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Severe *falciparum* malaria in young children is associated with an increased risk of post-discharge hospitalization: a prospective cohort study

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Abstract

Background Few studies have described post-discharge morbidity of children with specific manifestations of severe malaria (SM) beyond severe malarial anaemia or cerebral malaria.

Methods Children 6 months to 4 years of age admitted at Jinja and Mulago hospitals in Uganda, with one or more of the five most common forms of SM, cerebral malaria (n = 53), respiratory distress syndrome (n = 108), malaria with complicated seizures (n = 160), severe malarial anaemia (n = 155) or prostration (n = 75), were followed for 12 months after discharge, alongside asymptomatic community children (CC) (n = 120) of similar ages recruited from the households or neighbourhoods of the children with SM. Incidence and risk of hospitalizations, death or outpatient clinic visits were compared between children with SM and CC.

Results 312/551 (56.6%) of children with SM had one or more post-discharge hospitalization over 12 months, compared to 37/120 (30.8%) of CC. Frequency of hospitalization was similar across all forms of SM. Compared to CC, children with SM had a significantly higher risk of all-cause hospitalization (adjusted hazard ratio (aHR) 1.91, 95% confidence interval (CI) 1.39–2.63, $p < 0.001$) and hospitalization for severe malaria (aHR 1.94, CI 1.36–2.78, $p < 0.001$), but a similar risk of outpatient clinic visits for malaria (aHR 1.24, 95% CI 0.89–1.73, $p = 0.20$). 82% of hospitalizations in children with SM (575/700) and CC (50/61) were due to malaria.

Conclusions In this malaria endemic region, children with the five most common forms of SM had higher rates of post-discharge hospitalization than asymptomatic community children, and > 80% of hospitalizations were due to severe malaria. Studies of post-discharge malaria chemoprevention are urgently needed for children with SM, to determine if this treatment can reduce post-discharge morbidity.

Keywords Severe malaria, Post-discharge, Hospitalization, Mortality, Children

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Background

Severe *Plasmodium falciparum* malaria remains a leading cause of mortality in children, accounting for an estimated 608,000 deaths worldwide in 2022 [1]. Although severe malaria is a single disease entity, it presents in patients with a wide range of clinical manifestations. The common manifestations of severe malaria in Uganda, and in many other malaria endemic areas, are cerebral malaria (CM), respiratory distress syndrome (RDS), malaria with complicated seizures (MS), severe malarial anaemia (SMA), and prostration. Together, these common manifestations of severe malaria affect about 6 million African children and account for > 75% of paediatric malaria hospitalizations [2].

Despite the broad clinical typology of severe malaria, malaria research tends to focus on only two of its manifestations—CM and SMA. CM is the most lethal manifestation of severe malaria with an inpatient case fatality rate of 15–20% [3], whereas SMA is the most common presentation affecting 7.5–34% of the children that acquire severe malaria [4–6]. Mortality and morbidity in SMA are not limited to the inpatient period alone; survivors suffer significant post-discharge morbidity which can lead to hospitalization or death. A Malawian study found a 12.6% post-discharge all-cause mortality rate among children with SMA after 18 months. Similar studies from Uganda and Kenya revealed that between 10 and 16% of SMA survivors died or were readmitted within 6 months after discharge from the hospital [7–9]. Whether the other manifestations of severe malaria suffer similar rates of post-discharge morbidity and mortality is not well described.

In a prior study among children in Kampala, post-discharge morbidity was compared between children with SMA or CM and community children (CC) [10]. Compared with CC, children with CM had a higher risk of outpatient sick visits and both children with CM and SMA had greater odds of post-discharge hospitalizations [10]. However, children < 18 months of age were excluded from the study, although many children < 18 months in this area develop severe malaria and younger children may be prone to poor post-discharge outcomes [10, 11]. In malaria endemic regions other co-morbid conditions like severe acute malnutrition (SAM), severe pneumonia, HIV and severe anaemia have also been found to be associated with a high rate of post-discharge morbidity [11, 12]. The present study expands this research by documenting post-discharge morbidity or mortality across the five most common manifestations of severe malaria in young children living in malaria endemic areas. The effect of co-morbid conditions like SAM and HIV on post-discharge morbidity were also examined amongst the five different manifestations of severe malaria.

In this study, the incidence and risk of hospitalizations, death and outpatient clinic visits over a 12-month follow-up period in a cohort of children 6 months to 4 years of age admitted was evaluated. This was conducted at two tertiary hospitals in Uganda for one or more of the five common forms of severe malaria by comparing them to asymptomatic community children of similar ages with no known chronic illness or acute illness in the past 4 weeks. The community children were recruited from the same households or neighbourhoods as the children with severe malaria.

