MAJOR ARTICLE

Predicting the Clinical Outcome of Severe Falciparum Malaria in African Children: Findings From a Large Randomized Trial

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Background. Data from the largest randomized, controlled trial for the treatment of children hospitalized with severe malaria were used to identify such predictors of a poor outcome from severe malaria.

Methods. African children (<15 years) with severe malaria participated in a randomized comparison of parenteral artesunate and parenteral quinine in 9 African countries. Detailed clinical assessment was performed on admission. Parasite densities were assessed in a reference laboratory. Predictors of death were examined using a multivariate logistic regression model.

Results. Twenty indicators of disease severity were assessed, out of which 5 (base deficit, impaired consciousness, convulsions, elevated blood urea, and underlying chronic illness) were associated independently with death. Tachypnea, respiratory distress, deep breathing, shock, prostration, low pH, hyperparasitemia, severe anemia, and jaundice were statistically significant indicators of death in the univariate analysis but not in the multivariate model. Age, glucose levels, axillary temperature, parasite density, heart rate, blood pressure, and blackwater fever were not related to death in univariate models.

Conclusions. Acidosis, cerebral involvement, renal impairment, and chronic illness are key independent predictors for a poor outcome in African children with severe malaria. Mortality is markedly increased in cerebral malaria combined with acidosis.

Clinical Trial Registration. ISRCTN50258054.

Falciparum malaria can progress rapidly from an uncomplicated febrile illness that usually resolves with oral medication to a potentially lethal multisystem disease, despite in-hospital parenteral treatment. The mortality risk in uncomplicated falciparum malaria is thought to be under 0.1%, rising toward 1% as treatments fail in the context of antimalarial drug resistance [1]. The mortality due to severe malaria in young children usually exceeds 10% and increases with age [2]. Several predictive factors for death in severe childhood malaria have been identified [3]; among them,

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coma [2, 4–36], convulsions [2, 13, 18, 27, 29, 34, 36–42], acidosis [2, 5, 6, 8–10, 12, 14, 17, 21, 22, 25, 30, 31, 34, 42–51], respiratory distress [6–9, 12, 19, 26, 30, 31, 35, 38, 39, 41, 45, 46, 50–58], hypoglycemia [7, 10, 14, 16, 18, 20, 25, 27, 37, 41, 47], retinal changes [4, 11, 15, 25, 28, 29, 38, 59–61], increased concentrations of lactate in blood and cerebrospinal fluid [18, 62–64], increased concentrations of tumor necrosis factor [65–69], and the presence of malarial pigment in 0.5% or more of peripheral blood neutrophils [70]. Combinations of prognostic indicators or scoring systems have also been evaluated to identify patients who have an increased risk of death [53, 57].

Outcomes in severe falciparum malaria depend on the nature and degree of vital organ dysfunction. This differs between adults and children. For example, severe malaria with renal failure is an important cause of death in adults but acute renal failure from malaria-induced acute tubular necrosis is rare in children from any cause and is very rarely reported in African children with severe malaria [2, 53, 71, 72]. In contrast, severe anemia is a very common presentation of severe malaria in young children in high-transmission settings, but is relatively unusual in adults. Universal indicators can be used in clinical trials to define severe malaria, and can also direct studies of the pathogenesis of severe malaria and guide the identification of new targets for intervention. Using data from the largest severe malaria treatment trial to date [73], we analyzed the relationship between clinical and laboratory characteristics collected on admission and the risk of death.

METHODS

This analysis is based on a randomized clinical trial comparing parenteral artesunate with parenteral quinine in African children with severe falciparum malaria [73]. The trial was conducted between 2005 and 2010 in 11 participating centers in 9 African countries (Table 1). The spectrum of participating hospitals ranged from university hospitals and research institutes to rural hospitals without prior research experience. Human immunodeficiency virus (HIV) testing was approved at 4 sites (Beira, Muheza, Rwamagana/Nyanza, and Kilifi). The reported HIV prevalence (Table 1) relied on historical data from adults [74].

