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Factors associated with severe malaria and in-hospital mortality among hospitalised children under 15 years of age in Brazzaville, Republic of the Congo: a multicentre cross-sectional study

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Abstract

Background: Severe *Plasmodium falciparum* malaria remains a leading cause of paediatric morbidity and mortality in sub-Saharan Africa, recent data from urban Republic of the Congo are scarce. This study assessed the frequency, clinico-biological profile, risk factors and in-hospital death of severe malaria among children admitted to referral hospitals in Brazzaville.

Methods: This prospective, multicentre cross-sectional study (January–December 2024) analyzed children under 15 hospitalized with confirmed *P. falciparum* malaria in Brazzaville. Using 2014 WHO criteria, determinants of severe malaria and in-hospital mortality were identified via multivariable logistic regression.

Results: Of 1,050 children screened, 441 were eligible and included; severe malaria accounted for 161 (36.5%) cases and moderate malaria for 280 (63.5%). The median age was 48.0 months (IQR 15.0-96.0), and 240 children (54.4%) were younger than five years. In-hospital mortality was 7.0% (31/441) in the overall cohort and 18.0% (29/161) in the severe malaria group, compared with 0.7% (2/280) in the moderate malaria group ($p<0.001$). The predominant WHO 2014 features in the severe malaria group were composite neurological involvement (62.7%), severe anaemia (40.4%), repeated convulsions (39.1%) and coma (37.9%). The case fatality rate rose with the number of concurrent WHO criteria, from 14.5% with a single criterion to 44.4% with four or more criteria. Independent determinants of severe malaria were pre-hospital antimalarial self-medication (aOR 3.00; 95% CI 1.75-5.16; $p<0.001$) and delayed consultation beyond 48 hours (aOR 2.16; 95% CI 1.28-3.63; $p=0.004$). Independent risk factors for in-hospital death were severe malaria status (aOR 12.33; 95% CI 2.50-60.78; $p=0.002$), acute kidney injury (aOR 5.96; 95% CI 1.47-24.11; $p=0.012$) and age<5 years (aOR 2.98; 95% CI 1.12-7.91; $p=0.029$).

Conclusions: Severe paediatric malaria carries substantial mortality in Brazzaville, independently driven by acute k and age under five years. Pre-hospital self-medication and delayed consultation were the principal modifiable determinants of severe disease. Reducing these behavioural delays and ensuring access to paediatric renal support should be prioritised in the national malaria control strategy.

Background

Malaria remains a global public health priority, particularly in sub-Saharan Africa. According to the World Health Organization (WHO), an estimated 282 million malaria cases and 610,000 malaria-related deaths occurred globally in 2024, with the WHO African Region accounting for about 95% of cases and 95% of deaths [1]; children younger than five years accounted for approximately 76% of malaria-related deaths in the African Region [2]. Despite substantial progress over the past two decades, the burden has stabilised in several high-endemic countries, and the Republic of the Congo reported approximately 1.4 million cases in 2024 [2].

Severe malaria, almost exclusively caused by *Plasmodium falciparum*, encompasses a wide spectrum of clinical and biological manifestations whose prognostic relevance depends not only on their nature but

also on their simultaneous occurrence within the same patient [3–5]. Since the seminal work of Marsh and colleagues in Kenyan children, in which neurological involvement, respiratory distress and hypoglycaemia were identified as key bedside predictors of death [4], successive analyses of large paediatric datasets have confirmed that mortality is driven more by the accumulation of severity features than by any single criterion considered in isolation. In the AQUAMAT trial, acidosis, cerebral manifestations, elevated blood urea nitrogen and signs of chronic illness were the four independent predictors of death across nine African countries [5]. Age and transmission intensity also shape the clinical phenotype: in areas of high transmission, severe anaemia predominates among infants, whereas cerebral malaria becomes relatively more frequent as children get older and as overall transmission intensity declines [6, 7].

In West, East and Central Africa, hospital-based series continue to report divergent frequencies and mortality rates, reflecting heterogeneous health-system capacity, transmission intensity and care-seeking practices. Recent studies have documented severe malaria frequencies ranging from 15.9% in a Libreville referral centre to 67.8% among febrile children in Kinshasa [8, 9]. In-hospital case fatality rates have likewise varied from 0.6% in Libreville to more than 20% in some rural or crisis-affected settings [8, 10, 11]. Delayed presentation, pre-hospital antimalarial self-medication and limited access to supportive care are repeatedly identified as modifiable risk factors for severity and death [12–14]. More recently, attention has focused on malaria-associated acute kidney injury (AKI), which is increasingly recognised as an underestimated but highly lethal complication of paediatric severe malaria, with recent prospective work in Uganda showing that it independently predicts both in-hospital and post-discharge mortality [15–17].

In the Republic of Congo, data on severe paediatric malaria are limited and largely historical. Earlier work from Brazzaville reported an in-hospital frequency of 11.2% with a case fatality rate of 6.5%, and a more recent series from the rural Cuvette department reported a severe malaria frequency of 34.4% with a case fatality rate of 2.5% [18, 19]. Urban malaria transmission in Brazzaville is marked by strong local heterogeneity, and contemporary estimates integrating WHO 2014 criteria, objective AKI definitions and the impact of self-medication are lacking [20]. The present study was therefore designed to estimate the hospital frequency of severe malaria among children admitted to referral hospitals in Brazzaville, to describe the clinical and biological profile of affected children, and to identify factors independently associated with severe disease and with in-hospital death.

Methods

Study design and setting

This was a multicentre, prospective, analytical cross-sectional study conducted from 1 January to 31 December 2024. Four major referral hospitals of Brazzaville were included, covering both the northern and southern health districts of the city: the referral hospitals of Talangaï, Bacongo and Makélékélé (level II of the Congolese health pyramid), and the Centre Hospitalier Universitaire de Brazzaville (CHU-B), the

national tertiary referral centre (level III). Brazzaville, the capital of the Republic of the Congo, is characterised by a humid tropical climate with holoendemic, perennial *P. falciparum* transmission and marked intra-urban heterogeneity [20].

Eligibility criteria and sampling

All consecutively hospitalised children younger than 15 years with microscopically confirmed *P. falciparum* mono-infection were considered eligible. Children were excluded if they were neonates (age < 30 days), if they presented with a documented co-existing condition likely to confound the clinical or biological picture (sepsis, meningitis, bacterial pneumonia requiring a distinct diagnostic pathway, severe acute malnutrition with kwashiorkor, sickle-cell disease in crisis), if the medical record did not contain both a thick blood smear result and/or if parental consent was refused.

