

The Relationship between Age and the Manifestations of and Mortality Associated with Severe Malaria

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(See the editorial commentary by Olliario on pages 158–60)

Background. The reported case-fatality rate associated with severe malaria varies widely. Whether age is an independent risk factor is uncertain.

Methods. In a large, multicenter treatment trial conducted in Asia, the presenting manifestations and outcome of severe malaria were analyzed in relation to age.

Results. Among 1050 patients with severe malaria, the mortality increased stepwise, from 6.1% in children (age, <10 years) to 36.5% in patients aged >50 years ($P < .001$). Compared with adults aged 21–50 years, the decreased risk of death among children (adjusted odds ratio, 0.06; 95% confidence interval, 0.01–0.23; $P < .001$) and the increased risk of death among patients aged >50 years (adjusted odds ratio, 1.88; 95% confidence interval, 1.01–3.52; $P = .046$) was independent of the variation in presenting manifestations. The incidence of anemia and convulsions decreased with age, whereas the incidence of hyperparasitemia, jaundice, and renal insufficiency increased with age. Coma and metabolic acidosis did not vary with age and were the strongest predictors of a fatal outcome. The number of severity signs at hospital admission also had a strong prognostic value.

Conclusion. Presenting syndromes in severe malaria depend on age, although the incidence and the strong prognostic significance of coma and acidosis are similar at all ages. Age is an independent risk factor for a fatal outcome of the disease.

Every year, an estimated 1.21 million people die of severe malaria [1]. Once *Plasmodium falciparum* malaria takes a severe course, multiple organs are affected and mortality is high. Severity can be defined according to criteria developed by the World Health Organization (WHO) [2], but presenting symptoms and mortality patterns vary widely according to patient age and malaria transmission intensity. In areas with high, stable

transmission in sub-Saharan Africa, severe anemia in infants with relatively good prognosis is the main presentation, and severe malaria does not occur in adults with acquired immunity. In areas with moderate transmission, cerebral malaria in young children is the most common presentation [3, 4]. In areas with low transmission, such as South and Southeast Asia, severe malaria occurs in all age groups, but young adults are the most affected; cerebral malaria, renal failure, severe jaundice, and pulmonary edema are the main manifestations in this young adult population. Although assumptions about age-specific manifestations and their prognostic impact on patients with severe malaria can be found in many textbooks on malaria, only few detailed data are available to support this phenomenon [5]. We recently performed a large, multicenter, multi-

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national clinical trial including patients with severe *P. falciparum* malaria in South and Southeast Asia. In this trial, we compared intravenous artesunate with quinine for malaria treatment [6]. Further analysis of this large data set has allowed us to report age-specific manifestations of severe malaria and their prognostic significance.

MATERIALS AND METHODS

This multicenter trial was conducted in Bangladesh, Myanmar, India, and Indonesia from June 2003 through May 2005 [6]. A patient was enrolled if the admitting physician suspected severe malaria and the patient had a positive result of a *P. falciparum* histidine-rich protein 2 antigen-based rapid test. Diagnosis of malaria was confirmed subsequently by examination of the patient's peripheral blood film. Patient history and physical examination findings were recorded on a standard form. Blood concentrations of sodium, potassium, chloride, blood urea nitrogen (BUN), glucose, hemoglobin, and acid-base parameters were measured using a hand-held point-of-

care biochemical analyzer (i-Stat analyzer with EC8+ card; Abbott).

Patients were randomized to receive either intravenous artesunate (2.4 mg/kg of body weight at hospital admission and at 12 h and 24 h after hospital admission and, thereafter, once daily) or quinine dihydrochloride (20 mg salt/kg of loading dose, followed by 10 mg/kg 3 times daily). Supportive treatment was given according to WHO guidelines [2], but availability of blood transfusions, renal replacement therapy, and mechanical ventilation was limited.

