

Published in final edited form as:

Clin Infect Dis. 2005 October 1; 41(7): 948–957.

The Prognostic Value of Measures of Acid/Base Balance in Pediatric *Falciparum* Malaria, Compared with Other Clinical and Laboratory Parameters

Charles R. J. C. Newton^{1,4}, Clarissa Valim^{6,8}, Sanjeev Krishna^{2,3}, David Wypij^{6,7,8,9}, Christopher Olola⁴, Tsiri Agbenyega⁵, Terrie E. Taylor¹⁰, and for the Severe Malaria in African Children Network^a

¹Institute of Child Health and

²Department of Cellular and Molecular Medicine, St. George's Hospital Medical School, London, United Kingdom;

³Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon;

⁴Centre for Geographic Medicine (Coast), Kenya Medical Research Institute, Kilifi, Kenya;

⁵Department of Physiology, School of Medical Sciences, University of Science and Technology, Kumasi, Ghana;

⁶Clinical Research Program and

⁷Department of Cardiology, Children's Hospital Boston,

⁸Department of Biostatistics, Harvard School of Public Health, and

⁹Department of Pediatrics, Harvard Medical School, Boston, Massachusetts; and

¹⁰Department of Internal Medicine, College of Osteopathic Medicine, Michigan State University, East Lansing

Abstract

Background—Identifying severe, life-threatening *falciparum* malaria in African children allows for the prompt institution of appropriate management. In the past 2 decades, hyperlactatemia and acidosis have been identified as being associated with mortality in patients with severe malaria, but measurement of blood lactate concentration and base excess is expensive and technically demanding. In this large, prospective study, we examined the prognostic value of acidosis and hyperlactatemia and compared these markers to clinically assessed variables.

Methods—We examined several clinical and laboratory measurements as prognostic markers of mortality in 14,605 parasitemic children admitted to 3 hospitals in Africa. Whole-blood lactate concentration and acid/base status were used to identify subjects who had hyperlactatemia and acidosis.

Results—Using cut-points established by sensitivity and specificity curves, the sensitivities and positive predictive values for both lactate concentration and base excess were low, the specificities were moderate, and the negative predictive values were high (>97%). No reliable clinical surrogates for hyperlactatemia or acidosis were identified. Addition of lactate concentration and base excess to predictive models with previously identified clinical features (Blantyre Coma Score, deep breathing,

Reprints or correspondence: Prof. Charles R. J. C. Newton, P.O. Box 230, Kilifi, Kenya (cnewton@kilifi.mimcom.net)..

^aMembers of the Severe Malaria in African Children Network are listed at the end of the text.

prostration, and weight-for-age Z score) and 1 laboratory measure (blood glucose level) did not appreciably improve models to predict mortality.

Conclusions—Measurements of lactate concentration and acid/base balance are expensive to perform, and performance of the latter can be problematic. Severe falciparum malaria may be readily recognized in children at admission to hospitals in sub-Saharan Africa with use of simple, inexpensive means and does not require knowledge of lactate concentration and base excess.

Falciparum malaria is responsible for >1 million deaths per year, with >70% of the burden of infections, morbidity, and mortality occurring in children in sub-Saharan Africa [1]. Most of these children are cared for in health facilities that are underresourced, particularly in terms of laboratory investigations. However, whether laboratory investigations (beyond simple clinical observations) have significant prognostic value for identification of children with severe malaria is unclear.

In 1986, the World Health Organization produced criteria for the definition of severe malaria that included laboratory investigations, such as determination of parasitemia, glucose level, and base excess (BE) value and assessment of renal function [2]. These criteria were based mainly on studies that involved semi-immune adults. The criteria were revised in 2000 [3], incorporating data from studies of African children that identified acidosis [4] and hyperlactatemia [5] as factors strongly associated with mortality. Although recent studies have confirmed that lactate concentration and acid/base status [6–11] are valuable prognostic indicators, health care providers have been slow to incorporate these measures into standard practice, largely because measurement of these values with conventional equipment is relatively expensive, and determination of acid/base status can be problematic.

We examined established clinical and laboratory prognostic markers of mortality for 3 sites in Africa. In particular, we examined whether the expensive and difficult laboratory investigations—estimation of blood lactate concentration and BE value—added significantly to the prognostic value of a combination of simple clinical observations and readily available and affordable laboratory investigations, including blood glucose concentration, in predicting mortality.

METHODS

Subjects

This study was conducted through the Severe Malaria in African Children (SMAC) research network. Subjects were enrolled at the time of admission to the following hospitals: Queen Elizabeth Central Hospital (Blantyre, Malawi; April 2001 through December 2003), Kilifi District Hospital (Kilifi, Kenya; June 2001 through December 2003), and Komfo-Anokye Teaching Hospital (Kumasi, Ghana; January 2001 through December 2003). Details about these sites are described elsewhere (T.E.T. et al., unpublished data). Children (from birth to the age of 180 months) who had asexual *Plasmodium falciparum* parasites detected in peripheral blood samples at hospital admission were eligible for the study.

Clinical examination and laboratory tests

After obtaining informed consent, patient history and clinical examination findings were recorded, including history of fever, seizures, and vomiting; temperature; respiratory rate; prostration (inability to sit); Blantyre Coma Score [12]; and spleen size. Respiratory pattern was defined as deep “Kussmaul-type” breathing [13] or as an irregular pattern of breathing. Clinical details were recorded before the results of the laboratory investigations were available. Venous blood samples were collected at the time of admission to the hospital to determine parasite count (by thick and thin film stained with 10% Giemsa), hematocrit (by

microhematocrit centrifuge in Blantyre, and by Sysmex KX-21N [Sysmex Corporation] in Kumasi) or hemoglobin level (by Coulter MDII [Coulter Electronics] in Kilifi), glucose level (by ACCU-CHEK [Roche Diagnostics] in Blantyre, by 2300 Statplus analyzer [YSI Corporation] Kumasi, and by Analox GL5 [Analox Instruments] in Kilifi), and blood gas levels (by StatProfile pHox Blood Gas/Oximeter [Nova Biomedical] in Blantyre and Kumasi, and by IL 1620 [Instrument Laboratories] in Kilifi). Reliable means to measure lactate concentrations were available only in Blantyre (Arkey LactateProLT-1710; Instruments Ltd.) and Kumasi (2300 Stat plus analyzer) only. Outcomes (patient died, survived, or absconded) were recorded for each patient.

