Scientific Research Publishing

Open Journal of Pediatrics, 2023, 13, 866-878
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

Descriptive and Analytical Study of Factors Associated with Mortality in Severe Malaria among Children in Dakar Emergency Departments from July to December 2022

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How to cite this paper: Thiongane, A., Ba, A., Ly, F., Ndongo, A.A., Boiro, D., Kéita, Y., Basse, I., Niang, B., Ly, I.D., Dieng, Y.J., Cissé, D.F., Seck, N., Thiam, L., Faye, P.M., Fall, A.L., Sylla, A. and Ndiaye, O. (2023) Descriptive and Analytical Study of Factors Associated with Mortality in Severe Malaria among Children in Dakar Emergency Departments from July to December 2022. *Open Journal of Pediatrics*, **13**, 866-878.
https://doi.org/10.4236/ojped.2023.136095

Received: September 27, 2023
Accepted: November 7, 2023
Published: November 10, 2023

Abstract

Background: Malaria is the most widespread parasitic disease and remains a public health priority worldwide. The severe form is fatal if not treated early and appropriately. The aim was to carry out a descriptive and analytical study of the factors associated with mortality during severe malaria in children attending emergency departments in Dakar, Senegal. **Methods:** This is a prospective, observational and analytical study conducted over a 6-month period (July 1 to December 31, 2022), focusing on children hospitalized for severe malaria according to WHO severity criteria. **Results:** A total of 403 patients were hospitalized, including 78 cases of severe malaria (19.35%). Males predominated (60.26%) (sex ratio 1.51). The average age was 6.56 years [8 months - 14 years], with the [5 - 10 years] age group the most represented (40.26%). The average consultation time was 5.33 days (1 - 19 days). The main reasons for consultation were fever (70.51%), vomiting (24.35%) and convulsions (14.10%). Biological signs of severity were severe anemia (17.95%), renal failure (6.4%) and hypoglycemia (3.85%). Thrombocytopenia was noted in 52.56% of patients, including 32.05% of severe cases (<100,000), and hyperleukocyto-

sis in 61.41% of cases. Hyponatremia was noted in 39.74% of cases and hyperkalemia in 2 patients. Artesunate was the main drug used (93.59% of cases). Mortality was estimated at 1.5%. Factors leading to death were coma ($P < 0.01$), respiratory distress ($P < 0.01$) and renal failure ($P < 0.01$). **Conclusion:** Malaria is still a public health problem, with a high mortality rate in emergency departments. Reducing this mortality rate requires effective management of the factors associated with death.

Keywords

Children, Malaria, Death, Factors

1. Introduction

Malaria is a febrile erythrocytopathy caused by a haematozoan parasite of the genus Plasmodium. It is transmitted by the infecting bite of a mosquito called the female Anopheles. There are two forms of malaria: uncomplicated malaria, which generally progresses well under treatment, and severe malaria, which is fatal if not treated early and appropriately [1]. Malaria is a public health priority. It is the most widespread transmissible infectious disease in the world. It is responsible for very high morbidity and mortality, especially in low- and middle-income countries, notably in Sub-Saharan Africa, South-East Asia and South America. According to the WHO 2022 malaria report, the number of cases worldwide rose between 2020 and 2021. It was estimated at 247 million in 2021, compared with 245 million in 2020. The number of deaths rose from 625,000 in 2020 to 619,000 in 2021 [2]. The WHO African Region continues to bear a large and disproportionate share of the global burden of this disease. In 2021, 95% of malaria cases and 96% of malaria deaths were recorded in this Region. Children under 5 accounted for 80% of all deaths due to the disease. In Senegal, the year 2021 saw a rise in malaria cases in the country, from 445,313 cases in 2020 to 536,850 in 2021 [3]. Malaria is one of the leading causes of death in children. The severe form is fatal if not treated early and appropriately. Several factors are thought to be associated with these deaths, including bacterial superinfection, severe and poorly tolerated anemia, hypoglycemia, respiratory distress and coma. Since 2015, the national malaria control program has recommended the use of artesunate as a first-line molecule in the etiological treatment of malaria, in line with WHO recommendations. This study will assess the impact of artesunate treatment on mortality, as well as changes in factors associated with death, in comparison with previous studies, in a context of improving the quality of emergency care. In this context that we conducted this descriptive and analytical study over a 6-month period from July 1 to December 31, 2022, in the emergency department of the Centre Hospitalier National d'Enfants Albert Royer, the main pediatric referral facility for severe forms of malaria in Dakar.