A total of 1461 patients were included in the original study. Of these patients, 1050 subsequently fulfilled the prospectively defined modified WHO criteria for severe malaria, defined by ≥ 1 of the following syndromes or biochemical abnormalities: cerebral malaria (Glasgow coma score, <11) or repeated convulsions, renal impairment (BUN concentration, >17 mmol/L), severe anemia (hematocrit, $<20\%$), acidosis (bicarbonate concentration, <15 mmol/L; or base excess, <-3.3 mmol/L), hemodynamic shock (systolic blood pressure, <90 mm Hg, with

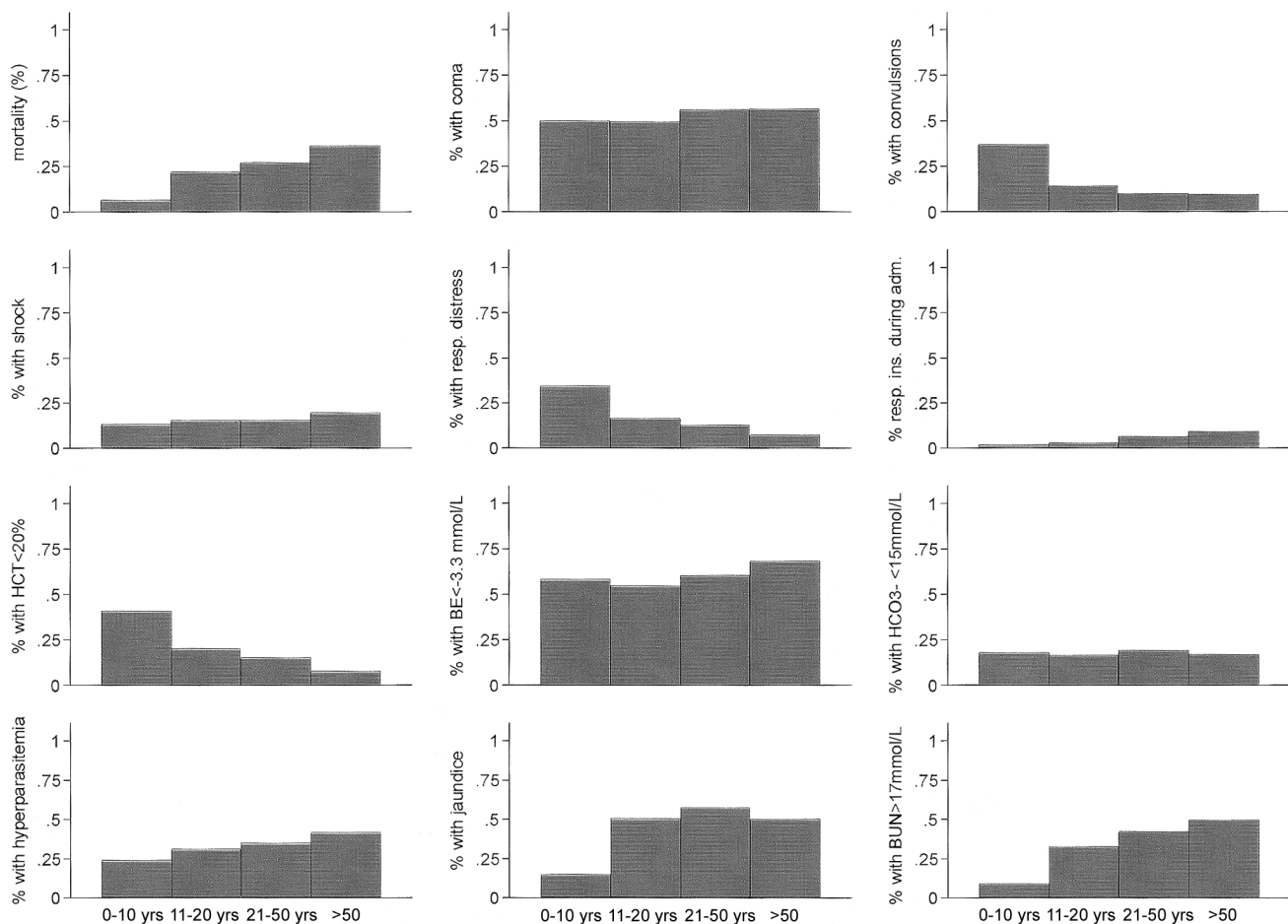


Figure 1. Mortality and presenting severity syndromes among 1050 patients with severe malaria, by age group. Incidence of respiratory (resp.) insufficiency (ins.) during hospital admission (adm.), by age group, is also shown. BE, base excess; BUN, blood urea nitrogen level; HCO_3^- , bicarbonate concentration; HCT, hematocrit; yrs, years.

Table 1. Severity criteria and malaria-associated mortality at presentation.

