FACTORS ASSOCIATED WITH ACUTE RENAL FAILURE IN ADULTS WITH SEVERE FALCIPARUM MALARIA

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Abstract. We conducted a retrospective study of patients with severe falciparum malaria to determine factors associated with malarial acute renal failure (MARF). We reviewed 262 medical records of adults hospitalized with severe falciparum malaria in Thailand from 2004 to 2008. The incidence of MARF in our study population was 44% (115/262); 75% (86/115) of these had MARF on admission and 25% (29/115) developed MARF during hospitalization. The majority of MARF patients presented in a hypercatabolic state (62%, 68/109) and were non-oliguric (48%, 55/115) or oliguric (44%, 51/115). Forty-six percent of MARF patients (53/115) required renal replacement therapy for a median duration of 4.5 days. Patients with MARF had significantly higher complication rates (p<0.001), longer duration of hospitalization (p<0.001) and a higher case fatality rate (p=0.001). Using stepwise multiple logistic regression analysis by backward selection method, factors associated with MARF were advanced age [odds ratios (OR); 95% confidence intervals (CI) 1.037 (1.011-1.063), p=0.005], being referred from another hospital [2.876 (1.447-5.714), p=0.003], an elevated total bilirubin level [(1.168 (1.101-1.241), p<0.001], requiring inotropic drugs [4.879 (2.255-10.557), p<0.001] and developing a hospital acquired infection [3.425; 1.406-8.343, p=0.007]. Clinicians should be aware of these factors associated with MARF.

Keywords: acute renal failure, severe malaria, falciparum malaria, associated factors

INTRODUCTION

Malaria is a life-threatening parasitic disease found in many tropical countries. *Plasmodium falciparum* is the most common cause of severe malaria and responsible for high morbidity and mortality throughout the world (White and Bremen, 2008). Malarial acute renal failure (MARF) is one of the most serious complications in severe malaria patients with a mortality rate >70% in untreated patients (Robinson *et al*, 2006; Dondorp and Day, 2007). Appropriate anti-malarial drugs and renal replacement therapy (RRT) can improve chances of survival and recovery of renal function in MARF patients (Dondrop and Day, 2007).

The incidence of MARF varies widely,

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from 0.6% to 60% worldwide and ranges from 13% to 18% in Southeast Asia due to differences in study populations and definitions of acute renal failure (Mehta *et al*, 2001; Abdul Manan *et al*, 2006). In Thailand, a previous study showed the incidence of MARF among children was only 4.8% (Niphakasem *et al*, 2006). The incidence of MARF among adults in South and Southeast Asia has been reported to range from 13% to 30% (Bouth and Giboda, 1987; Barsoum, 2000; Mehta *et al*, 2001). Immune status and availability of appropriate anti-malarial drugs are associated with the incidence of MARF (Barsoum, 2000; Day *et al*, 2000). There have only been a few studies of the incidence of MARF and their associated factors among adult patients with severe falciparum malaria. In this study, we assessed the incidence and associated factors for MARF among adult patients hospitalized with severe falciparum malaria in order to obtain information that might decrease case fatality rates and improve quality of care.