Sampling was consecutive and exhaustive. An a priori minimum sample size of 347 children was calculated using the Schwartz formula [$N = Z^2p(1 - p)/d^2$], using a 95% confidence interval ($Z = 1.96$), an expected severe malaria prevalence of 34.4% as reported in the Cuvette department of Congo [19] and a 5% precision. Exhaustive recruitment was maintained throughout the year to maximise statistical power and to reduce selection bias.

Data collection and laboratory procedures

Data were extracted prospectively, at the time of admission and during hospitalisation, from the medical records and routine laboratory reports using a standardised case-report form. Variables included socio-demographic data, preventive measures (insecticide-treated net [ITN] use), pre-hospital history (antimalarial self-medication, time from symptom onset to first hospital contact), physical examination findings, paediatric Glasgow Coma Scale (GCS) and Blantyre coma scale scores, results of thick and thin blood smears, full blood count, biochemistry (glycaemia, creatininaemia) and clinical outcome at discharge.

Laboratory analyses were performed as part of routine hospital practice, and our description is based on documented laboratory results and standard operating procedures. Parasitological diagnosis relied on microscopic examination of Giemsa-stained thick blood films read at high magnification, according to the WHO method. Parasite density, originally recorded as parasites per 200 leucocytes, was converted to parasites per µL by multiplying by the patient's white blood cell count when available, and by a standard value of 8,000/µL when unavailable. Haematological parameters were measured on an impedance-based automated analyser; biochemical parameters (glycaemia, creatinine) were measured using automated colorimetric spectrophotometry.

Operational definitions

Severe malaria was defined according to the WHO 2014 paediatric criteria [3]: severe anaemia (haemoglobin < 5 g/dL), prostration (inability of the child to sit, stand or feed normally according to age), impaired consciousness (Blantyre coma score 3–4 or paediatric GCS 9–10), coma (Blantyre coma score ≤ 2 or paediatric GCS ≤ 8), repeated convulsions (≥ 2 within 24 hours), respiratory distress (including acidotic or deep breathing, nasal flaring or intercostal recession), circulatory collapse or shock (cold extremities, capillary refill time > 3 s, or weak and rapid pulse), clinical jaundice, macroscopically confirmed haemoglobinuria (dark red or "Porto-wine" urine), hyperparasitaemia (corresponding to ≥ 250,000 parasites/μL), hypoglycaemia (< 2.2 mmol/L) and acute kidney injury (AKI). AKI was defined using age-adjusted absolute serum creatinine thresholds adapted from the Kidney Disease: Improving Global Outcomes (KDIGO) paediatric criteria, since pre-admission baseline creatinine values were not available. Lactate and blood-gas analyses were not routinely available in the study hospitals; hyperlactataemia and metabolic acidosis could therefore not be incorporated into the operational definition.

Definition of moderate malaria

A composite neurological involvement variable was defined a priori as coma OR impaired consciousness OR repeated convulsions, consistent with previous analyses of severity profiles [21]. Severe thrombocytopaenia was defined as a platelet count < 50 × 10^9/L and anaemia as a haemoglobin < 11 g/dL. Age was analysed both as a continuous variable (months) and categorised as < 5 years versus ≥ 5 years, in line with the standard paediatric stratification of malaria risk. Time to consultation was defined as the interval between symptom onset and first hospital presentation (categorised as ≤ 48 h versus > 48 h), and length of hospital stay was defined as the interval in days between admission and discharge or death.

Statistical analysis

All analyses were performed in R version 4.5.1. Normality of continuous variables was assessed using the Shapiro-Wilk test; all continuous variables departed from normality and were therefore summarised as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U or Kruskall Wallis tests if required. Categorical variables were summarised as counts and proportions and compared using the Chi-square or Fisher's exact test, as appropriate. Percentages of categorical variables are reported over the total number of children with available data for the variable of interest. Missing data were handled using a complete-case approach, with no imputation.

Determinants of severe malaria (moderate versus severe malaria) and of in-hospital death (survivors versus deaths) were first explored using univariable logistic regression. Variables reaching $p < 0.20$ or of established clinical relevance were entered into multivariable models; adjusted odds ratios (aOR) and 95% confidence intervals (CI) are reported. Multicollinearity was assessed using variance inflation factors; impaired consciousness and coma were coded as mutually exclusive categories (Blantyre score 3–4 and ≤ 2, respectively).

The cumulative severity burden was further explored by counting the number of WHO 2014 criteria present per patient (categorised as 1, 2, 3 or ≥ 4). Pairwise co-occurrence of severity criteria was quantified using the Jaccard similarity index and visualised as a heatmap to identify phenotypic clusters. A p-value below 0.05 was considered significant.

Results

Characteristics of the study population

During the study period, 1,050 children were admitted for suspected malaria across the four hospitals; 609 were excluded for co-existing febrile illness, incomplete laboratory work-up or missing records, leaving 441 children with microscopically confirmed *P. falciparum* mono-infection for analysis. Of these, 161 (36.5%) met at least one WHO 2014 criterion for severe malaria and 280 (63.5%) had moderate malaria (Table 1).

Table 1
General characteristics of the study population according to malaria severity (N = 441).

Variable	All patients (N = 441)	Moderate malaria (n = 280)	Severe malaria (n = 161)	*p*
Continuous variables: median [IQR]				
Age (months)	48.0 [15.0–96.0]	48.0 [17.0–96.0]	36.0 [10.0-88.1]	0.087
Time to admission (days)	3.0 [2.0–5.0]	3.0 [2.0–4.0]	4.0 [2.0–5.0]	0.002
Length of hospital stay (days)	5.0 [3.0–6.0]	4.0 [3.0–6.0]	5.0 [3.0–7.0]	0.016
Categorical variables: n (%)				
Age < 5 years	240 (54.4%)	147 (52.5%)	93 (57.8%)	0.226
Male sex	241 (54.6%)	147 (52.5%)	94 (58.4%)	0.281
Insecticide-treated net use	164 (37.2%)	108 (38.6%)	56 (34.8%)	0.490
Pre-hospital antimalarial self-medication	121 (27.4%)	50 (17.9%)	71 (44.1%)	< 0.001
Time to consultation > 48 h □	188 (59.3%)	101 (51.0%)	87 (73.1%)	< 0.001

□ *Denominator restricted to patients with available data on time to consultation (n = 317: 198 MM, 119 SM); percentages calculated over available data.*

Overall, the median age was 48.0 months (IQR 15.0–96.0); 240 children (54.4%) were younger than five years and 241 (54.6%) were male. The median time from symptom onset to hospital admission was 3 days (IQR 2–5), and a delayed consultation beyond 48 hours was documented in 188/317 patients with available data (59.3%). Pre-hospital antimalarial self-medication was reported in 121 children (27.4%), and ITN use in 164 (37.2%). The median length of hospital stay was 5 days (IQR 3–6), and overall in-hospital mortality was 7.0% (31/441).