Variable	No. of severity criteria, proportion (%) of patients				
	1	2	3	4	≥5
Age group, ^a years					
0–10	21/114 (18.4)	37/114 (32.5)	25/114 (21.9)	18/114 (15.8)	13/114 (11.4)
11–20	49/274 (17.9)	83/274 (30.3)	70/274 (25.6)	36/274 (13.1)	36/274 (13.1)
21–50	86/566 (15.2)	145/566 (25.6)	143/566 (25.3)	108/566 (19.1)	84/566 (14.8)
>50	13/96 (13.5)	18/96 (18.8)	31/96 (32.3)	25/96 (26.0)	9/96 (9.4)
All	169/1050 (16.1)	283/1050 (27.0)	269/1050 (25.6)	187/1050 (17.8)	142/1050 (13.5)
Mortality ^b	16/169 (9.5)	34/283 (12.0)	58/269 (21.6)	74/187 (39.6)	71/142 (50.0)

NOTE. From a total of 9 severity criteria (range, 1–7 severity criteria), including cerebral malaria (Glasgow coma score, <11), convulsions, renal impairment (blood urea nitrogen level, >17 mmol/L), severe anemia (hematocrit, <20%), acidosis (bicarbonate concentration, <15 mmol/L; or base excess, <–3.3 mmol/L), hemodynamic shock (systolic blood pressure, <90 mm Hg, in combination with cold extremities), respiratory distress, jaundice, and hyperparasitemia (parasite load, >200,000 parasites/ μ L).

^a $\chi^2 = 19.2$, with 12 df; $P = .08$.

^b By test for trend, $P < .001$.

cold extremities), respiratory distress, and hyperparasitemia (parasite count, >200,000 parasites/ μ L). All of these patients had asexual stages of *P. falciparum* found in their peripheral blood specimens.

Statistical methods. All analyses were stratified by age group, as follows: young children (age, ≤ 10 years), older children (age, 11–20 years), adults (age, 21–50 years), and the elderly population (age, >50 years). Relationships between presenting severity syndromes (as dichotomized variables) and age group were explored using the χ^2 test or Fisher's exact test. For significant associations, a test for trend was applied. The likelihood of a fatal outcome, according to presenting severity syndromes, was examined using Mantel-Haenszel (MH) ORs and a test of homogeneity to assess differences in risk between age groups. The choice of antimalarial treatment (artesunate or quinine) significantly affected mortality (19.8% vs. 28.1%; $P = .002$) [4]; therefore, all multivariate analyses were adjusted for treatment. However, treatment was not associated with any of the presenting severity syndromes and, therefore, was not considered to be a potential confounder in the univariate analysis.

To determine the prognostic significance of age, a logistic regression model was constructed with mortality as a dependent variable and with age group and all presenting syndromes that are listed above, with the addition of clinical, severe jaundice and the number of presenting severity syndromes, as independent variables. With use of a backward stepwise approach, only variables with $P < .05$ were retained in the model that was adjusted for treatment. A similar procedure was repeated within each age group. Appropriate model fit was confirmed using the Pearson goodness-of-fit test or the Hosmer-Lemeshow goodness-of-fit test, when appropriate. Overall predictive ability of the combined significant presenting syndromes was quantified using a receiver operating characteristic analysis [7]. Analyses were conducted with Stata, version 9 (StataCorp).

RESULTS

Of the 1050 patients included in the study, 114 (10.9%) were ≤ 10 years of age (62 of these patients were ≤ 5 years of age), 274 (26.1%) were 11–20 years of age, 566 (53.9%) were 21–50 years of age, and 96 (9.1%) were >50 years of age.

Mortality. Overall mortality was 24.1% (253 of 1050 patients died). There was a statistically significant association between mortality and age group ($P < .001$), with a stepwise increase in mortality with increasing age ($P < .001$, by test for trend) (figure 1). Mortality was 6.1% (7 of 114 patients died) among children aged ≤ 10 years, 21.9% (60 of 274) among patients aged 11–20 years, 26.7% (151 of 566) among adults aged 21–50 years, and 36.5% (35 of 96) among patients aged >50 years. The risk of death increased with increasing number of severe criteria at presentation ($P < .001$, by test for trend), with a mortality of 9.5% (16 of 169 patients died) among patients who fulfilled 1 criterion and 50% (71 of 142) among patients who presented with ≥ 5 syndromes (table 1). The number of severity syndromes at hospital admission did not differ significantly among age groups ($P = .08$) (table 1).

