Inter-Relationships of Cardinal Features and Outcomes of Symptomatic Pediatric Plasmodium falciparum Malaria in 1,933 Children in Kampala, Uganda

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Abstract. Malaria remains a challenging diagnosis with variable clinical presentation and a wide spectrum of disease severity. Using a structured case report form, we prospectively assessed 1,933 children at Mulago Hospital in Kampala, Uganda with acute Plasmodium falciparum malaria. Children with uncomplicated malaria significantly differed from those with severe disease for 17 features. Among 855 children with severe disease, the case-fatality rate increased as the number of severity features increased. Logistic regression identified five factors independently associated with death: cerebral malaria, hypoxia, severe thrombocytopenia, leukocytosis, and lactic acidosis. Cluster analysis identified two groups: one combining anemia, splenomegaly, and leukocytosis; and a second group centered on death, severe thrombocytopenia, and lactic acidosis, which included cerebral malaria, hypoxia, hypoglycemia, and hyper-parasitemia. Our report updates previous clinical descriptions of severe malaria, quantifies significant clinical and laboratory interrelationships, and will assist clinicians treating malaria and those planning or assessing future research (NCT00707200) (www.clinicaltrials.gov).

INTRODUCTION

Children with malaria have a wide variety of signs and symptoms. The World Health Organization recognizes numerous hallmark features of severe malaria (Table 1).1 Acute malaria syndromes carry diagnostic value and prognostic importance, but do not occur with equal prevalence among different age groups and across different regions. The severity of clinical infection in malaria depends on complex interactions of host, parasite, and environmental factors.1

Numerous previous studies have analyzed clinical features in malaria. Early work by Marsh and others established that three overlapping syndromes were found in severe disease: cerebral malaria (CM), respiratory distress (RD), and severe malaria anemia (SMA).2,3 Subsequent reports further characterized the clinical findings of malaria and established fundamental patterns of the illness.4–14 These patterns include the importance of impaired consciousness as a risk-factor for fatal outcome, the value of blood transfusion in the treatment of severe anemia, hypoglycemia during acute illness, and the observation of RD as a manifestation of lactic acidosis (LA). These studies were published more than 15 years ago and most were based on < 500 patients.

During 2000–2010, additional reports refined the case definitions of severe malaria. Two studies of children with severe malaria in Gabon and a third study from Mali reported that mortality was associated with CM, hypoglycemia, RD and L.A.15–17 These reports were unable to assess the contribution of increased blood lactate levels, thrombocytopenia, and leukocytosis to outcomes. Idro and others18 provided a detailed description of 100 children with CM treated in Uganda and identified RD, circulatory failure, hyporeflexia, and hyper-parasitemia as additive risk factors for fatal outcomes. In a subsequent report of more than 9,000 children in Kenya with malaria, they confirmed that acidosis, hypoglycemia, and circulatory collapse were associated with neurologic signs.19 Smaller studies from Ghana20 and Gabon21 and a multicenter sub-Saharan study22 further defined complications of severe disease. In a review of 25 previously published studies, Roca-Feltrer and others reported that the age distribution for SMA was consistently younger than that for CM.23 Recently, Vekemans and others24 provided a thorough review of the published literature through 2010 and suggested a standardized case definition for severe malaria for use in a multicenter phase III vaccine trial. Their report provides the most up-to-date approach to classifying severe malaria on the basis of previously available data.

In this report, we present results of a prospective observational study of clinical and laboratory features among 1,933 children with acute Plasmodium falciparum malaria at Mulago Hospital during 2007–2009. We used newer clinical assays, including blood lactate levels, oximetry, and complete blood counts. We present data on the prevalence of major malaria syndromes; the impact of specific syndromes on case-fatality rates; and, for the first time, a cluster analysis of the extent of association between different clinical features present in a large cohort of children with severe malaria. Our findings update the clinical description of severe malaria in children, respond to requests for improved case definitions for severe malaria,25 and may suggest new research targets and novel treatments for specific sub-groups of patients.

