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Can the Assessment of Malaria Severity be Simplified for Non-immune African Children?

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Abstract

Background: Whether there are alternative indicators than WHO criteria to assess malaria severity and outcome is not addressed in non-immune children.

Methods: To assess outcome of severe malaria among non-immune children, we conducted a prospective hospital-based study in Dakar (Senegal), a low transmission setting which delays development of clinical immunity.

Results: Of 311 falciparum cases (median age: 8 years), 233 (75%) matched 2000 WHO definition of severe malaria. The fatality rate was 9% (n=28). Logistic-regression analysis identified seven key prognostic factors : thrombocytopenia (platelets <100,000/mm3) (44.3%; odds ratio (OR), 6.1; 95% confidence interval (CI), 1.7 to 20.9), respiratory distress (30.5%; OR 3.2; 95% CI, 1.02 to 9.9), unrousable coma (inability to localize a painful stimulus with Blantyre coma score (BCS) ≤ 3) (26.3%; OR 8.1; 95% CI, 2.1 to 33.4), sluggish pupils (12.2%; OR 4.1; 95% CI, 1.1 to 14.7), hypoglycemia (11.2%; OR 5.8; 95% CI, 1.6 to 21.1), acute renal failure (2.2%; OR 17.9; 95% CI, 2.4 to 133), and the combination of jaundice, macroscopic hemoglobinuria and abnormal bleeding (21.2%; OR 3.1; 95% CI, 1.04 to 9.2). Gathering together children with impaired consciousness (BCS <5), thrombocytopenia or respiratory distress, the three most frequent conditions associated with malaria, we found the same discriminatory performance in predicting outcome than the 2000 WHO criteria (overlap, 87%, sensitivity, 100%, specificity, 28%, positive predictive value, 80%, negative predictive value, 100%).

Conclusions: WHO criteria (2000) provide a highly sensitive definition of severe malaria than can be replaced by three simple indicators in non-immune Senegalese children.

Keywords: Malaria; Children; Thrombocytopenia

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Abbreviations

WHO: World Health Organization; CM: Cerebral Malaria; OR: Odds Ratio; CI: Confidence Interval; IQ_{25-75}: Iinter-Quartile interval; CFR: Case Fatality Rate

Introduction

Severe Plasmodium falciparum (P. f.) infection is one of the leading causes for death among children living in tropical areas despite better knowledge on its pathogenesis and management [1]. To improve detection and treatment of severe malarial attacks, the World Health Organization (WHO) defined as early as 1986 ten criteria of severe and complicated malaria, completed in 1990 with five additional criteria, more appropriate for non-immune people, e.g. travelers and African children [2,3]. Over the last ten years, several reports from Africa revealed important aspects of severe malarial disease such as the close association between age and clinical features [4,5], or the influence of transmission level both on background immunity and clinical presentation [6,7]. Hence, current descriptions generally agree that within any single area, the mean age of children presenting the two major clinical syndromes of severe malaria, i.e., severe anemia and cerebral malaria, is significantly different. Thus, severe anemia is always encountered at a younger age than cerebral malaria whilst the latter condition is seldom observed in infants [8]. However, recent detailed clinical analysis on prognosis highlighted the relevance of a third major syndrome, respiratory distress (malaria hyperpneic syndrome) [9-11], which is indicative of severe metabolic acidosis and poor outcome [12], especially when associated with severe anemia [13,14], cerebral malaria [10,15,16] or both syndromes [9,11]. These studies, performed in countries with moderate to high endemicity [9-16], led Marsh and Snow to summarize the clinical presentation of severe childhood malaria to three

simple bedside criteria, i.e., severe anemia, impaired consciousness and respiratory distress [8]. Subsequently, WHO experts proposed a new definition of severe falciparum malaria which includes henceforth sixteen criteria [17]. However, though the problem has been addressed in adults [18], applying WHO criteria to non-immune subjects without previous evaluation was still questionable, in particular for traveling children [19]. In fact, such extrapolation purported that immunological differences in hosts to parasites relationships, or differences in health care facilities, would not change the outcome of severe malaria whatever the setting concerned. To elicit this question as much to gain a sufficient recruitment, we performed a prospective cohort study of severe pediatric falciparum malaria within a well-equipped hospital, based in Dakar, Senegal, an hypoendemic for malaria [20], where fatal cases are seen in children [5] and adults [4] due to a lesser effective clinical immunity [4,20]. Our principal objectives were to assess and to simplify the outcome of severe malaria in non-immune Senegalese children. Subsidiary, we aimed to propose a model susceptible to be extrapolated in other naïve populations, especially traveling children. The data presented herein clearly demonstrate the usefulness of the overlapping combination of impaired consciousness, respiratory distress and thrombocytopenia which proved the same discriminatory performance than fifteen 2000 WHO criteria in predicting outcome of pediatric malaria.