In the logistic regression model, increased mortality with age was independent of the variation in presenting syndromes among age groups. The model was adjusted for treatment, interaction between treatment and log-parasitemia, log-parasitemia, Glasgow coma score, hematocrit, BUN concentration, and base excess. Compared with adults (age, 21–50 years), children (age, ≤ 10 years) were less likely to die when presenting with severe malaria (adjusted OR [AOR], 0.06; 95% CI, 0.01–0.23; $P < .001$), and the risk of death among patients in the oldest age group was nearly 2 times higher (AOR, 1.88; 95% CI, 1.01–3.52; $P = .046$). Mortality risk among the older children (age, 11–20 years) was the same as that in the adult group (age, 21–50 years; AOR, 1.06; 95% CI, 0.66–1.69; $P = .82$). Mortality was different among study sites. Reanalyses, stratified

Table 2. Univariate analysis of risk of death among patients with and without severity syndromes (SS) at hospital admission.

Age group, years	Coma				Convulsions				Severe anemia			
	Patients who died, %		OR (95% CI)	P	Patients who died, %		OR (95% CI)	P	Patients who died, %		OR (95% CI)	P
	With SS	Without SS			With SS	Without SS			With SS	Without SS		
0-10	11.7	0	NA	.01	7.1	5.6	1.31 (0.28-6.19)	.73	2.3	4.8	0.47 (0.05-4.70)	.51
11-20	32.6	10.5	3.29 (1.73-6.25)	<.001	23.7	21.6	1.13 (0.50-2.53)	.77	21.6	21.8	0.99 (0.47-2.09)	.97
21-50	35.5	15.8	3.11 (2.03-4.76)	<.001	32.1	26.1	1.34 (0.74-2.44)	.33	25.6	25.6	1.00 (0.58-1.74)	.99
>50	48.3	16.7	4.25 (1.5-11.48)	.002	66.7	33.3	4.0 (0.90-17.82)	.05	28.6	37.4	0.67 (0.12-3.71)	.65
All	33.6	12.6	3.44 ^a (2.46-4.79)	<.001	24.8	24.0	1.41 ^a (0.92-2.18)	.11	18.9	24.2	0.94 ^a (0.62-1.44)	.79

NOTE. The ORs for patients with coma, convulsions, and severe anemia were not significantly different between age groups ($P = .46$, $P = .50$, and $P = .90$, respectively, by test for homogeneity). The ORs for shock differed significantly between age groups ($P = .01$, by test for homogeneity). The ORs for metabolic acidosis (base excess < -3.3 mmol/L), metabolic acidosis (sodium concentration < 15 mmol/L), hyperparasitemia, jaundice, and renal impairment were not significantly different between age groups ($P = .62$, $P = .99$, $P = .68$, $P = .87$, and $P = .42$, respectively, by test for homogeneity). NA, not applicable.

^a Mantel-Haenszel OR.

by study site to adjust for transmission intensity, gave very similar results, with only minor changes in the ORs.

Neurological syndromes. Coma, defined as a Blantyre coma score of 1 or 2 (on a scale of 5) in preverbal children or a Glasgow coma score < 11 (on a scale of 15) in the remainder of the patients, was present in 563 (53.6%) of the 1050 patients; the prevalence of coma was not associated with age group ($P = .29$) (figure 1). Presence of coma had a predictive value for a fatal outcome that was similar in all age groups (MH OR, 3.44; 95% CI, 2.46-4.79; $P = .46$, by test for homogeneity) (table 2). Convulsions at or before hospital admission were present in 145 (13.8%) of the 1050 patients (table 2) and were significantly more common in children ($P < .001$, by test for trend) (figure 1). Presence of convulsions was not associated with increased mortality in any age group (MH OR, 1.41; 95% CI, 0.92-2.18; $P = .50$, by test for homogeneity) (table 2).