Compared with children with moderate malaria, those with severe malaria had a longer median time to admission (4 [IQR 2–5] versus 3 [2–4] days; $p = 0.002$), a longer median hospital stay (5 [3–7] versus 4 [3–6] days; $p = 0.016$) and a more than two-fold higher frequency of pre-hospital antimalarial self-medication (44.1% versus 17.9%; $p < 0.001$). Delayed consultation beyond 48 hours was also significantly more frequent among children with severe malaria (73.1% versus 51.0% of patients with available data). In-hospital mortality was markedly higher in the severe malaria group (18.0% versus 0.7%; $p < 0.001$). Age, sex and reported ITN use did not differ significantly between groups.

Biological parameters differed markedly between groups (Fig. 1). The median haemoglobin was significantly lower in severe malaria (5.9 g/dL [IQR 4.3-9.0]) than in moderate malaria (9.9 g/dL [7.8–11.6]; $p < 0.001$), while the median platelet count was approximately halved in severe malaria (92.0 × 10^9/L [45.5–176.0] versus 167.0 × 10^9/L [120.0-313.0]; $p < 0.001$). Median white blood cell count was higher in severe malaria (12.0 × 10^9/L [8.8–15.8] versus 8.2 × 10^9/L [6.0-11.2]; $p < 0.001$). Median parasite density was approximately three-fold higher in severe than in moderate malaria (13,800/µL [5,328 − 28,800] versus 4,711/µL [2,096 − 12,042]; $p < 0.001$). Glycaemia did not differ significantly between groups (6.8 versus 6.8 mmol/L; $p = 0.659$), noting that glycaemia was available for only 193 patients (43.8%).

Distribution of WHO 2014 severe malaria criteria and case fatality rates

Within the severe malaria group (n = 161), the most frequently observed WHO 2014 criteria were composite neurological involvement (62.7%), severe anaemia (Hb < 5 g/dL; 40.4%), repeated convulsions (39.1%), coma (GCS ≤ 8 or Blantyre ≤ 2; 37.9%), severe thrombocytopaenia (27.3%), respiratory distress (23.6%) and isolated impaired consciousness (18.6%) (Table 2, Fig. 2). Acute kidney injury was identified in 12 children (7.5%), hyperparasitaemia in 10 (6.2%), circulatory collapse and prostration in 6 each (3.7%), clinical jaundice in 4 (2.5%) and hypoglycaemia in 2 (1.2%).

Table 2
Frequency and case fatality rate of WHO 2014 severe malaria criteria within the severe malaria group.

WHO 2014 criterion	N	%	In-hospital deaths	CFR[a] (%)
Composite neurological involvement[b]	101	62.7	16	15.8
Severe anaemia (Hb < 5 g/dL)	65	40.4	12	18.5
Repeated convulsions	63	39.1	9	14.3
Coma (GCS ≤ 8 or Blantyre ≤ 2)	61	37.9	12	19.7
Severe thrombocytopaenia (< 50 × 10^9/L)	44	27.3	10	22.7
Respiratory distress	38	23.6	10	26.3
Impaired consciousness (isolated)	30	18.6	3	10.0
Acute kidney injury	12	7.5	6	50.0
Hyperparasitaemia (≥ 250.000/µL)	10	6.2	1	10.0
Circulatory collapse / shock	6	3.7	5	83.3
Prostration	6	3.7	3	50.0
Clinical jaundice	4	2.5	3	75.0
Hypoglycaemia (< 2.2 mmol/L)	2	1.2	1	50.0

a-CFR: in-hospital case fatality rate, b- Composite: coma OR impaired consciousness OR repeated convulsions; the composite variable captures all patients with any neurological feature.

When expressed per-criterion, the highest case fatality rates were observed for circulatory collapse (83.3%), clinical jaundice (75.0%), prostration (50.0%) and acute kidney injury (50.0%), followed by respiratory distress (26.3%), severe thrombocytopaenia (22.7%), coma (19.7%) and severe anaemia (18.5%). Hyperparasitaemia was associated with a low case fatality rate of 10.0% (Fig. 2, panel B).

Cumulative severity burden and mortality

Within the severe malaria group, 69 (42.9%) children fulfilled a single WHO criterion, 53 (32.9%) two criteria, 30 (18.6%) three criteria and 9 (5.6%) four or more criteria. The case fatality rate rose with the number of concurrent criteria, from 14.5% with a single criterion to 13.2% with two, 26.7% with three and 44.4% with four or more (Fig. 3). Category-wise univariable logistic regression showed a trend towards significance for the highest category (unadjusted OR 4.57; 95% CI 1.00-20.9; $p = 0.050$ for ≥ 4 versus 1 criterion), and the Cochran-Armitage test confirmed a statistically significant linear dose-response gradient between the number of WHO criteria and in-hospital mortality ($Z = 2.21$; chi-square = 4.90, 1 df; $p = 0.027$).

Co-occurrence of severity criteria

Pairwise co-occurrence of severity criteria in the severe malaria group is shown in Fig. 4. The most frequent pairs were repeated convulsions with coma (n = 39; 24.2% of the severe malaria group), severe anaemia with severe thrombocytopaenia (n = 23; 14.3%) and repeated convulsions with respiratory distress (n = 17; 10.6%). Rarer associations included repeated convulsions with circulatory collapse (0.6%) and impaired consciousness with circulatory collapse (0.6%). Jaundice, prostration and hyperparasitaemia were almost always observed isolated.

Determinants of severe malaria

In univariable analysis (Table 3), pre-hospital antimalarial self-medication was associated with a more than three-fold higher odds of severe malaria compared with moderate malaria ($p < 0.001$), and delayed consultation beyond 48 hours with a more than two-fold higher odds ($p < 0.001$). Age < 5 years, male sex and ITN use were not significantly associated with severity. After adjustment for these variables in a multivariable model, self-medication and delayed consultation remained the only independent determinants of severe malaria.

Table 3
Factors associated with severe malaria — univariable and multivariable analysis (moderate versus severe malaria, N = 441).