Statistical methods

Tests for comparison of continuous variables across sites were based on analysis of variance and Kruskal-Wallis tests. Comparisons of proportions were based on Pearson χ^2 tests. Because of heterogeneity across sites, all analyses were site-specific. Optimal cut-points for BE value and lactate concentration for predicting mortality were chosen as the points at which the sensitivity and specificity curves crossed. To identify clinical markers of BE value and lactate concentration, we estimated Spearman rank correlation coefficients for continuous predictors and mean levels for binary predictors (with P values for comparisons based on Student's t test results). Linear regression methods were used to assess the effects of multiple predictor variables. Model selection was performed with the all-possible subsets regression procedure, to maximize the adjusted R^2 value.

Assessment of the ability of BE value and lactate concentration, in conjunction with other clinical and laboratory predictors, to predict malaria-related deaths was based on logistic regression methods. Clinical predictors or demographic variables were retained in the model if the P values were $<.05$ for all sites or if they increased the c statistic (a measurement of the predictive ability or concordance of the fitted model probabilities to the observed outcomes, equivalent to the area under the receiver operating characteristic curve) by ≥ 0.01 for at least 2 sites. We added readily available and affordable laboratory test measures to the model. Finally, we added BE value and lactate concentration to the selected models. To assess the predictive ability of BE value and lactate concentration, we examined the changes in the c statistic, comparing the model with clinical predictors, demographic variables, and standard laboratory investigations only with models in which BE value and/or lactate concentration were added. All P values are 2-tailed. Statistical analyses were performed using SAS software, version 9 (SAS Institute), and SPSS software, version 11.5 for Windows (SPSS).

RESULTS

The 14,605 subjects enrolled at the 3 sites were comparable with respect to demographic characteristics, temperature at the time of hospital admission, hematocrit, and blood glucose concentration (table 1). As a result, in part, of the large sample sizes, there were statistically significant differences across sites. By most measures, subjects from Kumasi were the most ill, and those from Blantyre were the least ill; subjects from Kilifi tended to have lower BE values than other subjects, and in Blantyre, hyperlactatemia was more common than it was elsewhere. Mortality rates were lowest in Blantyre and highest in Kumasi, consistent with the trends in severity.

Identifying cut-points for base excess value and lactate concentration

The distribution of BE values varied across sites, with lower values for the subjects who died (figure 1A). Using a cut-point BE value of less than or equal to -8 [7], the respective sensitivities and specificities were 36% and 98% in Blantyre, 78% and 57% in Kilifi, and 67% and 76% in Kumasi. With use of a cut-point BE value of less than or equal to -12 [14], the sensitivities

were 21% in Blantyre, 57% in Kilifi, and 45% in Kumasi, with specificities of $\geq 84\%$. The respective positive and negative predictive values for a BE value of less than or equal to -8 were 30% and 98% in Blantyre, 7% and 99% in Kilifi, and 13% and 98% in Kumasi; for a BE value of less than or equal to -12 , they were 60% and 98% in Blantyre, 12% and 98% in Kilifi, and 22% and 97% in Kumasi. The optimal cut-points to predict mortality were -0.1 in Blantyre, -9.3 in Kilifi, and -7.1 in Kumasi (figure 2A), suggesting that optimal BE cut-point selection can be heterogeneous across sites.

The distribution of lactate concentrations was similar in Blantyre and Kumasi (figure 1B). With use of the cut-point for lactate concentration of >5 mmol/L [5, 15, 16], the sensitivities and specificities were moderate in magnitude: 72% and 71% in Blantyre and 60% and 77% in Kumasi, respectively. The positive predictive values for a lactate concentration of >5 mmol/L were low (6% in Blantyre and 12% in Kumasi), although the negative predictive values were extremely high (99% in Blantyre and 97% in Kumasi). The optimal cut-points to predict mortality were 5.1 mmol/L in Blantyre and 4.1 mmol/L in Kumasi (figure 2B).

Surrogate clinical markers for BE value and lactate concentration

At all sites, mean BE values were significantly lower ($P < .001$) for all binary risk factors, except for vomiting in Blantyre, seizures in Kilifi, and vomiting and seizures in Kumasi (table 2). Similarly, BE value was significantly correlated ($P < .001$) with continuous clinical and laboratory test predictors, except for hemoglobin level, hematocrit, and temperature in Kilifi; weight-for-age Z score, spleen size, and hematocrit in Blantyre; and temperature in Kumasi. However, the Spearman rank correlation coefficients between BE and continuous predictors were only moderate in magnitude. At all sites, the strongest correlations with BE value were positive associations with Blantyre Coma Score ($r = 0.22$ in Blantyre, $r = 0.20$ in Kilifi, and $r = 0.22$ in Kumasi) and with glucose level in Kilifi ($r = 0.19$) and Kumasi ($r = 0.21$), with inverse associations between BE value and parasitemia in Blantyre ($r = -0.15$) and Kilifi ($r = -0.16$).

In multiple linear regression models to predict BE on the basis of clinical, demographic, and laboratory candidate predictors, the maximum adjusted R^2 values attained in Blantyre, Kilifi, and Kumasi were 0.19, 0.42, and 0.26, respectively. When lactate concentration was included as a covariate in the model selection, the maximum adjusted R^2 increased to 0.22 in Blantyre and to 0.40 in Kumasi. Therefore, at most, $\sim 40\%$ of the variability in BE value was accounted for by the other covariates, suggesting that these variables (alone or in combination) cannot serve as good surrogate measures for BE value. The factors that were consistently selected in models that had the highest adjusted R^2 at the 3 sites included deep breathing, parasitemia, age, hematocrit, temperature, and glucose level.