Respiratory distress. Respiratory distress, defined as a combination of a high respiratory rate (> 32 breaths/min for adults and > 40 breaths/min for children aged < 5 years) and increased work of breathing (as judged by the treating physician), was present in 361 (34.4%) of 1048 patients; the prevalence of respiratory distress decreased with increasing age ($P < .001$, by test for trend) (figure 1). Overall, 80 (22.2%) of the 361 patients who presented with respiratory distress died, compared with 172 (25.0%) of 687 patients who died when this criterion was not present (MH OR, 1.03; 95% CI, 0.76-1.41; $P = .84$). In contrast, the risk of developing respiratory distress during hospitalization increased with age ($P = .001$, by test for trend) (figure 1). Respiratory distress developed in 56 (5.3%) of the 1050 patients after enrollment and was associated with high mortality, independent of age (MH OR, 12.8; 95% CI, 6.30-26.1; $P = .99$, by test for homogeneity).

Severe anemia. Severe anemia (hematocrit, $< 20\%$) was present in 180 (18.4%) of 977 patients; the prevalence of severe anemia decreased stepwise with age ($P < .001$, by test for trend) (figure 1). Severe anemia did not have prognostic significance

with regard to mortality in any age group in univariate analysis (table 2).

Acidosis. Metabolic acidosis, defined as standard base excess < -3.3 mmol/L, was found in 564 (59.4%) of 949 patients and was not associated with age ($P = .13$) (figure 1). Among patients presenting with metabolic acidosis, the odds of death were 7.22 (95% CI, 4.56-11.45) times higher than that among patients who did not present with metabolic acidosis (table 2). The difference was statistically significant for all of the groups of patients aged > 10 years. Similarly, acidosis-defined plasma (bicarbonate concentration, < 15 mmol/L; according to the WHO criterion) was predictive of death (MH OR, 9.0; 95% CI, 5.88-13.76; $P = .99$, by test for homogeneity) and was not associated with age ($P = .81$) (table 2 and figure 1).

Shock. Hemodynamic shock, defined as a combination of low blood pressure and cold extremities, was present in 165 (15.7%) of the 1050 patients; there was no association between shock and age group ($P = .62$) (figure 1). In the univariate analysis, shock was associated with a fatal outcome only in the youngest group of children (age, ≤ 10 years) (table 2).

Hyperparasitemia. Three hundred fifty (33.3%) of the 1050 patients presented with a peripheral blood parasite load $> 200,000$ parasites/ μ L; this proportion increased with age ($P = .004$, by test for trend) (figure 1), and parasitemia was associated with increased mortality (MH OR, 2.10; 95% CI, 1.56-2.83; $P = .68$, by test for homogeneity) (table 2). After stratification by age, the increased risk of death was only statistically significant among the adults (age, 21-50 years; MH OR, 2.20; 95% CI, 1.49-3.24). Hyperparasitemia, defined according to the WHO criterion of parasitemia $> 10\%$ RBCs, was found in 229 (21.8%) of the 1050 patients and was also predictive of death (MH OR, 2.26; 95% CI, 1.63-3.13; $P = .38$, by test for homogeneity).

Jaundice. Jaundice was diagnosed clinically; plasma bilirubin concentrations were not measured. Jaundice was present in 529 (50.4%) of the 1050 patients. The frequency of jaundice

Table 2. (Continued.)

Metabolic acidosis (base excess <-3.3 mmol/L)				Metabolic acidosis (sodium concentration <15 mmol/L)				Shock			
Patients who died, %		OR (95% CI)	P	Patients who died, %		OR (95% CI)	P	Patients who died, %		OR (95% CI)	P
With SS	Without SS			With SS	Without SS			With SS	Without SS		
5.3	0	NA	.14	11.8	1.1	10.52 (0.89–98.67)	.08	20.0	4.0	5.94 (1.13–1.31)	.02
34.3	7.1	6.80 (2.90–15.92)	<.001	60.0	14.7	8.70 (3.86–19.61)	<.001	11.6	23.8	0.42 (0.16–1.13)	.08
38.1	6.8	8.40 (4.41–5.74)	<.001	64.7	16.7	9.14 (5.34–15.66)	<.001	29.6	26.2	1.18 (0.72–1.96)	.51
46.6	18.5	3.83 (1.22–12.09)	.01	78.6	30.0	8.56 (1.93–37.99)	<.001	26.3	39.0	0.56 (0.18–1.73)	.31
34.8	7.0	7.22 ^a (4.56–11.45)	<.001	59.4	15.8	9.0 ^a (5.88–13.76)	<.001	23.6	24.2	0.93 ^a (0.63–1.38)	.73

was increased in the older age groups ($P < .001$, by test for trend) (figure 1); its presence was not associated with mortality (MH OR, 1.20; 95% CI, 0.90–1.62; $P = .87$, by test for homogeneity) (table 2).