MATERIALS AND METHODS

Study site and population

This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. A retrospective study was conducted by reviewing medical records of hospitalized patients with severe falciparum malaria during 2004-2008, at Mae Sot General Hospital, Tak Province, Thailand. Inclusion criteria were: 1) adult patients (aged ≥15 years); 2) patients with a confirmed diagnosis of falciparum malaria by either peripheral blood smear microscopy or a positive rapid diagnostic test for malaria antigen; and 3) patients with severe falciparum malaria determined by WHO 2006 criteria (WHO, 2006). In our study, the WHO (2006) criteria for severe malaria were used with slightly modifications due to availability of data. These were: 1) impaired consciousness by a Glasgow coma scale (GCS) score ≤10; 2) a convulsion ≥ 2 times within 24 hours; 3) shock defined as a systolic blood pressure ≤80 mmHg or requiring inotropic drugs; 4) pulmonary edema or acute respiratory distress syndrome (ARDS) assessed clinically and having an abnormal chest roentgenorgraphy consistent with these syndromes; 5) hyperbilirubinemia defined as a total bilirubin ≥3 mg/dl; 6) hypoglycemia defined as a blood sugar <40 mg/dl; 7) severe anemia defined as a hematocrit (Hct) level <15% or a hemoglobin (Hb) level <5 g/dl; 8) spontaneous bleeding; 9) evidence of disseminated intravascular coagulation (DIC); 10) severe metabolic acidosis defined as an arterial blood pH <7.35 or a bicarbonate level <15 mmol/l; and 11) hemoglobinuria defined as dark colored urine or heme positive with <2 red blood cells (RBC) per high power field (HPF) in the urine; and 12) prostration. MARF was defined as malaria patients with a serum creatinine (Cr) ≥3 mg/dl while having euvolemic status during hospitalization. Exclusion criteria were: 1) patients with a history of pre-existing renal disease; or 2) patients with mixed infections. Demographic data, clinical and laboratory findings were collected from the medical records and entered into case record forms.

Sample size calculation

The incidence of MARF among adults has been reported to be 13% to 30% for South and Southeast Asia (Bouth and Giboda, 1987; Barsoum, 2000; Mehta *et al*, 2001). According to the hospital registry of Mae Sot General Hospital, 25% of adult patients with severe malaria had MARF; therefore, we estimated the incidence of

MARF in this study to be 25% with a 95% confidence interval (CI) and the precision to be within 5% of the true value. A required sample size of at least 289 medical records of hospitalized patients with severe falciparum malaria was needed for our study.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using the statistical package SPSS for Windows version 18.0 (SPSS, Chicago, IL). Categorical variables were summarized as frequencies and percentages and then analyzed by the chi-square test or the Fisher's exact test where appropriate. Numerical variables were tested for normality using the Kolmogorov-Smirnov test. Variables with non-normal distribution were summarized as median and inter-quartile range (IQR) and compared by the Mann-Whitney *U* test for two group comparison. Univariate logistic regression analysis was used to determine if the different investigated clinical and laboratory parameters were associated with the clinical outcome. Any parameter with a $p \leq 0.2$ on univariate logistic regression analysis was considered statistically significant. These parameters were then included in the stepwise multiple logistic regression analysis using a backward selection method for determining independent associated factors for clinical outcomes. All tests for significance were 2- sided, with a $p<0.05$ indicating statistical significance.

RESULTS

A total of 435 medical records of severe falciparum malaria patients admitted to Mae Sot General Hospital, Tak Province, Thailand during 2004-2008 was reviewed. Sixty-two medical records did not have sufficient data and 111 patients did not fulfill study criteria; 262 patients were eligible for the study.

Demographic, baseline characteristics and laboratory findings

The majority of patients were males (190/262, 72.5%) and 98 patients (37.4%) were cases referred from elsewhere. The median age (IQR) of the patients was 31.0 (22.0-40.0) years with fever duration prior to admission of 3.0 (3.0-5.0) days. The common presenting symptoms were fever (245/247, 99.2%), chills (102/109, 93.6%), convulsions (37/262, 14.1%) and coma (20/262, 7.6%). Physical examination showed the median temperature (IQR) was 38.7 (37.7-39.5)°C, the pulse was 110 (98-120) beats/min and mean arterial pressure (MAP) was 77 (70-90) mmHg. Other presenting signs were impaired consciousness (79/245, 32.2%), hepatomegaly (47/235, 20.0%) and splenomegaly (8/234, 3.4%).

