FACTORS ASSOCIATED WITH ACUTE RENAL FAILURE IN FALCIPARUM MALARIA INFECTED PATIENTS

Noppadon Tangpukdee[1], Sakhr Badawi Omar Elshiekh[1], Weerapong Phumratanaprapin[1], Srivicha Krudsood[2] and Polrat Wilairatana[1]

[1]Department of Clinical Tropical Medicine, [2]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Abstract. To identify factors associated with acute renal failure among patients with severe falciparum malaria (MARF), we studied 189 severe malaria patients admitted to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, in Bangkok, Thailand. Among these, 63 had MARF, and 126 did not. Baseline clinical demographics and laboratory variables were evaluated with univariate analysis. Logistic regression was used to ascertain adjusted odds ratios. By univariate analysis, factors associated with MARF included male gender, fever duration >4 days, patients who lived in a non-endemic area prior to malaria infection, body mass index >18.5 kg/m^2, oliguria, abdominal pain, impaired consciousness, jaundice, anemia, liver enlargement, total white blood cell count >10x10^9/l, total bilirubin >3 mg/dl, aspartate aminotransferase >120 U/l, alanine aminotransferase >120 U/l, albumin <3 g/dl, fever clearance time >72 hours, and parasite clearance time >72 hours. A hemoglobin >10 g/dl, patients living in a malaria endemic area, non-oliguria on the day of admission, and splenomegaly were negatively associated with MARF. After multivariate logistic regression, oliguria during the first 24 hours of admission and a history of living in a non-endemic area prior to malarial infection were factors associated with MARF. We conclude the most significant factors associated with MARF were oliguria on the day of admission and living in a non-endemic area prior to malaria infection.

Keywords: *Plasmodium falciparum*, severe malaria, renal failure, risk factor

INTRODUCTION

Severe malaria is most often caused by *Plasmodium falciparum*, among persons with no or low pre-existing malarial immunity. The WHO criteria for severe malaria includes acute renal failure (ARF) which is common among adults living in low malaria transmission areas who acquire malaria (WHO, 2010). ARF is associated with mortality in severe malaria (Tangpukdee *et al*, 2010). The incidence of ARF in falciparum malaria (MARF) is fewer than 1-4.8% in endemic areas, and between 25-30% for non-immune Europeans (Barsoum, 2000). Hospital admissions for MARF vary from 2-39% among total admitted malaria patients (Sitprija, 1988; Barsoum and Sitprija, 1996). Early

Correspondence: Dr Polrat Wilairatana, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Ratchathewi, Bangkok 10400, Thailand.
Tel: +66 (0) 2354 9159; Fax: +66 (0) 2354 9158
E-mail: tmpwl@mahidol.ac.th

diagnosis of MARF and prompt appropriate treatment may reduce morbidity and mortality for severe malaria patients. The objective of this study was to identify the factors associated with MARF among severe falciparum malaria patients admitted to the Hospital for Tropical Diseases, at the Faculty of Tropical Medicine, Mahidol University, in Thailand.

MATERIALS AND METHODS

Patient population and study design

Patients at the Hospital for Tropical Diseases who matched the WHO criteria for severe falciparum malaria were included in this study (WHO, 2010). All patients were 15 years of age or older with microscopy-confirmed by asexual *P. falciparum* malaria on a blood film. Surviving patients stayed in the hospital for 28 days. Patients were excluded from the study if they had known chronic renal failure, had concurrent significant illness (including hypertension, diabetes mellitus, viral hepatitis, leptospirosis, or scrub typhus), were pregnant or lactating, had a mixed malarial infection, and had been treated with other anti-malarial drugs during 1 month prior to hospital admission. Baseline clinical demographics and laboratory variables were recorded upon admission. Thick and thin blood films were obtained from fingerprick blood samples and stained with Giemsa. Clinical evaluation was conducted every 4 hours during the 28 days of their hospital stay. Fingerprick parasite counts for thick and thin blood films were conducted every 6 hours until parasite counts were negative for parasitemia, after which only thick films were obtained daily for the remainder of their stay. Other laboratory tests were performed on admission (pre-treatment), and after antimalarial treatment, as appropriate. A total of 189 severe malaria patients were included in the study. The patients were divided into 2 groups: those with and without ARF. MARF was defined as oliguria with a urine output <400 ml/24 hours and failure to improve after rehydration and a serum creatinine >3 mg/dl. Parasite clearance time (PCT) was defined as the time from the start of antimalarial treatment until the thick blood films remained negative for the next 24 hours. Fever clearance time (FCT) was obtained as the period from the start of treatment until the oral temperature decreased to <37.5°C or the rectal temperature decreased to <38.0°C, and remained below that temperature for 48 hours. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Thailand.