Renal impairment. Of 993 patients with available data, 368 (37.1%) had renal impairment at hospital admission (table 2). The frequency of renal impairment increased with age ($P < .001$, by test for trend) (figure 1). The odds of death were 4 times higher among patients who presented with renal impairment than among patients who did not present with renal impairment (MH OR, 4.01; 95% CI, 2.87–5.59; $P = .42$, by test for homogeneity) (table 2). Stratified by age group, the increased odds were statistically significant among patients aged 10–20 years and 21–50 years but not among the oldest age group. A total of 48 patients received peritoneal dialysis, and another 6 patients received hemodialysis.

Prognostic value of presenting syndromes, by age group. Mortality among the youngest age group was low (7 patients died); therefore, a multivariate analysis of the prognostic significance of presenting syndromes was not possible. In the group of patients aged 11–20 years, the following variables contributed to the overall model (adjusted for treatment): plasma standard base excess (AOR, 0.89; 95% CI, 0.84–0.94), Glasgow coma score (AOR, 0.83; 95% CI, 0.75–0.92), hematocrit (AOR, 1.06; 95% CI, 1.01–1.12), and BUN concentration (AOR, 1.03; 95% CI, 1.01–1.04). The resulting area under the receiver operating characteristic curve for this model was 0.87, indicating good ability of the model to predict outcome. In the group of patients aged 21–50 years, the contributing variables (adjusted for treatment) included Glasgow coma score (AOR, 0.78; 95% CI, 0.72–0.84) and standard base excess (AOR, 0.81; 95% CI, 0.77–0.85), with a corresponding area under the receiver operating characteristic curve of 0.88. In the group of patients aged >50 years, Glasgow coma score (AOR, 0.73; 95% CI, 0.60–0.90), standard base excess (AOR, 0.68; 95% CI, 0.53–0.88), and BUN concentration (AOR, 1.03; 95% CI, 1.00–1.06) were prognostic factors that contributed significantly to the model. There was significant interaction between standard base

excess and BUN concentration ($P = .006$); the area under the receiver operating characteristic curve was 0.86.

DISCUSSION

In this very large prospective study of mortality among patients selected on the basis of uniform criteria defining severe malaria, mortality gradually increased with age, from 6.1% among children aged ≤ 10 years to 36.5% among patients aged >50 years. The study was performed in Asian regions with low and unstable transmission, where protective immunity in the population is generally low. An increase in the case-fatality rate with age has been noted previously in studies involving Indonesian transmigrants [8], Indians [9], and returned travelers [10], but these smaller studies did not control for presenting syndromes. There were relatively few young children and no infants (they were excluded from the treatment trial); therefore, further dissection of age effects within the first years of life was not possible. In areas with intense transmission and where malaria is confined to the first few years of life, severe malaria is unusual during the first 6 months of life, but when it does occur, the mortality is high [11]. Part of the increase in mortality with age in this series can be explained by a high frequency of renal impairment in adults, which is associated with mortality, and the high incidence of severe anemia in children, which is associated with a lower mortality. However, when differences in presenting syndromes are taken into account, increasing age was still correlated with higher mortality.

Coma (cerebral malaria) was equally frequent and had similar prognostic significance in all age groups, although convulsions were much more common in small children, as is the case in other CNS diseases, such as bacterial meningitis [12]. Some convulsions at hospital admission may have been febrile convulsions, which do not usually occur in persons aged >6 years. Hypoglycemia may also have contributed to the incidence of convulsions.

A clinical diagnosis of respiratory distress—defined by both deep (acidotic) breathing and pulmonary pathologies (pul-

Table 2. (Continued.)

