

Care pathway factors associated with death among patients with severe malaria in selected hospitals in Ghana: a multicentre unmatched case-control study

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Abstract

Background

Severe malaria can progress rapidly after presentation, making prompt recognition, parenteral treatment, supportive care, and referral essential. Contemporary multicentre evidence on where fatal care pathways fail in Ghana is limited. We assessed care processes, factors associated with death, and adjusted attributable proportions among observed deaths.

Methods

We conducted a multicentre retrospective unmatched case-control study of 543 independently verified severe malaria admissions from 33 hospitals in eight regions of Ghana between January 2021 and June 2024. Cases were 205 deaths and controls were 338 recoveries. Facility-stratified conditional logistic regression compared cases and controls within hospitals. Complete parenteral care required treatment within two hours and concordance with medicine choice, dosage, administration, and required doses. Referral and transfusion analyses were restricted to applicable subgroups.

Results

Out of 543 severe malaria admissions, triage was not performed for 104 patients (19.2%), 198 (36.5%) did not receive parenteral treatment within two hours or received none, and 222 (40.9%) met all effective management criteria. Death was associated with no triage (adjusted odds ratio [aOR] 2.12, 95% confidence interval [CI] 1.26 to 3.55), residence outside the admitting district (aOR 3.28, 95% CI 1.83 to 5.88), and incomplete parenteral care (aOR 1.74, 95% CI 1.16 to 2.60). Insurance was inversely associated with death (aOR 0.25, 95% CI 0.15 to 0.40). Among applicable subgroups, late referral (aOR 10.53, 95% CI 2.40 to 46.15) and transfusion delay (aOR 2.29, 95% CI 1.26 to 4.18) were associated with death. Adjusted attributable proportions were 13.9% for no triage, 29.8% for residence outside the district, 30.9% for being uninsured, 31.8% for late referral, and 38.6% for transfusion delay.

Conclusions

Severe malaria deaths were associated with failures in triage, rapid parenteral treatment, referral, and transfusion, as well as geographical and financial barriers. Standardized severe malaria admission protocols, coordinated referral, timely access to blood, and prospective monitoring using exact timestamps should be priorities for quality improvement.

Background

Malaria remains a leading preventable cause of illness and death. In 2024, an estimated 282 million cases and 610,000 deaths occurred globally, with the WHO African Region accounting for approximately 95% of deaths and children younger than 5 years bearing most of the fatal burden [1]. Severe falciparum malaria can progress rapidly to coma, metabolic acidosis, shock, hypoglycaemia, acute kidney injury, respiratory distress, and profound anaemia. Parenteral artesunate reduces mortality compared with quinine, but effective antimalarial treatment alone is insufficient once organ dysfunction has developed [2, 3]. Survival depends on a coordinated emergency response that combines immediate assessment, rapid treatment, repeated physiological monitoring, correction of metabolic abnormalities, timely transfusion when indicated, and referral when the presenting facility cannot provide definitive care.

The narrow interval available for effective intervention makes the reliability of the care pathway central to malaria mortality reduction. In a multicentre study of more than 26,000 African children, 58% of severe malaria deaths occurred within 24 hours of admission, and mortality patterns varied substantially between hospitals [4]. Established prognostic studies identify coma, deep breathing or acidosis, hypoglycaemia, shock, renal failure, and impaired perfusion as major indicators of death [5–8]. These findings have two implications. First, patients must be triaged and stabilized without delay. Second, studies of care quality must distinguish the effect of care processes from the severity that prompted those processes, because patients at greatest risk may receive more intensive care and still die.

Evidence from African hospitals shows that severe malaria guidelines are not implemented consistently. A national survey in Malawi found discordance between recorded severe malaria diagnoses and the clinical evidence documented in patient records [9]. At a Ugandan regional referral hospital, only 3% of children received all recommended components of severe malaria care; confirmatory testing, completion of artesunate doses, and dose timing were frequent gaps [10]. A subsequent quality improvement programme at the same hospital improved diagnostic testing, completion of artesunate treatment, and dose timing through a structured admission checklist and workflow changes [11]. A 2025 mixed methods study across three hospitals in northern Uganda similarly found that only one third of reviewed records met guideline adherence criteria [12]. Before patients reach referral hospitals, delays in care seeking and referral can allow uncomplicated infection to progress to severe disease [13]. Trials, implementation studies, and WHO guidance on prereferral rectal artesunate also demonstrate that initial treatment cannot compensate for failure to complete referral or for inadequate definitive care at the receiving hospital [14–18].