Baseline hematological findings showed the median Hb (IQR) was 10.6 (8.3-12.9) g/dl, hematocrit (Hct) 31.9 (24.7-38.3) %, and platelet count was 32.0 (17.0-64.0) $x10^3/\mu l$. These values were lower than reference ranges, but the white blood cell (WBC) count [median (IQR), 8.3 (5.4-12.3) $x10^3/\mu l$] was within the reference range. The elevated baseline biochemical findings were: median blood urea nitrogen (BUN) (IQR) was 44.0 (22.0-72.8) mg/dl, serum Cr 1.8 (1.2-4.1) mg/dl, total bilirubin 5.0 (2.2-11.1) mg/dl, direct bilirubin 1.5 (0.7-3.8) mg/dl and aspartate transaminase (AST) 124.0 (58.8-232.3) U/l. The median serum bicarbonate (IQR) [16.7 (12.9-19.4) mmol/l] and albumin [2.8 (2.4-3.3) g/dl] levels were lower than the reference ranges. The other biochemical findings were within the reference ranges. Urinalysis showed a median specific gravity (IQR) of 1.020 (1.015-1.025). He-

maturia (RBC ≥3 cells/HPF in urine) and leukocyturia (WBC ≥10 cells/HPF in urine) were observed in 49.4% (79/160) and 8.8% (14/160) of the patients, respectively.

Folowing the WHO 2006 criteria for severe malaria, prostration was observed in 69.8% (178/255), hyperbilirubinemia in 62.1% (139/224), MARF in 43.9% (115/262), impaired consciousness in 43.3% (110/254), severe metabolic acidosis in 43.1% (109/253), shock in 33.3% (86/258), convulsions in 11.6% (30/258), spontaneous bleeding in 9.6% (7/73), pulmonary edema or ARDS in 9.1% (23/252), hypoglycemia in 6.9% (13/187) and severe anemia in 6.2% (16/258).

Of the 262 patients with severe falciparum malaria who had complications, 95 (36.3%) required mechanical ventilation and 74 (28.2%) required inotropic drugs. Hospital acquired infections were observed in 14.5% (38/262) of patients, including pneumonia (17, 44.7%), urinary tract infection (9, 23.7%) and others (12, 31.6%). The median duration of hospitalization (IQR) was 6.0 (4.0-10.0) days; 56 (21.4%) patients died.

Factors associated with MARF

Of the 115 patients with MARF, 86 (74.8%) had MARF on admission and 29 (25.2%) developed MARF during hospitalization. Among the MARF patients, non-oliguric renal failure occurred in 55 patients (47.8%), oliguric renal failure occurred in 51 patients (44.3%), anuric renal failure occurred in 3 patients (2.6%) and the data was incomplete in 6 patients (5.2%). A hypercatabolic state was observed in 62.4% of patients (68/109). Of the 115 patients with MARF, 53 (46.1%) underwent RRT: 22 patients (41.5%) had acute peritoneal dialysis (APD), 21 patients (39.6%) had intermittent hemodialysis (IHD) and 10 patients (18.9%) had combined APD and IHD. The median duration of RRT (IQR) was 4.5 (2.0-10.0) days.

The majority of baseline characteristics and laboratory parameters were similar between patients with MARF and those without MARF (Tables 1, 2) except age (p=0.005), WBC (p=0.001), BUN (p<0.001), Cr (p<0.001), serum potassium (p<0.001), total bilirubin (p<0.001), direct bilirubin (p<0.001), AST (p<0.001), ALT (p=0.015), alkaline phosphatase (p=0.016) which were significantly higher among MARF patients and temperature (p=0.001), Hb level (p=0.038), Hct level (p=0.014), platelet count (p=0.004), serum bicarbonate (p<0.001) and albumin (p<0.001) which were significantly lower among MARF patients. The percent of referrals (p=0.002) was more common among MARF patients than those without MARF.

Complications included prostration (p=0.006), hyperbilirubinemia (p<0.001), shock (p=0.001), pulmonary edema or ARDS (p<0.001), severe metabolic acidosis (p<0.001), required mechanical ventilator (p<0.001), required inotropic drugs (p<0.001), and hospital acquired infections (p=0.001) were more common among MARF patients. The median duration of hospitalization was significantly longer among MARF patients (p<0.001). The requirement for RRT (p<0.001) and expired cases (p=0.001) were more common among MARF patients (Table 1).

