RISK FACTORS OF SHOCK IN SEVERE FALCIPARUM MALARIA

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Abstract. The objective of this study was to determine the risk factors for the development of shock in adult patients admitted with severe falciparum malaria. As an unmatched case-control study, the records of patients who were admitted to the Bangkok Hospital for Tropical Diseases, Thailand, between the years 2000-2010, were reviewed. One hundred patients with severe falciparum malaria and shock, and another 100 patients with severe malaria but without shock were studied. Demographics, presenting symptoms, physical observations, and laboratory data of these patients were analyzed. Five risk factors for the development of shock were identified: female gender (OR 6.16; 95% CI 3.17-11.97), red cell distribution width (RDW) >15% (adjusted OR 2.90; 95% CI 1.11-7.57), anorexia (adjusted OR 2.76; 95% CI 1.03-7.39), hypoalbuminemia (adjusted OR 2.19; 95% CI 1.10-4.34), and BUN-creatinine ratio >20 (adjusted OR 2.38; 95% CI 1.22-4.64). Diarrhea was found to be a protective factor (adjusted OR 0.33; 95% CI 0.14-0.78). Metabolic acidosis was only weakly correlated to mean arterial blood pressure on admission (r_s = 0.23). Female gender was the strongest risk factor for the development of shock. We concluded that female gender, RDW >15%, anorexia, hypoalbuminemia, and BUN-creatinine ratio >20 were risk factors of shock development in severe falciparum malaria.

Keywords: malaria, shock, risk factor

INTRODUCTION

Malaria continues to be a major global health problem, with over 40% of the world's population at risk of malaria, and the disease caused an estimated 655,000 deaths in 2010 (WHO, 2012). Even with treatment, severe malaria has a case mortality rate of approximately 10-20% (Bruneel *et al*, 2010). Much research has investigated many of these complications, but one for which there is a relative paucity of research is the development of shock. There are many potential causes of hypotension or shock in severe malaria (WHO, 2000). These include secondary bacterial sepsis, dehydration from vomiting or fever, hemorrhage from gastrointestinal bleeding, splenic rupture, and cardiac dysfunction. The objective of this study was to investigate the risk factors for the development of shock in adult patients admitted with severe *Plasmodium*

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falciparum malaria in a tertiary referral center in Bangkok.

MATERIALS AND METHODS

Study site and recruitment procedure

This study was conducted at the Hospital for Tropical Diseases, Bangkok, Thailand, which is a tertiary referral center for malaria and other tropical diseases. This was an unmatched case-control study. All the records of adult patients admitted to the Bangkok Hospital for Tropical Diseases with a diagnosis of severe *Plasmodium falciparum* malaria were eligible for inclusion in this study. The inclusion criteria were as follows: adults patients aged ≥18 years, microscopically confirmed asexual forms of *P. falciparum* malaria, and having at least one severe manifestation of malaria, that is, impaired consciousness or unrousable coma (Glasgow Coma Score <11), ≥2 convulsions in a 24-hour period, prostration, shock with systolic blood pressure <90 mmHg, abnormal spontaneous bleeding or blood tests suggestive of disseminated intravascular coagulation, respiratory distress as evidenced by respiratory rate ≥32/minute, radiological evidence of pulmonary edema, severe metabolic acidosis (with venous bicarbonate level <15 mEq/l, pH <7.35, or lactate >5 mmol/l), severe anemia (with hemoglobin <5 g/dl or hematocrit <15%), visible hemoglobinuria, hyperparasitemia (with *P. falciparum* parasite density of >250,000 /μl or >5%), acute renal failure (with creatinine >3 mg/dl or urine output <400 ml/day), hyperbilirubinemia (with total bilirubin >3 mg/dl), plasma glucose level <40 mg/dl.

Patients with a documented systolic blood pressure <90 mmHg at any point during their admission were included as cases, and those without this criteria were included as controls. Exclusion criteria were having mixed malaria infection, co-infection at the time of admission (for example, dengue virus, leptospirosis, or scrub typhus), medical records missing or unavailable (records with partially missing data were not excluded), pregnancy, significant other prior medical co-morbidity (for example, liver cirrhosis, chronic kidney disease, or heart disease).

