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Predicting mortality for paediatric inpatients where malaria is uncommon

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Abstract

Objective—As the proportion of children living low malaria transmission areas in sub-Saharan Africa increases, approaches for identifying non-malarial severe illness need to be evaluated to improve child outcomes.

Design—As a prospective cohort study, we identified febrile paediatric inpatients, recorded data using Integrated Management of Childhood Illness (IMCI) criteria, and collected diagnostic specimens.

Setting—Tertiary referral centre, northern Tanzania.

Results—Of 466 participants with known outcome, median age was 1.4 years (range 2 months–13.0 years), 200 (42.9%) were female, 11 (2.4%) had malaria and 34 (7.3%) died. Inpatient death was associated with: Capillary refill >3 s (OR 9.0, 95% CI 3.0 to 26.7), inability to breastfeed or drink (OR 8.9, 95% CI 4.0 to 19.6), stiff neck (OR 7.0, 95% CI 2.8 to 17.6), lethargy (OR 5.2, 95% CI 2.5 to 10.6), skin pinch >2 s (OR 4.8, 95% CI 1.9 to 12.3), respiratory difficulty (OR 4.0, 95% CI 1.9 to 8.2), generalised lymphadenopathy (OR 3.6, 95% CI 1.6 to 8.3) and oral candidiasis (OR 3.4, 95% CI 1.4 to 8.3). BCS <5 (OR 27.2, p<0.001) and severe wasting (OR 6.9, p<0.001) were independently associated with inpatient death.

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Contributors JAC conceived and oversaw the study. HOR, LJM, BNN and GDK managed the day-to-day operations of the research. DCC conducted analyses and wrote the first draft of the manuscript under the mentorship of AMB and JAC. All authors provided critical feedback on revision of the manuscript.

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Ethics approval The study was approved by the KCMC Research Ethics Committee, the Tanzania National Institute for Medical Research Ethics Coordinating Committee, and an Institutional Review Board of Duke University Medical Center.

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Conclusions—In a low malaria transmission setting, IMCI criteria performed well for predicting inpatient death from non-malarial illness. Laboratory results were not as useful in predicting death, underscoring the importance of clinical examination in assessing prognosis. Healthcare workers should consider local malaria epidemiology as malaria over-diagnosis in children may delay potentially life-saving interventions in areas where malaria is uncommon.

INTRODUCTION

An estimated 7.6 million children <5 years of age died in 2010. In sub-Saharan Africa, one out of every eight children died before the age of 5 years.[1] Many child mortality studies in sub-Saharan Africa have been performed in areas highly endemic for malaria.[2–7] However, as interventions to combat malaria are increasingly implemented, there have been associated declines in disease.[8] If such declines continue, a growing proportion of sick children in sub-Saharan Africa will be managed in areas where malaria is uncommon.

Previous studies have shown that the majority of inpatient child deaths occur shortly after admission.[379–11] To avert inpatient death, clinicians must quickly identify and respond to clinical signs associated with adverse outcomes. Implementation of a formal triage programme has been shown to reduce child mortality in a low-resource setting.[12] Previous child mortality studies have focused on specific disease processes,[13–19] children under the age of 5 years[2–4131520–25] and rural settings.[2620212425] Studies that comprehensively examine child death are needed to improve the approach to triage.

We aimed to evaluate the performance of the Integrated Management of Childhood Illness (IMCI) criteria[26] to predict adverse outcomes among paediatric admissions in an area of low malaria intensity. As acute febrile illness is a common reason for hospitalisation and death among African children,[27] we studied children presenting with febrile illness at a consultant referral hospital in northern Tanzania.