The methods and the outcome of the trial have been reported in detail elsewhere [73]. Febrile children less than 15 years of age with a positive *Plasmodium falciparum* histidine-rich protein 2–based rapid test (Optimal) for falciparum malaria were eligible for enrolment based on a clinical judgment of severe malaria, which included at least 1 of the following conditions: coma, defined by a Blantyre Coma Scale (BCS) score $\leq$2 for children less than 2 years of age or a Glasgow Coma Scale (GSC) score $\leq$9 for older children; prostration, defined as the inability to sit unsupported (for children over 6 months of age) or the inability to drink or breast-feed in younger children; convulsions with a duration longer than 30 minutes or a frequency of 2 or more in the 24 hours preceding admission; compensated shock, defined as a peripheral capillary refill time $\geq$3 seconds or the presence of a temperature gradient with a normal systolic BP ($\geq$70 mmHg); decompensated shock, defined as a systolic blood pressure $<$70 mmHg; severe respiratory distress, defined as nasal alar flaring, costal indrawing, or use of accessory muscles, severe tachypnea, or deep breathing; hypoglycemia, defined as blood glucose $<$3 mmol/L or clinical improvement in the level of consciousness immediately after administration of 10% dextrose; severe symptomatic anemia, defined as severe pallor combined with respiratory distress; blackwater fever; clinical jaundice; hyperparasitemia, defined as asexual parasitemia

Table 1. Age Distribution, Case Fatality Rate, and Adult HIV Prevalence by Study Center

Study Center	Number of Children	Median Age (IQR, Years)	Mortality (%)	HIV/AIDS Adult Prevalence Rate (%) [78]
Banjul, The Gambia	502	4.4 (3.0, 6.1)	55 (11%)	1
Beira, Mozambique	664	3.8 (2.5, 5.3)	75 (11%)	12
Ilorin, Nigeria	450	2.8 (1.8, 4.2)	41 (9%)	3
Rwamagana and Nyanza, Rwanda	271 and 115	3.3 (1.7, 5.1)	20 (5%)	2
Kilifi, Kenya	442	3.3 (2.3, 4.8)	44 (10%)	8
Kinshasa, DRC	422	2.4 (1.6, 4.2)	18 (4%)	4
Korogwe, Tanzania	540	2.3 (1.3, 3.5)	80 (15%)	8
Kumasi, Ghana	436	3.0 (2.0, 4.3)	21 (5%)	1
Mbarara, Uganda	663	1.8 (1.0, 2.8)	42 (6%)	4
Teule, Tanzania	921	2.2 (1.2, 3.3)	131 (14%)	8
Total	5426	2.8 (1.7, 4.3)	527 (10%)	6[a]

Abbreviations: DRC, Democratic Republic of the Congo; HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Weighted mean.

above 10%. Patients were enrolled after a relative or guardian gave informed written consent.

Definitions of Clinical Features on Presentation

Seizures were defined as a history of convulsion of 30 minutes or longer reported by the caregiver or observed by the health care provider. On admission, the axillary temperature was measured with a digital thermometer, and the respiratory rate was recorded. Coma, respiratory distress, deep breathing, and shock were defined as stated in the inclusion criteria [56]. Blood pressure was measured using a digital sphygmomanometer. The presence of lymphadenopathy, candidiasis, nuchal rigidity, visible severe wasting, and edematous malnutrition were noted following standard guidelines [75].

Baseline Laboratory Results

A venous blood sample was collected for malaria rapid diagnostic tests, thin and thick blood films, and a point-of-care assessment of standard base excess (BE), negative logarithm of the blood hydrogen ion concentration (pH), glucose, blood urea nitrogen (BUN), hematocrit (HCT), and hemoglobin (Hb) using an automated handheld blood analyzer (i-STAT, Abbott Laboratories, Abbott Park, IL). In total, 419 i-STAT results were excluded from the analysis because of instrument malfunction. The blood films were read at the reference laboratory at the Mahidol Oxford Research Unit in Bangkok. Malaria parasites were quantified using the readings from the thin blood film, or if not available, calculated from the thick blood film (40 $\times$ count/200 white blood cells).

Statistical Analysis

The univariate association between various clinical indictors and mortality from severe malaria was initially examined visually using box plots and histograms. Factors that were considered potential independent predictors of mortality were recorded at admission, and are included in (Table 2). Lymphadenopathy, malnutrition, candidiasis, severe visible wasting, and desquamation were combined into a single variable as an indicator of chronic disease, which was also examined as a risk factor. Compensated shock and decompensated shock were also combined into a single variable. The BCS scores (used for preverbal children; n = 3417) and the GCS scores (n = 2004) were combined into a single coma score (1–5). In Rwanda, 2 smaller sites (Rwamagana and Nyanza), run by the same investigators, were combined. The *P* values for the univariate analysis were derived by logistic regression analysis, stratified by site, and adjusted for treatment. Correlations between variables were evaluated using Spearman's rank correlation coefficients or the 2-sample Wilcoxon rank-sum (Mann-Whitney) test.