Ethical considerations

The Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, approved this study (MUTM 2010-47-01; 2010 Nov 2).

Sample size calculation

Previous severe malaria studies, characterizing risk factors, have mostly focused on predicting morbidity. There have been no studies of which we are aware that specifically investigated risk factors for the complication of shock. Consequently, it was difficult to anticipate the magnitudes of the effects for different risk factors and the proportion of controls with possible exposures. Assuming that the proportion of the control group with an exposure was somewhere between 0.15-0.45 (15-45%), we used a cases-to-control ratio of up to 1:4, an alpha value of 0.05, and a power of 0.80. We would find significant correlations with an odds ratio of ≥3.0, and therefore a sample size of at least 40 cases and at least 160 controls, using the Kelsey method for sample size calculation. After starting the study, it became apparent that cases were more frequent than we had anticipated, and we were subsequently able to improve the cases to control ratio to 1:1, with an improved ability to detect significant correlations with odds ratio of ≥2.5.

Statistical analysis

Clinical data including demograph-

ics, presenting symptoms, complications, and laboratory results were described using descriptive statistics. For continuous data, the central tendency was reported as either means with standard deviations (normally distributed data) or medians with interquartile ranges (IQR, non-normally distributed data). Percentages were reported for categorical variables. The distribution of continuous variables was assessed for normality with the Kolmogorov–Smirnov test.

Associations between categorical variables were assessed using a two-sided Pearson's chi-square test with Yates' correction for continuity, or Fisher's exact test, as appropriate. Student's *t*-test and Mann-Whitney *U* test were used to assess differences between normally and non-normally distributed continuous variables, respectively. Data with repeated observations were assessed with paired *t*-test or Wilcoxon signed- rank test.

Crude and adjusted odds ratios (Mantel-Haenszel test) for the predictors of shock were calculated for categorical and dichotomized continuous variables. Statistical significance was accepted as a two-tailed 95% confidence level, with a *p*-value of <0.05.

RESULTS

Demographic data

The demographic results are presented in Table 1. The median age was 25 years (IQR 21-32 years), and this was almost identical between groups. Female gender was a significant risk factor for shock, with 77% of all females developing shock versus 35% of males ($p < 0.01$). Gender proportions in different blood pressure subgroups are shown in Table 2.

The largest ethnic group represented was Mon (29.1%), followed by unspecified Burmese (24.1%), Thai (23.6%), Karen (22.1%), and Laotian (1%), and there was no association between ethnicity and shock outcome. A history of malaria infection in the previous year was documented in 31 patients (15.5%), but there was no association with (or protection from) shock outcome. The median days of fever prior to admission was 4 days (IQR 3.0-7.0) and was similar between the shock group and the control group (5 versus 4 days, $p = 0.05$).

There were significantly more reports of dizziness and anorexia in the shock group ($p < 0.05$). Diarrhea was less common in the shock group compared to the control group ($p = 0.02$). There were no differences between the groups with any of the other symptoms recorded (fever >38ºC, weakness, chill/rigors, headache, myalgia, abdominal pain, and nausea). There were significantly higher respiratory rates, but there were significantly lower systolic, diastolic, and mean arterial blood pressure; height; weight; and body mass index (BMI) ($p < 0.05$) (Table 1). There was no difference in urine output on the first day of admission between groups. There were significantly lower findings of hemoglobin, hematocrit, red cell count (RBC), total protein, albumin, venous bicarbonate, and BUN-creatinine ratio in the shock group ($p < 0.01$). Red cell distribution width (RDW) >15% was significantly higher in the shock group ($p < 0.01$).

Of the 200 patients in the study, 81 had at least one set of blood cultures taken, of which there were only two positive results. The first grew *Streptococcus pneumoniae* in a patient with a right lower lobe consolidation on x-ray. The second grew a coagulase-negative *Staphylococcus* in one blood culture bottle only; positive only after three days of culture, and so likely a contaminant.

Table 1
Demographic data of severe malaria patients (*N*=200).