METHODS

Study population. Children 6 months to 12 years of age with either uncomplicated or severe malaria were enrolled in a prospective observational study conducted at the Acute Care Unit of Mulago Hospital in Kampala, Uganda.26 Mulago Hospital is a 1,500 bed national referral center and teaching hospital of Makerere University College of Health Sciences where a previous study documented a 4.2% case-fatality rate among 23,342 children with malaria.27 Children were enrolled during October 2007–October 2009. The diagnosis of malaria
counts were determined by two independent observers counting Brea, CA), blood lactate (LactatePro LT-1710; Arkray, Kyoto, blood grouping was determined by using commercial reagents (Ascensia Contour; Bayer HealthCare LLC, Mishawaka, IN).

All enrolled persons were tested for infection with human immunodeficiency virus (HIV); twenty-six were positive and forty-five were assigned to either uncomplicated malaria or severe malaria were not enrolled in the study so that analysis was suspected on the basis of clinical symptoms and a positive thick blood smear examined by an experienced laboratory technician, and subsequently confirmed by two expert reviewers from a reference parasitology laboratory who examined in a blinded fashion thick and thin blood smears from each person. Uncomplicated malaria was defined as the absence of any impairment of consciousness or hypoxia, with peripheral blood lactate levels < 5 mM and hemoglobin (Hb) levels > 7 g/dL without transfusion. Severe malaria was defined as impaired consciousness, arterial oxygen saturation < 90%, lactate blood levels > 5 mM, or an Hg level < 5 g/dL (or < 6 g/dL if tested after transfusion). Children who did not meet the above criteria for either uncomplicated or severe malaria were not enrolled in the study so that analysis would contrast the spectrum of malaria severity.

All enrolled persons were tested for infection with human immunodeficiency virus (HIV); forty-five were positive and were excluded from the analysis so that the clinical description would represent the effects of malaria alone. For each child, a parent or guardian provided written informed consent for participation in accordance with guidelines of the research ethics committees of the Makerere University College of Health Sciences and the University of Toronto.

Data collection. Two physicians (CM and AD) experienced in malaria care of children enrolled, evaluated, and recorded all information. All available clinical resources were used to assess the presence of coexisting bacterial infection or other medical conditions. Commercially available devices were used to measure complete blood count (ACT®; Beckman Coulter, Brea, CA), blood lactate (LactatePro LT-1710; Arkray, Kyoto, Japan), oxygen saturation (Nonin, Plymouth, MN), and glucose (Ascensia Contour; Bayer HealthCare LLC, Mishawaka, IN). The presence of Hb S was tested by using a commercial solubility assay (SickleDex; Streck, Omaha, NE). ABO and rhesus blood grouping was determined by using commercial reagents according to manufacturer’s directions. Quantitative parasite counts were determined by two independent observers counting the number of parasitized erythrocytes indexed to 200 leukocytes and then corrected for the actual leukocyte count. Structured clinical data for each person were collected in a uniform fashion by using a case report form (CRF) (www.cd36malaria.org). Data from the hard-copy CRF was transferred to a digital CRF (prepared with FileMaker Pro 9.0 version 1; FileMake, Santa Clara, CA) for subsequent analysis. Data accuracy and quality control were performed as reported.

Severe malaria categories. On the basis of their clinical and laboratory results, children with severe malaria were assigned to one or more of the following categories: severe malaria anemia (Hb level < 5 g/dL, or < 6 g/dL after transfusion); lactic acidosis: blood lactate levels > 5 mM; severe thrombocytopenia: platelet count < 50,000/μL; leukocytosis: total leukocyte count > 10,000 cells/μL; hyper-parasitemia: > 5% of erythrocytes parasitized; hypoxia: peripheral oxygen saturation < 90% while breathing ambient air; and hypoglycemia: blood glucose level < 2.2 mM.

We categorized persons as having CM if they met both of the following two criteria. First, the patient had coma or a Blantyre Coma Scale ≤ 2 provided that the coma was present for > 6 hours and was not attributable to hypoglycemia, meningitis, non-malaria-related pre-existing neurologic abnormalities, or drugs such as anticonvulsants or other agents with sedative/hypnotic effects. Second, the patient met either or both of the following two severity criteria: the patient had > 3 of the following 10 World Health Organization severity criteria: 1) > 2 seizures in 24 hours, RD, jaundice, hemoglobinuria, spontaneous bleeding, hypoglycemia (glucose level < 2.2 mM), LA (lactate level > 5 mM), normocytic severe anemia, hyper-parasitemia > 5%, or new acute renal failure; or 2) the patient had a cumulative score of ≥ 3 points on a previously reported scale of neurologic involvement.