The prognostic importance of these admission variables was assessed in a multivariate logistic regression model.

Table 2. Indicators Evaluated[a]

1. Age (years)
2. Base excess (BE, mmol/L)
3. Blackwater fever/dark urine
4. Coma score based on the Blantyre Coma Scale (BCS; 0–5) or Glasgow Coma Scale (GCS; 3–15)
5. Blood urea nitrogen (BUN, mg/dL)
6. Chronic disease (candidiasis, lymphadenopathy, malnutrition, severe visible wasting, desquamation of skin)
7. Convulsions (30 min or longer or ≥2 convulsions in 24 h preceding admission)
8. Glucose (mg/dL)
9. Hemoglobin (g/dL)
10. Heart rate (beats/min)
11. Log parasitemia (μL)
12. pH
13. Prostration (unable to sit unsupported; if under 6 months old, unable to breastfeed)
14. Respiratory distress (severe tachypnea, nasal alar flaring, costal indrawing or use of accessory muscles)
15. Deep breathing (labored breathing pattern with abnormally deep chest excursions)
16. Respiratory rate (breaths/min)
17. Sex
18. Shock (compensated and decompensated)
19. Systolic blood pressure (mmHg)
20. Axillary temperature (°C)
21. Visible jaundice

[a] Alphabetical order.

All clinical indicators that were significant in the univariate analysis were included in the model, with death as the dependent variable. A priori specified interactions between respiratory rate and shock, respiratory rate and age, respiratory rate and base excess, and base excess and age were assessed. A visual examination of the univariate associations between the clinical factors and death indicated possible nonlinear associations with some of the continuous variables (eg, glucose, log parasitemia, and respiratory rate; Figure 1). Therefore, multivariable fractional polynomials were used in conjunction with logistic regression to identify the model that would best predict the outcome [76]. Fractional polynomials indicated that the best fitting final model was achieved with linear values. Because a large set of potential predictors was compared, there was a risk that at least 1 indicator would reach the .05 level of significance purely by chance [77]. Hence, only variables with a *P* value less than .01 were retained in the final model, which was also adjusted for treatment (artesunate or quinine) and stratified by site. Receiver operating characteristic (ROC) analysis was used to evaluate the prediction ability of the final model. The logistic regression models made use of continuous variables. The fit of multivariate regression models was compared using likelihood