Parameters	With shock (*n*=100)	Without shock (*n*= 100)	*p*-value
Male/Female	46/54	84/16	[a]<0.01
Age (years)	25.0 (19.5-30.5)	25.0 (18.5-31.5)	0.90
Temperature (°C)	38.5 (37.8-39.0)	38.6 (37.9-39.4)	0.18
Pulse rate (min^{-1})	102 (90-117)	100 (90-112)	0.53
Respiratory rate (min^{-1})	28 (24-32)	24 (22-28)	[a]<0.01
Blood pressure (mmHg)			
Systolic	80 (79-90)	106 (97-110)	[a]<0.01
Diastolic	50 (49-55)	60 (58-70)	[a]<0.01
MAP	60 (57-65)	77 (70-83)	[a]<0.01
Height (cm)	160 (155-163)	162 (159-169)	[a]<0.01
Weight (kg)	50 (45-55)	54.0 (50-60)	[a]<0.01
BMI (kg/m^2)	19.7 (18.4-21.4)	20.3 (19.0-22.6)	[a]0.01
Urine output (ml)	1,200 (800-1,702)	1,050 (669-1,500)	0.28
% Parasitemia on admission	4.1 (1.1-11.8)	4.1 (1.5-8.7)	0.97
Parasite density (/ml)	136,242 (57,915-509,525)	161,508 (73,950-452,700)	0.52
Parasite clearance time (hrs)	57 ± 27	55 ± 20	0.85
Fever clearance time (hrs)	79 ± 52	72 ± 46	0.36
Hemoglobin (g/dl)	11.1 (9.3-12.4)	12.0 (9.9-14.4)	[a]<0.01
Hct (%)	33.0 (27.6-36.5)	35.0 (29.0-42.6)	[a]<0.01
RBC ($x10^{12}$/l)	4.11 (3.65-4.58)	4.60 (3.73-5.29)	[a]<0.01
RDW (%)	15.2 (14.3-15.8)	14.1 (13.6-15.0)	[a]<0.01
WBC ($x10^9$/l)	6.6 (4.4-9.4)	6.6 (4.7-8.9)	0.74
Platelet count ($x10^9$/l)	31 (20-50)	38 (24-52)	0.11
Glucose (mg/dl)	126 (102-157)	119 (98-150)	0.32
Liver function tests			
AST (U/l)	73 (40-155)	67 (41-105)	0.68
ALT (U/l)	47 (27-89)	48 (33-82)	0.42
ALP (U/l)	106 (77-142)	101 (78-152)	0.97
Total bilirubin (mg/dl)	3.8 (2.1-8.2)	4.6 (2.7-6.7)	0.30
Direct bilirubin (mg/dl)	1.6 (0.8-3.7)	1.9 (0.9-3.7)	0.74
Total protein (g/dl)	6.0 (5.6-6.5)	6.5 (5.9-7.0)	[a]<0.01
Albumin (g/dl)	2.8 (2.5-3.4)	3.2 (2.7-3.7)	[a]<0.01
Bicarbonate[b] (mmol/l)	20 (18-22)	21 (19-23)	[a]0.01
BUN (mg/dl)	32 (20-51)	26 (17-39)	0.08
Cr (mg/dl)	1.1 (0.8-1.6)	1.1 (0.9-1.3)	0.62
BUN-Cr ratio	26.5 (20.6-36.5)	22.4 (16.6-26.7)	[a]<0.01

[a]Statistically significance, [b]Venous bicarbonate
MAP, mean arterial blood pressure; BMI, body mass index; Hct, hematocrit; RBC, red blood cell count; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine.

Table 2
Lowest systolic blood pressure during admission by gender.

	Blood pressure subgroup				
	n (%)	≥90 mmHg	80 - 89 mmHg	<70-79 mmHg	<70 mmHg
Male	130 (65%)	84 (84%)	21 (38.2%)	18 (52.9%)	7 (63.6%)
Female	70 (35%)	16 (16%)	34 (61.8%)	16 (47.1%)	4 (36.4%)

Table 3
Severe malaria complications in severe malaria patients (*N*=200).