Methods

Study participants

This was a prospective cohort study performed at Jinja Regional Referral, Jinja and Mulago National Referral Hospital, Kampala, in eastern and central Uganda, respectively, as part of a larger parent study assessing neurodevelopmental impairment in children. The Ugandan Ministry of Health classifies Kampala as an area of low malaria transmission, while Jinja is classified as an area of moderate to high malaria transmission [13]. In the parent study, children meeting any of the pre-specified criteria for severe malaria (SM), as defined in Table S1, and community children (CC) were enrolled if they were between 6 months and 4 years of age and had no known chronic illness requiring medical care. For the SM group, children were recruited if either their blood smear or rapid diagnostic test (RDT) (SD Bioline Malaria Ag *P. falciparum* /Pan, Abbott, Chicago, Illinois, USA) result were positive for malaria from the performing clinical laboratory at each hospital. Microscopy was then repeated in the research laboratory and children with confirmed *P. falciparum* on blood smear in the research laboratory or with *P. falciparum* infection documented by RDT were included in analysis. The manifestations of severe malaria were graded in a hierarchical order based on severity of case fatality rates as follows: cerebral malaria (CM) > respiratory distress syndrome (RDS) > malaria with complicated seizures (MS) > severe malarial anaemia (SMA) > prostration (Pros). Children meeting more than one criterion for severe malaria were included in the higher-order group. Asymptomatic community children (CC) enrolled in the parent study were used as the comparator for the present analysis. CC were enrolled in the study if they met the criteria outlined in Table S1, including no acute illness within the past 4 weeks requiring medical care. CC were recruited in the same age range and from the families or neighbourhoods of children with SM. To recruit CC, parents of children with SM were provided information about the study, asked if any age-eligible children were present in their extended family, and invited to bring the eligible children to the clinic for evaluation. Parents of age-eligible children in the household compound of a child with SM were also notified about the study during a home visit. Children with severe acute malnutrition or known chronic diseases like cerebral palsy or epilepsy were excluded, irrespective of study group (Table S1).

Clinical, laboratory and demographic assessment

At enrolment, all study children underwent a medical history and physical examination. Nutrition was assessed by height- and weight-for-age z-scores using the World Health Organization standards. A blood smear for malaria and quantification of density of parasitaemia was done by two independent microscopists with a third reading if results were discrepant. For all children with severe malaria, malaria blood smears were repeated every 24 h during the admission until the smear was negative. Human Immunodeficiency Virus (HIV) testing was done as per standard clinical care for all admitted children in Uganda. Socioeconomic status was measured using a previously described scoring system in healthy Ugandan children $\geq$ 5 years [14].

Inpatient clinical care

Children with severe malaria were managed according to the Ugandan Ministry of Health treatment guidelines current at the time of the study. These included intravenous artesunate treatment for at least 24 h followed by a full dose of artemether-lumefantrine once the child was able to take it orally. All children with a haemoglobin $\leq$ 5 g/dL received a blood transfusion. Other medical problems were treated as per the standard protocols applicable at the study hospitals.

Study follow-up

All study children received an insecticide-treated bed net. Study children were asked to return hospital at one month (severe malaria group only) for evaluation of interim health, and at 12 months for neuropsychology testing. Caregivers were asked to bring their children back to study hospitals whenever the children fell sick during the follow-up period. Transportation costs were reimbursed for these visits, and all clinical care was provided free of charge. During each hospital visit, the children were assessed and managed by study clinicians as per national guidelines. All children who presented with a history of fever or had fever on examination had a malaria blood smear performed at the research laboratory as described above. At the end of the follow-up period, the vital status of study participants was noted and any deaths that occurred during the follow-up period were recorded. The primary outcome for this study was hospitalizations and secondary outcomes were death and outpatient clinic visits.

Statistical analysis

Analysis was done using Stata v18 (StataCorp., College Station, Texas). Enrolment characteristics of children with SM and CC were compared using Pearson Chi-square or Fisher's exact tests for categorical variables (where appropriate) or Wilcoxon rank-sum tests for continuous variables. The incidence and risk of study outcomes (hospitalizations, deaths and outpatient clinic visits) over the 12-month follow-up were compared between children with SM and CC using the Prentice-Williams-Peterson Total-Time (PWP-TT) approach for recurrent events. The PWP-TT approach is advantageous when assessing the risk of recurrent events as it allows the underlying risk of failure (and the effects of covariates) to vary between repeated events while simultaneously correcting for within-subject correlations of failure times over follow-up [15]. Results are reported as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Analyses were adjusted for various correlates of morbidity or mortality in this population, including age (years), study site, nutritional status as measured by height-for-age and weight-for-age z-scores (HAZ and WAZ, respectively), presence of HIV infection, sickle cell genotype, and socioeconomic status (SES) at enrolment. All study participants contributed person-time to the analyses and were censored when they died, withdrew from the study, were lost to follow-up or at their 12-month follow-up visit. Risk and incidence of study outcomes were measured from discharge for children with SM and from enrolment for CC. There was no significant interaction between study site and SM group for all outcomes ($p > 0.05$ for all) (Table S5), so all analyses used pooled data from both sites. Missing covariate data were modest (0.1% for WAZ, 0.5% for HIV infection, and 10.1% for SES). To retain all eligible children, multiple imputation using chained equations was used to impute missing data for these three covariates in Stata using the *mi impute* command. No outcome data were imputed. A comparison of the primary analysis according to treatment of missing data is provided in Table S7.