Patient and Methods

Study area and population

The study took place in the pediatric department of the "Hôpital Principal" in Dakar, Senegal, from October 01, 1997 to March 31, 1999. This hospital is one of the 3 main hospitals in Dakar and it serves a predominantly urban population. It has been managed for more than a hundred years by French military physicians specialized in tropical medicine and is partly supported by the French Ministry of Co-operation. About 3,500 children are admitted annually to its 120-bed pediatric ward. All children (0-15 years) with clinical signs and a P. falciparum-positive thick blood film were prospectively enrolled to assess prognostic factors of pediatric malaria in a low seasonal area (entomological inoculation rate <1 infective bite per person per year). Clinical and biological data were collected for medical management with informed consent from first-degree relatives, according to recommendations of the Ethical Committee of the "Hôpital Principal" de Dakar.

Clinical assessment

Main clinical features associated to malaria, 1990 WHO severity criteria [3] and respiratory distress [9] were systematically collected by a physician on ad hoc designed forms which also allowed the definition of severe cases using 2000 WHO guidelines [17]. Malnutrition was defined by a weight/age ratio more than two steps below the reference standard for the appropriate sex [21]. Patients with mild malaria were admitted to rule out other causes of fever, e.g., severe sepsis, typhoid fever, pneumonia, meningitis, dysenteric. The status of consciousness was assessed using Blantyre coma scale [22] and the revised Glasgow coma scale (scores 3 to 15) [23] which is widely used in French pediatric intensive care units. Prostration (Blantyre=5 and Glasgow=15 but inability to sit or to drink), mild impaired consciousness (Blantyre >3 and <5, or Glasgow score >9 and <15), or cerebral malaria (CM) (unrousable coma or inability to localize a painful stimulus with Blantyre ≤ 3 or Glasgow ≤ 9) were considered present if symptoms persisted more than one hour after a seizure or anticonvulsivant drug administration. Sluggish pupils were defined as unequal or dilated pupils in response to a light stimulus. Hyperparasitemia was first defined beyond the cut-off of 5% parasitized red blood cells. It was redefined beyond the cut-off of 4% to fulfill the 2000 WHO definition in non-immune children [17].

Laboratory procedures

On admission, children were weighted and blood was withdrawn for following measurements: parasitemia (percentage of infected red blood cells estimated on Giemsa stained blood thin smear); hematocrit and hemoglobin rates, mean corpuscular volume, complete blood cell count, determined by ST KS® Coultronics automation (Coulter Inc, Miami, Florida, USA). In case of severe thrombocytopenia (platelet counts less than 20,000/mm^3) or hemorrhage, controls on citrate tube and blood coagulation tests (for prothrombin time, partial thromboplastin time, and fibrinogen) were performed using manual chronometric tests. Blood glucose, bilirubin, urea, and creatinine were measured by the RA 1000® method (Bayer, Leverkusen, Germany). Electrolytes were measured using flame emission spectrophotometry by the IL 943® method (Instrument Laboratory, Milano, Italy). Plasma bicarbonate concentrations and arterial pH were determined by the AVL 990® method (Roche, Basel, Switzerland).

Case management

Malaria was treated following WHO 1990 guidelines [3]. Mild forms received oral chloroquine (25 mg/kg for 3 days). Children presenting with severe forms or vomiting received quinine formate (10 mg/kg salt, e.g., 8.3 mg/kg base) infused intravenously every 8 hours for 2-3 days, followed by oral chloroquine. No loading dose of quinine was given because of frequent undocumented treatments prior to admission. In cases of CM or multiple convulsions, a loading dose of 5 mg/kg to 15 mg/kg phenobarbital was given by slow intravenous infusion. If that failed, escalating doses of continuously infused clonazepam were given, and thiopental as a last resort. Comatose children with a Blantyre coma score ≤ 2 or a Glasgow coma score ≤ 7, seizures requiring thiopental or severe circulatory collapse, were intubated and mechanically ventilated. Whole blood transfusions for severe anemia (hemoglobin <5 g/dL or hematocrit <15%) were restricted to children with respiratory distress. After rehydration and parenteral furosemide, severe persistent renal failure was treated with hemodialysis.