Symptoms	*n*	With shock (*n*=100)	Without shock (*n*=100)	*p*-value
Cerebral malaria	40	16	24	0.22
Multiple convulsions	5	1	4	0.37
Abnormal bleeding	10	6	4	0.75
Metabolic acidosis	16	9	7	0.79
Severe anemia	0	0	0	1.00
Hyperbilirubinemia	134	60	74	0.05
Hyperparasitemia	110	54	56	0.89
Acute renal failure	30	14	16	0.84
Pulmonary edema/ARDS	15	11	4	0.19
Respiratory distress	66	39	27	0.10
Hypoglycemia	2	0	2	0.50
Macroscopic hematuria	0	0	0	1.00
Prostration	3	1	2	1.00

Complications of severe malaria

The most common complication was hyperbilirubinemia in 134 cases (67%), followed by hyperparasitemia in 110 cases (55%). However, there were no differences found in other complications between the shock group when compared to the control. These results are summarized in Table 3.

Treatments and outcomes

Antibiotics were given in 58% of shock cases and 40% of the control group (p = 0.02). Dopamine was used in 89% of the shock group but also in 10% of the control group. Adrenaline was used as a second vasoactive agent in four shock cases only. Intravenous artesunate was given to all malaria patients. Schedule and dosing of artesunate were similar between groups.

Only six patients out of our sample of 200 died. Two were females and four were males, with ages ranging from 22-58 years. There were four deaths in the shock group and two in the control group, but this was not a statistically significant difference. The most common complication resulting in death was cerebral malaria. When the occurrence of death was analyzed in blood pressure subgroups, there was a trend towards more deaths occurring in the lower blood pressure group (systolic

Table 4
Crude and adjusted odds ratios for dichotomized risk factors for shock.

Risk factor	Crude OR	95% CI	Gender Adjusted OR [b]	95% CI
Female gender	6.16	3.17-11.97[a]	-	-
RDW > 15.0%	3.47	1.48-8.16[a]	2.90	1.11-7.57[a]
Anorexia	2.93	1.20-7.17[a]	2.76	1.03-7.39[a]
Albumin < 3.5 g/dl	2.78	1.48-5.23[a]	2.19	1.10-4.34[a]
BUN-Cr ratio > 20	2.57	1.38-4.76[a]	2.38	1.22-4.64[a]
Diarrhea	0.37	0.17-0.79[a]	0.33	0.14-0.78[a]
Dizziness	2.55	1.24-5.25[a]	2.11	0.96-4.66
RBC < 4.5 x10^{12}/l	2.47	1.38-4.40[a]	1.79	0.95-3.36
Hemoglobin < 12.0 g/dl	1.98	1.12-3.52[a]	1.16	0.61-2.22
Bicarbonate[c] < 23 mmol/l	1.89	0.97-3.69	1.54	0.75-3.15
Respiratory rate ≥ 32/min	1.73	0.95-3.14	1.64	0.87-3.08
BMI < 18.5 kg/m^2	1.62	0.83-3.16	1.47	0.73-3.00

[a]Statistically significance with 95% confidence interval exclusive of 1.
[b]Odds ratio adjusted for gender strata by Mantel-Haenszel method.
[c]Venous bicarbonate.
RDW, red cell distribution width; BUN, blood urea nitrogen; Cr, creatinine; RBC, red blood cell count; BMI, body mass index

blood pressure <70 mmHg) (p <0.01).

Analysis of risk factors for shock

Crude odds ratios were calculated for identified risk factors for shock (Table 4). Continuous variables were dichotomized according to upper or lower limits of the normal reference ranges as appropriate. The largest odds ratio was seen with female gender (OR 6.11; 95% CI 3.17-11.97) followed by RDW >15% (OR 3.47; 95% CI 1.48-8.16). These results are presented in Table 4. Venous bicarbonate, respiratory rate ≥32/min, and BMI <18.5 failed to remain significant once dichotomized.

Several of the identified risk factors have the potential to be influenced by gender so adjusted odds ratios were calculated. BUN-creatinine ratio remained significant, but hemoglobin, red blood cell count, and dizziness failed to remain significant.

DISCUSSION

The most recent version of the WHO malaria treatment guidelines (WHO, 2010) defines circulatory collapse (shock) as a systolic blood pressure of <70 mmHg. The WHO criteria have been used to classify patients into uncomplicated and complicated (severe) malaria, as the latter have worse outcomes. First, this is to guide clinicians in the appropriate management of patients with malaria. Second, this classification attempts to standardize the admission of patients into clinical trials. The criterion of systolic blood pressure of <70 mmHg is intended as a predictor of increased mortality, rather than as a threshold for treatment initiation.