Statistical analysis. Continuous data are reported as a median with inter-quartile ranges (IQRs), and were compared by using the Wilcoxon test. Categorical data were compared using the chi-square test. All comparisons were two-tailed and a P value < 0.05 was considered significant. Associations between pairs of categories of severe malaria are presented as odds ratios. Logistic regression was used to determine the odds ratios for the outcome of death using input terms found to have significant association with death in 2 × 2 analysis or known to have a published biologic relationship to adverse outcomes in malaria: presence of CM, hypoxia, severe thrombocytopenia, leukocytosis, LA, hyper-parasitemia, SMA, Hb S, blood group A, age < 1.5 years, and female sex. Of the 855 children with severe malaria, 798 had recorded values for the above 11 input terms and formed the basis for the regression. The enrollment of approximately 1,000 uncomplicated and 1,000 severe malaria patients was designed to detect a difference of ≥ 6% with 80% power between uncomplicated and severe malaria patients for clinical features with a prevalence of 25–50%.

Ethics. The study was approved by the Makerere University School of Medicine Research Ethics Committee, the Toronto Academic Health Science Network Research Ethics Board, and the Uganda National Council for Science and Technology. The study was registered at www.clinicaltrials.gov as NCT00707200.

RESULTS

A total of 2,092 children six months to 12 years of age with either uncomplicated malaria or severe malaria were
enrolled. After study completion, 159 were excluded, leaving 1,933 available for analysis. Reasons for exclusion (specified before the study) were: HIV positivity (n = 45), not infected with *P. falciparum* (n = 35), and not meeting pre-study definitions for uncomplicated or severe disease (n = 79). Illness was attributed exclusively to malaria in nearly all children. For example, among those categorized as having CM (n = 174), one-third (n = 56) had a lumbar puncture performed and none of these children showed evidence of meningitis. Only 38 children received antibiotics for uncomplicated but suspected coexisting bacterial infections. Levels of parasitized erythrocytes were > 2,500/µL in 94% of children and > 5,000/µL in 91%.24

All patients were treated by pediatricians expert in malaria care. Intravenous quinine was used in 99% of children with severe malaria. Intravenous hydration, oxygen, and anti-seizure medications were used as needed. Transfusion therapy was readily available. Among 653 patients for whom blood was requested for transfusion, only one failed to receive a transfusion, three received fewer than the prescribed units, and 29 experienced some delay before the start of transfusion because of blood availability.

Clinical and laboratory features of 1,933 children are shown in Table 2. Of these children, 1,078 were classified as having uncomplicated malaria and 855 children were classified as having severe malaria on the basis of enrollment features of neurologic involvement, SMA, LA, or hypoxia. In addition to these enrollment features, children with severe malaria differed from those with uncomplicated malaria for 17 other clinical or laboratory findings. The age distribution of children is shown in Figure 1A. Severe malaria was more common among children < 1.5 years of age.

Clinical and laboratory features among the 855 children with severe malaria are shown in Table 3. The prevalence of findings for each of eight major clinical factors is shown.

**Cerebral malaria (n = 174).** Hypoglycemia was excluded as a cause of impaired consciousness in nearly all (93%) children categorized as having CM. Patients with CM were distinct from those with SMA; only 36 (4%) of 855 patients had both syndromes. As reported,23 children with CM were significantly older (median age = 2.5 years, IQR = 1.5–3.9 years) than those without CM (median age = 1.7 years, IQR = 1.0–2.9 years) (P < 0.0001) (Figure 1B). Among 855 patients with any form of SM, those with CM had a higher median Hb level (6.9 g/dL, IQR = 5.2–8.2 g/dL versus 4.2 g/dL, IQR = 3.4–4.9 g/dL; P < 0.0001) and a lower median platelet count (73,000/µL, IQR = 43,000–129,500/µL versus 110,000/µL, IQR = 66,000–170,000/µL; P < 0.0001) than children without CM.