Statistical methods

Clinical and biological data from the first 24 hours of hospitalization were computed for bivariate and multivariate analysis, considering two possible outcomes at discharge, i.e., alive or dead, using Stata® (Stata Statistical Software: release 7; Stata Corp. 2001). Proportions were compared by Chi square [2] or Fisher Exact tests as appropriate. Odds ratio (OR) and 95% confidence intervals (CI) were calculated for the risk of death. An alpha P value <0.05 was considered statistically significant.

Multivariate models were fitted by a stepwise procedure of covariates selection (P value to enter criteria ≤ 0.30 and P value to remove criteria >0.30 in the initial main-effects model; P value to enter criteria ≤ 0.05 and P value to remove criteria >0.05 in the second minimal-effects model). In the first model (data not shown), abnormal bleeding was not selected because all children affected by this condition died and so, this variable prevented any adjustment. In the second model, this criterion was included with clinical jaundice and macroscopic hemoglobinuria as a dichotomous and collapsed clue. All the interaction terms between the variables included

Table 1: Comparison of alternatives combinations of prognostic criteria, 1990 WHO and 2000 WHO definitions in predicting outcome of severe malaria, among 311 children hospitalized in Dakar, Senegal.

Criteria *	Prevalence n(%)	Mortality N(%)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Well classified
1. WHO 1990	161 (51.8)	28 (17.4)	100%	53%	70%	100%	57%
2. WHO 2000	233 (74.9)	28 (12.0)	100%	28%	80%	100%	34%
3. Unrousable coma and / or respiratory distress	133 (42.8)	27 (20.3)	96%	63%	66%	96%	66%
4. Unrousable com and/or thrombocytopenia §	183 (58.8)	28 (15.3)	100%	45%	72%	100%	50%
5. Impaired consciousness and / or respiratory distress	184 (59.2)	28 (15.2)	100%	45%	72%	100%	50%
6. Impaired consciousness and / or respiratory distress and / or severe anemia †	197 (63.4)	28 (14.2)	100%	40%	74%	100%	46%
7. Impaired consciousness and/or thrombocytopenia §	219 (70.4)	28 (12.8)	100%	33%	78%	100%	39%
8. Impaired consciousness and / or severe respiratory distress and / or thrombocytopenia §	232 (74.6)	28 (12.1)	100%	28%	80%	100%	34%

* See the methods section and footnotes to (Table 1 and 2) for definitions. Note that impaired consciousness includes all cerebral malaria cases. § Thrombocytopenia was defined as a platelet count under 100,000/mm^3. † Bedside simplification of severe childhood malaria according to Marsh and Snow [8].

Table 2: Prevalence, mortality, and odds ratios for the risk of death according to age and main malaria-associated conditions among 311 children hospitalized in Dakar, Senegal.

Indicator	Prevalence n (%)	Mortality N (%)	Odds ratio	95% CI	*P* values
Age					
0 - 4 years	69 (22.2)	4 (5.8)	1		
5 - 9 years	118 (37.9)	9 (7.6)	1.34	0.36 , 6.20	0.771
10 - 15 years	124 (39.9)	15 (12.1)	2.24	0.67 , 9.62	0.21
Malnutrition*	95 (30.5)	9 (9.5)	1.09	0.41, 2.64	0.832
Coexisting diseases**	35 (11.2)	5 (14.3)	1.83	0.51, 5.43	0.223
Other infections***	42 (13.5)	9 (21.4)	3.59	1.31, 9.31	0.006
Temperature > 40°C	30 (9.6)	7 (23.3)	3.77	1.21, 10.44	0.011
Sluggish pupils †	38 (12.2)	16 (42.1)	15.8	6.07, 41.18	< 0.001
Abnormal posturing ‡	27 (8.7)	12 (44.4)	13.4	4.80, 36.35	< 0.001
Thrombocytopenia §					
< 100 000 / mm^3	138 (44.4)	22 (15.9)	5.28	2.08, 13.42	< 0.001
Leukocytosis					
> 15 000 / mm^3	65 (20.9)	10 (15.3)	2.3	0.99, 3.63	0.051
Natremia §					
< 125 mmol / L	32 (10.3)	6 (18.7)	2.7	1.01, 7.25	0.048