We assessed the relationships between acidosis (BE value, less than or equal to -8) and deep breathing, irregular breathing, hyperlactatemia, and hypoglycemia (blood glucose level, <2.2 mmol/L). The proportions of acidotic subjects who did not have deep breathing (63% in Blantyre, 81% in Kilifi, and 68% in Kumasi) or irregular breathing (71% in Blantyre, 96% in Kilifi, and 89% in Kumasi) were high at all sites, suggesting that not all subjects with acidosis present with either deep or irregular breathing. The proportions of subjects without acidosis but with deep breathing (3% in Blantyre, 4% in Kilifi, and 11% in Kumasi), irregular breathing (4% in Blantyre, 1% in Kilifi, and 4% in Kumasi), or hypoglycemia (1% in Blantyre, 2% in Kilifi, and 2% in Kumasi) were relatively low. Therefore, when present, these markers are highly specific and rarely misclassify subjects as having false-positive results. Hyperlactatemia and acidosis were dissociated in a moderate number of subjects in Blantyre and Kumasi. The absence of hyperlactatemia misclassified as false negatives 33% of acidotic subjects in Blantyre and 44% in Kumasi; the presence of hyperlactatemia misclassified as false positives 29% of nonacidotic subjects in Blantyre and 15% in Kumasi.

Mean lactate concentrations were typically 1.5–2-fold higher in subjects who had a risk factor for severe disease, compared with subjects who did not have such risk factors (table 2). In Blantyre and Kumasi, mean lactate values were significantly higher ($P < .001$) for all binary risk factors, except for vomiting in Blantyre and seizures in Kumasi. Lactate concentration was significantly correlated with continuous clinical and laboratory test predictors ($P < .001$), except for weight-for-age Z scores and temperature in Blantyre and for weight-for-age Z scores and glucose level in Kumasi. Spearman rank correlations were only moderate in magnitude, with the largest correlations with Blantyre Coma Score ($r = -0.21$ in Blantyre and $r = -0.25$ in Kumasi) and hematocrit ($r = -0.20$ in Blantyre and $r = -0.34$ in Kumasi). BE value and lactate concentration had a weak-to-moderate inverse association ($r = -0.17$ in Blantyre and $r = -0.41$ in Kumasi). In multiple linear regression models to predict lactate concentration that were based on all candidate predictors, the maximum adjusted R^2 values were 0.15 in Blantyre and 0.42 in Kumasi. When BE value was allowed as a covariate in the model selection, these values increased to 0.17 in Blantyre and 0.53 in Kumasi.

Prognostic models for mortality

We chose to assess the predictive ability of acidosis and hyperlactatemia using BE value and lactate concentration as continuous covariates, because the optimal cut-points for BE value differed across sites, and both variables were approximately linearly associated with the log odds of the probability of death. Lower BE value and higher lactate concentration were associated with mortality. The crude ORs per unit decrease in BE value were 1.29 in Blantyre (95% CI, 1.23–1.34; $c = 0.81$), 1.22 in Kilifi (95% CI, 1.18–1.25; $c = 0.78$), and 1.22 in Kumasi (95% CI, 1.18–1.25; $c = 0.76$). The crude ORs per unit increase in lactate concentration were 1.19 in Blantyre (95% CI, 1.14–1.25; $c = 0.76$) and 1.24 in Kumasi (95% CI, 1.20–1.28; $c = 0.74$). The P values for all BE value and lactate concentration ORs were $<.001$. BE value and lactate concentration had the highest predictive abilities (i.e., c statistics) among all univariate models considered.

In the multiple logistic regression analysis of predictors of mortality with candidate clinical and demographic variables, the following covariates attained P values of $\leq .01$ at all sites: deep breathing, Blantyre Coma Score of ≤ 2 , inability to sit, and weight-for-age Z score. The c statistics for models including each of these variables for Blantyre, Kilifi, and Kumasi were 0.85, 0.84, and 0.80, respectively. Other predictor variables that were statistically significantly associated with mortality included vomiting in Blantyre; irregular breathing, seizures, and indrawing in Kilifi; and irregular breathing and seizures in Kumasi. However, the addition of these variables to the model did not increase the c statistic by >0.01 , nor did they appreciably confound the other covariates in the model.

Next, we added affordable laboratory tests to the logistic regression model (i.e., tests other than those for BE value and lactate concentration). In all sites, the only statistically significant laboratory test ($P < .01$) was hypoglycemia, which increased the c statistic to 0.85, 0.86, and 0.81 in Blantyre, Kilifi, and Kumasi, respectively. Neither hyperparasitemia nor severe anemia achieved P values $<.1$ or increased the c statistic by more than 0.01.

When added separately to this multivariable model, both BE value and lactate concentration reached statistical significance ($P < .001$) at each site. Table 3 presents the ORs for the logistic regression models including both BE value and lactate concentration. The adjusted associations of individual predictors and mortality tended to be stronger in Blantyre. When BE value was included with lactate concentration in multivariable models, the P value for the coefficient of lactate was $>.1$ for each site. The c statistic of this model was high (0.88, 0.87, and 0.83 in Blantyre, Kilifi, and Kumasi, respectively). Although BE value remained a statistically significant predictor of mortality at all sites, the addition of BE value and lactate concentration only slightly improved the predictive ability of the model that included the clinical predictors

and hypoglycemia (c statistic increases of 0.03 in Blantyre, 0.01 in Kilifi, and 0.02 in Kumasi). The receiver operating characteristic curves of these model-based criteria, with and without BE value and lactate concentration, were comparable (figure 3).