Factors associated with MARF on univaritate analysis $p \leq 0.2$ were age (p=0.054), being referred from another hospital (p=0.002), temperature (p=0.001), Hb level (p=0.132), WBC count (p=0.002), total bilirubin (p<0.001), requiring inotropic drugs (p<0.001), requiring a mechanical ventilator (p<0.001) and hospital acquired infection (p<0.001). On stepwise multiple logistic regression analysis using backward

Table 1
Baseline characteristics, complications and outcomes among patients with malarial acute renal failure and malaria without acute renal failure

Variables	Malarial acute renal failure			Without-malarial acute renal failure			*p*-value[d]
	n	No. (%)	Median (IQR[a])	*n*	No. (%)	Median (IQR[a])	
Baseline characteristics							
Referred cases	115	56 (48.7)		143	42 (29.4)		0.002
Age (years)	115		33.0 (27.0-42.0)	143		27.0 (20.0-39.0)	0.005[e]
Gender: male	115	91 (79.1)		143	99 (69.2)		0.099
Fever prior to admission (days)	114		3.5 (3.0-5.0)	143		3.0 (2.0-5.0)	0.147[e]
Physical examinations							
Temperature (°C)	115		38.2 (37.4-39.2)	141		38.9 (38.0-39.8)	0.001[e]
Pulse rate (/min)	115		110 (96-124)	141		110 (98-120)	0.763[e]
Mean arterial pressure (mmHg)	111		77 (70-90)	138		77 (70-90)	0.760[e]
Hepatomegaly	103	27 (25.7)		127	19 (15.0)		0.060
WHO 2006 criteria for severe malaria							
Prostration	115	90 (78.3)		143	88 (61.5)		0.006
GCS[b] ≤10	112	54 (48.2)		142	56 (39.4)		0.203
Convulsion	115	13 (11.3)		143	17 (11.9)		1.000
Severe anemia	115	5 (4.3)		143	11 (7.7)		0.397
Spontaneous bleeding	40	5 (12.5)		33	2 (6.1)		0.446
Hyperbilirubinemia	104	78 (75.0)		120	61 (50.8)		<0.001
Shock	115	51 (44.3)		143	35 (24.5)		0.001
Pulmonary edema/ARDS[c]	112	19 (17.0)		140	4 (2.9)		<0.001
Severe metabolic acidosis	115	77 (67.0)		138	32 (23.2)		<0.001
Hypoglycemia	90	8 (8.9)		97	5 (5.2)		0.474
Complications							
Mechanical ventilator	115	57 (49.6)		143	37 (25.9)		<0.001
Inotropic drugs	115	50 (43.5)		143	23 (16.1)		<0.001
Hospital acquired infection	115	26 (22.6)		143	11 (7.7)		0.001
Outcomes							
Renal replacement therapy	115	53 (46.1)		142	1 (0.7)		<0.001
Hospitalization (days)	115		10.0 (5.0-15.0)	143		5.0 (4.0-7.0)	<0.001[e]
Death	115	36 (31.3)		143	19 (13.3)		0.001

[a] IQR, Interquartile range. [b] GCS, Glasgow coma scale. [c] ARDS, Acute respiratory distress syndrome.
[d] *p*-values were calculated using the chi-square test or Fisher's exact test where appropriate.
[e] *p*-values were calculated using the Mann-Whitney *U* test.

Table 2
Laboratory data on admission among malarial acute renal failure and without-malarial acute renal failure patients.