Bivariate analysis; *assessed by NCHS Growth Charts; **pre-existent respiratory, cardio-vascular or neurological conditions able to interfere with patient management; ***severe sepsis, typhoid fever, pneumonia, meningitis, dysenteric; † unequal or dilated pupils in response to a light stimulus; ‡ opisthotonus, decorticate or decerebrate rigidity; § platelet and white blood cell counts were available respectively among 288 and 305 patients and considered as normal for the remainder patients.

in these models were tested. The adequacy of both models was determined by Lemeshow and Hosmer [24] goodness of fit test. To simplify the prediction of outcome, we calculated the discriminatory performance, i.e. sensitivity, specificity, positive predictive value, negative predictive value, proportion of well classified, of several combinations of variables, including 1990 and 2000 WHO definitions (Table 1).

Results

Population characteristics

A total of 319 consecutive children were admitted with falciparum malaria, 8 of whom with mild illnesses were excluded due to missing data, leaving 311 children for inclusion. The sex ratio (male: 185, female: 126) was 1.46. The median age was 8 years (Inter-quartile $(IQ)_{25\text{-}75}$: 5-11 years). All ages were represented: 0-4 years: n=69 (22%), 5-9 years: n=118 (38%), 10-15 years: n=124 (40%). The median duration of illness before admission was 3 days ($IQ_{25\text{-}75}$: 2-6 days). 163 (52%) children had been treated prior to admission with anti-malarial drugs, of whom 123 (40%) had received a quinine infusion and 32 (10%) oral chloroquine. The frequency of main co-morbidities and of the principal conditions associated to malaria is presented in (Table 2). Among the 311 patients, the prevalence of severe forms was 52% (n=161) according to 1990 WHO criteria and 75% (n=233) according to 2000 WHO criteria. The distribution of severe malaria criteria is detailed in (Table 3). The outcome distribution was: 28 (9%) patients died, of whom 15 (53.6%) were deceased before the 24th hour, 269 (86.5%) recovering without sequelae, and 14 (4.5%) discharged with neurologic sequelae.

Bivariate analysis of outcome according to age and malaria-associated conditions

The mortality correlates with age as follows: 5.8% in children aged 0-4 years, 7.6% in children aged 5-9 years, 12.1% in children aged 10-

Table 3: Prevalence, mortality and odds ratios for the risk of death related to 2000 WHO criteria of severe malaria, among 311 children hospitalized in Dakar, Senegal.

Criterion	Prevalence n (%)	Mortality N (%)	Odds ratio	95% CI	*P* values
Neurological impairment					
Unrousable coma [a*]	82 (26.3)	23 (28)	50.68	7.74, 2102	< 0.001
Mild impaired consciousness [b*]	76 (24.3)	4 (5.2)	7.22	0.36, 6.20	0.062
Prostration [c*]	22 (7.1)	0 (0)	0	–	1
Multiple convulsions [d]	63 (20.2)	11 (17.5)	3.47	1.50, 8.02	0.002
Respiratory distress [e]	99 (30.5)	21 (21.2)	7.88	3.05, 22.68	< 0.001
Jaundice [f]	54 (17.4)	9 (16.6)	2.51	0.93, 6.24	0.038
Metabolic acidosis [g]	50 (16.1)	13 (26)	4.07	1.60, 10.15	0.002
Severe anemia [h]	47 (15.1)	5 (10.6)	1.25	0.35, 3.61	0.59
Parasitemia ³ 4 % [i]	42 (13.5)	4 (9.5)	1.07	0.25, 3.37	0.078
Hypoglycemia [j]	35 (11.2)	7 (20)	3.04	1.01, 8.24	0.025
Macroscopic hemoglobinuria [f]	12 (3.8)	3 (25)	3.65	0.59, 15.82	0.083
Acute renal failure [k]	7 (2.2)	3 (42.8)	8.37	1.15, 51.80	< 0.001
Circulatory collapse [l]	7 (2.2)	3 (42.8)	8.37	1.15, 51.80	< 0.001
Abnormal bleeding [f]	6 (1.9)	6 (100)	+ ¥	13.8, +¥	< 0.001
Pulmonary edema [m]	2 (0.6)	0 (0)	0	_	1