Clinical implications

We investigated the number of deaths that would have been misclassified as being of low risk at hospital admission on the basis of simplified clinical criteria, compared with use of additional information on BE value and lactate concentration. Classification of a child as being at high risk if he or she had coma, deep breathing, inability to sit, or hypoglycemia at admission captured 84% of 432 deaths. Addition of acidosis (BE value, less than or equal to -8) to these criteria increased this percentage by 6%, to 90% (389 of 432 deaths). Addition of hyperlactatemia (lactate concentration, >5 mmol/L) instead of acidosis would have increased this percentage in Blantyre and Kumasi by 5%, from 87% (223 of 257 deaths) to 92% (236 of the 257 deaths). Among subjects who died and who had acidosis, 91% met at least 1 of the clinical or hypoglycemic criteria. Among subjects who died and who had hyperlactatemia, 92% satisfied at least 1 of the clinical or hypoglycemic criteria. Therefore, acidosis and hyperlactatemia were captured by at least 1 of the clinical or hypoglycemic criteria in most subjects who died.

DISCUSSION

Both acidosis and hyperlactatemia were significantly associated with mortality in children with severe falciparum malaria admitted to these hospitals in sub-Saharan Africa. However, neither of these laboratory tests on venous blood, used alone, appeared to predict death accurately, and the cut-points for BE value varied with site. These tests did not appreciably add to the predictive ability of a model based on clinical features and a relatively simple laboratory test, blood glucose, which prompts immediate therapy.

The predictive ability of some clinical features varied across sites. Efforts to standardize observations within the SMAC network were made before the start of the study, so these results should be extrapolated with caution to other settings in which the staff have had less training. The variability may represent differences in the patient populations at each hospital; differences related to measurements of these parameters are possible but are less likely, given the standardized methods employed. The clinical predictors suggested that children admitted to Kumasi were more ill than were those at the other 2 sites.

There was variability in measurements of acid/base balance. The optimal cut-points for venous BE value varied across sites, but a cut-point of 5 mmol/L for hyperlactatemia was nearly optimal at the 2 sites that assessed this parameter. The differences between sites could reflect differences in the types of patients admitted to each hospital or different methods of processing the sample. The latter is less likely, because identical Lactate Pro machines were used in Blantyre and Kumasi, and the appropriate quality controls were used for all 3 blood gas machines. Both tests were strong univariate predictors of malaria mortality. However, our analyses suggest that neither of these tests, taken alone, will effectively predict malaria deaths at any cut-point. The high negative predictive values for these tests are unlikely to influence clinical management.

None of the standard clinical observations or laboratory investigations were reliable surrogate markers for acidosis or hyperlactatemia. Although deep and/or irregular breathing, coma, and hypoglycemia were associated with hyperlactatemia and acidosis across all 3 sites, none of these features, either alone or in combination, can be used to identify children with acidosis or hyperlactatemia reliably. Although deep breathing was reported to be specific and sensitive for detection of acidosis in a small study of well-trained clinicians [13], we did not find that it

was a sensitive marker of acidosis in this larger study, which was more representative of practice in Africa. However, it was specific in Blantyre and Kilifi. In Kumasi, the clinicians occasionally knew the results of some laboratory investigations before assessing the clinical findings, but this does not appear to have improved the relationship between the clinical features and the results of these tests. Acidosis and hyperlactatemia are likely to have a number of different causes [17], and their clinical manifestations are probably influenced by other pathophysiological perturbations in falciparum malaria. Furthermore, interobserver variability in detecting these clinical signs may reduce their sensitivity and specificity for acidosis or hyperlactatemia.

Thus, although the measurement of levels of blood gases and lactate help identify children admitted to African hospitals who are likely to die of severe falciparum malaria, these parameters add little to the prognostic significance of a simpler, less expensive, model-based decision rule that includes clinical features and blood glucose level. The measurements of blood gas and lactate concentrations, however, may be useful in identifying children for trials of interventions targeted specifically against acidosis and/or hyperlactatemia. Findings from this large prospective comparison suggest that these measures are not essential laboratory investigations for the management of severe falciparum malaria in sub-Saharan African hospitals.

MEMBERS OF THE SMAC NETWORK

This article is published on behalf on the SMAC network, which includes contributions from the following individuals: Dominic Kwaitkowski, Emmanuel Onyekwelu, David Ameh, Ismaela Abubakar, Janet Fullah, Jalli Mori, Abdou Bah, Pamela Esangbedo, Kalifa Bojang, Mariatou Jallow, Stanley Usen, and Augustine Ebonyi (Banjul, The Gambia); Lloyd Bwanaisa, Alfred Njobvu, James Mwenechanya, Beatrice Mkondiwa, Timothy Mnalemba, Dina Kayaya, Collins Qongwane, Maganizo Chagomerana, and Sophie Kazembe (Blantyre, Malawi); Joshua Ngala, Rachael Odhiambo, Sadik Mithwani, Kathryn Maitland, Betty Wamola, Brett Lowe, and Norbert Peshu (Kilifi, Kenya); Daniel Ansong, Osei Yaw Akoto, Emmanuel Asafo-Adjei, Alex Owusu-Ofori, Cynthia Donkor, Sampson Antwi, Justice Sylverkyn, Kingsley Osei-Kwakye, David Sambian, Victor Degenu, Mbort Atan Ayibo, Evelyn Anane-Sarpong, Vida Asante, Emmanuel Owusu-Ansah, and Esther Esumming (Kumasi, Ghana); and Peter Kremsner, Saadou Issifou, Pierre Blaise Matsiegui, Bertrand Lell, Steffen Borrmann, Tim Planche, Maryvonne Kombila, Arnaud Dzeing, Frankie Mbadinga, and Nestor Obiang (Lambaréne, Gabon).

Acknowledgements

Financial support. US National Institutes of Health, Institute of Allergy and Infectious Diseases (AI45955; to C.V., D.W., C.O., and T.E.T.); the Wellcome Trust, United Kingdom (050533; to C.R.J.C.N.); St. George's Hospital Medical School, London, United Kingdom (to S.K.); and the University of Science and Technology, Kumasi, Ghana (to T.A.).