2. Methods

2.1. Type and Duration of Study

This is a descriptive and analytical study of severe malaria cases in children admitted to paediatric emergency departments. The duration of the study was 6 months, from July 1 to December 31, 2022.

2.2. Study Population

This study involved children hospitalized for severe malaria in the emergency department of the Centre National Hospitalier d'Enfants Albert Royer in Dakar.

2.2.1. Inclusion Criteria

All children hospitalized in emergency departments during the study period for severe malaria with:

- Rapid Diagnostic Test (RDT) or microscopy positive
- Age between 3 months and 15 years
- Presence of one or more of the WHO clinical or biological severity criteria.

2.2.2. Non-Inclusion Criteria

- Outpatients
- Patients with uncomplicated malaria

2.3. Data Collection and Analysis

2.3.1. Collecting Clinical Data

Data were collected on pre-established collection forms, based on the patient's history and clinical examination at the bedside.

2.3.2. Epidemiological Data

- Patient gender
- Patient age, classified into 4 age groups: 2 - 24 months, 24 - 60 months, 60 - 120 months et superior 120 months
- Geographical origin
- Parents' socio-economic level
- Mode of admission: referral or not
- The consultation delay, corresponding to the number of days between the onset of symptoms and the patient's admission to the department
- Consultation reasons

2.3.3. Clinical and Paraclinical Data

- Various severe forms
- Biological signs: blood count, renal and hepatic function, blood ionogram

2.3.4. Therapeutic and Evolutionary Data

- Curative treatment: artesunate, artemether, ACT
- Adjuvant and symptomatic treatment: oxygen therapy, anticonvulsants, antipyretics, transfusion, antibiotics

- Mortality

2.3.5. Analytical Study of Factors Associated to Death

Data were entered using Excel 2010. Analysis was performed with the following software: Excel 2010 and Epi info 7.2. For descriptive analysis, categorical variables were described using frequency tables and bar charts.

We performed a multivariate analysis on certain parameters to assess the risk of death in relation to these factors.

Quantitative variables were described by a histogram and their position (mean, median and mode) and dispersion (standard deviation, extremes) parameters.

Bivariate analysis enabled us to search for associations between variables, using the appropriate statistical tests according to their applicability conditions. The alpha risk of error was set at 5% and the CI at 95%.

The variables analyzed were:

- Age and death
- Disturbed consciousness and death
- Respiratory distress and death
- Renal failure and death
- Biological signs and death

2.3.6. Ethical Concerns

All ethical rules have been respected. Informed consent was obtained from the parent or carer prior to inclusion for patients meeting the inclusion criteria.

3. Results

3.1. Social and Demographic Data

During the study period, a total of 78 patients were included for severe malaria according to WHO criteria, among the 403 patients admitted to the emergency department, representing a frequency of 19.35%. The mean age of the patients was 78.72 months (8 - 168 months), with the 60 - 120 months age group predominating. Children under 60 months of age are the main target for prevention strategies in the national malaria control program, as they are less likely to develop malaria or severe malaria. Boys predominated (60.26%), with a sex ratio of 1.51. Peak visits were noted in October and November, at 29.49% and 33.33% respectively. More than half the patients came from the city center (66.67%). The socio-economic level was low to average for the vast majority (73.07%). Comorbidities were mainly sickle cell disease (6.41%) and acquired heart disease (3.85%). Fewer than half the patients were referred (35.90%). **Table 1** summarizes the socio-demographic characteristics for patients.

3.2. Data from Clinical Examination

The average consultation time was 5.33 ± 2.8 days, with extremes of 1 and 19 days. Of our patients, 53 (67.95%) had consulted before 7 days, and 19 (24.36%)

Table 1. Distribution of patients according to socio-demographic data.