Bivariate analysis; [a)] Blantyre score ≤ 3 or Glasgow score ≤ 9 with inability to locate a painful stimulus; [b)]Blantyre score > 3 and < 5, or Glasgow score > 9 and < 15; [c)] inability to drink or to sit; * tested together against reference "normal consciousness"; [d)] more than one reported or witnessed convulsion during the first 24 hrs; [e)] sustained chest recession or deep acidotic (Küssmaul) breathing; [f)] clinical criterion; [g)] HCO_3^- < 15 mmol/L (145 patients tested); [h)] Hemoglobin < 5 g/dL or hematocrit < 15%; [i)] Cut-off for non immune patients; [j)] Glucose < 2.2 mmol/L; [k)] Abnormal creatinine/age; [l)] Systolic blood pressure < 60 or 80 mm Hg before or after 5 years; [m)] X-Ray criterion.

Table 4: Minimal-effects logistic regression model for major predictors of mortality, among 311 children hospitalized in Dakar, Senegal.

Predictors	Prevalence n (%)	Mortality N (%)	Odds ratio	95% CI	*P* values
Thrombocytopenia [§]					
< 100 000 / mm³	138 (44.3)	22 (15.9)	6.1	1.7, 20.87	0.004
Respiratory distress [a]	99 (31.8)	21 (21.2)	3.19	1.02, 9.91	0.045
Unrousable coma [b]	82 (26.3)	23 (28.0)	8.12	2.12, 33.38	0.002
Abnormal bleeding, macroscopic hemoglobinuria or jaundice [c]					
	66 (21.2)	15 (22.7)	3.08	1.04, 9.16	0.043
Sluggish pupils †	38 (12.2)	16 (42.1)	4.09	1.14, 14.69	0.031
Hypoglycemia [d]	35 (11.2)	7 (20)	5.83	1.61, 21.10	0.007
Acute renal failure [e]	7 (2.2)	3 (42.8)	17.92	2.41, 132.9	0.005

Multivariate analysis; [§] platelet counts were available among 288 patients and considered as normal for the remainders; [a)] sustained chest recession or deep acidotic (Küssmaul) breathing; [b)] Blantyre score ≤ 3 or Glasgow score ≤ 9 with inability to locate a painful stimulus; [c)] clinical criterion; † unequal or dilated pupils in response to a light stimulus; [d)] Glucose < 2.2 mmol/L; [e)] Abnormal creatinine/age.

15 years. Malnourished children were not more likely to die (30.1%; OR 1.9; 95% CI, 0.4 to 2.6) as all those affected by a coexisting disease at admission (11.2%; OR 1.8; 95% CI, 0.5 to 4.3). Hyperthermic children had a significant increased risk for death (9.6%; OR 3.8; 95% CI, 1.2 to 10.4) likewise those presenting with concomitant infections (13.5%; OR 3.6; 95% CI, 1.3 to 9.3). Among obvious neurological features, children with sluggish pupils (12.2%; OR 15.8; 95% CI, 6.1 to 41.2) or abnormal posturing (8.7%; OR 13.4; 95% CI, 4.8 to 36.3) were more likely to die. Out of biological features, thrombocytopenia (platelet counts < 100,000/mm³) (44.3%; OR 6.1; 95% CI, 1.7 to 20.9) and hyponatremia (<125 mmol/L) (10.3%; OR 2.7; 95% CI, 1.01 to 7.2) were significant indicators of fatal outcome whereas leukocytosis (white blood cells counts >15,000/mm³) (20.9%; OR 2.3; 95% CI, 0.99 to 3.6) was not (Table 2).