Potential conflicts of interest. All authors: no conflicts.

References

1. World Health Organization (WHO). The world health report. Geneva: WHO, 2001
2. World Health Organization Malaria Action Programme. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1986;80(Suppl):3–50. [PubMed: 3523867]
3. World Health Organization. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000;94 (Suppl):S1–90. [PubMed: 11103309]
4. Taylor TE, Borgstein A, Molyneux ME. Acid-base status in paediatric *Plasmodium falciparum* malaria. *Q J Med* 1993;86:99–109. [PubMed: 8464997]

5. Waller D, Krishna S, Crawley J, et al. Clinical features and outcome of severe malaria in Gambian children. *Clin Infect Dis* 1995;21:577–87. [PubMed: 8527547]
6. Maitland K, Pamba A, Newton CR, Levin M. Response to volume resuscitation in children with severe malaria. *Pediatr Crit Care Med* 2003;4:426–31. [PubMed: 14525636]
7. Maitland K, Levin M, English M, et al. Severe *P.falciparum* malaria in Kenyan children: evidence for hypovolaemia. *QJM* 2003;96:427–34. [PubMed: 12788961]
8. Planche T, Agbenyega T, Bedu-Addo G, et al. A prospective comparison of malaria with other severe diseases in African children: prognosis and optimization of management. *Clin Infect Dis* 2003;37:890–7. [PubMed: 13130399]
9. Planche T, Onanga M, Schwenk A, et al. Assessment of volume depletion in children with malaria. *PLoS Med* 2004;1:e18. [PubMed: 15526044]
10. Dzeing-Ella A, Nze Obiang PC, Tchoua R, et al. Severe falciparum malaria in Gabonese children: clinical and laboratory features. *Malar J* 2005;4:1. [PubMed: 15638948]
11. Maitland K, Pamba A, Fegan G, et al. Perturbations in electrolyte levels in Kenyan children with severe malaria complicated by acidosis. *Clin Infect Dis* 2005;40:9–16. [PubMed: 15614686]
12. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989;71:441–59. [PubMed: 2690177]
13. English M, Murphy S, Mwangi I, Crawley J, Peshu N, Marsh K. Interobserver variation in respiratory signs of severe malaria. *Arch Dis Child* 1995;72:334–6. [PubMed: 7763067]
14. English M, Waruiru C, Amukoye E, et al. Deep breathing in children with severe malaria: indicator of metabolic acidosis and poor outcome. *Am J Trop Med Hyg* 1996;55:521–4. [PubMed: 8940984]
15. Stacpoole PW. Lactic acidosis. *Endocrinol Metab Clin North Am* 1993;22:221–45. [PubMed: 8325284]
16. Agbenyega T, Planche T, Bedu-Addo G, et al. Population kinetics, efficacy, and safety of dichloroacetate for lactic acidosis due to severe malaria in children. *J Clin Pharmacol* 2003;43:386–96. [PubMed: 12723459]
17. Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. *Pharmacol Ther* 1998;79:1–53. [PubMed: 9719344]

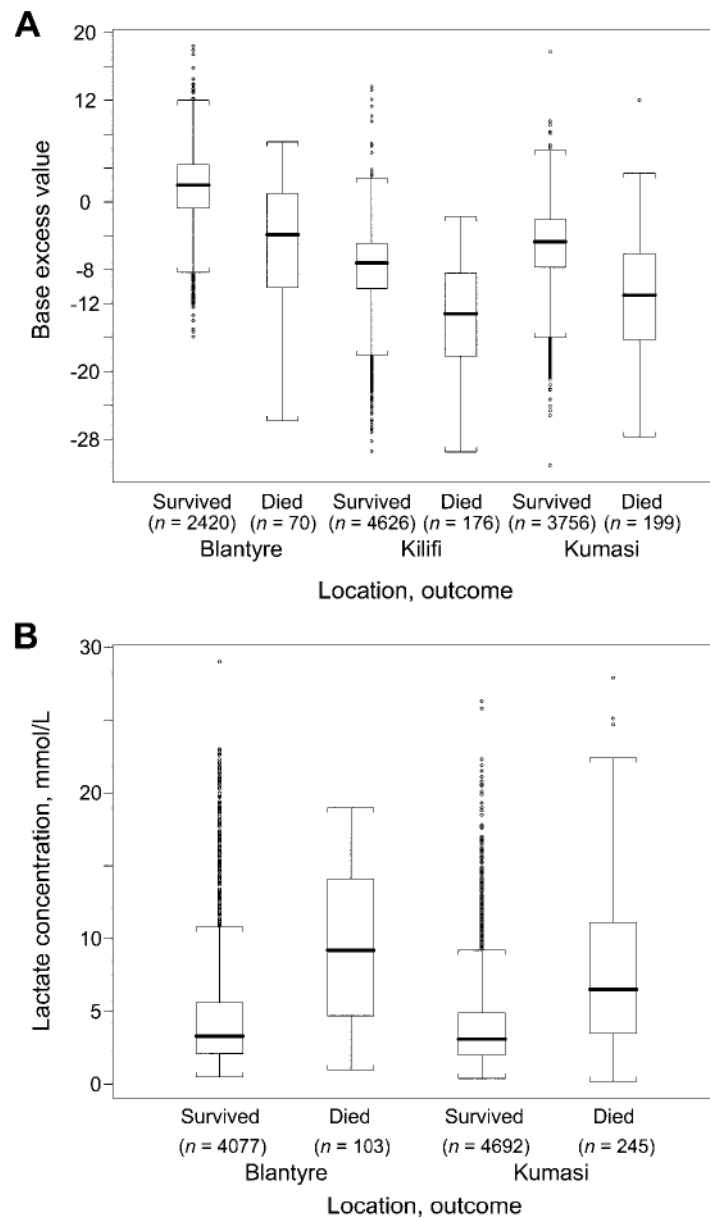


Figure 1.