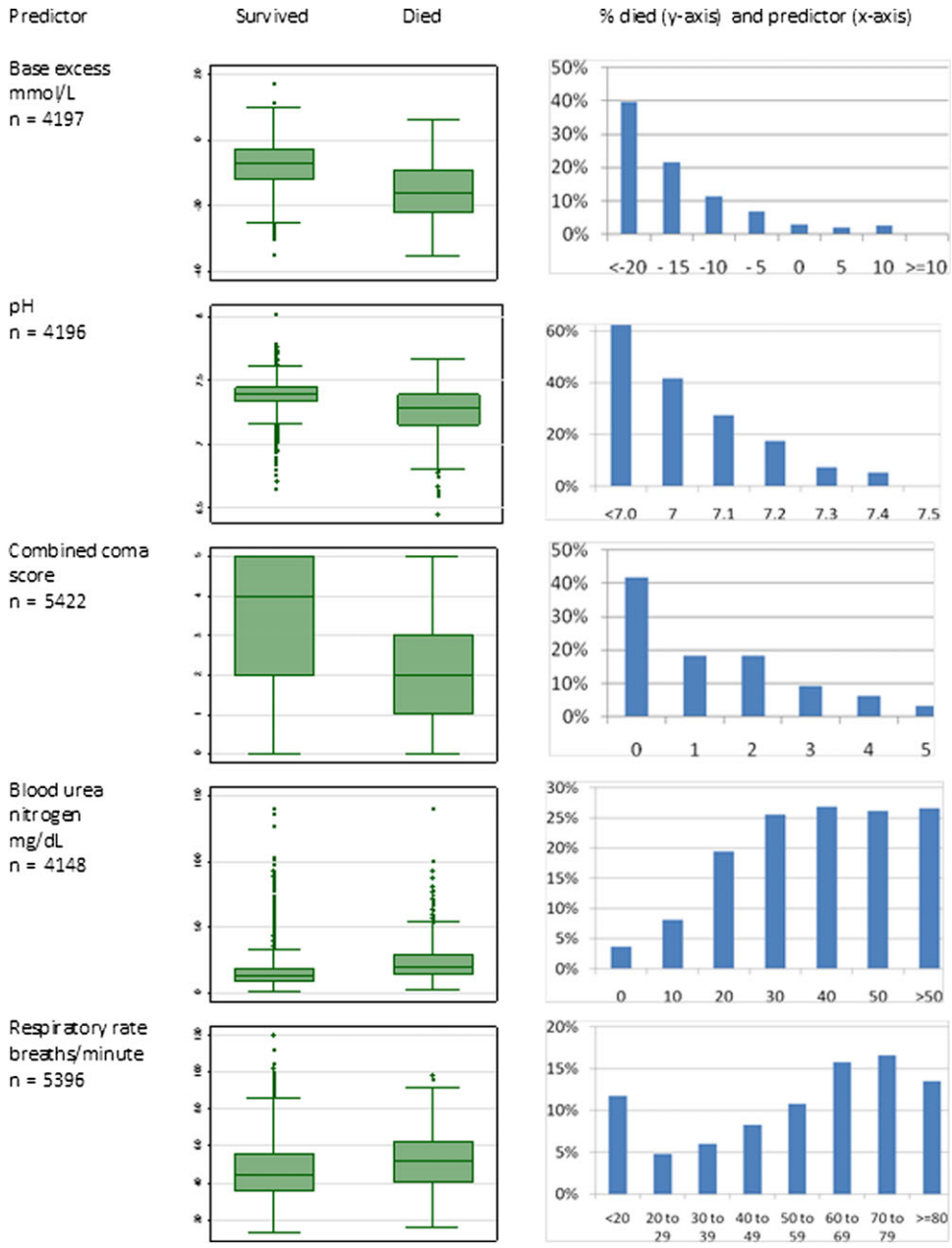


Figure 1. Baseline distribution of continuous variables in relation to outcome: survival or death.

ratios and Wald tests. In the Venn diagram approach, children with a combined coma score <3 were considered comatose, with a BE less than −8 mmol/L as acidotic, and with a BUN equal or larger than 20 mg/dL as uremic. All analyses were performed using Stata software, version 11 (StataCorp, College Station, TX).

Ethical Review

The trial protocol was approved by each local ethical review board, the Oxford Tropical Research Ethics committee, and the Institutional Review Board of the London School of Hygiene and Tropical Medicine.

RESULTS

There were 5426 children <15 years of age that participated in the study at 11 sites, of whom 9.7% (527) died (Table 1). Thirteen of the 21 variables examined were significantly associated with death in univariate models and were included in the multivariate model (Tables 3 and 4, Figure 1). The final model was fitted with data from 4089 children. The case fatality rate of children included and excluded from the model was 9.8%. There were 5 highly significant independent predictors of mortality from severe malaria in children,