Treatments and outcome measures

Patients were treated with artemisinin combination therapy (ACT) as part of the clinical protocol for severe falciparum malaria, *eg*, a loading dose of IV artesunate 2.4 mg/kg, followed by IV artesunate 1.2 mg/kg 12-hourly. Once the patients were able to take medication orally, they were switched to oral artesunate 4 mg/kg until completion of 5 days' treatment, with an additional 2 doses of oral mefloquine (25 mg/kg in 2 divided doses, 8 hours apart). Other than specific antimalarial medication, symptomatic and supportive treatment were also given, including hemodialysis for acute renal failure, mechanical ventilation for respiratory failure, and tepid sponging and fanning to reduce fever. A patient was designated "cured" with the absence of asexual malaria parasites after 28 days hospitalization.

Statistical methods

Demographic data and baseline clinical

Table 1
Demographic, therapeutic and baseline data.

	Severe malaria without acute renal failure (n = 126)		Severe malaria with acute renal failure (n = 63)		p-value
	Median	Range	Median	Range	
Age (years)	23	15-67	26	15-54	0.050
Body mass index (kg/m^2)	20.0	15.1-33.6	20.2	13.96-29.76	0.063
Duration of fever prior to admission (days)	4	2-14	5	1-15	0.022
Temperature (ºC)	38.2	36.0-40.2	38.0	36.0-40.8	0.037
Respiratory rate (/min)	24	12-44	28	16-44	0.036
Pulse rate (/min)	100	60-150	100	74-142	0.629
Systolic blood pressure (mmHg)	100	70-150	110	76-166	0.114
Diastolic blood pressure (mmHg)	60	38-90	60	40-100	0.616
Parasite counts (/µl)	289,770	33-283,5000	139,860	60-2,137,100	0.027
Parasite clearance time (hours)	56	12-141	66	8-251	0.025
Fever clearance time (hours)	80	4-188	82	4-232	0.362
Urine volume in first 24 hours	1,040	220-4,100	1,550	75-5,495	0.019

characteristics were summarized using descriptive statistics. Quantitative data were tested for normality with the Kolmogorov-Smirnov test and analyzed using the Mann-Whitney *U* test. Chi-square tests or Fisher's exact tests were used to compare proportions, where appropriate. The Spearman's correlation was used to identify relationships between MARF and other risk factors. A p-value <0.05 was considered statistically significant. Risk verification was expressed as a crude odds ratio (OR) with 95% confidence interval (CI). Logistic regression analysis was performed to eliminate confounding factors and to ascertain the adjusted OR, along with a 95% CI.

RESULTS

In this study, there were 189 severe falciparum malaria patients, 128 were males (67.7%) and 61 were females (32.3%); there was one death. One hundred twenty-six patients (79 males and 47 females) were diagnosed with severe malaria without ARF and 63 patients (49 males and 14 females) were diagnosed with MARF. Of the 63 patients with MARF, 46 (73%) underwent hemodialysis and 17 (27%) were treated without hemodialysis. In terms of demographics and baseline data, no differences were found between the groups with and without MARF in terms of patient age, height, pulse rate, blood pressure or FCT. However, there was a significant difference between the two groups in weight, duration of fever prior to admission, temperature, respiratory rate, urine output on the day of admission and PCT (p<0.05) (Table 1). No differences were found in glucose, total protein, alkaline phosphate, calcium, phosphate, or magnesium levels between those with

Table 2
Hematological and biochemistry data of patients on admission.