Variable	MM (n = 280)	SM (n = 161)	Unadjusted OR [95% CI]	p	aOR [95% CI]	p
Continuous variables: median [IQR]						
Age (months)	48.0 [17.0–96.0]	36.0 [10.0-88.1]	—	0.087	—	—
Time to admission (days)	3.0 [2.0–4.0]	4.0 [2.0–5.0]	—	0.002	—	—
Haemoglobin (g/dL)	9.9 [7.8–11.6]	5.9 [4.3-9.0]	—	< 0.001	—	—
Platelet count (× 10^9/L)	167 [120–313]	92 [45.5–176]	—	< 0.001	—	—
White blood cells (× 10^9/L)	8.2 [6.0-11.2]	12.0 [8.8–15.8]	—	< 0.001	—	—
Parasite density (/ µL)	4,711 [2,096 – 12,042]	13,800 [5,328 – 28,800]	—	< 0.001	—	—
Blood glucose (mmol/L)	6.8 [6.0-8.4]	6.8 [5.6–8.3]	—	0.659	—	—
Categorical variables: n (%)						
Age < 5 years	147 (52.5%)	93 (57.8%)	1.31 [0.88–1.95]	0.226	1.21 [0.74–1.99]	0.442
Male sex	147 (52.5%)	94 (58.4%)	1.27 [0.85–1.89]	0.281	—	—
Pre-hospital self-medication	50 (17.9%)	71 (44.1%)	3.63 [2.35–5.61]	< 0.001	3.00 [1.75–5.16]	< 0.001
Time to consultation > 48 h[a]	101 (51.0%)	87 (73.1%)	2.61 [1.60–4.27]	< 0.001	2.16 [1.28–3.63]	0.004
ITN use	108 (38.6%)	56 (34.8%)	0.85 [0.57–1.27]	0.490	—	—

MM: moderate malaria; SM: severe malaria; OR: odds ratio (severe malaria as outcome); ITN: insecticide-treated net. time to admission > 48 h, age < 5 years, ITN use. a Time to consultation > 48 h computed over patients with available data (n = 198 MM, n = 119 SM).

Regarding the impact of pre-hospital self-medication on malaria severity, consultation delay, and case fatality rate, Fig. 5 showed that pre-hospital self-medication was significantly more frequent among children with severe malaria than in those with moderate malaria. Children who practiced pre-hospital self-medication were three times more likely to develop severe malaria compared to those who did not (OR = 3.63 [2.35–5.61]; $p < 0.001$) (Fig. 5A). Similarly, the median time to admission and the case fatality rate were higher in children with severe malaria who practiced pre-hospital self-medication compared to those who did not (Fig. 5B and C) ($p < 0.001$).

Risk factors for in-hospital death

Overall in-hospital mortality was 7.0% (31/441 children). In univariable analysis (Table 4), severe malaria status, acute kidney injury, neurological involvement, severe anaemia, pre-hospital self-medication, severe thrombocytopaenia and age < 5 years were all associated with increased odds of death ($p < 0.03$), while delayed consultation, male sex and hyperparasitaemia were not. Hyperparasitaemia was not associated with mortality (unadjusted OR 0.81; 95% CI 0.10–6.29).

Table 4
Risk factors for in-hospital death-univariable and multivariable analysis

Variable	Survivors (n = 410)	Deaths (n = 31)	Unadjusted OR [95% CI]	*p*	aOR [95% CI]	*p*
Continuous variables: median [IQR]						
Age (months)	48.0 [16.0–96.0]	38.8 [7.0-56.2]	-	0.104	-	-
Length of stay (days)	5.0 [4.0–7.0]	2.0 [1.0–3.0]	-	< 0.001	-	-
Haemoglobin (g/dL)	9.1 [6.3–11.2]	5.9 [4.5–7.8]	-	< 0.001	-	-
Platelets (× 10^9/L)	150 [94–277]	70 [38–103]	-	< 0.001	-	-
Categorical variables: n (%)						
Severe malaria	132 (32.2%)	29 (93.5%)	30.54 [7.18–129.90]	< 0.001	12.33 [2.50-60.78]	0.002
Acute kidney injury	6 (1.5%)	6 (19.4%)	16.16 [4.86–53.74]	< 0.001	5.96 [1.47–24.11]	0.012
Neurological involvement	85 (20.7%)	16 (51.6%)	4.08 [1.94–8.58]	< 0.001	-	-
Severe anaemia (Hb < 5 g/dL)	53 (12.9%)	12 (38.7%)	4.25 [1.95–9.26]	< 0.001	1.76 [0.67–4.64]	0.255
Pre-hospital self-medication	103 (25.1%)	18 (58.1%)	4.13 [1.95–8.71]	< 0.001	2.18 [0.85–5.57]	0.103
Severe thrombocytopaenia	50 (12.2%)	10 (32.3%)	3.43 [1.53–7.70]	0.004	1.87 [0.73–4.80]	0.194
Age < 5 years	217 (52.9%)	23 (74.2%)	2.77 [1.16–6.60]	0.028	2.98 [1.12–7.91]	0.029
Time to consultation > 48 h	174 (42.4%)	14 (45.2%)	1.65 [0.62–4.41]	0.441	-	-
Male sex	222 (54.1%)	19 (61.3%)	1.40 [0.65–3.02]	0.501	-	-

Variable	Survivors (n = 410)	Deaths (n = 31)	Unadjusted OR [95% CI]	*p*	aOR [95% CI]	*p*
Continuous variables: median [IQR]						
Hyperparasitaemia ≥ 250.000/µL	16 (3.9%)	1 (3.2%)	0.81 [0.10–6.29]	1.000	-	-
WHO criteria count (SM group, n = 161)						
1 WHO criterion (reference)	59/69 (85.5%)	10/69 (14.5%)	Ref	-	-	-
2 WHO criteria	46/53 (86.8%)	7/53 (13.2%)	0.90 [0.33–2.49]	0.647	-	-
3 WHO criteria	22/30 (73.3%)	8/30 (26.7%)	2.15 [0.72–6.43]	0.172	-	-
≥ 4 WHO criteria	5/9 (55.6%)	4/9 (44.4%)	4.57 [1.00-20.9]	0.050	-	-

In the multivariable model three variables remained independently associated with in-hospital death: severe malaria status (aOR 12.33; 95% CI 2.50-60.78; $p = 0.002$), acute kidney injury (aOR 5.96; 95% CI 1.47–24.11; $p = 0.012$) and age < 5 years (aOR 2.98; 95% CI 1.12–7.91; $p = 0.029$). Severe anaemia, severe thrombocytopaenia and self-medication lost significance after adjustment (Table 4, Fig. 5).