Bivariate analysis of outcome related to 2000 WHO criteria of severe malaria

Among 2000 WHO severe malaria criteria, the commonest harbingers of fatal outcome were respiratory distress (30.5%; OR 7.9; 95% CI, 3.0 to 22.7), unrousable coma (26.3%; OR 50.7; 95% CI, 7.7 to 2102), multiple convulsions (>1/24 hrs) (20.2%; OR 3.5; 95% CI, 1.5 to 8.0), metabolic acidosis (16.1%; OR 4.1; 95% CI, 1.6 to 10.1) and hypoglycemia (11.2%; OR 3.0; 95% CI, 1.01 to 8.2) while acute renal failure (2.2%; OR 8.4; 95% CI, 1.1 to 51.8), circulatory collapse (2.2%; OR 8.4; 95% CI, 1.1 to 51.8) and abnormal bleeding (1.9%; OR + ∞; 95% CI, 13.8-+ ∞) were scarce risk factors. Noteworthy, all children with abnormal bleeding died (Table 3).

Predictors for outcome in multivariate analysis

The first phase logistic regression model, fed with all variables identified in univariate analysis at P ≤ 0.30 (excepted abnormal bleeding), included following variables: age, unrousable coma, mild impaired consciousness, multiple convulsions, sluggish pupils, abnormal posturing, thrombocytopenia, respiratory distress, leukocytosis, jaundice, acidosis, hyperparasitemia, concomitant infections, hypoglycemia, coexisting diseases, hyponatremia,

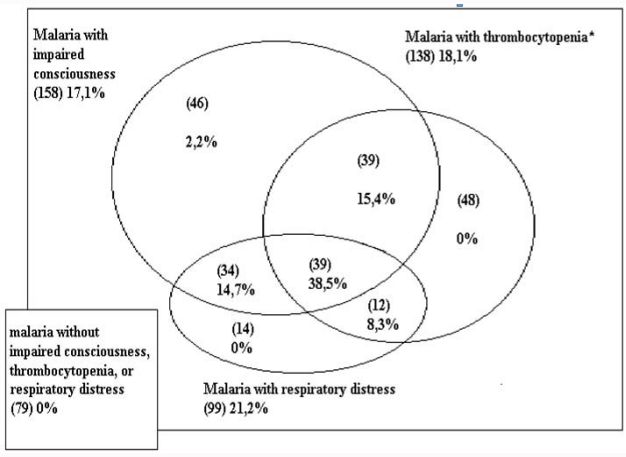

Figure 1: Numbers (n), overlap and mortality (%=N/n) of the three commonest conditions affecting the outcome of 233 severe malaria cases among 311 children hospitalized in Dakar, Senegal.
*Platelet counts were tested at admission for 288 children. Children without platelet counts available in the first 24 hours of hospitalization were considered non thrombocytopenic. This circle strictly features malaria cases with 2000 WHO criteria excluding those with impaired consciousness or respiratory distress (n=49, 20 of whom are thrombocytopenic, overlap 40.8%, lethality 0 %).

hyperpyrexia, macroscopic hemoglobinuria, renal failure and circulatory collapse. When the effect of all these variables was taken into account, age, multiple convulsions, jaundice, acidosis, hyperpyrexia, macroscopic hemoglobinuria were no longer significant (P>0.30). In consequence, these eight variables were dropped out, leaving fourteen variables in the main-effects model from the twenty pre-selected. Once controlled the effect of the remaining variables, only four indicators were significantly predictive of fatal outcome: unrousable coma (OR 41.4; 95% CI, 2.2 to 771), thrombocytopenia (OR 10.4; 95% CI, 1.7 to 20.9), hyponatremia (OR 9.6; 95% CI, 1.4 to 64) and hypoglycemia (OR 5.8; 95% CI, 1.02 to 33.4). In the second phase, abnormal bleeding was reintroduced in a combination with jaundice and macroscopic hemoglobinuria. The stepwise procedure excluded coexisting diseases, infections, mild impaired consciousness, hyperparasitemia, abnormal posturing and leukocytosis (P>0.05). The minimal-effects model identified seven independent predictors: thrombocytopenia (OR 6.1; 95% CI, 1.7 to 20.9), respiratory distress (OR 3.2; 95% CI, 1.02 to 9.9), unrousable coma (OR 8.1; 95% CI, 2.1 to 33.4), sluggish pupils (OR 4.1; 95% CI, 1.1to 14.7), hypoglycemia (OR 5.8; 95% CI, 1.6 to 21.1), renal failure (OR 17.9; 95% CI, 2.4 to 133), and the triplet jaundice, macroscopic hemoglobinuria, abnormal bleeding (OR 3.1; 95% CI, 1.04 to 9.2) (Table 4). No interaction among the variables included in those models was significant. The effect of thrombocytopenia on lethality was not affected by gender, age, parasitemia, or iron presumed deficiency.