METHODS

Setting

The study was conducted in Moshi (population >144 000), the administrative centre of the Kilimanjaro Region (population >1.4 million) and an area of low malaria transmission intensity.[28] Participants were recruited from Kilimanjaro Christian Medical Centre (KCMC), a consultant referral hospital serving several regions in northern Tanzania. Detailed methods for the parent study have been published elsewhere.[29]

Study population

In brief, participants were prospectively identified among consecutive admissions of paediatric inpatients at KCMC from 17 September 2007 through 25 August 2008. Admitted patients aged ≥2 months to <13 years with a history of fever in the past 48 h or an axillary temperature of ≥37.5°C or a rectal temperature of ≥38.0°C were eligible to participate. Sample size was determined by the parent study.[29]

Study procedures

Enrolment of participants was performed as soon as possible and prior to administration of antimicrobial therapy. A standardised clinical history and physical examination capturing IMCI criteria were performed by a trained clinical officer who was a member of the study team. Assays were performed in a laboratory operating to good clinical laboratory practices standards. Blood was drawn for aerobic blood culture (4 ml), complete blood count and differential, blood parasites and HIV antibody testing.[30] Thick and thin blood films stained

with Giemsa were examined for blood parasites by oil immersion microscopy. Parasite density was determined by standard methods.[31] For HIV seropositive infants aged <18 months, confirmatory testing with HIV-1 RNA PCR was performed.[3233] Data collection was standardised regardless of hospital outcome.

Clinical definitions

A Blantyre coma score (BCS) of ≤2 defined coma.[3435] Signs of respiratory difficulty included nasal flaring, respiratory grunting or chest indrawing. Abnormal breath sounds were defined as wheezing or crepitations on auscultation. Severe malnutrition was defined as mid-upper arm circumference (MUAC) <115 mm or weight-for-height z score (WHZ) < −3 in ages ≥6 to <60 months, body mass index-for-age z score <−3 in ages ≥60 months, or bilateral pitting oedema.[263637] Hypoglycaemia and severe anaemia were defined according to IMCI guidelines.[26] Clinical syndromes were based on the IMCI diagnostic guidelines and incorporated for those factors evaluated during data collection.[26] Typhoid fever was defined as IMCI-defined septicaemia and fever for >7 days.[26]

Statistical analysis

All statistical tests were performed at the 5% level of significance (two-sided) using JMP software 8.0.2 (SAS, Cary, North Carolina, USA). Analysis was restricted to study participants with known hospital outcome, death or discharge. Missing data were not included in the analysis and did not impact our findings to the best of our knowledge.

WHO AnthroPlus V.1.0.4 (WHO, Geneva, Switzerland) was used to calculate age and malnutrition parameters except weight-for-height. Distance from residence to KCMC was calculated using gvSIG, a geographic information system (Regional Ministry of Infrastructure and Transport of Valencia, Valencia, Spain) for previously mapped village locations.

The performance of IMCI guidelines to predict adverse outcomes was assessed. For binary data, Pearson's χ^2 test or Fisher's exact test (two-tailed) was performed.[38] ORs and 95% CIs were calculated. For continuous responses, a two-tailed t test was performed for approximated normal distributions and Wilcoxon rank sum tests for non-parametric data. Outliers were eliminated using standard techniques[39] except malnutrition parameters from WHO AnthroPlus which were eliminated using WHO-defined ranges.

A multivariable logistic regression analysis was performed. Sex, age and factors significantly associated with inpatient death in bivariable analysis that were assessed at admission, included >95% participants, and were not repetitive with another factor, were included in multivariable analysis. A Bonferroni correction, $p<0.05$ and $k=20$, was made to further select variables to be entered into the multivariable model.[40] Any factors that remained statistically significant ($p<0.05$) were included in the final model.

Standard measures of test validity including sensitivity (SN), specificity (SP), positive likelihood ratio (LR+) and positive predictive value (PPV) were performed for those factors in the multivariate model and for certain IMCI clinical syndromes.

Research ethics

The study was approved by the KCMC Research Ethics Committee, the Tanzania National Institute for Medical Research Ethics Coordinating Committee and an Institutional Review Board of Duke University Medical Center.