**Respiratory distress (n = 518) and lactic acidosis (n = 481).** The presence of labored or deep breathing, nasal flaring,
was observed in 65% of children with severe malaria. As noted in 209 children (70%) with severe malaria without SMA. 272 (49%) of 556 patients with SMA and in an additional 481 (25%) had levels all, among 1,903 children tested for blood lactate levels, LA (<94% had levels <3 mM. These results are consistent with previous investigators, who suggested that RD represents a respiratory compensation to LA, rather than those with hypoxia or lung disease.8,11 Over-all, among 1,903 children tested for blood lactate levels, 481 (25%) had levels >5 mM. Lactic acidosis was found in 272 (49%) of 556 patients with SMA and in an additional 209 children (70%) with severe malaria without SMA.

Severe malaria anemia (n = 558). Severe malaria anemia was observed in 65% of children with severe malaria. As noted by others,23 patients with SMA were younger (Figure 1B). Children with SMA had a slightly higher prevalence of splenomegaly (68% versus 51%; P < 0.0001) than those without SMA. Children with SMA also had higher absolute monocyte counts (median = 1,020/μL, IQR = 600–1,580/μL) than those without SMA (median = 547/μL, IQR = 319–886/μL) (P < 0.0001).

Severe thrombocytopenia (n = 166). Thrombocytopenia at admission was a strong indicator of disease severity (median platelet count = 103,000/μL in patients with severe malaria versus 136,000/μL in patients with uncomplicated disease) (P < 0.0001). The proportion of children with a platelet count <50,000/μL was nearly twice as high (19%) among those with severe syndromes than among those with uncomplicated malaria (10%) (χ² = 38, P < 0.0001). The number of patients with CM trebled with platelet counts <100,000/μL, suggesting that 100,000/μL may be a more informative threshold definition for severe thrombocytopenia (Figure 2).

Hyper-parasitemia (n = 402). The concentration of parasitized erythrocytes varied widely, and the median concentration was not statistically different between children with uncomplicated disease and those with severe disease. However, as shown in Table 2, the proportion of children with >5% parasitized erythrocytes was significantly higher among those with severe malaria (48%) than among those with uncomplicated malaria (25%) (P < 0.0001). Nevertheless, the presence of hyper-parasitemia had a positive predictive value of only 60% for severe malaria, and the absence of hyper-parasitemia had a negative predictive value of only 65% for severe malaria. Because the definition of hyper-parasitemia depends on the ratio of infected erythrocytes to total erythrocytes, the presence of anemia increases the likelihood of being classified as hyper-parasitemic for any given absolute concentration of parasitized erythrocytes per microliter of whole blood.

Leukocytosis (n = 490). The median leukocyte count was significantly higher in children with severe malaria (11,100/μL) than in those with uncomplicated malaria (7,800/μL) (P < 0.0001) (Table 2). Consistent with a host inflammatory response to severe disease, a leukocyte count >10,000/μL was found in 66% of those with SMA, 67% of those with hypoxia, and 77% of those with hypoglycemia (Table 3).

Case-fatality rate. The CFR was significantly different among patients with different severe malaria clinical features (Table 3). The most striking difference was the low CFR (2.8%) among patients with SMA than in those with CM (19%) or severe thrombocytopenia (14.5%). There were 48 deaths attributed to malaria. Major clinical features were found in the following percentages in fatal cases: LA in 79%, CM in 69%, hyper-parasitemia in 62%, severe thrombocytopenia in 50%, SMA in 31%, hypoglycemia in 33%, and hypoxia in 23%.

The relationship between CFR and the number of features present in the same patient are shown in Figure 3. The CFRs progressively increased with an increasing number of the following hallmark features of malaria: CM, LA, SMA, severe thrombocytopenia, and hyper-parasitemia. Logistic regression was used to determine the odds ratios of a fatal outcome according to the following 11 input variables: sex, age <1.5 years, CM, LA, SMA, severe thrombocytopenia,
### Table 3
Clinical and laboratory features among 855 children with severe *Plasmodium falciparum* malaria, Kampala, Uganda*