Influence of thrombocytopenia on clinical presentation of severe malaria

To test the impact of thrombocytopenia on outcome, we checked this condition with the two most common clinical features of severe malaria, i.e. impaired consciousness and respiratory distress. The prevalence, overlap and mortality related to the three conditions are shown in (Figure 1). Among severe malaria cases (n=233), 29 children had no impaired consciousness, respiratory distress or thrombocytopenia (overlap of these three indicators: 87.5%) whereas out of thrombocytopenic children (n=138), only 28 had no WHO criterion (overlap: 79.7%). Of the 28 children deceased, only one did not present at least two of these three prognostic indicators. For this purpose, the overlap of the three variables was predictive of more than half the deaths observed (n=15/28) and had a case fatality rate (CFR) of 38, 5%**.** The presence of two of these indicators predicted twelve deaths with a CFR between 8.3% and 15.4%. Among combinations of two indicators, the most pejorative was the overlap of a consciousness impairment and thrombocytopenia (CFR = 15.4%).

Discriminatory performance of combinations of prognostic indicators

WHO definitions (2000 and 1990) had 100% sensitivity in predicting death. Their comparison in terms of severity and lethality has been presented elsewhere [25]. The best compromise between sensitivity and specificity was observed with unrousable coma (sensitivity, 82%, specificity, 79%) and with thrombocytopenia (sensitivity, 79%, specificity, 59%). Taken together, these two prognostic indicators had a discriminatory performance compatible with that of 1990 WHO criteria. With addition of respiratory distress, the most frequent WHO criterion, the performance of this triplet was better than the 1990 WHO definition or than Marsh and Snow criteria in predicting fatal malaria. Finally, extending the combination to children presenting a mild impaired consciousness provided the same discrimination that fifteen 2000 WHO criteria joined together.

Discussion

In this study, we assessed for the first time the prognostic factors of *Plasmodium falciparum* malaria in an African setting with very low transmission rates. Previous surveys of life-threatening falciparum malaria have been conducted especially in areas with moderate to high endemicity rates [9-16]. Consequently, current clinical descriptions generally assumed that African children affected by severe malaria were aged less than five years [3,26,27]. In Dakar, the median age of Senegalese children hospitalized with malaria was eight years, and surprisingly 78% of the cases were older than five years. However, this issue was in agreement with two previous Senegalese studies which reported deaths equally among children and adults [4,5]. Altogether, these findings account for a significant delay in the development of clinical immunity in Dakar [4,20], which corroborates the correlation between age and severity, suggested by Baird et al. [26] in a series from Irian Java, and also supports the recent immunological evidence of a common IFN-γ response, both observed in non-immune subjects and people exposed to low transmission rates [28]. Thus, in view of these considerations, our population was composed of non-immune children implicitly more susceptible to severe malaria. Noteworthy, our hypothesis was strengthened by unequalled prevalence of severe forms reported from an hospital-based study, e.g., 52% (according to the 1990 WHO definition) in Dakar, Senegal (<1 infective bite per person per year), in comparison to the 38%, calculated from Marsh et al. [9] in Kilifi, Kenya (1990 WHO definition), a setting of stable endemicity (20 infective bites per person per year) [9].

In multivariate analysis, we identified seven key prognostic factors: cerebral malaria, respiratory distress, hypoglycemia, sluggish pupils, acute renal failure, abnormal bleeding and thrombocytopenia. In Dakar, impaired consciousness was the main clinical presentation of severe malaria and accounted for up to two thirds of severe cases, of which 26.3% had an authentic unrousable coma, i.e. inability to localize a painful stimulus defining cerebral malaria [2]. This prevalence rate confirmed previous surveys underlining CM as the most frequent clinical form predictive for death in African