Patients' characteristics	Number (n)	Percentage %
Demographic data		
Age group (months)		
Average: 78.72 (8 - 168 months)	-	-
[6 - 24]	6	7.69
[24 - 60]	21	27.27
[60 - 120]	31	40.26
>ou = 120	20	25.97
Gender		
Boys	47	60.26
Girls	31	39.74
Geographic origin		
City center	52	66.67
Periphery and others	26	33.33
Socio-economic status		
Low	26	33.33
Medium	31	39.74
Higher	21	26.92
Co-morbidities		
Sickle-cell disease	5	6.41
Acquired heart diseases	3	3.85
Asthma	2	2.56
Malnutrition	1	1.30
Cerebral Palsy	1	1.30
Treatment received before admission		
Herbal therapy	2	2.56
Oral antimalarial drug (ACT)	5	6.41
Injectable antimalarial drug (artésunate)	3	3.85
Antibiotics	10	12.82
Self-medication	7	8.97
Admission by referral		
Yes	28	35.90
No	50	64.10
Consultation period (days)		
<7	53	67.95
>7	19	24.36
Unspecified	6	7.69

had consulted 7 days after the onset of symptoms. The reasons for consultation were dominated by fever (70.51%), vomiting (24.36%), prostration (21.79%) and neurological signs including headaches and convulsions (19.23%, 14.10%) (Figure 1). Fever is the symptom common to all forms of malaria, and at the same time the main warning sign of the disease. It may be moderate or very high, depending on a number of factors. In some children with nutritional disorders or immune deficiencies, it may be mild or absent. Digestive signs are also quite common in children in the context of parasitic infection, but are most common in infants in the case of primary invasion, manifesting as acute gastroenteritis. Neurological signs are mainly observed in older children, who suffer less from anemia than infants, due to the sequestration phenomena that predominate in the brain at this age. The main signs of severity on admission were prostration (41.03%), jaundice (33.33%), respiratory distress (17.95%), altered consciousness (15.38%) and seizures (10.26%) (Figure 2). Prostration, reflecting generalized weakness, may be symptomatic of anemia. Jaundice reflects acute hemolysis, while respiratory distress indicates pulmonary involvement in acute pulmonary edema or decompensated anemia.

3.3. Biological Data

Biological diagnosis of malaria was based on RDT and microscopy. The RDT was positive in 87.18% of patients, negative in 3 and indeterminate in 7. Microscopy, considered by the WHO as the reference examination, was positive in all patients (100%), with a parasite density greater than 1000 parasites per microliter of blood in 42.31% of patients. CRP was positive (>25 mg/l) in the majority of cases (71.80%). The haemogram showed malarial anaemia (<5 g/dl) in 17.95% of patients, thrombocytopenia (<150,000 platelets/mm^3) in 52.56%, including

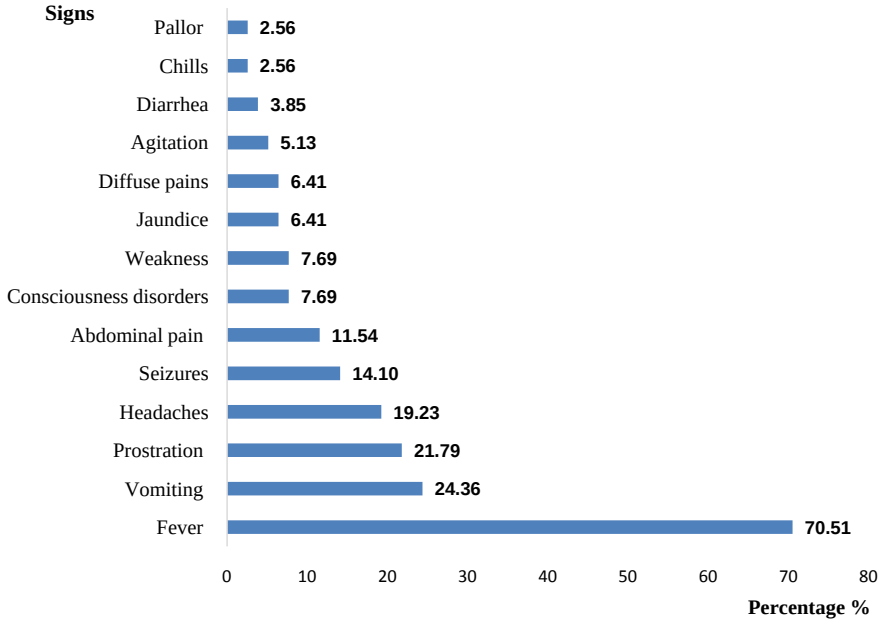

Figure 1. Distribution of patients by reasons for consulting (N = 78).