RESULTS

Over the study period, 1154 patients admitted to the paediatric services of KCMC were screened and 644 (55.8%) met eligibility criteria. Of 467 enrolled patients, one patient with unknown hospital outcome was excluded from analysis. Median (range) time from admission to initial assessment was 13.0 (0.0–36.5) h, IQR 1.0–18.5 h and mean of 11.1 h. Of 466 remaining participants, 34 (7.3%) died during admission. Median (range) age was 1.4 years (2 months–13 years) and 200 (42.9%) were female. Median (range) distance to residence from KCMC was 5 (0.6–262) km. Sixty (13.2%) participants were HIV-infected, 11 (2.4%) had positive malaria films and 17 (3.7%) had a bloodstream infection diagnosed by blood culture (table 1).

Demographic and clinical characteristics associated with in-hospital death

Table 1 shows the results of bivariable analysis of sociodemographic and clinical characteristics among those who did and did not die during the inpatient period. Death was more likely among participants presenting with fever of >7 days' duration (OR 3.8, p<0.001), those with history of difficulty breathing on admission (OR 5.9, p<0.001) and those referred from another inpatient facility (OR 2.5, p=0.010). History of antibacterial use, antimalarial use, diarrhoeal disease, vomiting and cough were not associated with inpatient death (table 1).

Among physical examination findings, death was more likely among participants presenting with inability to sit for those aged >9 months (OR 22.7, p<0.001), central cyanosis (OR 20.6, p=0.003), deep breathing (OR 19.0, p<0.001), capillary refill >3 s (OR 9.0, p<0.001), inability to breastfeed or drink (OR 8.9, p<0.001), stiff neck (OR 7.0, p<0.001), lethargy (OR 5.2, p<0.001), skin pinch >2 s (OR 4.8, p<0.001) and respiratory difficulty (OR 4.0, p<0.001). A BCS <5 was present in 15 (44.1%) participants who died compared with 14 (3.3%) discharged alive (OR 23.2, p<0.001). Other physical examination findings associated with inpatient death are shown in table 1. No patient who died had a positive malaria smear. Participants with severe anaemia (OR 5.3, p<0.0001) were more likely to die. Twenty (48.8%) of 41 participants with severe anaemia also had severe pallor. HIV infection, bloodstream infection and hypoglycaemia were not associated with hospital outcome (table 1).

Malnutrition

Participants who died in the hospital were more likely to exhibit visible severe wasting (OR 4.9, p<0.001) and a low weight-for-age z score (WAZ) (p=0.014). Severe malnutrition was identified among 97 (27%) of 338 participants but was not associated with inpatient death (OR 1.3, p=0.624) (table 1). Twenty-four (26.1%) of 92 participants with severe malnutrition also exhibited visible severe wasting.

Performance of IMCI criteria and admission diagnoses in predicting adverse outcomes

Table 2 shows the results of bivariable analysis of IMCI-defined syndromes and hospital outcome for those aged ≥2 to <60 months. Those who died were more likely to present with ≥1 IMCI danger sign (LR+ 2.08, SN 0.72, SP 0.65, PPV 0.15), with increasing likelihood of dying with ≥2 danger signs (LR+ 6.11, SN 0.52, SP 0.92, PPV 0.33) and ≥3 danger signs (LR+ 10.63, SN 0.98, SP 0.18, PPV 0.45). The presence of IMCI-defined septicaemia was associated with inpatient death (OR 3.0, p=0.003) but was not predictive of positive blood culture (LR+ 0.86, SN 0.27, SP 0.69, PPV 0.03). Participants meeting clinical criteria for typhoid fever were more likely to die (OR 6.0, p<0.001), but this did not identify the two participants with Salmonella typhi bloodstream infection. No participants with IMCI-defined non-severe malaria died (OR undefined, p=1.00). Of three participants meeting