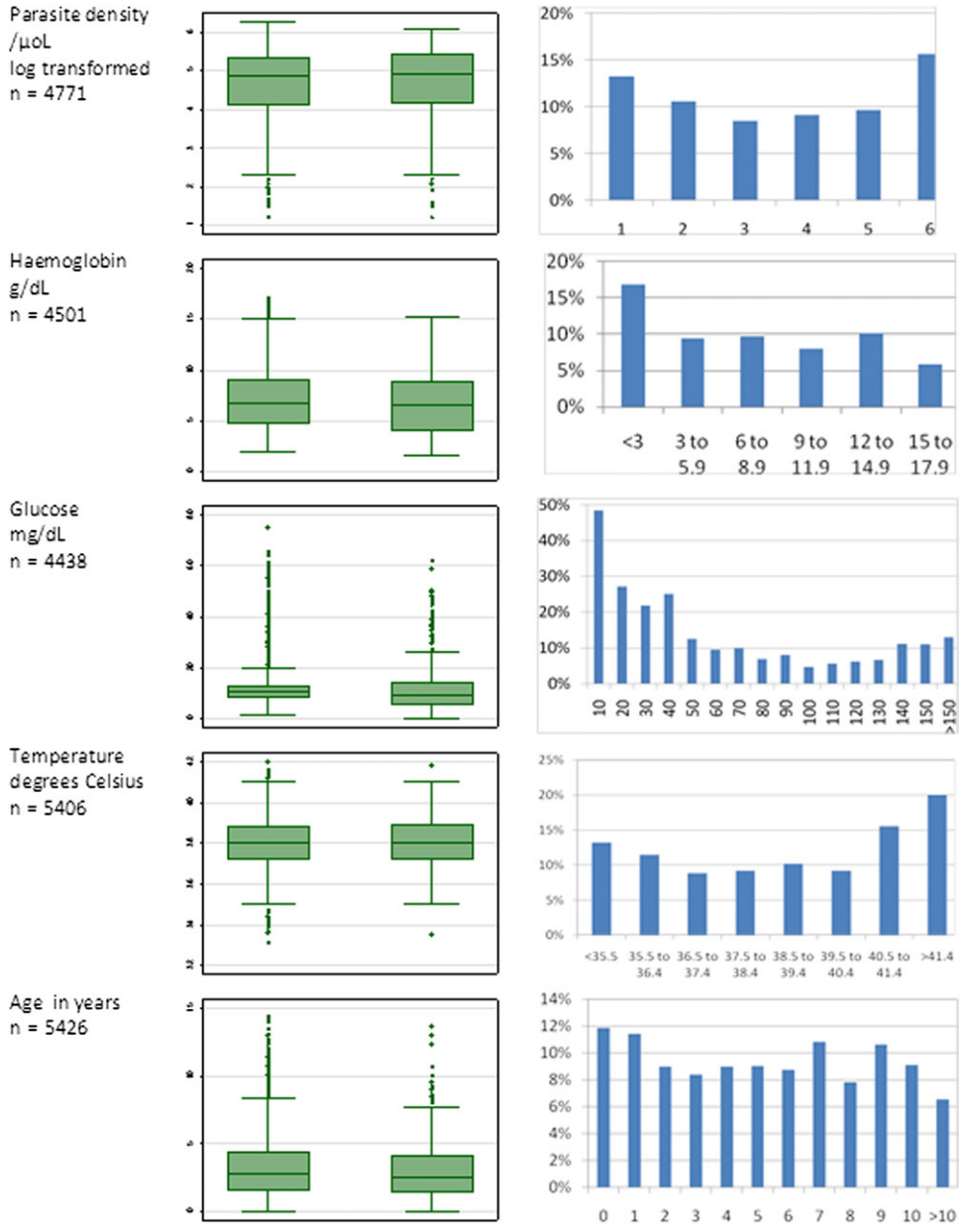


Figure 1 *continued.*

including base deficit (adjusted odds ratio [AOR] 1.12, 95% confidence interval (CI) 1.10–1.13), coma score (AOR 1.40, 95% CI 1.34–1.45), convulsions (AOR 1.72, 95% CI 1.30–2.30), BUN (AOR 1.02, 95% CI 1.02–1.03), and chronic illness (AOR 2.12, 95% CI 1.25–3.58). The area under the ROC curve indicated good ability of the model to predict mortality (area = 85%, 95% CI 83–87). None of the investigated interaction terms (respiratory rate and shock, respiratory rate, and age, respiratory rate and base excess, or base excess and age) were statistically significant. One or more of the independently significant variables from the final model were present at admission in 391/401 (98%) of children who died. There were 9 of 1065 (1%) children without any of potential risk factors on admission who died, in contrast to 66 of 124 (53%) children with 4 predictors (Table 5). In a Venn diagram that incorporates the 3 most frequent, independently statistically significant predictors, acidosis (BE < -8 mmol/L), impaired consciousness (combined coma score <3) or convulsions, and elevated blood urea (>20 mg/dL), the estimated mortality in children with all 3 predictors was 43% (Figure 2). In children with acidosis and impaired consciousness, the mortality was 23%. The sensitivity of acidosis as a prognostic indicator for death in this cohort was 78% (specificity 96%), impaired consciousness was 66% (specificity 95%), and elevated

Table 3. Association Between Childhood Severe Malaria Clinical Markers With Death: Continuous Variables[a]