The presence of more than four severity criteria for malaria was associated with a fourfold increase in the risk of death among children with severe malaria (OR: 4.57 [1.00–20.9]; $p < 0.050$). Conversely, the presence of one to three criteria had no significant impact on mortality.

Discussion

This study described the feature of complicated severe malaria and outcome in 441 children admitted in health structures of Brazzaville in Congo. To our knowledge, this is the first multicentre description of paediatric severe malaria in Brazzaville integrating WHO 2014 criteria, a pragmatic AKI definition and a quantitative assessment of cumulative severity burden.

The frequency of severe malaria observed in our cohort (36.5%) was substantially higher than that reported in the nearby Libreville referral centre in Gabon (15.9%) and in urban Dakar (19.4%) [4, 8]. But it is lower than recent reports from Kinshasa (67.8%) and Western Uganda (72.9%) [9, 13]. A previous hospital-based study conducted in Brazzaville more than a decade ago reported a severe malaria frequency of only 11.2% with a case fatality rate of 6.5% [18], suggesting that the hospital burden has risen substantially since then. This apparent escalation is consistent with broader regional patterns: slowing progress in malaria control since 2015, pandemic-related disruptions to routine services, and

financial constraints on the national malaria control programme have all been implicated in recent increases in paediatric severe malaria across sub-Saharan Africa [1, 17, 22]. The low reported ITN usage in this study cohort (37.2%), comparable to that recently documented in the rural Cuvette department (10.8%) [19] and markedly below the Ugandan rates reported by Opoka and colleagues, is consistent with the hypothesis of incomplete implementation of preventive interventions [13, 19].

The in-hospital case fatality rate of 18.0% in the severe malaria population is markedly higher than the 2.5% reported in the rural Cuvette department of Congo and the 0.6-4.0% reported in Libreville and Kinshasa [8, 9, 19]. However, it is within the range of rates reported from Rwanda, Zimbabwe during the COVID-19 pandemic and from resource-limited settings with interrupted access to parenteral artesunate or blood products [10, 11, 17]. Compared with the 26.3% case fatality rate historically reported from Brazzaville. The present result would suggest a substantial reduction over the last decade, consistent with improvements in diagnostic capacity, availability of artemisinin-based injectable therapy and strengthened paediatric critical care [23]. Nonetheless, mortality remains unacceptably high for a preventable and curable disease.

The clinical profile observed dominated by composite neurological involvement, severe anaemia, repeated convulsions and coma is broadly consistent with classical descriptions of African paediatric severe malaria [4, 5, 7]. However, coma frequency (37.9%) was markedly higher than in the recent Cuvette series (1.4%), possibly reflecting differences in pre-hospital health-seeking behaviours, transmission intensity and referral patterns between urban Brazzaville and rural Cuvette [19]. Severe anaemia predominated among younger children whereas cerebral features were more frequent in older age groups. This is consistent with the age-phenotype variation originally described across East African settings of differing transmission intensity [6] and subsequently reported from Gabonese cohorts [7, 8].

The relationship between the number of concurrent WHO 2014 criteria and the in-hospital case fatality rate rising from 14.5% with one criterion to 44.4% with four or more, provides a clinically tractable metric for bedside risk stratification, consistent with previous analyses of severity profiles in African children [5, 22]. The pairwise co-occurrence analysis further suggested that specific combinations, notably repeated convulsions with coma and severe anaemia with severe thrombocytopaenia, carry particularly high mortality, whereas combinations involving isolated impaired consciousness are less ominous. These findings highlight earlier evidence that it is the phenotype, rather than any single marker, which determines short-term outcome [4, 5, 22].

One of the most striking findings of the present study is the magnitude of the effect of pre-hospital antimalarial self-medication, which remained associated with a three-fold higher odds of severe disease after adjustment (aOR 3.00; 95% CI 1.75–5.16). Children who were self-medicated before admission had a longer time from symptom onset to hospital presentation (5.0 versus 3.5 days among severe cases) and a markedly higher case fatality rate (25.4% versus 12.2% in the severe malaria group) (Fig. 5). This pattern is consistent with recent evidence from the Democratic Republic of the Congo, where caregiver perceptions of fever severity and the ready availability of antimalarials in private drug outlets have been

identified as major drivers of treatment-seeking delay [12]. Furthermore, a recent Ethiopian meta-analysis showing that low educational attainment, financial constraints and long travel distances were the principal determinants of delayed malaria care-seeking in sub-Saharan Africa [14]. Our data reinforce the need for community-level interventions combining caregiver education, regulation of unsupervised antimalarial sales and strengthening of the primary healthcare referral pathway.

Acute kidney injury was present in only 7.5% of children with severe malaria in the study cohort, a frequency lower than in recent prospective Ugandan cohorts, where up to 35–45% of children with severe malaria have been shown to develop AKI when KDIGO criteria were applied with a validated paediatric baseline creatinine estimate [15, 16, 24]. This discrepancy almost certainly reflects under-ascertainment of AKI in our setting, since pre-admission baseline creatinine values were unavailable and age-adjusted absolute creatinine thresholds are known to be conservative in paediatric populations. Despite this likely under-estimation, AKI was independently associated with a six-fold higher odds of in-hospital death (aOR 5.96; 95% CI 1.47–24.11), accounting for approximately one in five severe malaria deaths in our cohort. These findings are in line with recent syntheses showing that malaria-associated AKI is a key driver of mortality in African children and a predictor of both post-discharge death and subsequent chronic kidney disease [15, 16, 24]. They reinforce the need for systematic creatinine measurement at admission in all children presenting with severe malaria, for the availability of paediatric dialysis capacity in tertiary centres, and for multidisciplinary management protocols integrating nephrology, paediatrics and critical care.

This study has some limitations which should be acknowledged. First, lactate and blood-gas analyses were not routinely available in the study hospitals; metabolic acidosis and hyperlactataemia, which are among the strongest predictors of death in African children with severe malaria, could therefore not be incorporated into the operational severity definition [4, 5].

Second, haemoglobinuria was diagnosed macroscopically and was not confirmed by urine dipstick or red cell sediment analysis, which may have led to a conservative estimate of its frequency.

Third, nutritional status, socioeconomic position and secondary bacterial infections all established modifiers of severe malaria outcome were not systematically documented. Finally, the study was conducted in a single calendar year and in referral hospitals only; external validation through multi-year, multicentre studies integrating peripheral health facilities is needed before the identified predictors can be generalised.

