Severe malaria and risk factors for death in the infectious diseases department of the University Hospital of Fann in Dakar, Senegal

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Abstract

The aim of this study was to describe the epidemiological, clinical, paraclinical and outcome aspects of severe malaria and to determine the risk factors for death.

methodology

This was a retrospective descriptive and analytical study of patients treated for severe malaria at the infectious and tropical diseases department of the University Hospital center of Fann between January 1, 2019 and December 31, 2021. Multivariate logistic regression was used to identify risk factors for death

Results

During our study, 138 patients were hospitalized for severe malaria over a period of 3 years, with a peak in the months of october and november. They were mostly from urban areas (68.11%). The average consultation time was 6.7 days ± 7.1 days. There was a clear male predominance, with a sex ratio of 3.18. The average age of patients was 33.96 ± 17 years. The main signs of clinical severity were coma (44.2%), prostration (36.95%) and jaundice (61.5%). Biological signs included anaemia (14.49%) and renal failure (9.42%). Severe malaria was associated with SARS Cov 2 infection in 4 patients. All patients were treated with injectable artesunate.The average length of hospitalization was 6 ± 6 days. Case fatality was 10.7.In multivariate analysis, coma (ORa=12.29 IC95%: 2.0 - 73.22 *P*=0.006) and severe anaemia(ORa=27.16 IC95%: 3.4 - 217.18 *P*=0.006) were risk factors associated with death.

Conclusion

Early recognition of the signs of seriousness and their early management thanks to improved technical facilities in intensive care units can improve the prognosis of patients.

Keywords: severe malaria, death, risk factors, Dakar

1. INTRODUCTION

Malaria is rife in tropical areas, particularly in sub-Saharan Africa, where almost all cases of severe malaria are attributable to the *plasmodium falciparum* species. According to WHO estimates, the number of malaria cases has fallen from 241 million in 2000 to 227 million in 2019, while at the same time there has been a reduction in the lethality rate **[1]**.Senegal is no exception, with the number of malaria cases falling from 492,253 in 2016 to 354,708 in 2019, a 28%

drop, and a 51% reduction in the number of deaths over the same period **[2]**. Despite these efforts, severe malaria is still a current disease in Senegal and figures prominently in the management of patients in intensive care units in the infectious diseases department **[3,4]**. Two major clinical trials have demonstrated a reduction in case fatality with the introduction of injectable artesunate as first-line treatment **[5,6]**. This strategy has been adopted in Senegal. It would be appropriate to verify the impact of this practice in our context. In addition, better knowledge of poor prognostic factors may have an impact on case management. It is in this context that we conducted this study, theaim of which were to describe the epidemiological, clinical , paraclinical ,evolutionary and to identify the risk factors for death from severe malaria at theinfectious and tropical diseases department of the University Hospital center of Fann

2. METHODOLOGY

Study design and population study

This was a retrospective study with descriptive and analytical aims covering the records of patients admitted to the infectious and tropical diseases department of the University Hospital center of Fann during the period from 01 January 2019 to 31 December 2021. All patients with a diagnosis of severe malaria according to the 2015 WHO definition criteria **[7]** were included.

Data collection

Data were collected from patients' medical records, hospitalization and treatment registers. The survey forms were filled in on the basis of information collected from the patients' medical records and hospitalization registers. For each patient, a form was drawn up which included socio-demographic aspects (number of cases, age, sex, geographical origin, co-morbidities), clinical aspects (time of consultation, clinical signs of malaria severity, associated clinical signs), paraclinical aspects (biological signs of severity, other associated biological signs), therapeutic aspects (antimalarial treatment, adjuvant treatment) and outcome aspects (duration of hospitalization, evolutionary modalities).

Statistical analysis

- **Description of variables**

Qualitative variables were expressed as numbers (n) and percentages (%). Quantitative variables were expressed as average and standard deviation when they were normally distributed or as median and extremes when they were not.