Baseline hematological and biochemistry data	Severe malaria without acute renal failure (n = 126)		Severe Malaria with acute renal failure (n = 63)		p-value
	Median	Range	Median	Range	
White blood cell (x10^9/l)	5.8	1.6 - 18.2	9.3	1.6 - 26.7	<0.001
Hemoglobin (g/dl)	12.3	5.2 - 17.3	10.9	5.4 - 18.4	<0.004
Glucose (mg/dl)	127	60 - 339	116	26 - 357	0.077
BUN (mg/dl)	23.1	6.0 - 78.0	89.0	17.0 - 161.7	<0.001
Creatinine (mg/dl)	1.0	0.4 - 2.6	3.7	0.9 - 12.8	<0.001
Direct bilirubin (mg/dl)	1.6	0.2 - 16.3	6.8	0.9 - 37.1	<0.001
Total bilirubin (mg/dl)	4.1	0.8 - 21.6	13.6	1.7 - 54.4	<0.001
Total protein (g/dl)	6.2	4.5 - 7.8	6.3	4.5 - 7.5	0.425
Albumin (g/dl)	3.4	1.7 - 4.8	2.7	1.5 - 3.9	<0.001
Globulin (g/dl)	3.0	1.9 - 4.1	3.1	2.2 - 26	0.022
Alkaline phosphatase (U/l)	116	6 - 328	130	28 - 468	0.055
AST (U/l)	58	11 - 372	131	39 - 1,758	<0.001
ALT (U/l)	49	4 - 267	67	16 - 475	0.004
Sodium (mmol/l)	133	120 - 145	130	121 - 152	0.009
Potassium (mmol/l)	3.7	2.7 - 7.4	3.9	2.9 - 5.7	<0.001
Chloride (mmol/l)	99	86 - 111	97	81 - 113	0.013
Bicarbonate (mmol/l)	21	14 - 31	18	6 - 44	<0.001

and without MARF. However, significant differences were found between the two groups for BUN, creatinine, direct and total bilirubin, albumin, globulin, transaminases, sodium, potassium, chloride, and bicarbonate (p<0.05) (Table 2).

Impaired consciousness, jaundice, metabolic acidosis, spontaneous bleeding, hypoglycemia, hyperparasitemia (≥5% parasite red blood cells infected) and prostration, were significantly more frequent among patients with MARF than without MARF (p<0.05). Impaired consciousness, jaundice, metabolic acidosis, spontaneous bleeding, hypoglycemia, hyperparasitemia and prostration were found in 38.1, 82.5, 33.3, 7.9, 7.9, 42.9, and 20.6% of MARF patients, respectively. Patients with MARF were more frequently overweight, as determined by body mass index (BMI), than patients without MARF (15.3% *vs* 5.7%, p<0.05). Correlation analysis showed MARF correlated negatively with a hemoglobin level >10 mg/dl (p=0.002), living in a malaria endemic area prior to malaria infection (p=0.002), non-oliguria on the day of admission (p=0.019) and splenomegaly (p=0.028).

Associated factors based on demographics and baseline clinical and laboratory variables recorded on admission are shown in Table 3. The crude OR (95% CI) showed that patients with a white blood cell count >10x10^9/l, jaundice or impaired

Table 3
Variables showing a significant odds ratio (risk indicators).

Variables	OR (95%CI)
WBC count >10x10^9/l	9.28 (4.11-20.97)
Jaundice	5.47 (2.55-11.77)
Impaired consciousness	5.38 (2.17-13.35)
AST >120 U/l	4.80 (2.49-9.28)
Hyperbilirubinemia > 3 mg/dl	4.41 (1.76-11.10)
Epigastric pain	3.63 (1.84-7.17)
ALT >120 U/l	3.47 (1.57-7.68)
Albumin ≤3 g/dl	3.39 (1.81-6.37)
Fever clearance time >72 hours	3.32 (1.58-6.97)
Oliguria during the first 24 hours of hospitalization	3.21 (1.16-8.88)
Patients from non-endemic area	3.20 (1.47-6.98)
Parasite clearance time >72 hours	2.98 (1.53-5.84)
Body mass index >18.5 kg/m^2	2.72 (1.13-6.60)
Liver enlargement	2.13 (1.14-4.00)
Duration of fever >4 days prior admission	2.09 (1.13-3.87)
Pallor	2.09 (1.07-4.09)
Male gender	2.08 (1.04-4.17)

consciousness had the greatest association with MARF. Four variables: hemoglobin >10 g/dl, living in endemic area prior this malaria infection, urine output on the day of admission >400 ml (non-oliguria), and splenomegaly were negatively associated with MARF. Logistic regression analysis was conducted to eliminate confounding factors that might affect the study results; it showed there were 2 true risk factors: oliguria on the day of admission (OR 6.69; 95% CI 5.10 - 8.29), and being from a non-malaria endemic area (OR 6.04; 95% CI 4.77 - 7.32).

DISCUSSION

Renal complications are common among adult falciparum malaria patients living in areas with unstable malaria transmission. Some oliguric ARF patients have dysfunction of other major organs on admission and in some patients ARF symptoms only become clear when patients recover from an acute phase of another severe disease. The former presentation is often associated with hepatic dysfunction and metabolic acidosis, which often results in fatal pulmonary edema. The subacute presentation of MARF carries a better prognosis (White, 2009).