	Died		Survived		
Risk factor	n	Mean (SD) or median (IQR)[b]	n	Mean (SD) or median (IQR)[b]	P[c]
BE, mmol/L	413	−15.6 (8.1)	3784	-7.8 (6.5)	<.001
pH	413	7.25 (0.19)	3782	7.38 (0.11)	<.001
Coma score[d]	525	2.2 (1.6)	4897	3.7 (1.5)	<.001
BUN, mg/dL	409	23.9 (17.2)	3739	14.9 (11.6)	<.001
Respiratory rate, breaths/min	517	52.6 (14.6)	4879	46.8 (14.1)	<.001
Hemoglobin, mg/dL	449	6.6 (3.0)	4052	7.0 (2.9)	<.001
Heart rate, beats/min	515	148.5 (32.2)	4878	144.3 (28.1)	.03
Age, years (median)	527	2.5 (1.5–4.1)	4899	2.8 (1.7–4.3)	.06
Axillary temperature, °C	521	38.1 (1.2)	4885	38.0 (1.1)	.24
Glucose, mg/dL	444	117 (97.4)	3994	120 (71.1)	.35
Systolic blood pressure, mmHg	403	94.5 (17.3)	3886	94.8 (15.5)	.67
Parasite density/μL[e]	450	45 533 (16–1 858 880)	4321	45 232 (16–1 251 227)	.82

Abbreviations: BE, base excess; BUN, blood urea nitrogen; IQR, interquartile range; SD, standard deviation.

[a] Sorted by P value.

[b] Unless otherwise specified.

[c] From logistic regression analysis, stratified by site and adjusted for treatment.

[d] Blantyre Coma Scale and Glasgow Coma Scale scores were combined into 1 variable for analysis.

[e] Geometric mean (range).

blood urea was 53% (specificity 95%). If 2 of the 3 prognostic signs (acidosis, impaired consciousness, or elevated blood urea) were detected, the sensitivity increased to 94% (specificity 98%).

Specific Predictors

Acidosis

Increasing levels of acidosis were associated with increasing mortality (Table 3). The mean (SD) BE on admission among the 413 children who died was −16 mmol/L (8.1) compared with −8 mmol/L (6.5) among the 3784 survivors ($P < .001$). Similarly, there was a statistically significant difference between the mean pH (SD) of the 413 children who died (pH = 7.25, 0.19) and the 3782 children who survived (pH = 7.38, 0.11; $P < .001$). When BE and pH were included in multivariate models, BE but not pH remained an independent and statistically significant covariable.

Impaired Consciousness and Cerebral Malaria

Mortality increased with decreasing coma scores. Of the of children with a combined coma score ≤2, 21% (347/1645) died in contrast to 5% (178/3777) of the remaining children ($P < .001$). Of the children who experienced convulsions, 14% (242/1692) died in contrast to 8% (285/3734) of the remaining children ($P < .001$). The coma score retained statistical significance in the multivariate model.

Blood Urea Nitrogen

Mortality increased with increasing BUN in the study population. The median BUN was 24 mg/dL among the 409 children who died and 15 mg/dL among the 3739 children who survived ($P < .001$). There was a statistically significant but weak correlation between increasing age of children and increasing BUN (Spearman $\rho = 0.08$; $P < .001$).

Underlying Chronic Illnesses

Clinical signs of an underlying chronic illness was observed in 189 (4%) of the 5379 children participating in the study. Lymphadenopathy on its own was associated with high mortality (21%; 17/82 compared with 9%; 504/5312; $P < .001$) but was not statistically significant in multivariate models. A combined variable representing signs of chronic illness was associated with a high mortality of 18% (34/189) compared with 9% (486/5190; $P < .001$) for separate variables, and the combined variable retained statistical significance in the multivariate model.

Respiration

The respiratory rate was significantly higher (Figure 1), and respiratory distress (Table 4) and deep breathing were significantly more frequently encountered in children who died than in children who survived. In a multivariate model, which included a base deficit, none of the clinical signs related to respiration were independently significant. There was a significant correlation between respiratory distress ($P < .001$), respiratory rate ($\rho = –0.3$; $P < .001$), deep breathing ($P < .001$), and base deficit. In a model without a base deficit, deep breathing and respiratory rate were significant; however, the model that included a base deficit had a significantly better fit (likelihood ratio test $P < .0001$).