Results

Baseline characteristics

In the parent study, 720 children were enrolled at the two sites, 600 children with severe malaria (SM) and 120 community children (CC). 49 children with SM were excluded from the present analysis because they withdrew from the study prior to discharge (n = 4), died during admission (n = 44) or met delayed exclusion criteria (n = 1). No children with SM left the hospital against medical advice. A total of 671 children (551 SM, 120 CC) were included in this analysis (Fig. 1). 374 (55.7%) of the study participants were from the Kampala site, and the distribution of the different manifestations of SM were similar in the two sites (Table S4). Age and sex were similar between children with SM and CC (Table 1). All children with SM were positive by rapid diagnostic test (RDT), blood smear or both tests. 401 (72.9%) children with SM and 11 (9.3%) CC were blood smear positive for *P. falciparum* at enrolment, while all children with SM tested by RDT were positive for *P. falciparum*. All children with SM cleared parasitaemia with artesunate and artemether-lumefantrine treatment prior to discharge. CC with parasitaemia were treated with a full course of oral artemether/lumefantrine.

Risk of hospitalizations

Overall, 761 hospitalizations occurred in 349 of 671 children: 700 events in children with SM and 61 events in CC. 625 of the 761 (82.1%) hospitalizations were due to malaria, and this was similar for children with SM (575/700) and CC (50/61). Hospitalization occurred in 312 of 551 children with SM after discharge (56.6%) and in 37 of 120 CC (30.8%). A total of 161 children with SM and 13 CC had multiple hospitalizations (range: 2 to 18) compared to 13 CC (range: 2 to 5). Over the 12-month follow-up, risk of hospitalization was nearly twice as high in children with SM than CC (aHR 1.91, 95% CI 1.39–2.63, $p < 0.001$, Fig. 2) adjusting for age, study site, nutritional status, presence of HIV infection, sickle cell genotype and socioeconomic status at enrolment. Risk of hospitalization for severe malaria and hospitalization for reasons unrelated to severe malaria or severe