Box plots of base excess value (A) and lactate concentration (B), according to outcome status and by site. The solid bar within each box represents median value; the upper boundary of the box represents the 75th percentile; the lower boundary of the box represents the 25th percentile; whiskers extend to the most extreme observation within 1.5 interquartile range units of the 25th and 75th percentiles. More extreme values are plotted with small circles.

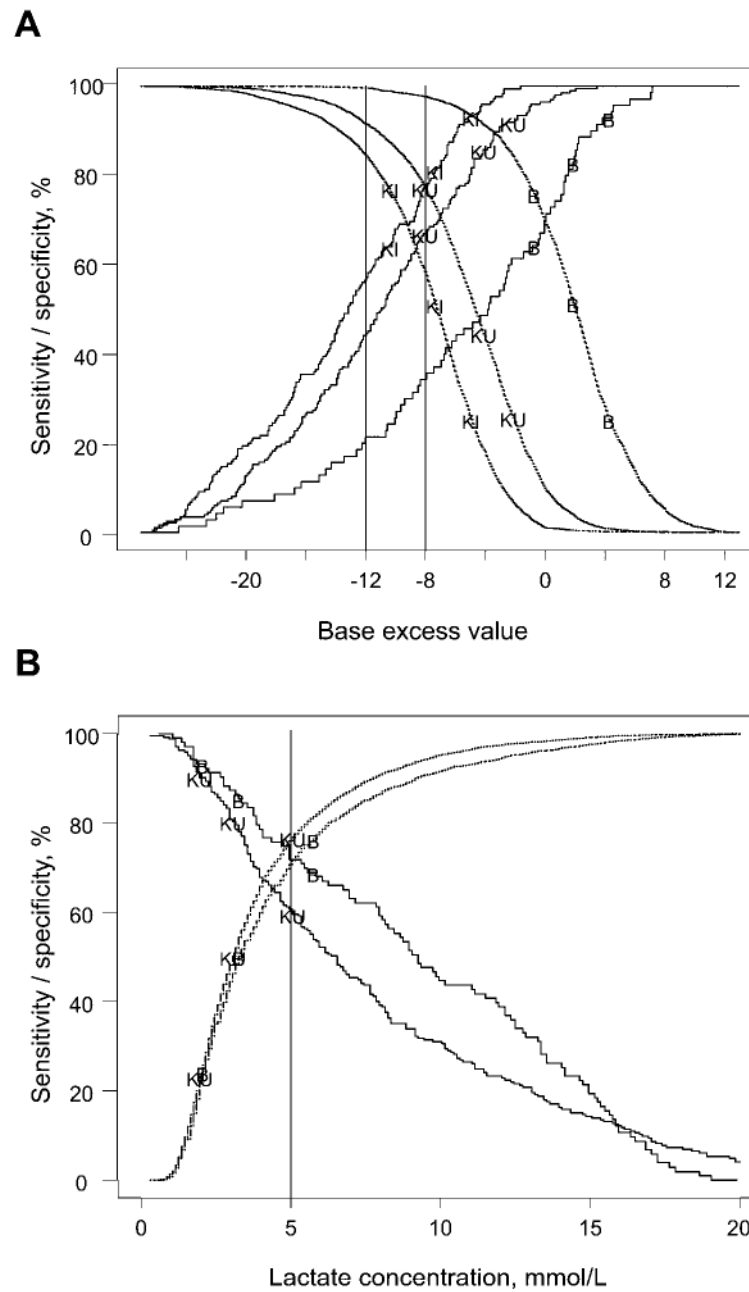


Figure 2. Sensitivity curves (*solid lines*) and specificity curves (*dashed lines*) for prediction of mortality as a function of base excess value (*A*) and lactate concentration (*B*), by site. Initials for the sites are positioned at the quartiles of the site-specific distributions of BE value and lactate concentration. B, Blantyre, Malawi; KI, Kilifi, Kenya; KU, Kumasi, Ghana.

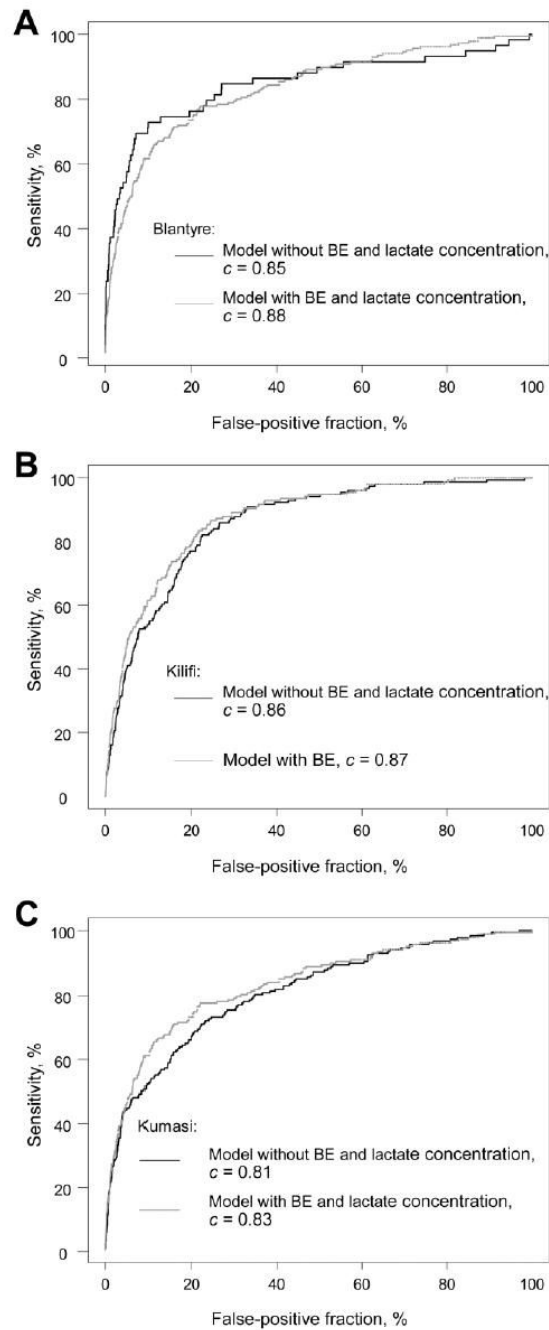


Figure 3.