Hyperparasitemia				Jaundice				Renal impairment			
Patients who died, %		OR (95% CI)	P	Patients who died, %		OR (95% CI)	P	Patients who died, %		OR (95% CI)	P
With SS	Without SS			With SS	Without SS			With SS	Without SS		
14.8	3.5	4.87 (0.98–24.27)	.05	5.9	6.2	0.95 (0.11–8.49)	.96	0	3.3	NA	.58
29.1	18.6	1.79 (0.99–3.26)	.05	23.0	20.7	1.14 (0.64–2.03)	.65	40.5	12.1	4.92 (2.52–9.60)	<.001
35.5	21.1	2.20 (1.49–3.24)	<.001	28.9	23.7	1.31 (0.90–1.93)	.16	41.5	14.4	4.22 (2.74–6.50)	<.001
46.0	30.4	1.88 (0.80–4.43)	.14	35.4	37.5	0.91 (0.40–2.11)	.83	45.7	25.5	2.45 (0.99–6.03)	.05
34.3	19.0	2.10* (1.56–2.83)	<.001	27.2	20.9	1.20* (0.90–1.62)	.22	40.8	13.0	4.01* (2.87–5.59)	<.001

monary edema or pneumonia)—at hospital admission was received more frequently by younger patients. Unexpectedly, respiratory distress was not associated with an adverse outcome. This finding should be interpreted with some caution, because the physiologically higher respiratory rates in young children may have been interpreted as respiratory distress in some of the children [13]. The development of respiratory insufficiency or deep breathing during hospital admission, resulting from pulmonary edema, secondary pneumonia, or metabolic acidosis, was more common in older patients and was associated with a high mortality. The lower risk of pulmonary edema among small children is in accordance with the published literature [14].

Severe anemia is an important manifestation of *P. falciparum* malaria in young children and is included in the rubric “severe malaria,” although it carries a significantly better prognosis than the other manifestations included. The frequency of severe anemia was highest in young children, decreased sharply in the adolescent group, and gradually decreased further with increasing age. There is no clear explanation for this increased risk of severe anemia among children, although lower premorbid hemoglobin levels in the younger children cannot be excluded. Less efficient removal of rigid, uninfected erythrocytes in adults, quantitatively the most important contributor in malarial anemia, could also contribute to the development of severe anemia in children [15]. Severe anemia was not associated with increased mortality in this series. In fact, multivariate analysis in the group of patients aged 11–20 years revealed a positive correlation between hematocrit and mortality, which can be explained by the good prognosis of anemia as a presenting syndrome in the absence of other severity syndromes.

The incidence of metabolic acidosis was similar among all of the age groups and was an important prognostic factor for mortality. This further suggests that respiratory distress was not specific for this lethal pathology. Acidosis in severe malaria is commonly a lactic acidosis caused by anaerobic glycolysis, mainly resulting from a compromised microcirculation caused by sequestration of parasitized erythrocytes and, to a lesser extent, by other adhesive forces between erythrocytes and by

decreased erythrocyte deformability [16]. Hepatic clearance of lactate is reduced [17]. If present, hemodynamic shock and severe intravascular dehydration can cause acidosis. Other organic acids also contribute to acidosis [18]. Renal failure is an important contributor to acidosis in adults. The prognostic significance of acidosis is revealed by the consistent observation of the symptom in both adults and children with severe malaria [17, 19].

The frequency of shock did not increase with age and was associated with high mortality in young children only. This may relate to higher frequencies of bacteremia complicating malaria in young children [20], but this hypothesis could not be confirmed in our study, because blood cultures were not routinely available. In children, the development of hypotension is a late feature of shock, which could explain the difference in prognostic significance of this syndrome.

The incidence of acute renal impairment at presentation increased gradually with age. The pathology of acute renal failure in severe malaria is acute tubular injury [21]. Children are generally less vulnerable to tubular damage resulting from ischemic or toxic insults. With increasing age, the kidney becomes more vulnerable to compromising prerenal factors. Unexpectedly, the prevalence of hyperparasitemia increased with age. It is possible that older, nonimmune patients have less efficient parasite clearance mechanisms than do younger patients. Because of smaller total numbers of patients in the oldest age group, renal failure and hyperparasitemia, which were most frequent in this age group, were not significant prognostic factors in this group, in contrast with patients aged 21–50 years.

Of all of the presenting syndromes, coma and metabolic acidosis (defined biochemically) were the most significant prognostic indicators of mortality in all of the age groups. Thus, despite the substantial differences in presentation of severe malaria with age, pathophysiological mechanisms responsible for a fatal outcome of the disease are likely to be similar. The number of presenting severity syndromes also correlated strongly with disease outcome, as reported elsewhere [14].

In conclusion, our study reports the clinical presentation of severe malaria in relation to age. Presenting syndromes vary

widely, and mortality increases sharply with age. However, the incidence and strong prognostic significance of coma and acidosis is similar among all age groups.

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