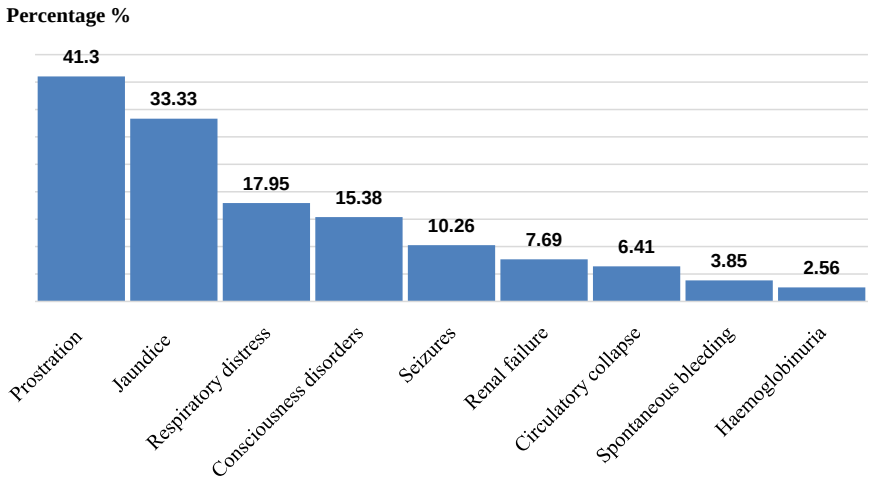

Figure 2. Patients distribution according to WHO severity signs.

32.05% with severe forms (<100,000 platelets/mm^3), and hyperleukocytosis (>16,000/mm^3) in 30.76%. CSF analysis after lumbar puncture was performed and normal in 5 patients. There was one case of urinary tract infection (**Table 2**). Hypoglycemia (<0.4 g/l) was noted in 3 patients. Urea was increased in 11.54% of patients, as was creatinine in 5. Blood ionograms showed hyponatremia in 39.74% of cases, and hypernatremia in 1 patient. Hypokalemia was noted in 8.97% of patients, and hyperkalemia in 2 (**Table 3**).

3.4. Therapeutic Data

Management was both symptomatic and etiological. Etiological treatment involved injectable antimalarial drugs, notably artesunate and artemether. The majority of patients were on injectable artesunate (93.59%), while artemether was used in 5 patients (6.41%). Symptomatic treatment included blood transfusion (47.43%), oxygen therapy (17.95%) and anticonvulsants (10.26%). Antibiotics were used to treat bacterial infections (35.90%) (**Table 4**).

3.5. Evolutionary Data

The majority (92.30%) had a favorable outcome. We noted a mortality rate of 1.5%. The factors significantly associated with these deaths were disorders of consciousness ($P < 0.01$), respiratory distress ($P < 0.01$) and renal failure ($P < 0.01$). There was no significant association with mortality for the other clinical and biological variables analyzed. There was no significant relationship between age and the number of deaths ($P = 0.40$), gender ($P = 1$), hypoglycemia ($P = 0.36$) and bacterial superinfection ($P = 1$) (**Table 5**).

4. Comments

The aim of our study was to investigate the clinical and biological factors associated with mortality during severe childhood malaria in the emergency department of the Albert Royer National Children's Hospital in Dakar, Senegal. Multivariate

Table 2. Distribution of patients according to biological signs.