Receiver operating characteristic curves and c statistics of the predicted probability of mortality from models including only clinical predictors and hypoglycemia (*solid lines*) and models including clinical predictors, hypoglycemia, base excess value (BE), and lactate concentration (*dashed lines*) for Blantyre, Malawi (A); Kilifi, Kenya (B); and Kumasi, Ghana (C).

Table 1
Demographic, clinical, and laboratory test characteristics of and outcomes for African children with malaria, by site.

Characteristic or finding, by class	Blantyre, Malawi (n = 4362)	Kilifi, Kenya (n = 5274)	Kumasi, Ghana (n = 4969)
Demographic			
Age, mean months $\pm$ SD	36 $\pm$ 32	34 $\pm$ 28	32 $\pm$ 29
Male sex	54	53	55
Weight, mean kg $\pm$ SD	12.0 $\pm$ 5.5	10.8 $\pm$ 4.5	11.5 $\pm$ 5.2
Weight-for-age Z score, mean $\pm$ SD	-1.8 $\pm$ 1.7	-2.4 $\pm$ 1.7	-1.7 $\pm$ 1.6
Medical history			
Seizures	18	18	44
Vomiting	42	31	56
Examination findings at admission			
Deep breathing	5	11	16
Indrawing	2	14	19
Irregular breathing	4	3	6
Unable to sit	28	26	47
Blantyre coma score ≤ 2	5	10	13
Blantyre coma score ≤ 4	9	20	25
Temperature, mean $^{\circ}\text{C} \pm \text{SD}$	38.4 $\pm$ 1.2	38.3 $\pm$ 1.2	37.8 $\pm$ 1.1
Spleen size, mean cm $\pm$ SD	0.7 $\pm$ 1.4	0.9 $\pm$ 1.7	1.6 $\pm$ 2.0
Laboratory test results at admission			
Parasite count, median parasites $\times 10^3/\mu\text{L}$ (IQR)	81 (33–177)	43 (3–214)	75 (17–265)
Hyperparasitemia ^a	4	8	12
Hematocrit, mean % $\pm$ SD	26.8 $\pm$ 7.9	24.7 $\pm$ 7.6	20.0 $\pm$ 7.4
Hemoglobin, mean g/dL $\pm$ SD	... ^b	7.8 $\pm$ 2.4	6.7 $\pm$ 2.5
Anemia ^c	8	12	28
Glucose, mean mmol/L $\pm$ SD	5.5 $\pm$ 1.9	5.4 $\pm$ 2.4	5.4 $\pm$ 2.9
Hypoglycemia ^d	2	5	5
Base excess value			
Mean $\pm$ SD	-1.5 $\pm$ 4.6	38.1 $\pm$ 4.7	35.5 $\pm$ 4.9
Less than or equal to -8	3	44	26
Less than or equal to -12	1	17	10
Lactate concentration, mean mmol/L $\pm$ SD	4.7 $\pm$ 3.9	... ^e	4.2 $\pm$ 3.3
Hyperlactatemia ^f	30	... ^e	25
Mortality	2.5	3.6	5.0

NOTE. Data are percentage of patients, unless indicated otherwise. To compare sites, Pearson χ^2 tests were used to compare proportions, the Kruskal-Wallis test was used to compare parasitemia levels, and analysis of variance was used to compare other continuous variables. *P* values for each comparison were $< .001$, except for sex ($P = .21$) and glucose level ($P = .10$). IQR, interquartile range.

^aParasite load, $> 500,000$ parasites $\times 10^3/\mu\text{L}$.

^bHemoglobin level was not measured in Blantyre.

^cDefined as a hematocrit of $< 15\%$ or a hemoglobin level of $< \text{g/dL}$.

^dGlucose level, ≤ 2.2 mmol/L.

^eLactate concentration was not measured in Kilifi.

^fLactate concentration, > 5 mmol/L.

Table 2
Base excess value and lactate concentration across levels of risk factors in African children with malaria, by site.