Ghana has made important gains in malaria control, but transmission and access to care remain unequal [19]. The 2022 Ghana Demographic and Health Survey found malaria parasitaemia in 10% of children aged 6 to 59 months, with substantial regional variation [20]. Earlier hospital studies in northern Ghana documented severe anaemia, neurological involvement, respiratory distress, hypoglycaemia, and concurrent infection as prominent clinical manifestations [21, 22]. More recently, Peprah and colleagues identified age younger than 5 years, severe pallor, sepsis, and short hospital stay as factors associated with malaria mortality in the former Northern Region [23]. That study focused mainly on patient characteristics and selected treatment variables from 2014. A Ghanaian quality assurance internship

later showed that structured mentorship could improve severe malaria assessment and strengthen referral relationships between primary care providers and district hospitals [24]. However, there remains little contemporary multicentre evidence examining how triage, treatment execution, referral, transfusion, insurance, and geographical access operate together after a patient with severe malaria enters the health system.

This evidence gap is programmatically important because severe malaria deaths may reflect both clinical severity and modifiable failures in recognition, referral, treatment, and supportive care. We therefore assessed patient, access, and care pathway factors associated with mortality among patients with independently verified severe malaria in selected Ghanaian hospitals. We also quantified component-specific gaps, evaluated referral and transfusion among clinically relevant subgroups, and estimated adjusted attributable proportions among observed deaths.

Methods

Study design and setting

We conducted a multicentre retrospective unmatched case-control study nested within a clinical audit of severe malaria care. Records covered admissions from 1 January 2021 to 30 June 2024. The analytical component compared patients who died during an admission recorded as severe malaria with patients who recovered, while the audit component assessed whether essential care processes were documented and completed. The study is reported in accordance with the STROBE recommendations for case-control studies [25]. Ghana has 16 administrative regions and a tiered health system comprising community-based services, health centres and clinics, district and municipal hospitals, regional hospitals, and tertiary teaching hospitals. Malaria transmission is perennial, with marked geographical and seasonal variation. Referral pathways link lower-level facilities to hospitals capable of providing definitive inpatient care.

Facility sampling

Regional sampling frames included inpatient facilities that had recorded at least one malaria death during the study period. Facilities were selected with probability proportional to the number of recorded malaria deaths. The final dataset contained 33 hospitals across Ashanti, Bono East, Eastern, Greater Accra, North East, Northern, Savannah, and Volta regions. Facilities without recorded malaria deaths were outside the sampling frame.

Study size determination

The sample size was calculated in Stata for an unmatched case control study. The calculation assumed a 15% exposure prevalence among controls, a minimum detectable odds ratio of 2.0, 80% statistical

power, a two sided 95% confidence level, and a planned ratio of two controls per case. At an odds ratio of 2.0, the corresponding expected exposure prevalence among cases was 26.1%. These assumptions produced a minimum sample of 151 cases and 302 controls, giving an initial total of 453 records. A design effect of 1.0 was applied. The sample was increased by 10% to account for incomplete or unavailable clinical records, resulting in a final target of 499 records. The final analysis included 543 records, comprising 205 deaths and 338 recoveries. Although the achieved control to case ratio was 1.65:1 rather than the planned 2:1 ratio, the total sample exceeded the calculated minimum requirement.

Participants, cases, and controls

The source population comprised patients admitted during the review period with a recorded diagnosis of severe malaria. Eligibility required an inpatient admission, an ascertainable outcome of death or recovery, and independent verification of severe malaria against the applicable WHO clinical criteria documented in the source records. Outpatient and uncomplicated malaria records, admissions outside the review period, records that did not meet the WHO criteria, and records without an ascertainable outcome were excluded. A case was an eligible admission ending in death attributed to malaria in the clinical record. A control was an eligible admission ending in recovery and discharge alive. Outcomes were determined from patient folders and cross-checked, where available, against admission, discharge, mortality audit, and cause-of-death records. All retrievable eligible deaths were included. Recoveries were sampled from the same hospital and study period, with a target of approximately two controls per death. The achieved ratio varied by hospital because the number and retrievability of eligible recovery records differed. The final sample comprised 205 deaths and 338 recoveries.