Biological signs	Number (n)	Percentage %
RDT		
Positive	68	87.18
Négative	3	3.85
Unspecified	7	8.97
Microscopy		
Positive	78	100
Negative	00	00
Parasite density (parasites/microlitre)		
<1000	38	48.72
>1000	33	42.31
Unspecified	7	8.97
CRP (mg/l)		
<6	12	15.38
6 - 24	10	12.82
≥25	56	71.80
Hemogram		
Haemoglobin level (g/dl)		
<5	14	17.95
[5 – 7]	22	28.20
[7- 10.9]	34	43.60
≥ 11	8	10.25
MCV (fl)		
≤80	54	69.23
80 - 100	22	22.21
≥100	2	2.56
White blood cells/mm³		
<4000	3	3.84
[4000 - 12,000]	31	39.74
[12,000 - 16,000]	12	15.38
≥16,000	24	30.76
Platelet/mm³		
<100,000	25	32.05
[100,000 - 150,000]	16	20.51
>150,000	37	47.44
CSF		
Normal	5	6.41
Unspecified	73	93.60

Continued

UCBE		
Urinary infection	1	1.28
Unspecified	77	98.71

RDT = Rapid Diagnostic Test, CRP = C-Reactive Protein, MCV = Mean Corpuscular Volume, CSF = cerebro-spinal fluid, UCBE = Urine Cyto-Bacteriological Examination.

Table 3. Distribution of patients according to metabolic signs.

Metabolic signs	Number (n)	Percentage %
Blood glucose level (g/l)		
≤0.40	3	3.85
0.40 - 1.26	43	55.13
>1.26	15	19.23
Unspecified	17	21.80
Urea		
≤0.45 g/l	30	38.50
>0.45 g/l	9	11.54
Unspecified	39	50.00
Creatininemia		
≤12 mg/l	42	53.85
>12 mg/l	5	6.41
Unspecified	31	39.74
Natremia		
<135	31	39.74
135 - 145	22	28.21
>145	1	1.28
Kaliemia		
<3.5	7	8.97
3.5 - 5.3	45	57.69
>5.3	2	2.56
Chloremia		
<98	24	30.77
98 - 108	27	34.62
>108	3	3.85
Transaminases		
High	8	10.25
Unspecified	70	89.75
Total Bilirubinemia		
High	7	8.97
Unspecified	71	91.03

Table 4. Therapeutic management.

Types of treatment	Number (n)	Percentage (%)
Antimalarial drug (IV)		
Artesunate	73	93.59
Artemether	5	6.41
Antibiotics	28	35.90
Blood transfusion	37	47.43
Oxygenotherapy	14	17.95
Antiepileptics	8	10.26
Others	10	10.82

Table 5. Clinical factors associated with death.

Clinical variables	Death					
	Yes		No			
	N	%	N	%	OR (CI 95%)	P value
Age (years)					0.57 [0.35 - 0.92]	0.40
<5	3	11.54	23	88.46		
≥5	3	6.00	47	94.00		
Genders					0.38 [0.16 - 0.90]	1
Girls	2	6.67	28	93.33		
Boys	4	8.51	43	91.49		
consciousness disorders					2.28 [1.31 - 3.96]	<0.01
Yes	2	100.00	0	0.00		
No	4	5.33	71	94.67		
Respiratory distress					2.18 [0.40 - 11.91]	<0.01
Yes	5	38.46	8	61.54		
No	1	1.56	63	98.44		
Renal failure					4.5 [1.53 - 13.10]	<0.01
Yes	3	60.00	2	40.00		
No	3	4.17	69	95.83		
Hypoglycemia					0.50 [0.10 - 0.95]	0.36
Yes	1	33.33	2	66.67		
No	5	6.94	67	93.05		
Bacterial superinfection						
Yes	4	30.76	9	69.23	0.45 [0.15 - 0.80]	
No	2	3.12	62	96.88		1

analysis showed 3 clinical factors strongly associated with death in children hospitalized for severe malaria in the emergency department. These were disorders

