the number of asexual parasite forms per 200 white blood cells on thick smears, and multiplying by the white-blood-cell count, or by counting the number of asexual parasite forms per 1 000 erythrocytes on thin smears, and multiplying by the red, blood-cell counts.

2.4. Outcome of treatment

Radical cure was defined as the absence of asexual parasites during 28 days' follow-up. Any antimalarial-drug-resistant responses (RI, RII, or RIII) were categorized according to WHO criteria, 1973[7]. Surviving cases were the patients who cured and discharged well after treatment. Fatal cases were the patients who died in the hospital during treatment.

2.5. Statistical analysis

Quantitative data were expressed as mean with standard deviation (SD) and qualitative data as number of observations with percentage(%). All reported *P*-values were from 2-tailed testing, and statistical significance was set at 0.05 probability. Descriptive statistics were used to summarize baseline values and demographic data. The Chi-square test or Fisher's exact test was used to compare proportions, as appropriate, and the *t*-test to analyze continuous data. Risk verification was expressed with odds ratio (OR) and 95% confidence interval (95%*CI*). Stepwise logistic regression analysis was conducted to eliminate confounding factors and to ascertain the adjusted odds ratio, revealing fatal indicators in severe malaria. Validation of the logistic model

was illustrated by positive and negative predictive values, and percentage accuracy.

3. Results

3.1. General baseline clinical description

Regarding the therapeutic results, patients were divided into 2 groups: 170 (84.1%) survived and 32 (15.9%) died. All surviving cases were cured and discharged well on day 28 after initial treatment. No antimalarial-drug-resistance responses were found in this group. In the fatal patients, death occurred between 1-5 days after admission. Some patients, therefore, could not be completed courses of artesunate-mefloquine therapy. The baseline clinical characteristics and laboratory data for both groups are shown in Table 1. There were statistically significant differences for body mass index, initial respiratory rate, and serum creatinine (P<0.05). Moreover, there were statistically significant differences in age, initial pulse rate, white blood cell count, serum blood urea nitrogen, direct and total bilirubin, aminotransferases, potassium and bicarbonate (P<0.01). From the hematology profile for all patients, on admission most patients had reduced numbers of white blood cells, red blood cells, and platelets. In contrast, we found leucocytosis only in the fatal group. On admission, most of the patients in both groups had high levels of aminotransferases, total bilirubin, blood urea nitrogen, and creatinine. In addition, hypoalbuminemia, and hyponatremia were found in both groups.

3.2. Clinical manifestations and fatal-outcome indicators

The patients' clinical manifestations on admission are shown in Table 2. Overall, the most common presentations were chill-rigor (72.2%), jaundice (68.8%) and hyperparasitemia (64.8%). In the fatal group, the most common findings were jaundice (93.7%), hyperparasitemia (62.5%), acute renal failure (59.3%), chill-rigor (56.2%), and metabolic acidosis (53.1%). To assess the importance of the clinical manifestations on admission, we conducted initial univariate analysis using the variables listed in Table 2. The results showed that only 7 variables-respiratory distress, cerebral malaria, metabolic acidosis, spontaneous bleeding, acute renal failure, jaundice, and circulatory collapse-were associated with an increased risk of death, with OR (95%*CI*) of 21.1 (6.9-64.2), 17.5 (6.0-50.7), 15.3 (6.0-38.7), 13.5 (4.3-42.3), 9.5 (3.8-23.5), 8.4 (1.9-36.3), and 8.3 (2.0-33.8), respectively. No variable was considered as protective against the risk of death.

Further analysis was conducted to eliminate any confounding factors that might affect the study results. To substantiate the initial results obtained, 20 statistically significant variables (Tables 1 and 2) were subjected to stepwise multiple logistic regression analysis. This yielded only 6 variables-jaundice, cerebral malaria, metabolic acidosis, body mass index, initial respiratory rate, and white blood cell count-as significant for the logistic model, with adjusted odds ratios (95%*CI*) of 15.2 (2.1-32.3), 4.3 (2.3-12.6), 3.3 (2.3-5.7), 2.4 (1.9-3.5), 2.2 (1.5-2.6), and 1.7 (1.2-3.1), respectively.

Table 1
Clinical characteristics and laboratory data of study patients on admission.