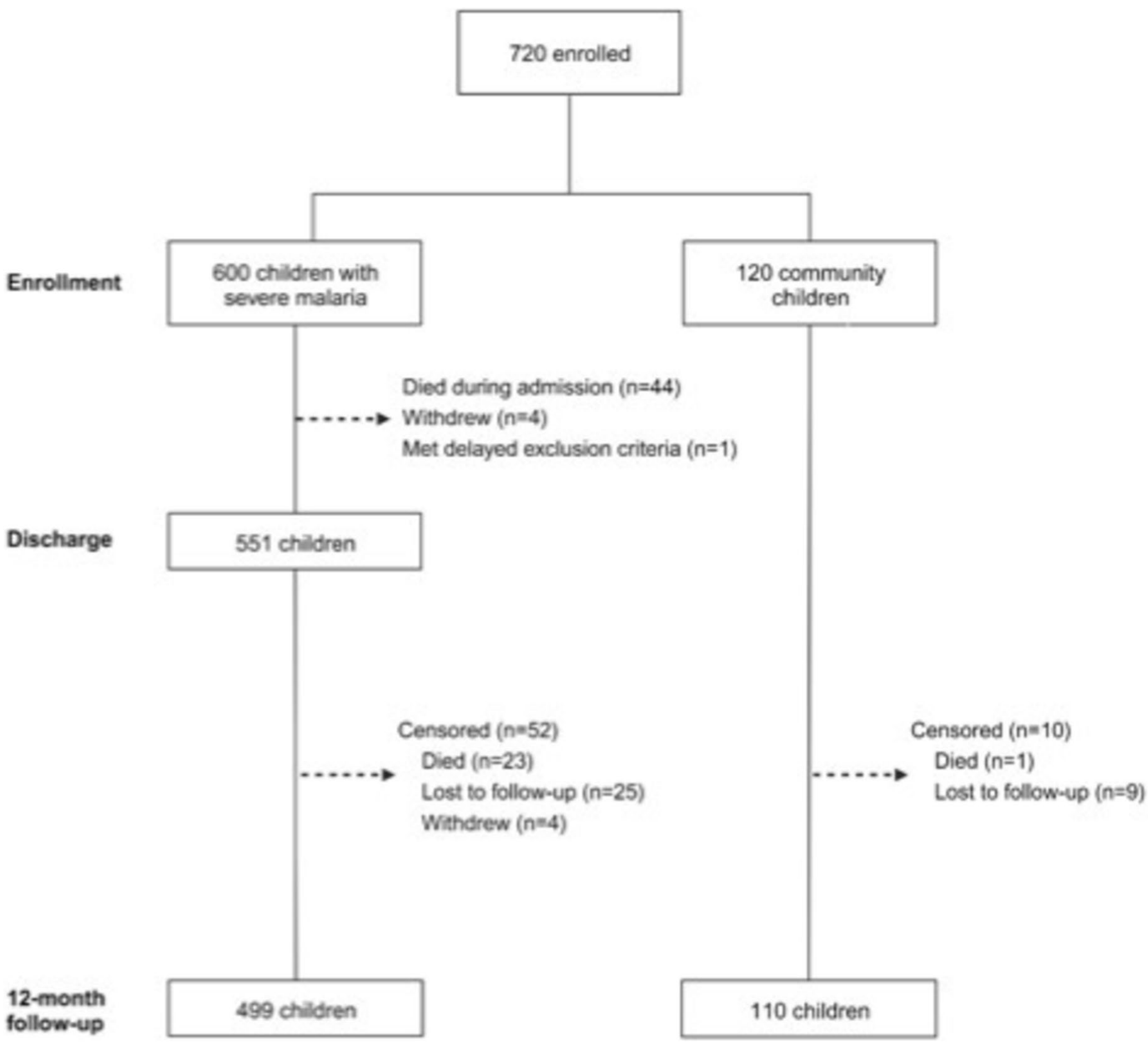


Fig. 1 Flowchart of study participants from enrolment to 12-month follow-up

Table 1 Demographic and clinical characteristics of study participants at enrolment

	SM (N = 551)	CC (N = 120)	P value[a]
Demographic characteristics			
Age (years)	2.0 (1.4, 2.9)	2.2 (1.4, 3.1)	0.53
Sex (male)	317 (57.5)	64 (53.3)	0.40
Site (Kampala)	307 (55.7)	67 (55.8)	0.98
Duration of hospitalization (days)	4.0 (3.0, 5.0)	–	–
Used insecticide-treated bed net previous night[b]	416 (84.6) (492)	93 (85.3) (109)	0.84
SES score	10 (8, 14) (494)	11 (9, 15) (109)	0.06
HIV positive	13 (2.4) (549)	0 (0) (119)	0.14
Sickle cell genotype			
HbAA	529 (96.0)	105 (87.5)	< 0.001
HbAS	10 (1.8)	14 (11.7)	
HbSS	12 (2.2)	1 (0.83)	
Clinical characteristics			
Height-for-age z-score	−1.0 (−1.9, −0.26)	−1.3 (−2.2, −0.37)	0.12
Weight-for-age z-score	−0.99 (−1.8, −0.32) (550)	−0.41 (−1.3, 0.26)	< 0.001
BS positive for malaria	401 (72.9) (550)	11 (9.3) (118)	< 0.001
Parasite density among BS + (parasites/uL)	59018 (5702, 211881)	3181 (1198, 12915)	< 0.001
RDT positive for malaria	538 (100.0) (538)	29 (25.2) (115)	< 0.001

SM severe malaria, *CC* community children, *SES* socioeconomic status, *HAZ* height-for-age z-score, *WAZ* weight-for-age z-score, *BS* + blood smear positive, *RDT* rapid diagnostic test

Data presented as n (%) or median (IQR). If data were missing, the non-missing N is listed in final parentheses

[a] P values obtained from Wilcoxon rank-sum tests for continuous variables, and Pearson's Chi-square or Fisher's exact tests for categorical variables (where appropriate)