In this study, we defined shock as a systolic blood pressure of <90 mmHg, as this was more in keeping with the standard definition of shock (Munford, 2008)

and critical care guidelines (Bone *et al*, 1992); this was a common threshold for initiation of vasoactive agents if a patient remains unresponsive to fluid resuscitation.

In our study, patients with shock, the vast majority (93%), either had shock on admission, or within the first 24 hours after admission. This was consistent with an earlier study in France (Bruneel *et al*, 2003).

Interestingly, there was a significant association between female gender and the occurrence of shock. From the female group, 54 out of 70 females (77%) developed shock versus only 46 out of 130 men (35%). As can be seen, females made up the majority (61.8%) of the patients in the group with systolic BP in the 80-89 mmHg range, despite representing only 35% of the total sample. Possibly this was because females normally had lower average blood pressures compared to men, and we simply captured more in our shock group by using the cut-off of <90 mmHg (which may not be as overtly abnormal for females). In the normal population, females generally do have a slightly lower blood pressure than males (Reckelhoof, 2001). However, the difference in usual blood pressure between healthy men and women was not typically that pronounced.

In a Thai survey, the average female blood pressure was 112.7/73.1 mmHg versus 115.7/76.2 mmHg for males, representing an average of only 3 systolic points difference (aged 35-44 years) (WHO, 2005). Additionally, the disproportionate representation of females held true even in the 70-79-mmHg systolic blood pressure group, suggesting the observed predisposition to the development of shock was real.

A gender difference in the development of shock in severe malaria has not been previously reported. An earlier study by Bruneel *et al* (1997) reported that 14 severe malaria patients with shock showed no gender imbalance. One possible explanation for this disparity was acquired immunity from previous infections or coinfections.

In our study, no protective effect from a history of malaria in the previous year with regards to shock could be demonstrated. However, previous malaria was much more common in males (21.5%) compared to females (4.3%) (p <0.01). There was no difference in days of fever prior to admission, treatment prior to admission, or treatment upon admission between males and females to explain the disparity.

Patients with shock reported more anorexia on admission, although it was a relatively common finding in both groups (91% versus 78%). Diarrhea was reported in a total of 21.1% of patients, but with a significant difference between groups; 13% in the shock group versus 30% in the control group.

This apparent reduction in the occurrence of shock in those who presented with a history of diarrhea, is a rather counter-intuitive finding. These patients might receive closer observation and more fluid resuscitation because of the presence of this symptom. However, its presence was not associated with shock.

Nausea, vomiting, and epigastric discomfort were frequently reported symptoms in severe malaria and were likely due to gastritis (Wilairatana *et al*, 1992), delayed gastric emptying, or small bowel dysfunction. Diarrhea as a symptom of severe malaria has been less commonly reported in the literature (Wilairatana *et al*, 2008).

An elevated BUN-creatinine ratio >20 is generally associated with pre-renal (hypovolemic) azotemia. We found a greater number of patients in the shock group compared to the control group with this complication, suggesting hypovolemia might be a contributing factor to shock in those patients. We also found a statistically significant change in the specific gravity (a marker of urine concentration) between the admission urine specimen and a subsequent urine specimen. This was seen in the shock group and not the control group, possibly suggesting that dehydration was a contributing factor to the complication of shock.

The change in urine specific gravity in the shock group was very minor (from a median value of 1.015 to 1.010), and the groups had relatively normal specific gravities on admission (median of 1.015 in both groups). This change in specific gravity might be influenced by administration of furosemide or intravenous fluid rehydration prior to admission to the intensive care unit, or a change in the urine concentrating ability of the kidney. Urine output on the first day of admission was not statistically different between groups. Therefore, on balance, dehydration and hypovolemia were not demonstrated to be contributing factors to the development of shock.

Regarding to the large effect of gender on the complication of shock, we adjusted the odds ratios to account for this influence. Several variables including hemoglobin, red blood cell count, and dizziness failed to remain significant.