Table 4. The Association Between Childhood Severe Malaria Clinical Markers With Death: Categorical Variables

Risk factor	n	Died (%)	P^a
Convulsions			
Yes	1692	242 (14)	<.001
No	3734	285 (8)	…
Prostration			
Yes	2974	142 (5)	<.001
No	2452	385 (16)	…
Shock[b]			
Yes	663	123 (19)	<.001
No	4763	404 (9)	…
Respiratory distress			
Yes	867	145 (17)	<.001
No	4559	382 (8)	…
Deep breathing			
Yes	938	218 (23)	<.001
No	4488	309 (7)	…
Jaundice			
Yes	114	22 (19)	<.001
No	5312	505 (10)	…
Chronic disease[c]			
Yes	189	34 (18)	<.001
No	5190	486 (9)	…
Sex			
Male	2815	275 (10)	.74
Female	2611	252 (10)	…
Blackwater fever			
Yes	237	22 (9)	.96
No	5189	505 (10)	…

[a] From logistic regression analysis, stratified by site and adjusted for treatment.

[b] Compensated and decompensated shock combined.

[c] Lymphadenopathy, malnutrition, candidiasis, severe visible wasting and desquamation combined as an indicator for chronic disease.

Table 5. Score Based on 5 Independently Significant Variables: Base Excess (<−8 mmol/L), Blood Urea Nitrogen (≥ 20 mg/dL), Combined Coma Score <3, Chronic Disease, and Convulsions.[a]

Score	Survived	Died (%)	Total
0	1056	9 (1)	1065
1	1339	75 (5)	1414
2	923	118 (11)	1041
3	311	131 (30)	442
4	58	66 (53)	124
5	1	2 (67)	3
Total	3688	402 (10)	4089

[a] Presence of each variable provides 1 point to the score.

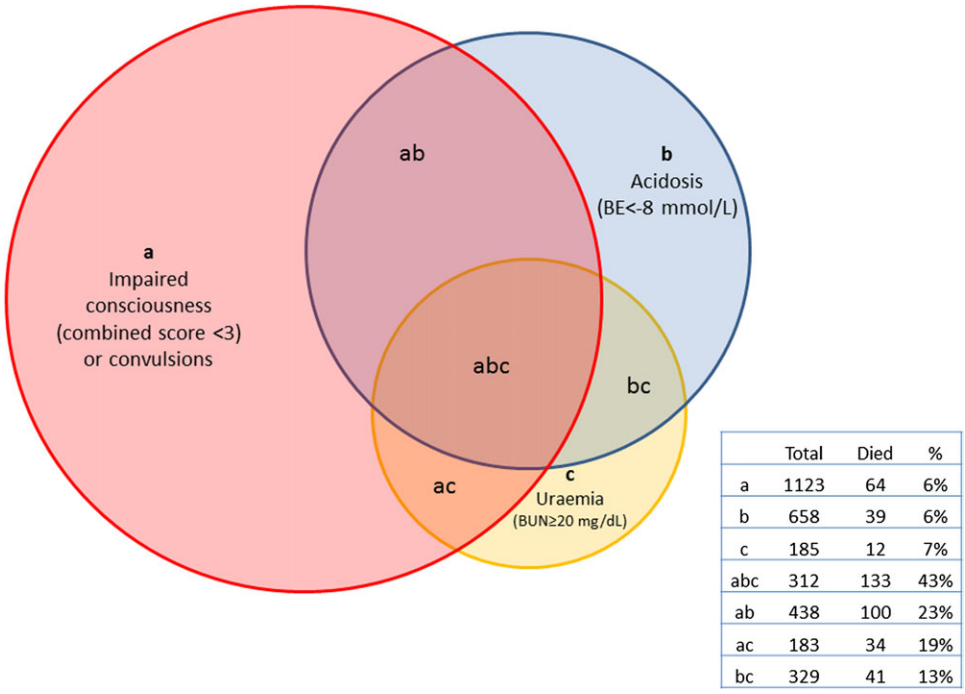
DISCUSSION

In this study, 4 predictors were independently associated with an increased risk of death: acidosis indicated by a large base deficit, cerebral manifestations of malaria (coma and/or convulsions), an elevated blood urea nitrogen, or signs of chronic illness on admission. The standard base deficit was found to be the single most relevant predictor of death in this series, which confirms findings from Malawian children [30] and adult Asians [43] with severe malaria. In our study, the specificity of impaired consciousness and acidosis were similar (95% vs 96%), but the sensitivity of acidosis as a prognostic marker was 78% compared with a sensitivity of 66% for impaired consciousness. Deep breathing and respiratory distress also had high specificities (93% and 92%), but the sensitivity of deep breathing was only 41% and that of respiratory distress was only 28%.