Nevertheless, the main strengths of this study are its multicentre prospective design covering the four main referral hospitals of Brazzaville, its use of the WHO 2014 criteria combined with a KDIGO-inspired AKI definition, and its systematic assessment of the cumulative severity burden.

Conclusions

Severe paediatric malaria remains a frequent and life-threatening condition in Brazzaville, with more than one in three hospitalized children meeting at least at least one WHO 2014 severity criterion and nearly one in five dying admission. Pre-hospital antimalarial self-medication and delayed consultation are the principal modifiable drivers of severity, whereas acute kidney injury and young age are independent predictors of death. The relationship between the number of concurrent WHO criteria and case fatality rate offers a simple, clinically tractable tool for risk stratification. These findings call for renewed investment in community education and strengthening of referral pathways. Multicentre prospective studies incorporating peripheral health facilities complete biological measurements and long-term follow-up are needed to refine prognostic models and inform triage algorithms adapted to the local context.

Abbreviations

AIC
Akaike Information Criterion
AKI
acute kidney injury
aOR
adjusted odds ratio
BCS
Blantyre coma scale
CFR
case fatality rate
CI
confidence interval
CHU-B
Centre Hospitalier Universitaire de Brazzaville
GCS
Glasgow coma scale
Hb
haemoglobin
IQR
interquartile range
ITN
insecticide-treated net
KDIGO
Kidney Disease:Improving Global Outcomes
MM
moderate malaria
OR

odds ratio
SM
severe malaria
VIF
variance inflation factor
WHO
World Health Organization.

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the Declaration of Helsinki. The study protocol and authorization measures were formally reviewed and approved by the institutional medical boards and directorates of the Faculty of Health Sciences, the Brazzaville University Hospital Center, and the reference hospitals of Talangaï, Bacongo, and Makélékélé. Written informed consent was obtained from the parents or legal guardians of all minor participants prior to enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified dataset that supports the findings of this study is available from the corresponding author on reasonable request, subject to the approval of the participating hospitals and compliance with local data-protection regulations.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

This work was carried out in collaboration among all authors.

Author BAMK designed the study, performed analyses and corrected final manuscript

Author OKAIL wrote the protocol and managed the analysis of the study

Authors KJ, SOG collected the field data and managed the analysis of the study

Author SOG wrote the manuscript and managed the literature searches

Author MBJR designed the study and revised the manuscript

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Figures

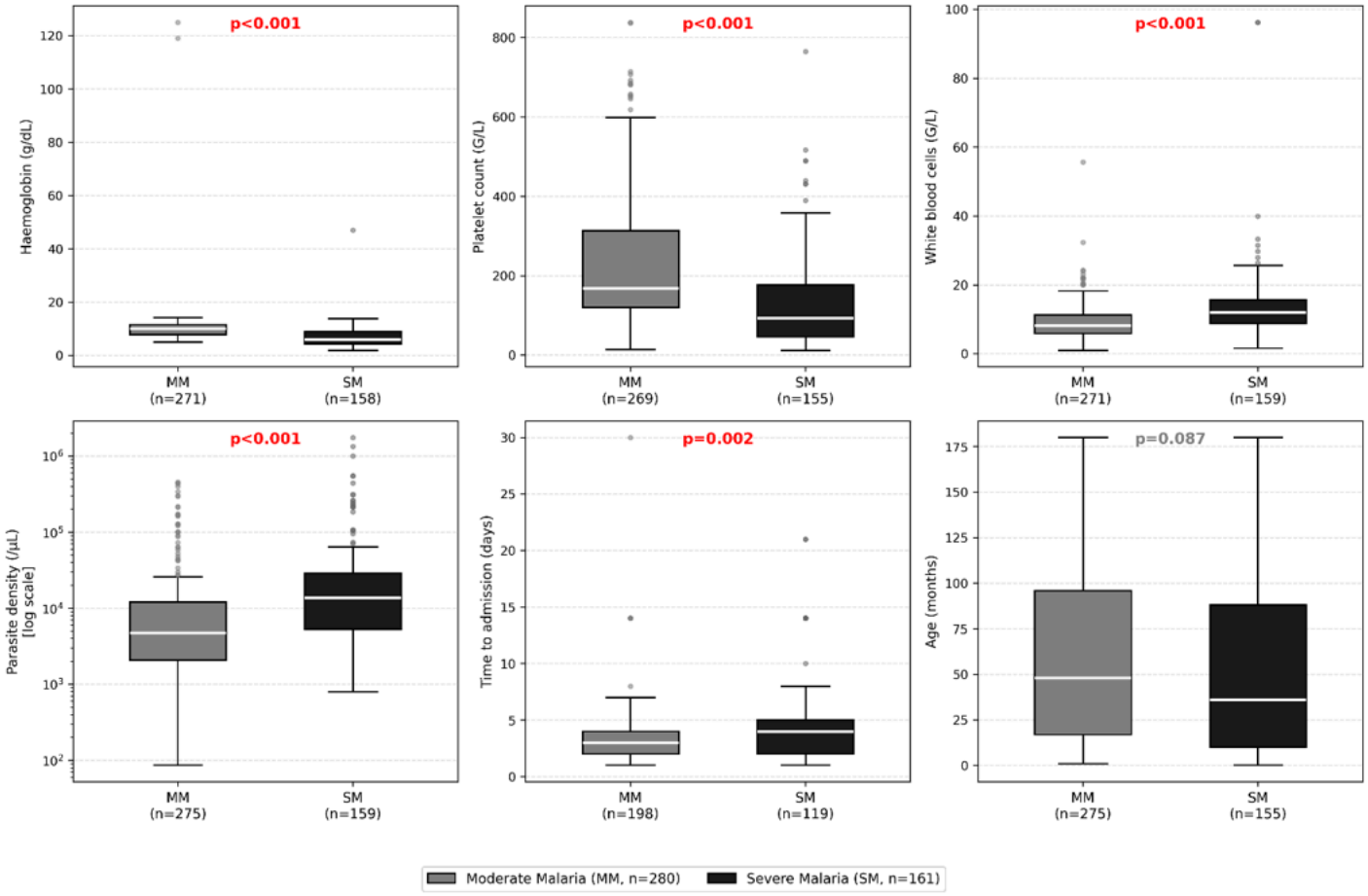


Figure 1

Distribution of biological variables in children with moderate (MM) and severe malaria (SM): haemoglobin, platelet count, white blood cell count, parasite density, time to admission and age. Dashed red lines indicate WHO 2014 severity thresholds when applicable.