Data sources and abstraction

Data were abstracted from patient folders and cross-checked, where available, against clinicians' notes, nursing and medication charts, admission and discharge registers, laboratory reports, referral notes, mortality audit reports, cause-of-death certificates, and autopsy reports. The abstraction tool captured facility characteristics; age, sex, residence, insurance, and chronic illness; WHO severe malaria manifestations; malaria testing; triage; antimalarial medicine, route, dose, administration, and timing; referral; transfusion; and discharge outcome. Severe malaria eligibility was independently verified against WHO clinical criteria recorded across these sources. Triage status was triangulated using patient folders, clinicians' notes, nursing notes, and admission and discharge records rather than a single entry. Discrepancies were reviewed by supervisors and resolved against the available source records. Thirty-three data collectors and seven supervisors completed two days of protocol and electronic-form training. The form was pretested outside the selected facilities. Supervisors reviewed submissions daily for completeness, duplicates, logical inconsistencies, and outliers, and queries were resolved against source documents.

Variables and operational definitions

The primary outcome was death versus recovery. Age was categorized as younger than 5 years, 5 to 14 years, and 15 years or older. Residence was classified as within or outside the district of the admitting hospital. Insurance status was recorded at admission. Clinical severity was represented by the count of 19 WHO severe malaria manifestations documented during the admission. The severe malaria classification itself was independently verified against the applicable WHO clinical criteria and was not based solely on the diagnosis written in the folder.

Triage was classified as completed, not completed, or indeterminate. A patient was classified as triaged when evidence of triage was found in at least one of the patient folder, clinicians' notes, nursing notes, admission record, or discharge record. A patient was classified as not triaged when all available sources had been reviewed and none contained evidence that triage was performed. Triage was indeterminate when relevant sources were unavailable, incomplete, illegible, or conflicting. Parenteral treatment within two hours required documented administration of a parenteral antimalarial within two hours of presentation. Guideline-concordant parenteral treatment required an appropriate parenteral medicine, correct dosage, correct administration, and receipt of the required doses. Patients explicitly recorded as receiving no parenteral antimalarial were classified as not treated within two hours and as non-concordant. Complete parenteral care required both treatment within two hours and guideline concordance.

Effective management required completed triage, malaria testing, and complete parenteral care. Management was classified as ineffective when any component showed a documented failure. It was indeterminate only when no failure was recorded but triage could not be ascertained. Late referral was defined from the source item indicating that referral was not timely and was analysed only among referred patients whose timing was classifiable as timely or late. Transfusion delay was defined as a recorded failure to provide timely transfusion and was analysed only among patients documented as requiring blood.

Statistical analysis

Analyses were conducted in Python 3.10 using pandas, NumPy, and SciPy. Participant characteristics and care processes were summarized using counts, percentages, medians, and interquartile ranges. Crude associations were expressed as odds ratios (ORs) with 95% CIs. The primary analysis used facility-stratified conditional logistic regression. Conditioning on hospital compared deaths and recoveries within the same facility, controlled characteristics that were constant within a hospital, and aligned the analysis with facility-based control sampling. Three facilities with no within-facility outcome variation contributed six records and were excluded by the conditional likelihood, leaving 537 records from 30 informative facilities.

The primary model included age group, sex, insurance, residence outside the admitting district, number of documented severe manifestations, triage status, and completeness of parenteral care. These variables were selected a priori because they represented demographic characteristics, access barriers, baseline clinical severity, emergency recognition, and definitive treatment processes. Treatment within

two hours and guideline concordance were combined as complete parenteral care because all 48 patients who received no parenteral antimalarial had structurally inapplicable downstream treatment fields; modelling separate missing-category indicators would have introduced deterministic collinearity.

Referral timing was analysed among referred patients with known timing, and transfusion delay among patients requiring blood. These reduced subgroup models adjusted for age younger than 15 years, sex, severe-manifestation count, and teaching-hospital status and used facility-clustered standard errors with a finite-sample correction. Insurance by teaching-hospital status and severity by age-group interactions were assessed using one-degree-of-freedom conditional likelihood-ratio tests.

Sensitivity analyses excluded indeterminate triage, combined indeterminate and no triage, fitted ordinary logistic regression with facility-clustered standard errors, and fitted an unconditional model with facility fixed effects. For no triage, residence outside the admitting district, lack of insurance, late referral, and transfusion delay, exploratory adjusted attributable proportions among observed deaths were estimated using the Miettinen case-distribution formula, $Pd(OR - 1)/OR$, where Pd was the proportion of deaths exposed and OR was the adjusted odds ratio. Confidence limits were obtained by applying the same transformation to the OR confidence limits. The estimates describe statistical attribution within the analysed deaths. Conditional likelihood calculations were checked against facility fixed-effect and clustered models.