In our study, hypoalbuminemia was associated with shock. This might be due to an increased inflammatory response and more transcapillary leak in these patients. Hypoalbuminemia in severe malaria has also been shown to be associated with renal failure (Vannaphan *et al*, 2010) and jaundice (Wilairatana *et al*, 1994), and has been suggested to aggravate pulmonary edema and acute respiratory distress syndrome (Lefebvre *et al*, 2007). Patients who turned from initially non-severe malaria to severe malaria also tend to have lower albumin (Tangpukdee *et al*, 2007).

Changes in serum albumin level were also seen in non-falciparum malaria (Tangpukdee *et al*, 2006). Hypoalbuminemia was commonly seen in other causes of critical illness and is linked to the systemic inflammatory response with decreased synthesis, increased catabolism, and redistribution of albumin into the extravascular space (due to increased capillary permeability) (Horowitz and Tai, 2007). The role of hypoalbuminemia as a predictor in severe malaria has not yet been particularly well delineated.

In this study, the red cell distribution width (RDW) of >15% was associated with shock (adjusted OR 2.90; 95% CI 1.11-7.57). RDW is a surrogate marker of increased erythropoiesis and has been shown to increase in response to anemia in malaria (Helleberg *et al*, 2005; Caicedo *et al*, 2009). It is possible that the shock group in our study had more hemolysis, thereby resulting in a greater release of young red blood cells and reticulocytes from bone marrow.

There was a statistically significant difference in hemoglobin between the groups, but this difference was small (median 11.1 versus 12.0 g/dl, $p < 0.01$), and was mostly accounted for by the female predominance in the shock group (gender adjusted OR 1.16; 95% CI 0.61-2.22). Alternatively, the shock group might simply have had a greater erythropoietic response for the same degree of anemia compared to the control group.

There was only a weak association between acidosis and shock in our study. Venous bicarbonate on admission was marginally lower in the shock group compared to the control group. It was possible that our definition of shock as a systolic blood pressure of <90 mmHg resulted in the inclusion of patients with simple hypotension rather than shock with impaired tissue perfusion, thereby weakening this correlation. Whether acidosis is caused directly by (hypovolemic) shock has been debated in earlier studies (Maitland and Newton, 2005; Planche, 2005).

The WHO recommend a low threshold for administering antibiotics in severe malaria, as there is a diagnostic overlap between septicemia and severe malaria, especially in African children (WHO, 2010). Nearly half (49%) of the patients in our study received an antibiotic during their admission. Patients might develop secondary infections while in hospital. These included aspiration or ventilator-acquired pneumonia (especially in the comatose patients), urinary tract infections as a result of catheterization, and infection of vascular devices.

Of 200 patients in our study, 81 (41.5%) had at least one set of blood cultures taken on admission. There was only one positive blood culture, and one contaminant. In total, only 11 patients had a positive culture from any source (six in the shock group, four in the control group). This was a very low rate of proven bacteremia or secondary infection compared to other studies. In our study, 12 of the 81 patients had received antibiotics prior to the blood culture being taken, which might partially explain the low rate of bacteremia. In addition, urine and sputum cultures were infrequently sampled.

There were only six deaths in our study, and it was mostly due to cerebral malaria. Extensive analysis of risk factors for death was limited due to the small sample size. There was a trend towards more deaths occurring in the lower blood pressure group, with four of the six deaths occurring in this group (systolic blood pressure <70 mmHg). This likely reflected peri-terminal physiological collapse, and its prevalence was influenced by how often the blood pressure was recorded moments before death.

In conclusion, shock was one of several complications that can occur in severe *Plasmodium falciparum* malaria, although little is known about the risk factors for the development of shock. We found that five risk factors for the development of shock were identified, including female gender, RDW>15%, anorexia, hypoalbuminemia and BUN-creatinine ratio >20. Female gender was the strongest risk factor for the development of shock in severe *Plasmodium falciparum* malaria.

ACKNOWLEDGEMENTS

This study was undertaken as partial fulfillment of Master of Clinical Tropical Medicine degree program (Brendan J Arnold) and supported by the Office of the Higher Education Commission and Mahidol University under the National Research Universities Initiative; and also the Faculty of Tropical Medicine, Mahidol University in Thailand.

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