<table>
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<tr>
<td>Age, years</td>
<td>2.5 (1.5–3.9)</td>
<td>174</td>
<td>1.70 ([1.1–3.0])</td>
<td>481</td>
<td>1.55 (1.0–2.6)</td>
<td>558</td>
<td>2.48 (1.4–4.0)</td>
<td>166</td>
<td>1.48 (1–2.5)</td>
<td>490</td>
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<tr>
<td>BMI</td>
<td>14.7 (13.3–16.7)</td>
<td>122</td>
<td>14.8 (13.7–16.5)</td>
<td>364</td>
<td>14.8 (13.6–16.2)</td>
<td>439</td>
<td>15.0 (13.8–16.5)</td>
<td>112</td>
<td>14.7 (13.5–16.3)</td>
<td>382</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>90:84</td>
<td>174</td>
<td>3 (4–3)</td>
<td>174</td>
<td>3 (3–5)</td>
<td>481</td>
<td>4 (4–5)</td>
<td>558</td>
<td>3 (3–4)</td>
<td>490</td>
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<td>Temperature, °C</td>
<td>37.9 (37.3–38.6)</td>
<td>82</td>
<td>38.0 (37.2–37.8)</td>
<td>301</td>
<td>37.8 (37.0–38.5)</td>
<td>321</td>
<td>37.9 (37.4–38.4)</td>
<td>102</td>
<td>37.8 (37.5–38.5)</td>
<td>294</td>
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<tr>
<td>Lactate (mM)</td>
<td>4.3 (2.7–8.1)</td>
<td>171</td>
<td>4.9 (3.0–9.0)</td>
<td>481</td>
<td>4.9 (3.0–9.0)</td>
<td>556</td>
<td>7.0 (4.6–10.2)</td>
<td>165</td>
<td>6.05 (3.3–9.9)</td>
<td>488</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>6.9 (5.2–8.2)</td>
<td>171</td>
<td>4.6 (3.4–6.8)</td>
<td>481</td>
<td>3.8 (3.2–4.4)</td>
<td>558</td>
<td>5.9 (4.3–7.7)</td>
<td>166</td>
<td>4.1 (3.3–5)</td>
<td>490</td>
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<tr>
<td>Platelet (×10(^9)/L)</td>
<td>84 (79–88)</td>
<td>174</td>
<td>83.5 (78–90)</td>
<td>481</td>
<td>85.5 (78–92)</td>
<td>558</td>
<td>84.4 (78–89)</td>
<td>162</td>
<td>83 (77–90)</td>
<td>490</td>
</tr>
<tr>
<td>Leukocytes (×10(^9)/L)</td>
<td>9.4 (7.1–14.3)</td>
<td>174</td>
<td>11.5 (8.1–18.2)</td>
<td>480</td>
<td>12.6 (8.5–18.8)</td>
<td>558</td>
<td>8.3 (5.4–13.9)</td>
<td>166</td>
<td>15.4 (12.2–21)</td>
<td>490</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>7 (6–9)</td>
<td>174</td>
<td>8 (6–11)</td>
<td>481</td>
<td>9 (7–11)</td>
<td>556</td>
<td>12 (9–15)</td>
<td>165</td>
<td>9 (7–12)</td>
<td>490</td>
</tr>
<tr>
<td>Platelet (×10(^9)/L)</td>
<td>57 (33)</td>
<td>174</td>
<td>121 (25)</td>
<td>481</td>
<td>69 (12)</td>
<td>558</td>
<td>68 (14)</td>
<td>166</td>
<td>90 (20)</td>
<td>490</td>
</tr>
<tr>
<td>Leukocytes (×10(^9)/L)</td>
<td>90 (43)</td>
<td>174</td>
<td>295 (61)</td>
<td>481</td>
<td>370 (66)</td>
<td>558</td>
<td>68 (41)</td>
<td>166</td>
<td>250 (62)</td>
<td>490</td>
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<tr>
<td>Monocytes (%)</td>
<td>0.6 (0.3–0.9)</td>
<td>174</td>
<td>0.81 (0.5–1.4)</td>