There were many factors associated with MARF in this study on univariate analysis. There were more male patients than females in this study, similar to other studies (Manan *et al*, 2006). Men may more likely be exposed to malaria infection because of working outdoors in endemic areas. A long duration of fever (>4 days) prior to admission was associated with MARF. This may indicate delayed diagnosis and treatment. In patients with

prior oral antimalarial drug treatment prolonged fever may be due to poor drug compliance, inappropriate treatment or drug resistance. FCT after artemisinin-based combination therapy (ACT) in uncomplicated malaria is usually <3 days in artemissinin sensitive areas. Patients who live in non-malaria endemic areas may be more prone to develop severe malaria than patients who live in endemic areas. Being overweight was associated with MARF. An earlier study showed overweight patients are more likely to develop severe malaria infections than normal weight patients (Tangpukdee *et al*, 2007). One study found15 times as many parasitized red blood cells sequestered in blood vessels of subcutaneous fatty tissue in severe malaria patients than in patients with uncomplicated malaria (Wilairatna *et al*, 2000). In MARF, patients may be oliguric or non-oliguric. The causes of oliguria may include hypovolemia and renal failure. The majority of MARF patients in this study had oliguria on day of admission to the hospital, even after rehydration.

Epigastric pain was associated with MARF. Acute malaria gastritis and distension of Glisson's capsule due to hepatomegaly can contribute to abdominal pain (Wilairatana *et al*, 1992). Liver enlargement was associated with MARF in this study. During malaria infection, Kupffer cell hypertrophy and hyperplasia contribute to enlargement of the liver (de Brito *et al*, 1969). There are no previous reports of a direct effect of hepatomegaly on MARF. Cerebral malaria has frequently been reported as factors associated with MARF in children and adults (Habte, 1990; Ehrich and Eke, 2007). Children with cerebral malaria have more severe course of renal failure than children with mild malaria (Ehrich and Eke, 2007).

A bilirubin >3 mg/dl was found to be associated with MARF in our study. Jaundice has also been found to be associated with severe malaria complications in other studies (Wilairatana *et al*, 1994; WHO, 2010); this can alert clinicians to look for other complications. Jaundice in severe malaria may be due to hemolysis or liver impairment (Wilairatana *et al*, 1994). Our study found increased levels of both aspartate and alanine aminotransaminases (AST and ALT) in severe malaria patients. A total bilirubin level >3 mg/dl and a three-fold increase in aminotransaminases (>120 U/l) were more frequently found in MARF patients than in patients without MARF.

Low albumin levels were found to be associated with of MARF. Low albumin levels may decrease intravascular fluid volume and diminish renal blood flow contributing to renal ischemia. Albumin administration was found to be associated with lower mortality rates in patients with severe malaria (Woodrow and Planche, 2007). Pallor was associated with MARF, hemoglobin levels were also significantly different in patients with and without MARF.

Leukocytosis was found in patients with and without MARF, but a white blood cell count $>10x10^9$/l was associated with MARF. This could be due to MARF patients having more severe disease and a greater inflammatory cell response than non-MARF patients. A FCT >72 hours and a PCT >72 hours were associated with MARF, possibly due to a delayed response to antimalarial treatment or severity of disease.

Four factors in this study were negatively associated with MARF: a hemoglobin level >10 g/dl, having living in a malaria endemic area, no oliguria on the day of admission and having splenomegaly. If malaria patients have higher

hemoglobin levels, well-developed malaria immunity due to regular exposure from living in an endemic area, or have no severe renal dysfunction, it is reasonable to expect a negative association with MARF. Repeated malaria infections may cause splenomegaly; therefore, splenomegaly may be correlated with patient immunity to malaria. Subsequent malaria infections may be less severe or patients may have a lower risk of MARF than patients with no previous malaria immunity.

In this study confounding factors were eliminated by multivariate logistic analysis. Only two factors were found associated with MARF after multivariate logistic analysis: oliguria on the day of admission and living in a non-malaria endemic area prior to malaria infection. Poor urine output may indicate dehydration, poor circulation or renal dysfunction. Oliguric MARF patients have an eightfold greater risk of requiring hemodialysis than non-oliguric patients (Wilairatana *et al*, 1999). A history of travel to a malaria endemic area is an important clue to suspect malaria in febrile patients with ARF. Patients without previous malaria immunity returning from malaria endemic areas are more vulnerable to developing MARF (Barsoum, 2000).

In conclusion, oliguria and living in a non-malaria endemic area were associated with MARF in this study. Early identification of oliguria and correct management, including rehydration and dialysis, may reduce morbidity and mortality in severe malaria patients.

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