In severe malaria, sequestration of red blood cells containing the mature parasites leads to tissue ischemia. Reduced red cell deformability, the clumping of uninfected to infected red cells (rosetting), and the clumping between infected red cells (auto-agglutination) further contribute to the impairment of microcirculatory flow, causing tissue hypoxia and a shift from aerobic to anaerobic metabolism. With anaerobic metabolism, pyruvate is converted into lactic acid, an important but not exclusive contributor to acidosis [44, 78]. A venous blood base deficit had a stronger prognostic value than pH, which has been confirmed in other studies [43]. This is not surprising because a base deficit better reflects metabolic acidosis, whereas the pH starts to drop only when respiratory compensation is insufficient and the blood's buffering capacity becomes exhausted [78]. Because respiratory signs in severe malaria are a response to acidosis, it should also not be surprising that respiratory signs are not independently significant predictors in models that include a base deficit. The sequestration of infected red blood cells in the cerebral microvasculature is thought to be the central pathological process preceding the cerebral manifestations of severe malaria [18, 21]. Coma and convulsions suggest advanced cerebral involvement, and deep coma can progress to central respiratory depression followed by death.

The association of an elevated BUN with poor outcome is of interest, as renal involvement is rarely reported in children [13, 35, 72] in contrast to adults with severe malaria [2, 53, 71]. The findings from this study suggest that renal involvement could be frequently overlooked in children with severe malaria. A number of factors can contribute to an increased BUN, including hypovolemia and increased protein breakdown. More research is required to explore the significance of elevated BUN in children with severe malaria.

Overall, 4% of the study participants were diagnosed with chronic debilitating illness, the causes of which include a diverse



	Total	Died	%
a	1123	64	6%
b	658	39	6%
c	185	12	7%
abc	312	133	43%
ab	438	100	23%
ac	183	34	19%
bc	329	41	13%

Figure 2. Venn diagram illustrating the combinations of presentations and associated mortality.

spectrum of pathologies, including malnutrition and HIV infection. It is likely that a proportion of the chronically debilitated children were suffering from AIDS, but only 4 sites conducted diagnostic tests for it. Increased morbidity and mortality from severe malaria in HIV-infected children has been reported previously [79, 80].

Independent of other factors, there was no association of severe anemia with death in our study. This may be because life-threatening severe anemia is accompanied by metabolic acidosis and prostration. Furthermore, early transfusion in life-threatening severe anemia in pediatric falciparum malaria can prevent death [81]. In the current series, only those children with extremely low hemoglobin concentrations (<3 g/dL) were at an increased risk of dying. Similarly, hypoglycemia can be reversed when detected early, and as a severity sign, it is, again, not independent of other severity symptoms, including metabolic acidosis. Hyperparasitemia has been associated with a poor outcome in severe malaria [18]. In our cohort, only extremely high parasite densities above 440 000/μL carried an increased risk of death. There was a small group of 25 severely ill children who presented with very low parasite densities, and the mortality in this subgroup was also high (20%). It is possible that the malaria in these children was not the primary cause of illness, but was instead a coincidental coinfection. Very high mortality in patients with malaria and bacteremia coinfections has been documented [82–84].

We observed a lower mortality in children with prostration (5%) compared with children without prostration (16%). Cerebral impairment caused by malaria exhibits a wide spectrum that consists of the relatively mild presentation of prostration as compared with convulsions and coma, which lie on the other end of this spectrum. Children whose presentation includes prostration have a lower mortality rate compared with children who have a more advanced impairment of their central nervous system, but have an increased mortality compared with children with uncomplicated malaria [1].

While the inclusion of a very large cohort from highly heterogeneous settings assures the generalizability of the findings, there is a risk that high interobserver variability occurred. This could explain, at least in part, the relatively poor performance of several clinical signs such as shock, prostration, and respiratory distress as indicators for severity in this study. It is reassuring that coma scales turned out to be valid prognostic indicators. A limitation of our study is the fact that not all participants in the trial had all test results assessed. The major reason for missing results was the unavailability of i-STAT results due to a malfunctioning analyzer or an interrupted supply of test cards.

Robust and locally affordable point-of-care tests to measure any base deficit would be highly desirable for the management of severe malaria patients in sub–Saharan Africa. Until such diagnostic tests are widely available, clinical signs

will have to suffice to guide clinicians. In the absence of a diagnostic test for respiratory acidosis, deep breathing signs can be a valuable marker for high risk patients in the hands of skilled observers. For large, multicenter studies, which employ observers with variable levels of training and skills, a standardized test for acidosis seems preferable.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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