<td>480</td>
<td>1.02 (0.6–1.6)</td>
<td>556</td>
<td>1.2 (0.8–1.8)</td>
<td>166</td>
<td>1.2 (0.8–1.8)</td>
<td>490</td>
</tr>
<tr>
<td>Infected erythrocytes/L (&lt;1%)</td>
<td>4.6 (11.1–16.2)</td>
<td>171</td>
<td>7.0 (19–16.8)</td>
<td>471</td>
<td>4.2 (0.9–11.9)</td>
<td>538</td>
<td>7.6 (1.9–18.0)</td>
<td>162</td>
<td>5.5 (1–15.5)</td>
<td>490</td>
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<tr>
<td>% Infected erythrocytes</td>
<td>85 (50)</td>
<td>171</td>
<td>267 (57)</td>
<td>471</td>
<td>253 (47)</td>
<td>538</td>
<td>100 (62)</td>
<td>166</td>
<td>252 (50)</td>
<td>480</td>
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<tr>
<td>Hemoglobin S</td>
<td>6 (4)</td>
<td>174</td>
<td>16 (3.4)</td>
<td>465</td>
<td>5 (5.5)</td>
<td>541</td>
<td>5 (3.1)</td>
<td>161</td>
<td>28 (5.9)</td>
<td>474</td>
</tr>
<tr>
<td>Platelet (×10(^9)/L)</td>
<td>71 (41)</td>
<td>174</td>
<td>183 (38)</td>
<td>480</td>
<td>206 (37)</td>
<td>558</td>
<td>39 (35.8)</td>
<td>165</td>
<td>182 (37)</td>
<td>490</td>
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<tr>
<td>SaO(_2) saturation</td>
<td>96 (94–98)</td>
<td>171</td>
<td>96.5 (94–99)</td>
<td>477</td>
<td>97 (94–99)</td>
<td>555</td>
<td>96 (94–98)</td>
<td>163</td>
<td>97 (94–99)</td>
<td>486</td>
</tr>
<tr>
<td>SaO(_2) saturation &lt;90%, (%)</td>
<td>10 (6)</td>
<td>174</td>
<td>32 (6.7)</td>
<td>467</td>
<td>23 (4.2)</td>
<td>544</td>
<td>11 (6.8)</td>
<td>163</td>
<td>29 (6)</td>
<td>485</td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>5.4 (3.6–6.9)</td>
<td>161</td>
<td>4.9 (3.7–6.1)</td>
<td>124</td>
<td>4.4 (3.6–5.4)</td>
<td>102</td>
<td>5.2 (4.2–6.8)</td>
<td>70</td>
<td>4.6 (3.6–5.4)</td>
<td>123</td>
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<tr>
<td>Deaths (%)</td>
<td>33 (19)</td>
<td>174</td>
<td>37 (7.7)</td>
<td>481</td>
<td>15 (2.7)</td>
<td>558</td>
<td>24 (14.5)</td>
<td>166</td>
<td>33 (6.7)</td>
<td>490</td>
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*Values are medians (interquartile range [IQR]) or no. For example, in the first column, there were 174 children with cerebral malaria. Of these children, body mass index (BMI) values were recorded for 122. The median BMI was 14.7 (IQR = 13.3–16.7) and 39 (32%) of 122 had BMI values <13.6 cm²/kg, arterial oxygen saturation; C = cerebral malaria.
leukocytosis, hyper-parasitemia, hypoxia, blood group A, and presence of Hb S. Five factors had significant associations with fatal outcome in the final model: CM, hypoxia, severe thrombocytopenia, leukocytosis, and LA. Test results for interactions among these five factors were found to be not significant. The results are shown in Table 4.