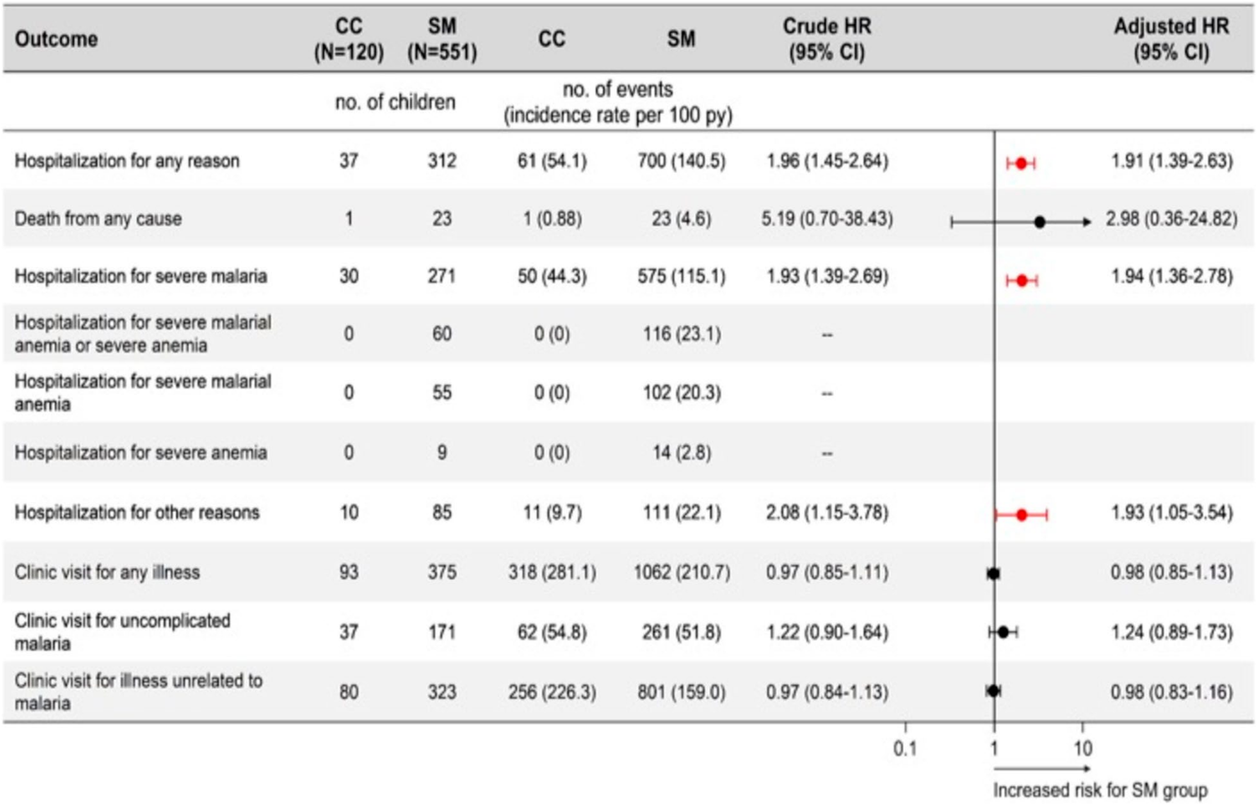
[b] Measured at 6-month follow-up visit

anaemia were also higher in children SM compared to CC (aHR 1.94, 95% CI 1.36–2.78, $p < 0.001$, and aHR 1.93, 95% CI 1.05–3.54, $p = 0.03$, respectively). Similar results across these outcomes were seen when the analysis was restricted to blood smear positive children with SM compared to CC (Table S2) and when restricting the comparator group to CC who were blood smear negative (Table S3). The risk difference in hospitalizations unrelated to severe malaria or severe anaemia between children with SM compared to CC increased with increasing age at enrolment (Table S6), but this age-dependent association was not observed for all-cause hospitalizations or hospitalizations for severe malaria.

Risk of hospitalization for any reason and hospitalization for severe malaria were higher for children with each individual manifestation of SM than for CC ($p < 0.01$ for all), except for children with prostration who did not differ from CC in their risk of hospitalization for severe malaria after correction for multiple comparisons ($p = 0.02$) (Table 2). Despite elevated hazard ratios, children with each form of SM and CC did not significantly differ in their risk of hospitalization for reasons unrelated to severe malaria or severe anaemia after correction for multiple comparisons ($p > 0.01$ for all), although the higher risk for children with MS compared to CC was significant prior to correction ($p = 0.03$). Overall, risk of post-discharge hospitalization was similar across the five manifestations of SM, correcting for multiple comparisons. However, children with SMA had an increased risk of hospitalization for severe malarial anaemia or severe anaemia compared to children with MS or prostration, and children with RDS had a higher risk of hospitalization for severe malarial anaemia than children with MS (Table 2).

Risk of death

A total of 24 study children (3.6%) died during 12-month follow-up, 23/551 with SM (4.2%) and 1/120 CC (0.8%). The risk of death over follow-up was higher in children with SM than in CC (aHR 2.98, 95% CI 0.36–24.82), though the difference did not reach statistical significance ($p = 0.31$) (Fig. 2). Children with RDS had the highest frequency of post-discharge deaths at 10 (9.3%), followed by children with SMA ($n = 8$, 5.2%) and prostration ($n = 3$, 4.0%) (Table 2). Most deaths (14/24, 58.3%) occurred in the community, and exact cause of death was difficult to ascertain, but often occurred after a short febrile illness. Seven (7) of the 10 follow-up deaths that occurred in-hospital were due to malaria-related severe anaemia.



Outcome	CC (N=120)	SM (N=551)	CC	SM	Crude HR (95% CI)	Adjusted HR (95% CI)
	no. of children		no. of events (incidence rate per 100 py)			
Hospitalization for any reason	37	312	61 (54.1)	700 (140.5)	1.96 (1.45-2.64)	1.91 (1.39-2.63)
Death from any cause	1	23	1 (0.88)	23 (4.6)	5.19 (0.70-38.43)	2.98 (0.36-24.82)
Hospitalization for severe malaria	30	271	50 (44.3)	575 (115.1)	1.93 (1.39-2.69)	1.94 (1.36-2.78)
Hospitalization for severe malarial anemia or severe anemia	0	60	0 (0)	116 (23.1)	--	
Hospitalization for severe malarial anemia	0	55	0 (0)	102 (20.3)	--	
Hospitalization for severe anemia	0	9	0 (0)	14 (2.8)	--	
Hospitalization for other reasons	10	85	11 (9.7)	111 (22.1)	2.08 (1.15-3.78)	1.93 (1.05-3.54)
Clinic visit for any illness	93	375	318 (281.1)	1062 (210.7)	0.97 (0.85-1.11)	0.98 (0.85-1.13)
Clinic visit for uncomplicated malaria	37	171	62 (54.8)	261 (51.8)	1.22 (0.90-1.64)	1.24 (0.89-1.73)
Clinic visit for illness unrelated to malaria	80	323	256 (226.3)	801 (159.0)	0.97 (0.84-1.13)	0.98 (0.83-1.16)