Risk factor	Mean value $\pm$ SD				
	Base excess value		Lactate concentration, mmol/L		
	Blantyre, Malawi	Kilifi, Kenya	Kumasi, Ghana	Blantyre, Malawi	Kumasi, Ghana
Vomiting					
Yes	1.2 $\pm$ 4.8	-9.1 $\pm$ 5.3	-5.6 $\pm$ 5.1	4.9 $\pm$ 4.1	4.4 $\pm$ 4.4
No	1.8 $\pm$ 4.3	37.7 $\pm$ 4.4	-5.4 $\pm$ 4.6	4.6 $\pm$ 3.8	3.9 $\pm$ 3.1
Seizures					
Yes	0.4 $\pm$ 5.0	-8.2 $\pm$ 4.3	-5.6 $\pm$ 4.9	5.5 $\pm$ 4.3	4.1 $\pm$ 3.1
No	1.8 $\pm$ 4.4	-8.1 $\pm$ 4.8	-5.4 $\pm$ 4.9	4.5 $\pm$ 3.8	4.2 $\pm$ 3.4
Deep breathing					
Yes	-3.6 $\pm$ 7.3	-13.3 $\pm$ 6.3	-8.9 $\pm$ 6.0	7.9 $\pm$ 5.3	7.1 $\pm$ 4.6
No	1.8 $\pm$ 4.2	-7.5 $\pm$ 4.1	-4.8 $\pm$ 4.4	4.5 $\pm$ 3.8	3.6 $\pm$ 2.6
Indrawing					
Yes	-3.2 $\pm$ 6.0	-10.0 $\pm$ 5.7	-8.0 $\pm$ 5.9	7.5 $\pm$ 5.2	6.3 $\pm$ 4.5
No	1.6 $\pm$ 4.4	-7.8 $\pm$ 4.5	-4.9 $\pm$ 4.4	4.6 $\pm$ 3.8	3.7 $\pm$ 2.6
Irregular breathing					
Yes	-2.8 $\pm$ 6.0	-12.0 $\pm$ 6.3	-9.0 $\pm$ 6.5	7.7 $\pm$ 5.3	6.9 $\pm$ 5.2
No	1.7 $\pm$ 4.4	-8.0 $\pm$ 4.7	-5.3 $\pm$ 4.7	4.6 $\pm$ 3.8	4.0 $\pm$ 3.0
Unable to sit					
Yes	0.1 $\pm$ 5.5	-10.0 $\pm$ 5.5	-6.7 $\pm$ 5.4	5.5 $\pm$ 4.3	5.1 $\pm$ 3.8
No	2.0 $\pm$ 4.0	-7.4 $\pm$ 4.2	-4.4 $\pm$ 4.1	4.4 $\pm$ 3.7	4.3 $\pm$ 2.3
Anemia					
Yes	-0.7 $\pm$ 6.5	-9.7 $\pm$ 5.7	-6.6 $\pm$ 5.5	8.0 $\pm$ 5.0	5.8 $\pm$ 4.5
No	1.7 $\pm$ 4.3	-7.9 $\pm$ 4.5	-5.1 $\pm$ 4.6	4.4 $\pm$ 3.6	3.5 $\pm$ 2.4
Hyperparasitemia					
Yes	-0.6 $\pm$ 5.2	-10.3 $\pm$ 4.8	-7.1 $\pm$ 5.2	5.9 $\pm$ 4.4	5.3 $\pm$ 3.2
No	1.6 $\pm$ 4.5	-7.9 $\pm$ 4.7	-5.3 $\pm$ 4.8	4.6 $\pm$ 3.9	4.0 $\pm$ 3.2
Hypoglycemia					
Yes	-5.0 $\pm$ 5.8	-13.0 $\pm$ 5.9	-11.8 $\pm$ 6.1	9.5 $\pm$ 5.6	8.8 $\pm$ 5.8
No	1.7 $\pm$ 4.4	-7.8 $\pm$ 4.5	-5.1 $\pm$ 4.6	4.6 $\pm$ 3.8	3.9 $\pm$ 2.9
Hyperlactatemia					
Yes	0.3 $\pm$ 5.1	...	-9.4 $\pm$ 5.3	...	...
No	2.1 $\pm$ 4.1	...	-4.2 $\pm$ 4.0	...	...
Blantyre coma score					
≤ 2					
Yes	-3.1 $\pm$ 7.1	-10.9 $\pm$ 5.5	-8.5 $\pm$ 6.3	8.8 $\pm$ 5.3	6.3 $\pm$ 4.7
No	1.8 $\pm$ 4.2	-7.8 $\pm$ 4.5	-5.1 $\pm$ 4.5	4.5 $\pm$ 3.7	3.8 $\pm$ 2.9
≤ 4					
Yes	-2.4 $\pm$ 6.5	-10.1 $\pm$ 5.5	-7.6 $\pm$ 6.0	7.8 $\pm$ 5.1	5.7 $\pm$ 4.3
No	1.9 $\pm$ 4.1	-7.6 $\pm$ 4.4	-4.8 $\pm$ 4.3	4.4 $\pm$ 3.6	3.6 $\pm$ 2.6
BE value less than or equal to -8					
Yes	...	...	...	10.1 $\pm$ 5.8	6.9 $\pm$ 4.7
No	...	...	...	4.6 $\pm$ 3.6	3.3 $\pm$ 1.8

NOTE. *t* Tests were used to compare base excess (BE) values and lactate concentrations across levels of risk factors, by site. *P* values for each BE comparison were $<.001$, except for vomiting in Blantyre ($P = .003$), seizures in Kilifi ($P > .10$), and vomiting and seizures in Kumasi ($P > .10$ for each). *P* values for each lactate comparison were $<.001$, except for vomiting in Blantyre ($P = .02$) and seizures in Kumasi ($P > .10$).

Table 3
Predictors of mortality via multiple logistic regression in African children with malaria, by site.

Characteristic	Blantyre, Malawi(<i>n</i> = 2159)	Kilifi, Kenya(<i>n</i> = 4670)	Kumasi, Ghana(<i>n</i> = 3730)
Weight-for-age Z score (per unit increase)	0.84 (0.71–1.01)	0.75 (0.68–0.82)	0.90 (0.81–0.99)
Deep breathing	3.78 (1.76–8.14)	1.53 (0.99–2.36)	2.26 (1.57–3.27)
Blantyre coma score ≤2	2.29 (1.05–5.03)	1.93 (1.25–2.99)	3.15 (2.18–4.56)
Unable to sit	3.64 (1.73–7.63)	2.65 (1.68–4.17)	1.83 (1.17–2.85)
Hypoglycemia ^a	2.17 (0.77–6.12)	2.48 (1.57–3.92)	2.10 (1.34–3.29)
Lactate (per mmol/l increase)	1.05 (0.99–1.12)	...	1.02 (0.98–1.07)
Base excess (per unit decrease)	1.14 (1.08–1.21)	1.13 (1.09–1.17)	1.11 (1.07–1.15)
c Statistic	0.88	0.87	0.83

NOTE. Data are OR (95% CI), unless otherwise indicated. There were a total of 59 deaths in Blantyre, 156 deaths in Kilifi, and 183 deaths in Kumasi. *P* values were <.05 whenever an OR of 1.0 was excluded from the 95% CI. Also, *P* = .06 for weight-for-age Z score, *P* = .14 for hypoglycemia, and *P* = .14 for lactate concentration in Blantyre; *P* = .06 for deep breathing in Kilifi; and *P* = .31 for lactate concentration in Kumasi.

^a Glucose level, ≤2.2 mmol/L.