Laboratory findings	Malarial acute renal failure			Without-malarial acute renal failure			*p*-value[c]
	n	Median (IQR[a])	No. (%)	*n*	Median (IQR[a])	No. (%)	
Hematology							
Hemoglobin (g/dl)	113	9.7 (8.0-12.4)		142	11.4 (8.8-13.2)		0.038
Hematocrit (%)	115	28.3 (23.5-36.1)		143	33.2 (26.9-39.0)		0.014
White blood cell (x10^3/µl)	115	10.2 (6.7-13.7)		143	7.5 (5.0-10.1)		0.001
Platelet count (x10^3/µl)	114	26.0 (15.8-43.0)		143	35.0 (18.0-88.0)		0.004
Biochemistry							
Blood sugar (mg/dl)	61	117.0 (98.0-158.0)		70	126.0 (101.3-142.0)		0.837
Blood urea nitrogen (mg/dl)	113	74.0 (57.5-112.0)		136	24.0 (16.3-39.8)		<0.001
Creatinine (mg/dl)	114	4.3 (3.0-6.5)		137	1.3 (1.0-1.6)		<0.001
Sodium (mmol/l)	110	133.9 (129.7-137.4)		132	134.7 (131.6-137.3)		0.098
Potassium (mmol/l)	110	4.0 (3.6-4.6)		132	3.7 (3.3-4.1)		<0.001
Bicarbonate (mmol/l)	109	14.4 (11.1-17.2)		132	18.9 (15.8-21.4)		<0.001
Total bilirubin (mg/dl)	100	7.4 (2.8-14.6)		122	3.2 (1.7-7.0)		<0.001
Direct bilirubin (mg/dl)	100	2.7 (0.9-5.3)		121	1.0 (0.5-2.0)		<0.001
Aspartate aminotransferase (U/l)	100	168.0 (82.5-310.3)		122	99.0 (52.5-210.0)		<0.001
Alanine amintransferase (U/l)	100	71.0 (42.0-129.0)		123	45.0 (30.0-106.0)		0.015
Alkaline phosphatase (U/l)	100	113.0 (89.0-140.0)		120	96.5 (70.3-134.0)		0.016
Albumin (g/dl)	100	2.6 (2.2-3.0)		120	2.9 (2.7-3.4)		<0.001
Globulin (g/dl)	100	2.9 (2.4-3.3)		120	2.9 (2.5-3.3)		0.608
Urinalysis							
Specific gravity	88	1.020 (1.015-1.025)		89	1.020 (1.015-1.025)		0.509
Red blood cells ≥3/HPF[b]	89		48 (53.9)	92		44 (47.8)	0.501[d]
White blood cells ≥10/HPF[b]	88		11 (12.5)	94		8 (8.5)	0.524[d]

[a]IQR, Interquartile range. [b]HPF, High power field.
[c] *p*-values were calculated using the Mann-Whitney *U* test.
[d] *p*-values were calculated using the chi-square test.

Table 3
Univariate and multivariate analysis of clinical and laboratory parameters during admission.

Variables	Univariate analysis		Multivariate analysis	
	OR[a] (95%CI[b])	*p*-value	OR[a] (95%CI[b])	*p*-value
Age	1.018 (1.000-1.037)	0.054	1.037 (1.011-1.063)	0.005
Referred cases	2.282 (1.366-3.813)	0.002	2.876 (1.447-5.714)	0.003
Temperature	0.702 (0.569-0.867)	0.001		
Hemoglobin	0.939 (0.866-1.019)	0.132		
White blood cell	1.076 (1.028-1.126)	0.002		
Platelet count	0.995 (0.990-0.999)	0.21		
Total bilirubin	1.128 (1.074-1.185)	<0.001	1.168 (1.101-1.241)	<0.001
Aspartate transaminase	1.000 (1.000-1.001)	0.288		
Alanine transaminase	1.000 (0.999-1.001)	0.848		
Required inotropic drugs	4.013 (2.250-7.159)	<0.001	4.879 (2.255-10.557)	<0.001
Required mechanical ventilator	2.815 (1.669-4.751)	<0.001		
Hospital acquired infection	3.506 (1.649-7.455)	<0.001	3.425 (1.406-8.343)	0.007

[a]OR, Odds ratios. [b]CI, Confidence intervals.

selection, factors associated with MARF were advanced age [1.037 (1.011-1.063), p=0.005], being referred [2.876 (1.447-5.714), p=0.003], total bilirubin [1.168 (1.101-1.241), p<0.001]; requiring inotropic drugs [4.879 (2.255-10.557), p<0.001]; and having a hospital acquired infection [3.425 (1.406-8.343), p=0.007] (Table 3).