Fig. 2 Incidence and risk of study outcomes between children with severe malaria and community children. Forest plot depicting adjusted hazard ratios (HR) and 95% confidence intervals (CI) from adjusted PWP-TT models for each recurrent outcome. Covariates in the models included age, study site, height-for-age and weight-for-age z-scores, presence of HIV infection, sickle cell genotype and socioeconomic status at enrolment. aHR significant at $p < 0.05$ depicted in red. aHR and 95% CI plotted on logarithmic scale. Abbreviations: SM, severe malaria; CC, community children; HR, hazard ratio; CI, confidence interval

Risk of outpatient clinic visits

468 (69.7%) study participants had outpatient clinic visits during the follow-up period, visiting the clinic 1,380 times, with 323 (23.4%) of these visits related to uncomplicated malaria. Although the incidence rates of outpatient clinic visits were higher in CC than in children with SM irrespective of the reason for the visit, the groups did not differ significantly in their risk of clinic visits over the 12-month follow-up (Fig. 2). Comparable results were seen when the analysis was restricted to blood smear positive children with SM compared to CC (Table S2) and when restricting the comparator group to blood smear negative CC (Table S3). Risk of clinic visits was similar between the individual forms of SM compared to CC, but children with MS had a greater risk of clinic visits overall and clinic visits related to uncomplicated malaria compared to children with SMA (Table 2).

Discussion

In this large prospective cohort study, it is shown that in malaria endemic areas, children with the five most common forms of severe malaria were all at significantly increased risk of hospitalization following their acute illness compared to asymptomatic community, and that the hospitalizations were mainly (>80%) due to malaria. In addition, the risk of uncomplicated malaria was not increased in children with severe malaria relative to community children, suggesting that children with severe malaria have underlying factors that specifically predispose them to development of recurrent severe malaria.

Overall, more than half (56.6%) of all children with severe malaria were hospitalized post-discharge, which was similar to the readmission rate after severe anaemia (45.9%) previously reported in the same setting [16]. A recent study of post-discharge malaria chemoprevention for children with severe anaemia in malaria endemic

Table 2 Incidence and risk of hospitalizations, death and outpatient clinic visits between severe malaria manifestations and community children

Outcome	CC (N = 120)	CM (N = 53)	RDS (N = 108)	MS (N = 160)	SMA (N = 155)	Pros (N = 75)
no. children with event, no. of events (incidence rate per 100 py) aHR compared to CC (95% CI)[a]						
Hospitalization for any reason	37, 61 (54.1)	31, 55 (114.4) 1.84 (1.26–2.68)	65, 175 (184.2) 2.18 (1.52–3.11)	90, 168 (114.2) 1.78 (1.26–2.52)	85, 213 (152.8) 2.04 (1.45–2.87)	41, 89 (129.6) 1.67 (1.13–2.47)
Death from any cause	1, 1 (0.88)	1, 1 (2.1) 1.93 (0.12–31.17)	10, 10 (10.3) 6.38 (0.65–62.49)	1, 1 (0.67) 0.53 (0.03–9.65)	8, 8 (5.7) 3.70 (0.40–34.49)	3, 3 (4.3) 3.14 (0.30–33.04)
Hospitalization for severe malaria	30, 50 (44.3)	29, 47 (97.6) 1.91 (1.26–2.90)	61, 151 (158.5) 2.24 (1.51–3.33)	75, 129 (87.5) 1.76 (1.18–2.62)	73, 178 (127.4) 2.10 (1.43–3.10)	33, 70 (101.7) 1.68 (1.07–2.62)
Hospitalization for severe malarial anaemia or severe anaemia[b,c]	0, 0 (0.0)	4, 6 (12.4)	19, 43 (44.6)	6, 9 (6.1)	27, 53 (37.8)	4, 5 (7.2)
Hospitalization for severe malarial anaemia[b,d]	0, 0 (0.0)	4, 6 (12.4)	18, 38 (39.4)	6, 7 (4.7)	23, 46 (32.7)	4, 5 (7.2)
Hospitalization for severe anaemia	0, 0 (0.0)	0, 0 (0.0)	3, 5 (5.2)	1, 2 (1.4)	5, 7 (5.0)	0, 0 (0.0)
Hospitalization for other reasons	10, 11 (9.7)	7, 8 (16.5) 1.70 (0.72–4.01)	13, 19 (19.6) 1.78 (0.79–3.99)	30, 37 (25.0) 2.12 (1.10–4.08)	22, 28 (19.9) 1.80 (0.89–3.63)	13, 19 (27.5) 2.08 (0.99–4.37)
Clinic visit for any illness[b]	93, 318 (281.1)	36, 103 (212.8) 1.08 (0.87–1.34)	73, 193 (198.9) 0.95 (0.78–1.16)	119, 385 (259.7) 1.04 (0.87–1.23)	93, 204 (144.8) 0.80 (0.66–0.96)	54, 177 (255.2) 1.01 (0.82–1.24)
Clinic visit for uncomplicated malaria	37, 62 (54.8)	16, 27 (55.8) 1.58 (0.94–2.64)	37, 60 (61.8) 1.26 (0.84–1.88)	54, 84 (56.7) 1.26 (0.85–1.86)	41, 56 (39.8) 1.12 (0.76–1.67)	23, 34 (49.0) 1.09 (0.69–1.72)
Clinic visit for illness unrelated to malaria	80, 256 (266.3)	32, 76 (157.0) 1.09 (0.84–1.41)	61, 133 (137.1) 0.94 (0.74–1.18)	108, 301 (203.0) 1.06 (0.87–1.29)	74, 148 (105.1) 0.80 (0.64–0.99)	48, 143 (206.2) 1.01 (0.81–1.26)