Inter-relationships of malaria syndromes. Inter-relationships between major clinical features of severe malaria are shown in Table 5 and Figure 4. Clinical findings were assembled into clusters on the basis of statistically significant positive odds ratios. Two clusters of associations emerged. In the first cluster, SMA, splenomegaly, and leukocytosis demonstrated mutually significant positive associations of similar magnitude. In the second cluster, seven features demonstrated significant positive inter-relationships. Strong associations centered on the triad of death, severe thrombocytopenia, and LA. Cerebral malaria was associated with death and severe thrombocytopenia; hypoxia and hypoglycemia were associated with death and LA; and hyper-parasitemia was associated with LA and severe thrombocytopenia.

**RESULTS**

Using a standardized assessment, we have analyzed the clinical features at hospitalization of 1,933 children with acute malaria at Mulago Hospital in Kampala, Uganda. We confirmed results of previous reports that SMA affects younger children and CM affects older children with malaria; that LA is found both in association with SMA and independent of SMA; and that RD was unrelated to hypoxia. Our data update existing information on risk factors associated with fatal outcomes in severe malaria.

The three largest recent studies on presenting features in malaria are those of Dzeing-Ella and others, Issifou and others, and Ranque and others, each of which enrolled children more than a decade ago. Our study agrees with the findings of those reports but includes a larger number of children and CM affects older children with malaria; that LA was unrelated to hypoxia. Our data update existing information on risk factors associated with fatal outcomes in severe malaria.

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![Cerebral Malaria cases](image)

**Figure 2.** Cerebral malaria according to platelet count at presentation, Kampala, Uganda.

![Increase in case-fatality rate (CFR) with increasing number of severe malaria features, Kampala, Uganda. CFRs are shown for 855 children with one or more combinations of the following features: cerebral malaria, lactic acidosis, severe anemia, severe thrombocytopenia, or hyper-parasitemia. The x-axis separates children into five groups based on an increasing number of co-existing severe malaria features present in combination. The groups show an increasing median CFR. The size of each bubble indicates the number of persons ranging from n = 558 for the single feature of severe anemia (lower left) to n = 4 for all five features simultaneously present (upper right).](image)

**Figure 3.** Increase in case-fatality rate (CFR) with increasing number of severe malaria features, Kampala, Uganda. CFRs are shown for 855 children with one or more combinations of the following features: cerebral malaria, lactic acidosis, severe anemia, severe thrombocytopenia, or hyper-parasitemia. The x-axis separates children into five groups based on an increasing number of co-existing severe malaria features present in combination. The groups show an increasing median CFR. The size of each bubble indicates the number of persons ranging from n = 558 for the single feature of severe anemia (lower left) to n = 4 for all five features simultaneously present (upper right).

**Table 4**

Logistic regression for fatal outcome based on 798 children with severe malaria, Kampala, Uganda.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral malaria (CM)</td>
<td>13.1</td>
<td>6.2–27.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>6.9</td>
<td>2.6–18.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Severe thrombocytopenia</td>
<td>3.6</td>
<td>1.7–7.5</td>
<td>0.0008</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>2.4</td>
<td>1.1–5.3</td>
<td>0.0030</td>
</tr>
<tr>
<td>Lactic acidosis (LA)</td>
<td>2.4</td>
<td>1.1–5.4</td>
<td>0.0351</td>
</tr>
<tr>
<td>Cerebral malaria anemia (SMA)</td>
<td>0.7</td>
<td>0.3–1.5</td>
<td>0.3466</td>
</tr>
</tbody>
</table>

* For the upper panel, \( Y = 2.4 \times CM + 1.9 \times Hypoxia + 1.3 \times Thrombocytopenia + 1.1 \times Leukocytosis + 0.9 \times LA - 5.86 \). For the lower panel, \( Y = 2.6 \times CM + 1.9 \times Hypoxia + 1.3 \times Thrombocytopenia + 0.9 \times Leukocytosis + 0.9 \times LA - 5.78 \). Upper panel shows the odds ratios and 95% confidence intervals for 11 input features of severe malaria. (Model \( \chi^2 = 96.7 \), degrees of freedom = 11, \( P < 0.0001 \)). Lower panel shows the results for the five statistically significant features. (Model \( \chi^2 = 82.9 \), degrees of freedom = 5, \( P < 0.0001 \)). CM, hypoxia, severe thrombocytopenia, leukocytosis, LA, hyper-parasitemia, and SMA were entered as dichotomous values as defined in the Methods.

DISCUSSION

Using a standardized assessment, we have analyzed the clinical features at hospitalization of 1,933 children with acute malaria at Mulago Hospital in Kampala, Uganda. We confirmed results of previous reports that SMA affects younger children and CM affects older children with malaria; that LA is found both in association with SMA and independent of SMA; and that RD was unrelated to hypoxia. Our data update existing information on risk factors associated with fatal outcomes in severe malaria.