- **Search for risk factors for death**

For the search for risk factors, we considered the variable «malaria-related death» as the variable to be explained, with the modalities «presence» or «absence» of death. A bivariate analysis was first carried out and gave us the crude Odds Ratio (ORb) with their 95% Confidence Intervals (CI95%). To compare the averages of potentially explanatory quantitative variables, we used Student's t test or the Wilcoxon MW test, depending on their applicability. To compare the proportions of potentially explanatory qualitative variables, we used Pearson's Chi2 test, Yates' corrected Chi2 test or Fisher's test, depending on their applicability.

We then performed a multivariate logistic regression in which all the explanatory variables whose p-values were less than 0.20 in the bivariate analysis were included. At the end of this analysis we had the adjusted Odds Ratio (ORa) for each explanatory variable framed by their CI95%. Their relationship with the death variable was statistically significant when the CI95% of the ORa excluded the value 1.

3. RESULTS

Epidemiological aspects

During the study period, 138 cases of severe malaria were hospitalized in the Fann infectious diseases department. The average age of the patients was 33.96 ± 17.09 years. The age group between 16 and 45 years was the most representative (72.46%), with a clear male predominance (76.10%) and a sex ratio of 3.18 **(Table 1)**. Severe malaria cases were admitted mostlý in october with 73 cases (52.9%) and november with 30 cases (21.7%). Most patients came from urban areas (68.11%), suburban areas (26.81%) in the Dakar region. In our series, 21 patients had an underlying chronic pathology dominated by High Blood Pressure (8 cases) followed by type 2 diabetes (6 cases).

Clinical aspects

The average consultation time was 6.7 ± 7.1 days. With regard to the clinical signs of severity, we found coma in 61 patients (44.20%), convulsions in 10 patients (7.24%), and prostration in 36.95% of patients. Jaundice was present in 61.59% of patients, and other signs such as macroscopic haemoglobinuria and cardiovascular collapse accounted for 6.52% and 2.89% of cases respectively. Other serious clinical signs were rarer **(Table 2)**. In addition to these WHO - defined clinical signs , we found other symptoms associated with severe malaria, including fever (93.3%), headache (68.9%) and vomiting (43%). A severe malaria Covid 19 co-infection was found in 4 patients.

Biological aspects

The average parasite density was 103940.4 ± 589280.4 trophozoites/mm^3 with a minimum of 7 trophozoites/mm3 and a maximum of 5100000 trophozoites/mm^3 ; with 5 cases of hyperparasitaemia with a parasite density higher than 100000 trophozoites/mm^3. The average haemoglobin level was 9.6 ± 3 g/dl, with a minimum of 3.9 g/dl and a maximum of 15 g/dl. Severe anaemia was noted in 20 patients, with a haemoglobin level of <7 g/dl (14.49%). The average creatinine level was 20.2 ± 21.7 mg/l, and 13 patients had kidney failure as a sign of severity, with creatinine levels above 30 mg/l (9.3%). Three cases of hypoglycaemiawere noted and 2 cases of metabolic acidosis were found. C- reactive protein was positive in 130 patients or 96.3%**.**

Table 1:Socio-demographic characteristics of severe malaria among patients at the infectious and tropical diseases department, Fann Hospital, Dakar, 2019-2021

Variables	Number of cases	Percentage (%)
Year		
2019	52	37,68
2020	26	18,84
2021	60	43,47
Age group (years)		
≤15	3	2,2
16 -45	100	72,46
46 – 60	20	14,50
61 – 90	15	10,90
Sex		
Male	105	76,10
Female	33	23,90
Geographical origin		
Urban district dakar	94	68,11
Sub urban district Dakar	37	26,81
Other regions	7	5,07
Hospitalization time (N=131)		
≤ 7days	107	81.67
> 7 days	24	18.32

Table 2:Clinical and biological manifestations of severe malaria at the infectious and tropical diseases department, Fann Hospital, Dakar, 2019-2021.