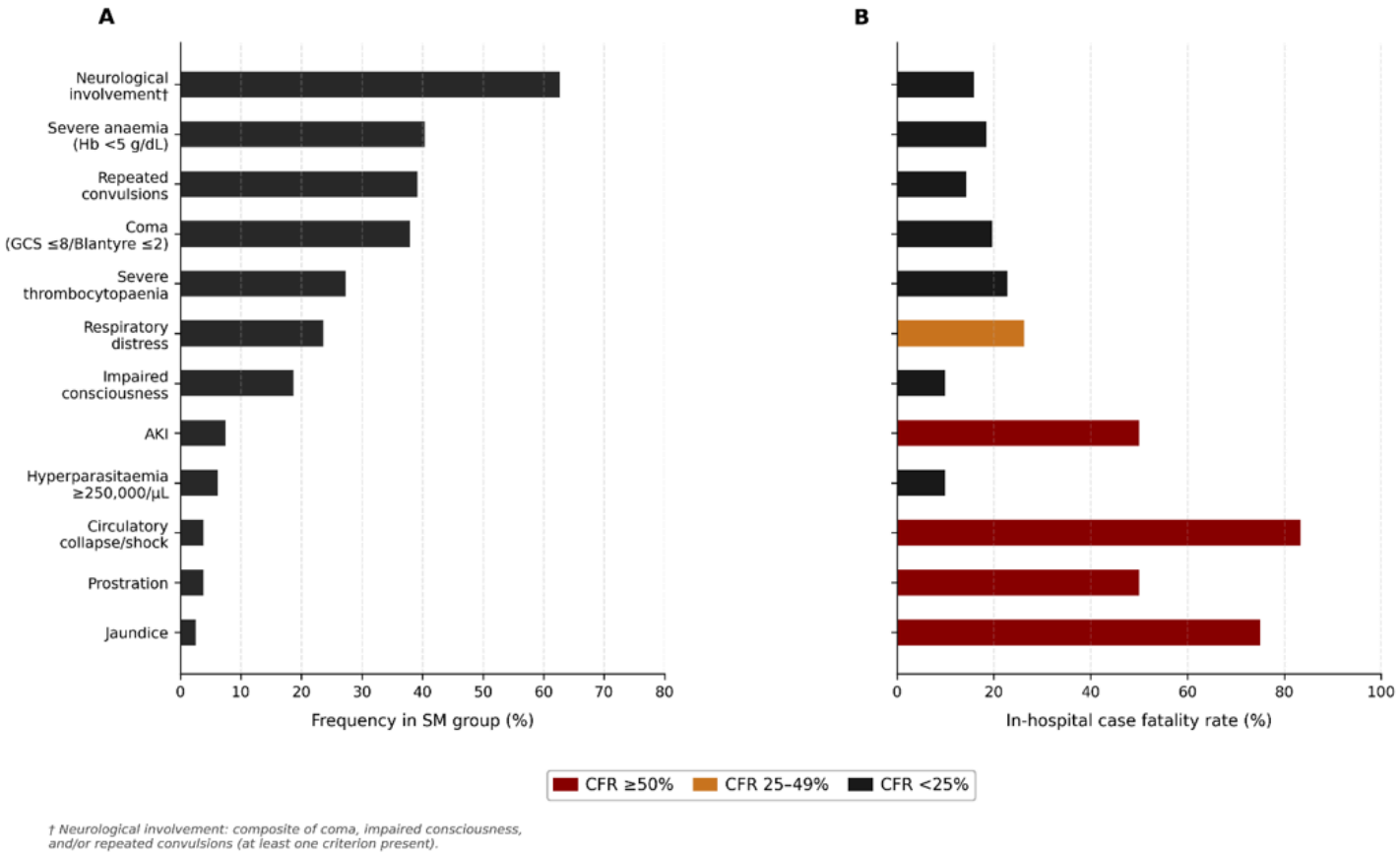


Figure 2

WHO 2014 severe malaria criteria-(A) frequency in the severe malaria group and (B) case fatality rate by criterion. Criteria with ≥ 50% CFR are shown in dark red; 25-49% in orange;<25% in black. The composite neurological involvement variable pools coma, impaired consciousness and repeated convulsions.