DISCUSSION

The mortality rate with untreated severe malaria is thought to approach 100% (White, 2003). With anti-malarial drugs, the mortality falls to 16-24% (Stanley, 1997; Robinson *et al*, 2006; Mishra *et al*, 2007; Dondorp *et al*, 2008). Acute renal failure is one of the most serious complications of falciparum malaria and is especially common among adults in Southeast Asian countries (Das, 2008) with a mortality rate of 70% if untreated (Dondorp and Day, 2007). The overall incidence of MARF in Southeast Asia has been reported to be 13% to 18% (Metha *et al*, 2001; Abdul *et al*, 2006). However, the incidence of MARF among severe malaria patients is 30-50%, particularly in regions nonendemic for malaria (Losert *et al*, 2000; Krishnan and Karnad, 2003; Koh *et al*, 2004; Gerritsen *et al*, 2008). In our study, the incidence of MARF among severe malaria patients was 44%, similar to previous reports (Day *et al*, 2000). The majority of MARF patients (75%, 86/115) had it on admission and the rest (25%, 29/115) developed MARF during hospitalization.

In our study, patients with MARF had high complication rates, longer durations of hospitalization and a higher case fatality rate (21.4%). The case fatalities in our study occurred from multi-organ failure, similar to a report from India (Kanodia *et al*, 2010). RRT was performed in 46% of MARF patients; most had a hypercatabolic state and severe metabolic acidosis. The

median duration of RRT was 4.5 days. Both APD and IHD were used in our study patients. APD was performed in 41% of patients undergoing RRT with a frequency of 22 cycles per day; IHD was performed in 40% of patients undergoing RRT at a frequency of 3 sessions per week; and combined APD and IHD was conducted in 19% of patients undergoing RRT. Our patients had a shorter duration of RRT than a previous study from the Hospital of Tropical Diseases in Bangkok, Thailand in which MARF patients received RRT for a median duration of 10 days (Wilairatana *et al*, 1999).

Using stepwise multiple logistic regression analysis with backward selection, advanced age, being referred from another institution, having an elevated total bilirubin level, requiring inotropic drugs and having a hospital acquired infection were independently associated with MARF. The hyperbilirubinemia could be due to intravascular hemolysis, DIC or malarial hepatitis (Anand and Puri, 2005). Hyperbilirubinemia has been associated with MARF, ARDS, septicemia and case fatality (Nacher *et al*, 2001). Patients with severe falciparum malaria usually present with multi-organ involvement (Krishnan and Karnad, 2003). Prompt effective treatment with anti-malarial drugs and antibiotics may reduce case fatality rates (Gomes *et al*, 2009). In our study, 55 patients with shock received inotropic drugs: dopamine (33 patients), adrenaline (5 patients) and combined dopamine with adrenaline (17 patients). A MAP of ≥70 mmHg was maintained using inotropic drugs in order to maintain an adequate glomerular filtration rate (Abuelo, 2007). Dopamine may be used safely in malaria patients, but adrenaline may cause lactic acidosis, which is associated with a decrease in renal blood flow (Dondrop and Day, 2007).

The incidence of MARF was 44% among patients with severe falciparum malaria at our hospital. Advanced age, being referred from another institution, having an elevated bilirubin level, requiring inotropic drugs and having a hospital acquired infection were factors associated with MARF. These findings may help clinicians be aware of the complications associated with MARF and is hoped will reduce case fatalities.

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