Results

Participant characteristics

The study included 543 admissions from 33 hospitals: 205 deaths and 338 recoveries. The median age was 5 years (interquartile range 3 to 11); 256 patients (47.1%) were younger than 5 years and 275 (50.6%) were male. Insurance coverage was lower among deaths than recoveries, 121 of 205 (59.0%) versus 275 of 338 (81.4%). Residence outside the admitting facility district was recorded for 88 deaths (42.9%) and 104 recoveries (30.8%) (Table 1).

Table 1
Participant characteristics by admission outcome

Characteristic	Recovered, n = 338	Died, n = 205	Crude OR (95% CI)	P value
Age < 5 years	156 (46.2)	100 (48.8)	1.11 (0.78–1.57)	0.595
Age 5–14 years	116 (34.3)	58 (28.3)	0.76 (0.52–1.10)	0.155
Age ≥ 15 years	66 (19.5)	47 (22.9)	1.23 (0.80–1.87)	0.383
Male	166 (49.1)	109 (53.2)	1.18 (0.83–1.67)	0.377
Insured	275 (81.4)	121 (59.0)	0.33 (0.22–0.49)	< 0.001
Residence outside facility district	104 (30.8)	88 (42.9)	1.69 (1.18–2.43)	0.005
Chronic illness documented	97 (28.7)	41 (20.0)	0.62 (0.41–0.94)	0.025
Teaching hospital	85 (25.1)	50 (24.4)	0.96 (0.64–1.44)	0.918
Regional hospital	14 (4.1)	7 (3.4)	0.82 (0.32–2.06)	0.820
District or other hospital	239 (70.7)	148 (72.2)	1.08 (0.73–1.58)	0.769

Severe malaria care audit

Triage was completed for 378 patients (69.6%), not performed for 104 (19.2%), and indeterminate for 61 (11.2%). Malaria testing was documented for 538 (99.1%). A total of 198 patients (36.5%) did not receive parenteral treatment within two hours or received no parenteral treatment, while 157 (28.9%) did not receive guideline-concordant parenteral treatment. Complete parenteral care was documented for 308 patients (56.7%). Overall management was effective for 222 patients (40.9%), ineffective for 292 (53.8%), and indeterminate for 29 (5.3%) (Table 2).

Table 2
Care processes by admission outcome

Care process	Status	Recovered, n (%)	Died, n (%)	Total, n (%)
Triage	Yes	244 (72.2)	134 (65.4)	378 (69.6)
	No	50 (14.8)	54 (26.3)	104 (19.2)
	Indeterminate	44 (13.0)	17 (8.3)	61 (11.2)
Malaria testing	Yes	333 (98.5)	205 (100.0)	538 (99.1)
	No	5 (1.5)	0 (0.0)	5 (0.9)
Parenteral treatment within two hours	Yes	240 (71.0)	105 (51.2)	345 (63.5)
	No	98 (29.0)	100 (48.8)	198 (36.5)
Guideline-concordant parenteral treatment	Yes	234 (69.2)	152 (74.1)	386 (71.1)
	No	104 (30.8)	53 (25.9)	157 (28.9)
Complete parenteral care	Complete	209 (61.8)	99 (48.3)	308 (56.7)
	Incomplete	129 (38.2)	106 (51.7)	235 (43.3)
Effective management composite	Effective	156 (46.2)	66 (32.2)	222 (40.9)
	Ineffective	159 (47.0)	133 (64.9)	292 (53.8)
	Indeterminate	23 (6.8)	6 (2.9)	29 (5.3)

***Complete parenteral care required both treatment within two hours and guideline concordance. Effective management required completed triage, malaria testing, and complete parenteral care.*

Facility-stratified multivariable analysis

After within-facility adjustment, no triage was associated with higher odds of death than completed triage (aOR 2.12, 95% CI 1.26 to 3.55). Residence outside the admitting district was associated with higher odds of death (aOR 3.28, 95% CI 1.83 to 5.88), while insurance was inversely associated with death (aOR 0.25, 95% CI 0.15 to 0.40). Incomplete parenteral care, defined using the two-hour treatment threshold, was independently associated with death (aOR 1.74, 95% CI 1.16 to 2.60) (Table 3).