	Baseline data	SMS(n=170)	SMD(n =32)
Clinical charateristics	Gender (male/female)	134/36	23/9
	Age (years)*	27.5±10.5	38.0±16.3
	Body mass index (kg/M^2)**	20.4±3.2	25.3±3.3
	Geometric mean parasite count (/μL)	87 796	106,546
		(320-1 154 250)	(256-1 335 320)
	Duration of fever before admission (days)	4.6±2.1	4.8±1.6
Initial vital signs	Auxiliary temperature (℃)	38.1±1.0	38.1±1.5
	Pulse rate (/min)*	99.7±14.8	112.4±18.9
	Respiratory rate (/min)**	25.8±4.9	31.8±6.7
	Systolic blood (mmHg)	107.7±15.6	110.8±28.2
	Diastolic blood (mmHg)	64.7±11.8	71.9±20.6
Hematology profiles	White blood cell count (×10^3/μL)*	7.4±4.1	15.3±10.5
	Red blood cell count (×10^6/μL)	4.4±1.0	4.1±0.9
	Hemoglobin (g/dL)	14.6±11.0	14.0±13.2
	Platelet count (×10^3/μL)	49.6±45.7	36.2±20.8
Biochemistry profiles	Glucose(mg/dL)	130.5±45.2	133.0±103.2
	Blood urea nitrogen(mg/dL)*	39.6±35.5	60.4±36.3
	Creatinine (mg/dL)**	1.7±1.5	2.8±1.8
	Direct bilirubin (mg/dL)*	3.8±2.9	8.2±5.8
	Total bilirubin(mg/dL)*	7.5±5.8	10.9±7.4
	Albumin(g/dL)	3.3±0.7	3.1±0.6
	Aspartate aminotransferase (U/L)*	106.3±101.7	466.7±442.9
	Alanine aminotransferase (U/L)*	69.1±61.5	212.9±181.5
	Sodium(mmol/L)	132.0±4.8	133.0±8.0
	Potassium(mmol/L)*	3.8±0.6	5.4±6.2
	Bicarbonate(mmol/L)*	20.1±3.9	15.5±8.6

*: P<0.01, **: P<0.05, SMS: severe *P. falciparum* malaria survival patients; SMD: severe *P. falciparum* malaria dead patients.

Table 2
Clinical manifestations of study patients and number of deaths.

Clinical manifestation	Total number of diagnostic patients (cases)	Number in fatal group (cases)	Odds ratio(95% *CI*)
Past history of malaria in last 1 year	45	3	0.5 (0.1–1.9)
Chill–rigors	146	18	2.9 (0.6–13.3)
Abdominal pain	57	3	0.9 (0.2–3.9)
Vomiting	95	3	0.3 (0.1–1.4)
Hepatomegaly	87	9	1.1 (0.4–2.7)
Splenomegaly	22	3	15 (0.4–5.6)
Cerebral malaria*	34	14	17.5 (6.0–50.7)
Severe anemia	17	5	4.4 (1.4–14.1)
Respiratory distress*	38	15	21.1 (6.9–64.2)
Hypoglycemia	9	3	4.8 (1.1–21.0)
Circulatory collapse*	9	4	8.3 (2.0–33.8)
Acute renal failure*	53	19	9.5 (3.8–23.5)
Spontaneous bleeding*	16	8	13.5 (4.3–42.3)
Multiple convulsion	8	2	3.0 (0.6–16.2)
Metabolic acidosis*	34	17	15.3 (6.0–38.7)
Hemoglobinuria	95	11	1.2 (0.5–3.2)
Hyperparasitemia	131	20	0.9 (0.4–1.9)
Jaundice*	139	30	8.4 (1.9–36.3)

*: $P<0.01$

3.3. Validation study

In the validation study logistic model, the positive predictive value was 92.9%, and the negative predictive value was 89.9%, with 90.0% accuracy.

4. Discussion

Although *P. falciparum* malaria is the major cause of death among malaria patients, particularly in tropical and subtropical regions, deaths may be reduced by early diagnosis of malaria and prompt effective treatment[8,9]. Thus, it is crucial to predict the most likely course of disease as accurately as possible, particularly for in-hospital patient management. Various study teams in different regions have studied the fatal indicators of severe malaria; however, few studies have been conducted in Southeast Asia. In the past decade, most reports have established the indicators of fatal outcomes in pediatric severe-malaria cases, focusing on endemic areas, such as Africa. This study described the clinical features of adult patients with severe *P. falciparum* malaria in the Intensive Care Unit of the Hospital for Tropical Diseases (HTD) and the clinical indicators associated with a lethal outcome. In a previous report, we noted the mortality rate among malaria patients admitted to the HTD was 1.8%[10]. The HTD was a tertiary-care setting for tropical diseases, particularly for the management of severe malaria; therefore, it is unsurprising that the malaria mortality rate was low compared with other recent reports[5,11,12]. In this study, however, we enrolled patients according to the randomization process along with the inclusion and exclusion criteria. As a result, the flaw of this study was the lack of epidemiological data for comparison with the previous report. However, the start-point was adult patients with complicated *P. falciparum* malaria. These patients were enrolled into the study after admission, without any selection bias, by clinicians. We were, therefore, confident that our results had described the complete spectrum of fatal indicators in this setting.