CC community children, *CM* cerebral malaria, *RDS* respiratory distress syndrome, *MS* multiple seizures, *SMA* severe malarial anaemia, *Pros* prostration, *aHR* adjusted hazard ratio, *CI* confidence interval

[a] Adjusted hazard ratios (aHR) obtained from PWP-TT analysis for each recurrent outcome comparing severe malaria manifestations to CC, adjusted for age, study site, presence of HIV infection, and socioeconomic status at enrolment. Significant aHR for each outcome following Bonferroni correction for 5 comparisons to CC are bolded ($p < 0.01$)

After Bonferroni correction for 10 comparisons between severe malaria manifestations for each outcome ($p < 0.005$), the following groups differed

[b] MS vs SMA

[c] SMA vs Pros

[d] RDS vs MS

areas showed a 35% reduction in hospitalization or death in this population [17]. The present study suggests that trials of post-discharge malaria chemoprevention should be conducted in children with severe malaria, as the study suggests that malaria chemoprevention might markedly reduce post-discharge hospitalization in children with all forms of severe malaria, as it did in children with severe anaemia.

This study shows that the effects of clinical malaria extend beyond the initial inpatient period. Prior research first uncovered the post-discharge impact of CM. Studies found that 11 to 26% of children with CM were discharged with gross neurological deficits [18–20], while a further 25% developed long-term cognitive impairments, or behavioural or mental problems [3, 21–25]. Later, SMA was shown to be associated with nearly two post-discharge deaths for every inpatient mortality [7, 8, 10], and was also shown to be associated with long-term cognitive and behavioural impairment [25, 26]. This study expands on this research by showing that other common manifestations of severe malaria are associated with marked post-discharge morbidity as well.

In terms of post-discharge mortality, the risk of death over the follow-up period was higher (aHR 2.98) in children with SM discharged from the hospital when compared to asymptomatic community children, though the difference did not reach statistical significance. Studies that have examined all-cause admissions in malaria endemic region have found that severe malaria was associated with lower 6-month post-discharge mortality than children without severe malaria [12]. Among children with a known cause of death, most were due to severe malarial anaemia (7 of 10, 70%). There is need for further studies to explore the effect of severe malaria on post-discharge mortality. In this study, however the risk of recurrent hospitalizations was greatly increased in children with each form of severe malaria compared to the community children. The study data suggest that, although different manifestations of severe malaria impact children's health distinctively, the effects of the disease may last for months after hospital discharge irrespective of the manifestation. Currently, most clinical care is limited to the inpatient period, thus the findings suggest that care should extend beyond discharge.

In this study, repeat malaria infections were the most common reason for recurrent hospitalizations in the follow-up period. All patients with severe malaria were treated according to clinical guidelines using intravenous artesunate followed by artemether/lumefantrine and had documented clearance of parasitaemia (negative blood smear) before discharge. Anti-malarial studies in Uganda show that artesunate is still effective for rapid parasite clearance [27]. In addition, during the follow-up period, insecticide-treated bed nets were reportedly used by most children with severe malaria and community children (over 80% in both groups). Currently an analysis to determine whether the follow-up visits for malaria were due to reinfection or recrudescence is being conducted [28, 29]. Further studies are needed to determine risk factors that predispose children to post-discharge morbidity in malaria endemic areas and to define and assess the effectiveness of tools that can identify children most likely to benefit from post-discharge interventions.

Regardless of the pathological mechanisms, the effects of the initial episode of severe malaria appear to predispose the child to repeated episodes of severe malaria in the immediate post-discharge period. In this study, the curve of post-discharge events was steep in the first 3 months and began to plateau by month 6. More than two-thirds of the outpatient visits and more than 80% of the hospitalizations and deaths happened in the first 6 months, suggesting this critical time is when children with severe malaria are most vulnerable to recurrent illness, including recurrent severe malaria. During this period of incomplete recovery, children remain susceptible to repeat malarial attacks, including repeated episodes of severe malaria. While children with severe malaria are also vulnerable to uncomplicated malaria in this follow-up period, they are at no more risk than community children without severe malaria for uncomplicated malaria. Instead, children with severe malaria appear to have specific increased vulnerability to repeated severe malaria. Furthers studies are needed to uncover the precise mechanisms that make children with severe malaria vulnerable to repeated episodes of severe malaria in the first 6 months after discharge. What is clear, however, is that children with severe malaria remain vulnerable beyond the inpatient period, and that interventions to decrease the rate of recurrent hospitalizations in children with severe malaria are urgently needed.