Table 3
Facility-stratified conditional logistic regression

Factor	Adjusted OR (95% CI)	P value
Age < 5 vs ≥ 15 years	0.98 (0.54 to 1.78)	0.941
Age 5–14 vs ≥ 15 years	0.70 (0.38 to 1.29)	0.256
Male	1.16 (0.78 to 1.71)	0.460
Insured	0.25 (0.15 to 0.40)	< 0.001
Residence outside admitting district	3.28 (1.83 to 5.88)	< 0.001
Each additional severe manifestation	0.91 (0.78 to 1.06)	0.229
Not triaged vs triaged	2.12 (1.26 to 3.55)	0.004
Triage indeterminate vs triaged	0.71 (0.36 to 1.41)	0.328
Incomplete vs complete parenteral care	1.74 (1.16 to 2.60)	0.007

****** Reference groups were age 15 years or older, female sex, uninsured, residence within the admitting district, completed triage, and complete parenteral care.

Attributable proportions

Among the 205 observed deaths, 54 patients (26.3%) were not triaged, 88 (42.9%) lived outside the admitting district, and 84 (41.0%) were uninsured. Their adjusted attributable proportions were 13.9% (95% CI 5.5% to 18.9%), 29.8% (95% CI 19.5% to 35.6%), and 30.9% (95% CI 24.5% to 34.8%), respectively. Among 54 deaths in referred patients with known timing, 19 (35.2%) followed a late referral, corresponding to an adjusted attributable proportion of 31.8% (95% CI 20.5% to 34.4%). Among 57 deaths in patients requiring blood, 39 (68.4%) had transfusion delay, corresponding to an adjusted attributable proportion of 38.6% (95% CI 14.0% to 52.1%) (Table 4).

Table 4
Adjusted attributable proportions among observed deaths

Exposure	Exposed deaths	Adjusted OR (95% CI)	Attributable proportion (95% CI)
No triage	54/205	2.12 (1.26 to 3.55)	13.9% (5.5% to 18.9%)
Residence outside admitting district	88/205	3.28 (1.83 to 5.88)	29.8% (19.5% to 35.6%)
Uninsured	84/205	4.06 (2.49 to 6.61)	30.9% (24.5% to 34.8%)
Late referral	19/54 referred deaths	10.53 (2.40 to 46.15)	31.8% (20.5% to 34.4%)
Transfusion delay	39/57 deaths requiring blood	2.29 (1.26 to 4.18)	38.6% (14.0% to 52.1%)

****Attributable proportions used $Pd(OR \text{ minus } 1)/OR$, where Pd is the exposure prevalence among deaths. The uninsured OR is the reciprocal of the insured OR.**

Pathway, interaction, and sensitivity analyses

Referral timing was classifiable for 92 referred patients, including 54 deaths and 38 recoveries. Late referral occurred among 19 deaths and two recoveries and was associated with death after reduced adjustment (aOR 10.53, 95% CI 2.40 to 46.15). Among 149 patients requiring blood, 85 experienced transfusion delay, including 39 of 57 deaths and 46 of 92 recoveries. Transfusion delay was associated with death after reduced adjustment (aOR 2.29, 95% CI 1.26 to 4.18) (Table 5).

There was no evidence that the insurance association differed between teaching and other hospitals (interaction $p = 0.508$) or that the association of severe-manifestation count differed between patients younger than 15 years and adults (interaction $p = 0.183$). The association between no triage and death persisted when indeterminate triage was excluded (aOR 2.16, 95% CI 1.28 to 3.64), in a model with facility fixed effects (aOR 2.19, 95% CI 1.29 to 3.73), and in ordinary logistic regression with facility-clustered standard errors (aOR 1.65, 95% CI 1.01 to 2.70). When indeterminate triage was combined with no triage, the estimate was attenuated and imprecise (aOR 1.45, 95% CI 0.93 to 2.28), supporting retention of indeterminate status as a separate category.