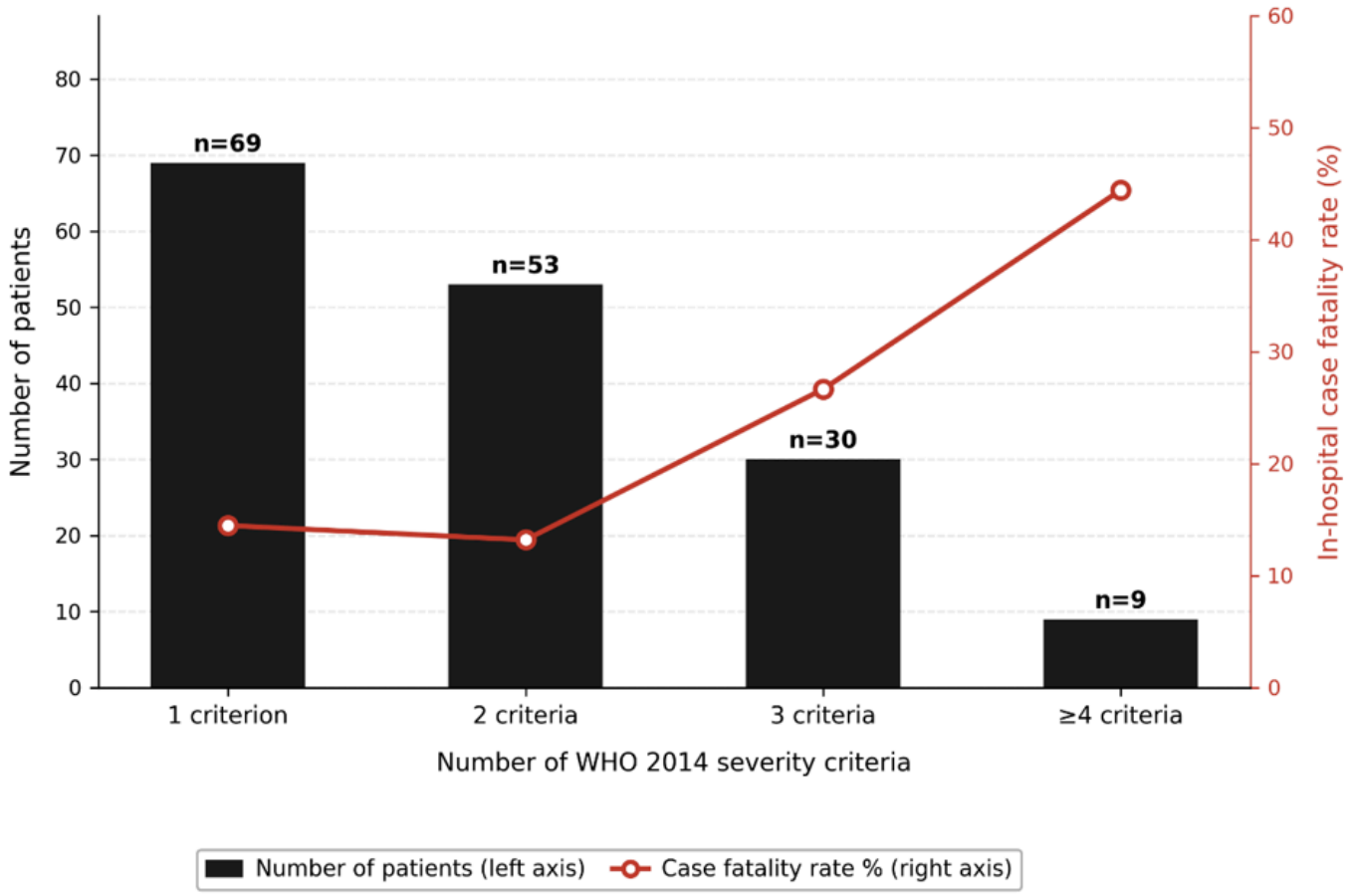


Figure 3

In-hospital case fatality rate according to the number of WHO 2014 severe malaria criteria fulfilled per patient (severe malaria group, n=161). Bars: number of patients; line: in-hospital case fatality rate.



Figure 4

Co-occurrence matrix of WHO 2014 severe malaria criteria within the severe malaria group (n=161). Diagonal cells (red border) show the individual criterion frequency; off-diagonal cells show the percentage of patients presenting both criteria. Prostration, jaundice, hyperparasitaemia and hypoglycaemia were too infrequent to produce interpretable pairwise estimates and are omitted from the matrix.

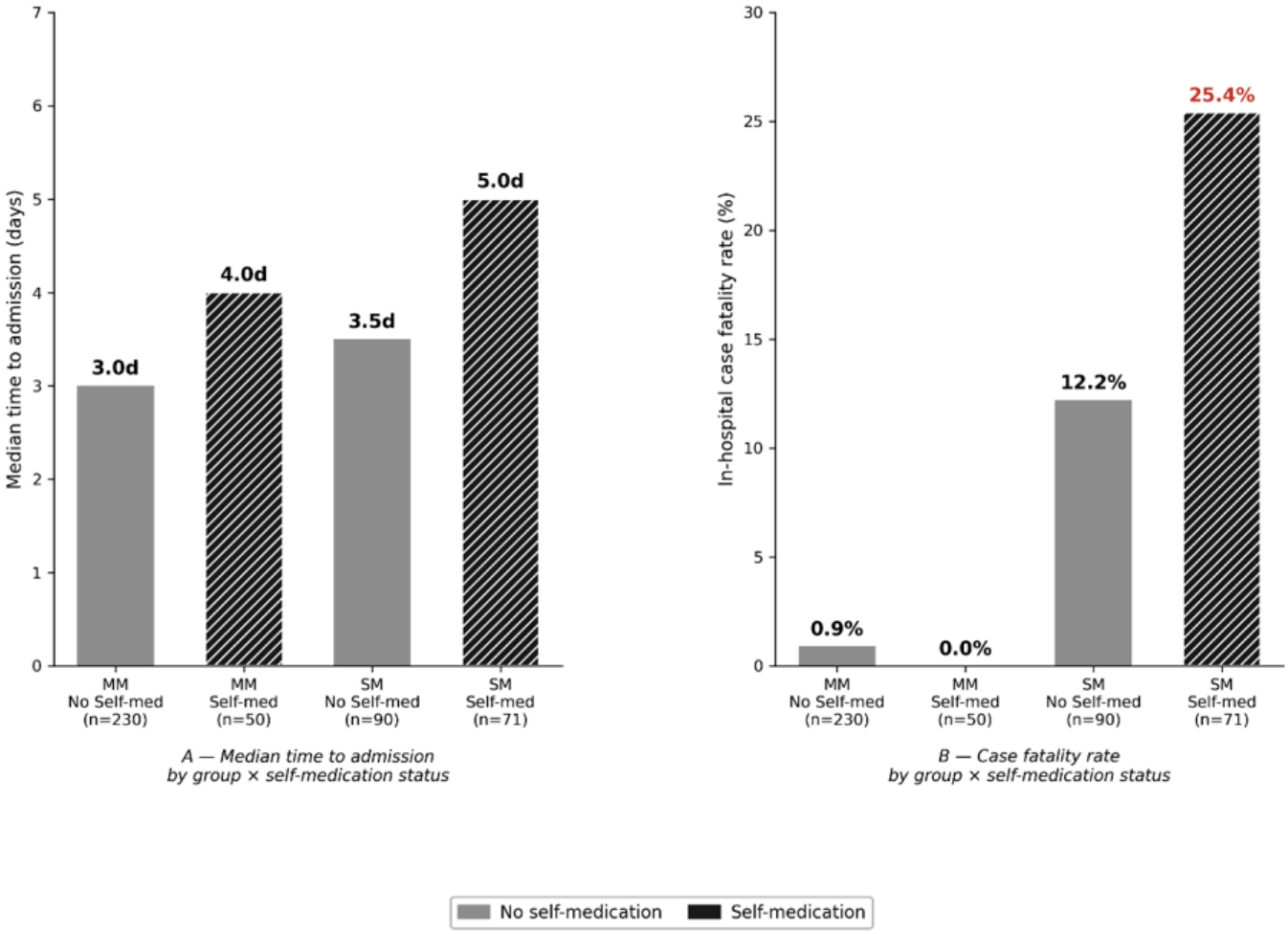


Figure 5

Impact of pre-hospital antimalarial self-medication on severity, time to admission and case fatality rate. (A) Prevalence of self-medication by severity group (B) Median time to admission, stratified by severity group and self-medication status. (C) In-hospital case fatality rate, stratified by severity group and self-medication status.