Phiri and colleagues showed that provision of malarial chemoprevention with artemether lumefantrine in the first 3 months was associated with 31% reduction in morbidity and mortality in children with SMA [30]. Recently, a larger study in Kenya and Uganda showed that in children with severe anaemia, 85% of whom had malaria, a monthly treatment course of dihydroartemether-piperaquine given for 3 months was associated with 35% reduction of all-cause readmission or death over 6 months [17]. In the first 3 months, the reduction was even greater at 70%. Malarial chemoprevention was most effective in reducing all-cause readmissions or mortality in the first 3 months in children who had malaria-related anaemia [17]. The study data led to a change in World Health Organization guidelines, which now state that a full therapeutic course of anti-malarial medicine should be given at discharge to children admitted to hospital with severe anaemia living in settings with moderate to high malaria transmission [31]. The present study adds to these findings, showing the severe malaria, even in the absence of anaemia, is a strong risk factor for post-discharge hospitalizations.

The overall rate of hospitalization observed in this study population is of public health concern. Although more children with severe malaria were hospitalized than CC, it is concerning that nearly a third (30.8%) of all asymptomatic community children at enrolment had at least one admission during the follow-up period. Over half (58.3%) of the deaths occurred in the community before the caretakers could bring the children back to hospital. This may be due to poor health-seeking behaviours or rapid progression of the condition in the community. Either case points to challenges in health services that need to be addressed. Future research should attempt to establish the reasons for the high post-discharge morbidity in this region to inform implementation of comprehensive measures to improve children's health outcomes.

Strengths of this study include the prospective study design encompassing two sites with different malarial transmission intensities and population characteristics (e.g., urban vs rural) and an asymptomatic community comparator group. In addition, children with severe malaria were clinically diagnosed at admission and post-discharge morbidity was carefully documented over time. This study is not without limitations. First, the comparator group was selected, in part, based on having no active acute illness within the past 4 weeks requiring medical care at the time of enrolment. It is, therefore, possible that some community children could have been exposed to severe malaria or other co-morbidities prior to the 4-week cut-off and the estimates in this study may be conservative. Second, it is also possible community children had different health-seeking behaviours from children with severe malaria although this is unlikely given that the rate of outpatient clinic visits were similar between the two groups. Caregivers of all study children were reimbursed for travel to the clinic, which likely helped to reduce potential variation in health-seeking behaviour or distance to the clinic between the groups. Therefore, the large difference in rate of recurrent hospitalizations found in this study is most likely reflective of the high burden of post-discharge morbidity in malaria amongst young children in endemic regions. Future studies should assess the risk of hospitalization, death and clinic visits with various comparisons groups to tease out the impact of disease severity and symptomology.

Conclusions

In conclusion, this study found that the rate of hospitalization was high in all the 5 most common types of severe malaria during the 12 months after discharge. Children with severe malaria had a nearly two-fold increased risk of all-cause hospitalization compared to asymptomatic community children, driven largely by repeat malarial infections in the post-discharge period. Further evaluation of post-discharge malarial chemoprevention for all children with severe malaria is needed in settings where it is not presently being implemented to determine the level of its efficacy for prevention of readmission or death after severe malaria.

Abbreviations

aHR	Adjusted hazard ratio
CC	Community children
CI	Confidence interval
CM	Cerebral malaria
HIV	Human immunodeficiency virus
MS	Malaria with complicated Seizures
PWP-TT	Prentice-Williams-Peterson total-time
RDS	Respiratory distress syndrome
RDT	Rapid diagnostic test
SES	Socioeconomic status
SM	Severe malaria
SMA	Severe malarial anaemia
USA	United States of America

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12936-024-05196-3.

Additional file 1: Supplemental Tables containing seven additional tables

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Author contribution

R.O.O. and C.C.J. designed the study. R.N., R.O.O and C.C.J. supervised the study. A.L.C and M.J.G. supervised data management and quality control and performed initial data analysis. A.L.C and K.A.M performed final data analysis. R.O.O. wrote the first draft of the manuscript. D.D., A.R and A.L.C. performed laboratory analyses, supervised laboratory processes, analyzed the results and monitored the study. A.L.C, K.A.M, M.J.G., R.N., R.O.O. and C.C.J. verified the underlying data and provided final data interpretation. All authors had full access to all study data, participated in the editing of the manuscript and accept responsibility of submission of the manuscript for publication.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Initial verbal consent from the parents or legal guardians of study participants was obtained for children fulfilling inclusion criteria, since most participants were critically ill and required emergency stabilization. Written informed consent was obtained once the participant was clinically stabilized. Ethical approval was granted by the Institutional Review Boards at Makerere University School of Medicine, the University of Minnesota, Indiana University, and regulatory approval granted by the Uganda National Council for Science and Technology. The study was conducted in accordance with the ethical standards of the Helsinki Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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