Table 5
Pathway-specific adjusted analyses

Pathway	Analysis population	Exposure	Adjusted OR (95% CI)	P value
Referral	Known referral timing, $n = 92$	Late referral	10.53 (2.40 to 46.15)	0.002
Transfusion	Required blood, $n = 149$	Transfusion delay	2.29 (1.26 to 4.18)	0.007

***Models adjusted for age younger than 15 years, sex, severe-manifestation count, and teaching-hospital status, with facility-clustered standard errors. Referral estimates were based on 17 facilities and transfusion estimates on 27 facilities.*

Discussion

Our assessment identified failures and barriers at several points in the severe malaria care pathway. Within the same hospitals, no triage more than doubled the adjusted odds of death, residence outside the admitting district more than tripled the odds, and insurance remained strongly protective. Using the two-hour threshold, incomplete parenteral care was associated with 74% higher adjusted odds of death. Late referral had the largest association among referred patients, while transfusion delay more than doubled the adjusted odds of death among patients requiring blood. The attributable analysis indicated appreciable potential service importance for each exposure.

The triage and treatment findings are clinically coherent. Severe malaria can deteriorate rapidly, with many deaths occurring soon after admission [4]. Triage should trigger immediate assessment for coma, respiratory distress, shock, hypoglycaemia, severe anaemia, renal dysfunction, and other manifestations requiring escalation [5–8]. Evidence from Malawi and Uganda similarly shows incomplete application or documentation of severe malaria standards [9, 10, 12], while structured admission checklists and workflow changes improved testing and artesunate administration in Uganda [11]. In the present study, triangulating multiple clinical and administrative sources strengthened classification of triage status. The two-hour treatment measure identifies whether parenteral therapy was initiated during the early emergency-care window. Together, the findings support a standardized admission bundle linking triage to bedside glucose and haemoglobin assessment, immediate parenteral artesunate, senior review, physiological monitoring, and an explicit decision on referral, transfusion, or critical care.

Residence outside the admitting district and late referral indicate delays that may begin before arrival at definitive care. Cross-district travel may reflect distance, repeated care seeking, bypass of nearby facilities, transport constraints, or referral from facilities without the required capacity. Evidence from the CARAMAL programme shows that prereferral treatment cannot prevent deaths when onward referral is incomplete or care after arrival is inadequate [15–17]. The association with transfusion delay extends this pathway into supportive care. Severe anaemia is a major manifestation of severe malaria in Ghana [21, 22], so delays in blood request, availability, compatibility testing, or administration may be consequential. Health services should define measurable referral and transfusion timelines, stabilize patients before transfer, communicate with receiving hospitals, maintain reliable transport and blood access, and reassess referred patients immediately on arrival.

Insurance coverage was substantially lower among deaths and remained inversely associated with mortality after within-hospital adjustment. Ghanaian evidence links insurance with greater formal care use and reduced household spending for malaria treatment [26–28]. Insurance may facilitate earlier presentation, diagnostic testing, acquisition of medicines or supplies, and completion of referral.

However, the attributable estimate for being uninsured should not be interpreted as the proportion of deaths that enrolment alone would prevent. Insurance may also represent socioeconomic position, health literacy, proximity to services, prior engagement with care, and willingness to seek treatment early. Prospective work should measure these pathways directly and examine whether active coverage reduces delays from symptom recognition through referral and definitive treatment.

The study has several strengths. Severe malaria eligibility was independently verified against WHO clinical criteria rather than accepted solely from the recorded diagnosis. Triage was triangulated across patient folders, clinicians' and nurses' notes, and admission and discharge records. The analysis included 205 deaths from 33 hospitals in eight regions, evaluated linked stages from recognition to referral and supportive care, and used facility stratification to compare deaths and recoveries within hospitals. The treatment measure used a clinically relevant two-hour threshold, and transfusion timing was analysed only among patients requiring blood. Subgroup analyses were confined to applicable patients, and alternative model specifications generally supported the triage finding.

Several limitations remain. Record retrievability may have affected control selection, and complete screening counts were unavailable. Although key variables were triangulated across sources, retrospective records may still omit care that occurred, and abstractors were not blinded to outcome. The count of documented severe manifestations may incompletely capture physiological severity, leaving residual confounding and potentially differential documentation between rapidly fatal and surviving patients. Referral timeliness was based on recorded classification rather than a common timestamp threshold. The referral estimate was imprecise, and both referral and transfusion analyses may be affected by indication, selection, and survivor-time biases. Insurance and residence may represent unmeasured socioeconomic and access factors.

The results identify actionable weaknesses in emergency recognition, early definitive treatment, transfer, and supportive care. Hospitals should implement a standardized severe malaria admission bundle, monitor the interval from presentation to the first parenteral antimalarial dose, establish objective referral and transfusion timelines, and prospectively record physiological severity and exact timestamps. Quality-improvement programmes should evaluate whether these changes reduce treatment delay and mortality while accounting for baseline severity and access barriers.