urban hospitals [5,10,29], whereas severe malarial anemia carries the major burden in the community [6,26]. Thus, in Senegalese children hospitalized with severe malaria, predictors of mortality were indicators well known to worsen CM. Respiratory distress had primarily been reported to complicate severe anemia in Kenya and in Gambia [13,15]. However, its prognostic significance in comatose children has been shown by several investigators [10,14,16]. Most, respiratory distress, namely malaria hyperpneic syndrome, is the manifestation of a severe metabolic acidosis [12], but sometimes it may raise from other mechanisms. Crawley et al. [30] have described three patterns of ventilation in CM: hypoventilation with nystagmus and salivation which are signs of a subtle status epilepticus, hyperventilation associated to extensor posturing, an expression of an intra-cranial hypertension, and lastly periodic respiration, predictive of transtentorial herniation. In Dakar, respiratory distress was more frequent in children aged of 10-15 years but only half of our population had a metabolic acidosis, while the overlap with comatose children was more important, suggesting multiple mechanisms for this frequent complication in non-immune Senegalese children. Hypoglycemia is a common harbinger of fatal pediatric malaria [9-11,31], to the extent that oversight of its correction, especially in young children, is often misleading and leads to overestimations of cerebral malaria cases [17]. Nonetheless, the overlap between these two complications is important and hypoglycemia currently worsens CM [16,22,32]. In our cohort study, hypoglycemia was more frequent in children less than ten years, confirming the susceptibility of young African children to this serious complication [17,33]. The prognostic value of sluggish pupils had not been yet reported in malaria series. In Dakar, they were present in 44% of CM cases while 97% of abnormal pupil reactions were observed in CM. Therefore, they could reflect more a CM-related brainstem involvement than a non-specific brain damage. Though it has been associated to CM in the Gambia [34], the acute renal failure in severe pediatric malaria had not been yet involved to alter the prognosis in a multivariate analysis [9-11]. Thus, our survey is the first demonstration in children of the independent prognostic value of malaria-related renal failure. However, of the four children surviving an acute renal failure, hemodialysis was life-saving only in two cases and considered not critical for the two others, whereas it was not performed for the three children deceased because of delayed management. Subsequently, if we assume a successful hemodialysis, this issue supported both the difficulties of our African ward to perform a rapid extra-renal clearance than an authentic indicator of life-threatening malaria in our setting. The significance of abnormal bleeding, e.g., spontaneous hemorrhages from gums, nose, gastrointestinal tract or venipuncture sites, in adult severe malaria is often related to a disseminated intravascular coagulopathy. In children, this complication is rare and was not incriminated to be a major prognostic factor in previous multivariate analysis [9-11]. In Dakar, although hemorrhages were observed in all children deceased from circulatory collapse, no disseminated intravascular coagulopathy was found. However, blood coagulations tests, performed at admission, were not controlled at time of death and could have underestimated occurrence of a late *pre-mortem* coagulopathy [35].

The prognostic value of thrombocytopenia in falciparum malaria has already been demonstrated in an hypoendemic area [36]. More recently, it was confirmed in a retrospective series of critically-ill Senegalese children requiring mechanical ventilation for life-threatening symptoms [37]. In the light of our previous findings, the data presented herein emphasize the interest of assessing platelet counts in pediatric malaria. Moreover, in the current study, we disclosed the important impact of considering thrombocytopenia as outcome measure in non-immune children. Thus, the overlap between thrombocytopenia and the two other principal conditions associated with malaria, i.e., impaired consciousness and respiratory distress, proved the same discriminatory performance in assessing outcome than fifteen 2000 WHO criteria joined together. A great sensitivity is welcome to ensure medical triage of pediatric malaria cases, i.e. an interesting property at the African district level, whereas a high negative predictive value is warranted to spare ICU resources or to restrict quinine use, i.e. an interesting property to advocate a PICU admission as recommended for severe imported malaria in modern countries [38]. Finally, the impact of thrombocytopenia led to simplify the assessment of both severity and prognosis in children exposed to low malaria transmission rates.

In conclusion, 2000 WHO criteria proved a highly sensitive definition in predicting outcome of severe malaria than can be replaced by three simple indicators in non-immune Senegalese children. This issue brings a novel insight into malaria clinical research and provides new tools for accurate prognosis of severe forms. We hope it will be considered for managing childhood falciparum malaria either in endemic and malaria free countries.

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