The three largest recent studies on presenting features in malaria are those of Dzeing-Ella and others, Issifou and others, and Ranque and others, each of which enrolled children more than a decade ago. Our study agrees with the findings of those reports but includes a larger number of children and CM affects older children with malaria; that LA was unrelated to hypoxia. Our data update existing information on risk factors associated with fatal outcomes in severe malaria.

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others in 1995,2 suggesting little therapeutic advance for this deadly syndrome. We extend existing reports by identifying with logistic regression five factors associated with fatal outcomes: CM, hypoxia, severe thrombocytopenia, leukocytosis, and LA.

The presence of severe thrombocytopenia was a clinically important finding in our study with prognostic significance. Children with severe malaria had lower median platelet counts than those with uncomplicated malaria (Table 2). In logistic regression analysis, death was 3.6 times more likely in the presence of severe thrombocytopenia. Recent interest has focused on the finding by McMorran and others29 that growth of *P. falciparum in vitro* was inhibited by co-culture with platelets. However, their non-flow, co-culture system was unable to assess the role of platelets in the cytoadhesion of parasitized erythrocytes to endothelium. Our clinical data support the view that thrombocytopenia is associated with poor outcomes30 and are consistent with the hypothesis that platelets actively participate in the pathophysiology of cytoadhesion in malaria.26,31–36

As shown in Figure 4, we determined inter-relations among the major clinical features of SM. We observed two clusters of relationships, one cluster in children with SMA, and a second cluster centered on death, severe...
thrombocytopenia, and LA. These inter-relationships are consistent with the three original major syndromes described by Marsh and others² (CM, SMA, and RD) and with three potential pathophysiologic pathways shown in Figure 5. One pathway emphasizes anemia that accompanies some patients with malaria. With blood transfusion, children with SMA can be rescued and fatal outcomes averted.⁶ Without transfusion, severe anemia will result in insufficient tissue oxygenation, LA, and RD. A second pathway emphasizes cytoadhesion and microvascular ischemia in the central nervous system resulting in CM. In our dataset, severe thrombocytopenia was strongly associated with CM (Figure 2, Figure 4, and Table 5), suggesting an important role for platelet-mediated cytoadhesion in the cerebral vasculature as suggested by several authors.³¹,³²,³⁴,³⁷ A third pathway, also directly associated with severe thrombocytopenia, is systemic LA in the absence of CM or SMA (Figure 4 and Table 5). Lactic acidosis with accompanying RD presumably results from microvascular tissue ischemia outside the central nervous system, and in severe cases is associated with hypoglycemia and death. Further research to identify which host or parasite factors favor cytoadhesion in the cerebral vasculature versus the non-cerebral circulation is expected to be of value in guiding new therapies.

Our study had the following limitations. Results are based only on children who were hospitalized. Thus, our data do not reflect general prevalence rates for children at risk for malaria. Serial laboratory data and clinical follow-up data were not collected. We did not collect data for renal function, levels of malaria pigment found in leukocytes, cytokines, retinal examination in all patients with suspected CM or the relative distribution of parasite maturity in peripheral blood. However, none of these features was considered essential in the clinical assessment of malaria by a recent panel of experts.²⁴

In summary, we update presenting features of pediatric malaria on the basis of a prospective, uniform, clinical and laboratory assessment of approximately 2,000 children treated at an urban medical center in Uganda. Our data emphasize the clinical distinction between uncomplicated and severe malaria, report the prevalence of cardinal features that characterize syndromes of severe malaria, quantify clustered inter-relationships among malaria syndromes, and identify the major risk factors for fatal outcomes. We hope that these results will not only assist in the care of children with malaria, but may also prove valuable in the planning and assessment of future research.

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Note: Supplemental video appears at www.ajtmh.org.

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Disclaimer: Christine M. Cserti-Gazdewich and Walter H. Dzik conceived and designed the study, analyzed data, and prepared the
manuscript. Aggrey Dhabangi, Charles Musoke enrolled patients and collected primary data. Isaac Ssewanyana, Henry Ddungu, Deborah Nakiboneka-Ssenabulya, Nicolette Nabukeera-Barungi, and Arthur Mpimbaza participated in the organization and design of the study, provided oversight, and assisted in data collection. All authors approved the final manuscript.

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