Conclusions

Among patients with independently verified severe malaria in selected Ghanaian hospitals, death was associated with no triage, incomplete parenteral care within two hours, residence outside the admitting district, lack of insurance, late referral, and transfusion delay. Their attributable proportions suggest substantial service improvement opportunities. Standardized emergency assessment, prompt parenteral treatment, reliable referral coordination, timely access to blood, and prospective audit using exact timestamps should be prioritized.

Abbreviations

CI, confidence interval; GHS ERC, Ghana Health Service Ethics Review Committee; IQR, interquartile range; NMEP, National Malaria Elimination Programme; OR, odds ratio; WHO, World Health Organization.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ghana Health Service Ethics Review Committee (GHS ERC 001/11/24). Administrative permission was obtained from participating health authorities and facilities. The Ghana Health Service Ethics Review Committee waived individual informed consent because the study involved retrospective abstraction of routinely collected clinical records.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

EK, KLM, NYP, and MAW conceptualized the study and developed the protocol. GAA, AGM, PB, DD, WM, and MBL contributed to data collection and management. EK and AGM conducted and verified the analysis and drafted the manuscript. MAW, FOA, AA, and MDO contributed to interpretation and critical revision. All authors read and approved the final manuscript.

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Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

References

1. World Health Organization. World malaria report 2025: addressing the threat of antimalarial drug resistance. Geneva: World Health Organization. 2025. ISBN 978-92-4-011782-2.
2. World Health Organization. WHO guidelines for malaria, 13 August 2025. Geneva: World Health Organization. 2025. WHO reference number 10.2471/B09514. Available from: <https://www.who.int/publications/i/item/guidelines-for-malaria> Accessed 21 August 2026.
3. Dondorp AM, Fanello CI, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children: an open-label, randomised trial. *Lancet*. 2010;376:1647–57. 10.1016/S0140-6736(10)61924-1.
4. Kendjo E, Agbenyega T, Bojang K, Newton CRJC, Bouyou-Akotet M, et al. Mortality patterns and site heterogeneity of severe malaria in African children. *PLoS ONE*. 2013;8:e58686. 10.1371/journal.pone.0058686.
5. Sypniewska P, Duda JF, Locatelli I, Rambaud-Althaus C, Althaus F, Genton B. Clinical and laboratory predictors of death in African children with features of severe malaria: a systematic review and meta-analysis. *BMC Med*. 2017;15:147. 10.1186/s12916-017-0906-5.
6. Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, et al. Indicators of life-threatening malaria in African children. *N Engl J Med*. 1995;332:1399–404. 10.1056/NEJM199505253322102.
7. von Seidlein L, Olaosebikan R, Hendriksen ICE, Lee SJ, Adedoyin OT, Agbenyega T, et al. Predicting the clinical outcome of severe falciparum malaria in African children: findings from a large randomized trial. *Clin Infect Dis*. 2012;54:1080–90. 10.1093/cid/cis034.
8. Namazzi R, Opoka RO, Datta D, Bangirana P, Batte A, Berrens Z, et al. Acute kidney injury interacts with coma, acidosis, and impaired perfusion to significantly increase risk of death in children with severe malaria. *Clin Infect Dis*. 2022;75:1511–9. 10.1093/cid/ciac246.
9. Shah MP, Briggs-Hagen M, Chinkhumba J, Bauleni A, Chalira A, Moyo D, et al. Adherence to national guidelines for the diagnosis and management of severe malaria: a nationwide, cross-sectional survey in Malawi, 2012. *Malar J*. 2016;15:369. 10.1186/s12936-016-1423-2.
10. Moffitt CA, Olupot-Olupot P, Onen JW, O'Brien N. Adherence to severe malaria treatment guidelines in children at a Ugandan regional hospital: a baseline assessment for a malaria treatment quality improvement project. *Malar J*. 2023;22:67. 10.1186/s12936-023-04507-4.
11. Moffitt CA, Olupot-Olupot P, Wamulugwa J, Abeso J, Muszynski JA, O'Brien N. Improving adherence to severe malaria treatment guidelines in children at a Ugandan regional hospital: assessment of a quality improvement initiative. *Malar J*. 2024;23:245. 10.1186/s12936-024-05076-w.