Clinical and biological	Number of	Percentage (%)

Manifestation	Cases	
Prostration	51	36,95
Impairedconsciousness /coma	61	44,20
Degree of coma G scale(N= 61)		
- G scale < 6	6	9,83
- G scale ≥ 7	55	90,16
Multiple convulsions	10	7,24
Jaundice	85	61,59
Severe anemia (Hb <7 g/dl)	20	14,49
Renal failure (creat> 30 mg/l)	13	9,42
Macroscopichaemoglobinuria	9	6,52
Hyperparasitaemia (> 100000/ mm3)	5	3,62
Cardiovascular collapse	4	2,89
Abnormalbleeding	4	2,89
Hypoglycemia(GC<0,4g/l)	3	2,17
Metabolicacidosis	2	1,44
Pulmonaryoedema	1	0,7

g scale : Glasgow scale

outcome and risk factors for death

All patients had received injectable artesunate at a dose of 2.4 mg/kg as an aetiological treatment ASSOCIATED with tThree thirds of patients (75%) had spent 6 days in hospital. The outcome was favourable in 121 patients (87.6%), with a fatality rate of 10.9% and 2 sequela cases. univariate analysis, neither sex nor age was associated with death (**Table 3**). In multivariate analysis, coma (ORa=12.29 CI95%: 2.0 - 73.22 p=0.006) and severe anaemia (ORa =27.16 CI95%: 3.4-217.18 p=0.006) were risk factors independently associated with death (**Table 4**).

Table 3 :Univariate analysis of risk factors for death of severe malaria at the infectious and tropical diseases department, Fann Hospital, Dakar, 2019-2021

Variables	Death		*p value*
	Yes N (%)	No N (%)	
Age group (years)			
1-60	15(12,0)	108(87,8)	0,17
> 60	0(0)	15(100)	
Sex			0,20
Male	10(9,5)	95(90,5)	

Female	5 (15,2)	28(84,8)	
Impaired consciousness			0,0006
No	2 (2,5)	72(97,3)	
Yes	13(21,3)	48 (78,7)	
Multiple Convulsion			
No	14(11,2)	111(88,8)	0,69
Yes	1 (10)	9(90)	
Jaundice			
No	5(10,2)	44(89,8)	
Yes	10(11,8)	75 (88,2)	0,40
Metabolic acidosis			
No	14(10,3)	122(89,7)	
Yes	1(50)	1(50)	0,1
Severe anemia			
No	8(6,8)	110 (93,2)	0,001
Yes	7 (35,0)	13 (65,0)	
Renal failure			
No	8 (5,80)	117 (93,6)	0,3
Yes	7 (53,84)	6 (46,15)	

Table 4:Risk factors for death of severe malaria atthe infectious and tropical diseases department, Fann Hospital, Dakar, 2019-2021

	Univariate analysis		**multivariate analysis**	
Variables	**OR (IC 95%)**	***p value***	**ORa (IC 95%)**	***p value***
Sex				
Female	1	-	-	-
Male	0,5 (0,15-1,66)	0,26	3,46 (0,42-28,61)	0,25
Metabolic acidosis				
No	1	-	-	-
Yes	9,33(0,55-158,95)	0,2	8,68 (0,07-1136,02)	0,385
Impaired consciousness				
No	1	-	-	-
Yes	8,31 (1,76-39,28)	0,0006	12,29 (2,06-73,22)	0,006
Severe anemia				
No	1	-	-	-
Yes	9,82 (2,83-34,06)	0,001	27,16 (3,4-217,18)	0,006

4.DISCUSSION

The particularity of this study is that all patients received injectable artésunate. In terms of frequency, these results are comparable to those of Diop in 2010, who reported 181 cases over 4 years **[8]**. A similar finding was made by Wade, who reported 87 cases over a 2-year period **[9]**. Elsewhere in Africa, a study carried out in Côte d'Ivoire noted 274 cases over 14 years **[10]**. The higher number of cases in 2021 may be explained by disruptions to malaria prevention, diagnosis and treatment services, as predicted by the WHO during the covid 19 pandemic in many countries **[1]**. Senegal was not outdone, which may explain the increase in the number of severe cases of malaria, with 60 cases in 2021. Other malaria-endemic countries have reported reductions of more than 20% in malaria tests by 2020 **[1]**. In addition, during the covid 19 pandemic, the similarity of the clinical signs of malaria with covid 19 can lead to misdiagnosis and longer consultation times, resulting in development to severe forms of malaria. The availability of the covid 19 rapid diagnostic test during the third wave in 2021 made it possible to diagnose severe co-infection with covid 19 malaria in 4 patients during this period.