of consciousness, respiratory distress and renal failure. There was no significant association between death and the other clinical and biological items, according to the results of the statistical analysis. Impaired consciousness (coma) was statistically associated with the risk of death in our study (OR = 2.28 95% CI [1.31 - 3.96]. This result is in line with the literature [4]. Coma results from sequestration of red blood cells in the cerebral circulation, with disruption of cerebral perfusion and oxygen supply [5]. This leads to neuronal damage, with cerebral edema and intracranial hypertension, which can result in brain stem compression and cardiorespiratory arrest. These phenomena justify the higher risk of death in children with these disorders of consciousness, as opposed to those without. In addition the risk of hypoglycemia, which make worse brain damage, and the risk of intracranial hypertension. Hypoglycemia in malaria results from 2 mechanisms: the use of quinine as an antimalarial drug induces insulin production and hypoglycemia, and the disruption of hepatic gluconeogenesis due to rheological disorders [6]. Other factors contributing to hypoglycemia include digestive disorders (diarrhea, vomiting, refusal to eat, anorexia) and dehydration. Respiratory distress (RD) was also identified as a factor associated with death during severe malaria in children hospitalized in emergency departments (OR = 2.18 95% CI [0.40 - 11.91]). In severe malaria, it generally results from an acute respiratory distress syndrome of lesional origin, leading to acute pulmonary edema with hypoxemia [7]. This picture of hypoxemic lesional edema often requires respiratory assistance, which is not always the case in our resource-constrained countries. Other factors increase the risk of death: refractory hypoxemia, in particular severe malarial anemia, and septic shock. Acute renal failure was the 3rd factor identified as associated with a risk of death among our patients in our study (OR = 4.5 95% CI [1.53 - 13.10]). Renal damage in malaria results from the phenomena of globular sequestration, but is favored by the occurrence of dehydration and hemodynamic disorders. The risk associated with renal damage is the occurrence of ionic complications such as hyponatremia and hyperkalemia. These ionic disorders can be complicated by intracranial hypertension and cardiac arrhythmia, leading to cardiorespiratory arrest and death [8]. These results have been reported by authors in Africa, notably Senegal, with young age (P = 0.025), coma (P = 0.007), respiratory distress (P = 0.04) or hypoglycemia (P = 0.001) as risk factors for death [7]. Other clinical and laboratory signs of severity were not associated with a higher risk of death, according to our results. It would be desirable to carry out a multicenter study over a longer period with a more representative sample in order to be able to draw conclusions. In our study, the most frequent signs of neurological severity were prostration, observed in 32 of our patients (41.03%). This result was similar to those reported by Senegalese authors [9] [10]. Other neurological signs were less frequent, including seizures and coma (10.26% and 7.69% respectively). Jaundice was found in 33.33% of our patients. Clinical anemia was noted in 57 patients (73.08%). The frequency of anemia in malaria can be explained by the importance of hemolysis due to high parasite density, the association with martial deficiency in

Africa due to malnutrition. Circulatory collapse was found in 6.41% of our patients, a higher rate than the 1.8% reported by other authors [9]. Macroscopic hemoglobinuria was found in 2.56% of cases, a lower rate than that reported by some authors, 10.18% and 6.9% [9] [11]. Biologically, microscopy was the reference test for the biological diagnosis of malaria according to WHO recommendations. It was positive in all patients, with a mean parasite density of 7462 parasites per micro-liter of blood (720 - 110,000 parasites/microliter). These results are in line with the literature [12]. In addition to microscopy, RDT was also routinely performed on all children admitted with fever. It is less sensitive than microscopy, but is recommended as first-line treatment by Senegal's national malaria control program [3] for all children admitted to emergency departments with fever. It was positive in 87.18% of children, while 10 children had a negative RDT (12.82%). These negative RDT results against a positive microscopy may suggest the occurrence of an HRP2 gene mutation, which is not yet the case in Senegal, although it has been described in some African countries [13] [14]. However, prevalence studies are needed to confirm or refute this hypothesis. Ionic disorders were observed in some children: hyponatremia (39.74%), hypernatremia (1.28%), hypokalemia (8.97%), hyperkalemia (2.56%). These ionic disorders are frequently described as complications of severe malaria [8] [15]. In terms of etiological treatment, almost all patients were treated with injectable artesunate in 93.59% of cases (73/78), while 6.41% (5 patients) were treated with artemether. As recommended by the WHO, the first-line treatment of severe malaria is based on the use of injectable artesunate [12] [15]. The majority (92.30%) had a favorable outcome. The mortality rate was 7.69% for patients admitted late, or with comorbidity or bacterial superinfection. However, our study has some limits. These include the small sample size (78 patients), the monocentric nature of the study, and the fact that the study period only covered the second half of the year (6 months). A prospective multi-center study with a more representative sample would enable us to confirm these findings through statistical analysis.

5. Conclusion

Severe malaria is still fatal in our health facilities. Some factors have been identified as being associated with this mortality. A prospective multicenter study with a more representative sample will confirm these results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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