12. Akello Z, Oloro J, Mukanyangezi MF, Asingizwe D. Adherence to severe malaria treatment guidelines in Northern Uganda: a mixed methods study. *Malar J.* 2025;24:417. 10.1186/s12936-025-05658-2.
13. Mousa A, Al-Taiar A, Anstey NM, Badaut C, Barber BE, Bassat Q, et al. The impact of delayed treatment of uncomplicated *Plasmodium falciparum* malaria on progression to severe malaria: a systematic review and pooled multicentre individual-patient meta-analysis. *PLoS Med.* 2020;17:e1003359. 10.1371/journal.pmed.1003359.
14. Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet.* 2009;373:557–66. 10.1016/S0140-6736(08)61734-1.
15. Lengeler C, Burri C, Awor P, Athieno P, Kimera J, Tumukunde G, et al. Community access to rectal artesunate for malaria: a large-scale observational implementation study in the Democratic Republic of the Congo, Nigeria and Uganda. *PLOS Glob Public Health.* 2022;2:e0000464. 10.1371/journal.pgph.0000464.
16. Brunner NC, Omoluabi E, Awor P, Okitawutshu J, Tshefu A, Signorell A, et al. Prereferral rectal artesunate and referral completion among children with suspected severe malaria in the Democratic Republic of the Congo, Nigeria and Uganda. *BMJ Glob Health.* 2022;7:e008346. 10.1136/bmjgh-2021-008346.
17. Lambiris MJ, Venga GN, Ssempala R, Okitawutshu J, Tshefu A, Omoluabi E, et al. Health system readiness and the implementation of rectal artesunate for severe malaria in sub-Saharan Africa: an analysis of real-world costs and constraints. *Lancet Glob Health.* 2023;11:e34–45. 10.1016/S2214-109X(22)00507-1.
18. World Health Organization. The use of rectal artesunate as a pre-referral treatment for severe *Plasmodium falciparum* malaria. Geneva: WHO; 2023.
19. World Health Organization. Malaria 2024 Ghana country profile. Geneva: World Health Organization. 2024. Available from: <https://www.who.int/publications/m/item/malaria-2024-gha-country-profile> Accessed 21 August 2026.
20. Ghana Statistical Service, Service GH. ICF. Ghana Demographic and Health Survey 2022. Maryland, USA: Accra, Ghana and Rockville; 2023.
21. Mockenhaupt FP, Ehrhardt S, Burkhardt J, Bosomtwe SY, Laryea S, Anemana SD, et al. Manifestation and outcome of severe malaria in children in northern Ghana. *Am J Trop Med Hyg.* 2004;71:167–72.
22. Oduro AR, Koram KA, Rogers W, Atuguba F, Ansah P, Anyorigiya T, et al. Severe *falciparum* malaria in young children of the Kassena-Nankana district of northern Ghana. *Malar J.* 2007;6:96. 10.1186/1475-2875-6-96.
23. Peprah NY, Mohammed W, Adu GA, Dadzie D, Oppong S, Barikisu S, et al. Patient socio-demographics and clinical factors associated with malaria mortality: a case-control study in the northern region of Ghana. *Malar J.* 2024;23:230. 10.1186/s12936-024-05038-2.
24. Asiedu A, Haws RA, Gyasi A, Boateng P, Malm K, Ntumy R, et al. Improving malaria case management and referral relationships at the primary care level in Ghana: evaluation of a quality

- assurance internship. *Glob Health Sci Pract*. 2023;11:e2300050. 10.9745/GHSP-D-23-00050.
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–7. 10.1016/S0140-6736(07)61602-X.
26. Fenny AP, Asante FA, Enemark U, Hansen KS. Malaria care seeking behavior of individuals in Ghana under the National Health Insurance Scheme. *BMC Public Health*. 2015;15:370. 10.1186/s12889-015-1696-3.
27. Dalaba MA, Akweongo P, Aborigo RA, Ataguba JE. Does the National Health Insurance Scheme in Ghana reduce household cost of treating malaria in the Kassena-Nankana districts? *Glob Health Action*. 2014;7:23848. 10.3402/gha.v7.23848.
28. Fenny AP, Asante FA, Arhinful DK, Kusi A, Parmar D, Williams G. Treatment-seeking behaviour and social health insurance in Africa: the case of Ghana under the National Health Insurance Scheme. *Glob J Health Sci*. 2014;7:296–314. 10.5539/gjhs.v7n1p296.