The pathophysiological processes causing severe malaria are complex and currently incompletely understood. Classification of disease severity, in malaria, is still crucial to the provision of effective care, particularly for in-hospital patient management. Various reports have shown the factors associated with treatment outcomes among malaria patients. Recently, metabolic acidosis and cerebral malaria have been reported as simple predictors of therapeutic outcome in adult patients with severe malaria[9]. There were some consistencies with another report, which showed that cerebral malaria, acute renal failure, needing ventilator support, and severe anemia, were indicators of mortality for adult malaria patients[13]. Robinson and coworker emphasized that unconsciousness, renal failure, and pulmonary edema, were significant predictors of mortality among adult patients with severe malaria[5]. The results of our study showed some agreement with these other studies; we have shown that cerebral malaria, metabolic acidosis, and initial respiratory rate, in adult patients with complicated *P. falciparum* malaria, were associated with fatal outcome. However, acute renal failure, severe anemia, and respiratory distress including need for ventilator support and pulmonary edema were not included in our study model. Regarding our study conditions, the hospital's facilities and treatment procedures probably contributed to the differences in results from these former studies. All severe malaria patients admitted to the HTD were monitored closely by medical staff, the blood bank unit was well-managed, and all life-support equipment (ventilator, hemodialyzer) was kept on stand-by as a matter of routine. For most patients, therefore, disease severity was detected before complications developed.

Recently, subcutaneous fatty tissue and overweight have also been established as factors associated with disease severity in malaria[8,14]; this may be why body mass index (BMI) was one clinical indicator associated with a fatal outcome among the malaria patients in our own study. Hematological changes during malaria infection have been well-described[15-17]. White-blood-cell counts might be high, normal, or low, in malaria infection. Three previous reports have confirmed the frequent presence of low white-

blood-cell counts in acute malaria[18-20]. In contrast, an African study of child malaria patients commonly found high white-blood-cell counts; however, this factor was not necessarily indicative of a poor prognosis[21]. Regarding our results, it was not surprising that white-blood-cell count was one of the fatal indicators. Since controversy still remains over this factor, more investigations should be undertaken, to distinguish on viral or bacterial co-infections, other inflammations or traumas and stress during malaria treatment. In severe *P. falciparum* malaria, jaundice was a common feature, attributed in part to liver damage and the hemolysis of both parasitized and non-parasitized erythrocytes[22]. In our study, jaundice was included as a predictor of mortality; this illustrated a inconsistency with another report which showed that jaundice was not associated with therapeutic outcome in severe malaria[13]. Regarding the results of this study, jaundice (total bilirubin>3 mg/dL) was seen in most patients. In this study, the direct parameters for hemolysis were not measured, but a decrease in red-cell mass, *e.g.*, hemoglobin, (without bleeding), concomitant with an increase in unconjugated bilirubinemia after admission, might explain the hemolytic jaundice.

Regarding validation of the study results, we found that the validity indices were slightly low. This might be due to the small sample size in the study, as we had a limited time to recruit patients.

In conclusion, a presentation of multiple complications in severe *P. falciparum* malaria patients after admission made clinical management difficult. Even in tertiary hospitals, clinical management difficulties may arise due to the deterioration of patient status at any time during hospitalization. In this situation, our results indicated that fatal indicators in severe malaria might differ in different settings. We recommended that further studies on fatal indicators in severe malaria should compare data from different geographical areas, to elicit evidence-based field data on potentially fatal indicators in different settings.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

This study was partially supported by Mahidol University grants. We thank the Faculty of Tropical Medicine, Mahidol University, for defraying the costs of printing. We also thank the staff and nurses of the Hospital for Tropical Diseases for their help. Thanks to Mr. Paul Adams for editing the English language of the manuscript.

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