Senegal is classified as a sub-Saharan African country where malaria is endemic, with seasonal transmission mainly during the rainy season, according to the National Malaria Control Programme**[2]**. The monthly breakdown showed higher numbers of cases in october and november, with 73 cases (52.9%) and 30 cases (21.7%) respectively. These results are similar to previous studies conducted on severe malaria in Africa **[9,11,12]**, with this period corresponding to the postrainy season, which is characterised by the peak of the malaria epidemic. A study conducted in Côte d'Ivoire by Eholié found that the majority of cases (62%) were recorded during and after the rainy season **[10]**.

The case-fatality rate was 10.9%, lower than previous data from Diop **[8]** and Lawson **[13]**, who found 17.1% and 18% respectively. This trend observed in our study is clearly in line with current WHO data, which show a reduction in case fatality in recent years, from 896,000 cases in 2000 to 558,000 cases in 2019 **[1]**. Similarly, in Senegal, the number of deaths fell from 526 to 260, a 51% reduction over the period 2016 to 2019 **[2]**. In addition, injectable artesunate, currently the first-line treatment for severe malaria, was the only antimalarial used in all patients in our series. Clinical trials had already established that the use of injectable artesunate reduced mortality and shortened hospital stays, as it leads to faster parasite clearance **[14,15]** .

We also looked for risk factors for death. In univariate analysis, although males predominated in our series (76.10%), this did not influence case fatality. This male predominance has been reported by other authors **[10,16,17,18]**. This difference could be explained in part by the fact that women are much better educated thanks to greater participation in awareness campaigns on measures to prevent this condition, especially during prenatal consultations.

Our study population consisted of young adults with an average age of 33.96 ± 17.09 years. In a study conducted in the same department **[19]** the average age was 28.2 ± 13.7 years. It was difficult to find a link between advanced age and death because the majority of our patients were young adults. However, other studies have reported a link between death and advanced age **[20]**.

Jaundice was found in 61.59% of our patients, and is often linked to liver damage, which is very common in adults, as other authors have pointed out **[4,21]**. These results could be influenced by traditional herbal medicine, which lengthens the consultation time **[21,22]**. However, we did not find an association with death in univariate analysis.

Other signs such as kidney failure and convulsions were not found to be predictive of death in our series.

Multivariate analysis showed that coma and severe anaemia were risk factors for death in our study. Coma was a factor independently associated with death (ORa=12.29 CI95% : 2.0 - 73.22). These data are consistent with those in the literature **[20,23]**. In Brunel's study **[20]**, 21% of patients who survived had consciousness disorders, compared with 62% of patients who died, with a statistically significant difference (ORa=1.32 CI95%:1.20-1.45). The severity of neuromalaria is linked to the sequestration of red blood cells, leading to vital dysfunction, which is mainly the preserve of *Plasmodium falciparum*.

Severe anaemia, found in 14.5% of patients, was independently associated with death (ORa =27.16 95% CI: 3.4 -217.18). These results corroborate those of Soumaré**[19]** who found 80% of deaths in patients with severe anaemia, and the same trend was reported by Diop **[8]**. However, in the study by Mengistu and Mutombo **[23,24]**, anaemia was not a predictive factor for death. Anaemia is due to haemolysis and is thought to be a poor prognostic factor, especially in children, as it results in insufficient oxygen transport to the brain, leading to cerebral hypoxia **[25]**.

Cases of metabolic acidosis represented only 1.5% in our series, probably underestimated because blood gas measurement was not systematically available in our public services, and this could constitute a bias. This result is much lower than that of Wade **[9]** who would have obtained 38% in a study of 87 patients. Hanson **[26]** found this acidosis to be a risk factor for death, and in an Ethiopian series **[23]** metabolic acidosis was associated with death 13.4 (3.2-56.3). In the latter study pulmonary oedema was also a poor prognostic factor **[23]**.

5. CONCLUSION

Severe malaria remains a public health issue in our resource-limited countries. Access to RDT has improved early diagnosis, and the use of injectable

artesunate has helped to reduce mortality. The risk factors for death identified in our study were coma and severe anaemia. Optimising early recognition of signs of seriousness and improving the technical facilities in intensive care units, as well as stepping up prevention, can improve patient outcomes.

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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