criteria for non-severe malaria, all three (100%) had a positive malaria smear (LR+ infinity (division by zero), SN 0.38, SP 1.00, PPV 1.00). Of 11 participants with ≥3 severe malaria predictors, three (27.3%) had a positive malaria blood smear (LR+ 0.34, SN 0.33, SP 0.02, PPV 0.27). The presence of ≥4 severe malaria predictors identified one of nine positive malaria smears (LR+ 13.72, SN 0.11, SP 0.99, PPV 0.25). There were no deaths with laboratory-confirmed typhoid fever or malaria as described previously.[29] Other clinical syndromes associated with death during admission are presented in table 2. Of 78 participants aged ≥60 months, four (5.1%) died, accounting for 11.8% of deaths; there was no association between IMCI syndromes and death in this age group.

Malaria and pneumonia were diagnosed clinically on admission in 274 (58.8%) and 232 (49.8%) participants, respectively. Admission diagnoses of malaria, pneumonia, typhoid fever and septicaemia were not associated with inpatient death.

Multivariable analysis

BCS <5 (OR 27.2, p<0.001) and visible severe wasting (OR 6.9, p<0.001) were independently associated with inpatient death. Presentation with one or more of these factors predicted 24 (70.6%) participants who died (LR+ 6.33, SN 0.71, SP 0.89, PPV 0.34).

Days spent in hospital and inpatient death

Inpatient death was associated with a shorter hospital stay (OR 6.5, p<0.001) with a median (range) of 4 (0–31) days for those who died in-hospital and 7 (1–99) days for those discharged alive. Participants who died were more likely to spend ≤2 days in the hospital compared to those discharged alive, who were more likely to spend >2 days (OR 6.5, p<0.001).

DISCUSSION

IMCI clinical signs and syndromes performed well for predicting inpatient death in a low malaria transmission setting. These findings suggest clinical signs often associated with malaria in high transmission areas are indicative of severe non-malarial illnesses in areas where malaria is uncommon. Given that children often present at a healthcare facility before death[2541] and often die soon after admission,[379–11] identifying those at high risk for death and focusing on this group for immediate use of potentially life-saving interventions is essential. To avert inpatient death, healthcare workers should utilise IMCI criteria along with malaria testing to prevent malaria over-diagnosis and to prevent delayed recognition of severe non-malarial illnesses in areas where malaria is uncommon.

Signs of respiratory distress and abnormal mental status have been associated with child death in areas of high malaria transmission.[57102042] We have shown these signs are also important in non-malaria endemic areas. Presentation with BCS <5 or severe wasting identified 71% of children who died of non-malaria illness in an area where malaria is uncommon. IMCI-defined syndromes effectively predicted inpatient death in children aged ≥2 to <60 months, but were poorly predictive of laboratory diagnoses, suggesting these syndromes may be useful to identify a child at risk for an adverse outcome but less useful to guide more specific diagnosis and treatment. Besides severe anaemia, laboratory diagnoses did not predict inpatient death. We demonstrate the importance of considering non-malaria causes of anaemia. Despite enhanced laboratory diagnostics, many deaths were not explained with microbiological evaluations, underscoring the importance of clinical evaluation.[29] Our findings support a prior study that showed a subset of clinical signs may be useful to predict risk of inpatient death.[10]

We confirmed that a low WAZ, a measure that does not differentiate chronic from acute malnutrition,[264344] is a risk factor for child death.[214445] The prevalence of severe acute malnutrition was high but not associated with increased risk for death. HIV-infected participants were more likely to be mal-nourished. Although visible severe wasting was independently associated with death, this accounted for only a quarter of participants with severe malnutrition by anthropometric measurements, suggesting that healthcare workers identified only a subset of malnourished children and should not rely on observation of severe wasting alone.

Our study confirmed that sub-Saharan African children who die in-hospital often die soon after admission.[379–11] While the majority of deaths in prior studies occurred within 48 h of admission, the median time to death was 4 days in our study. Many of these prior studies were in rural district hospitals with high malaria transmission rates. A subset of severely ill children may have died before reaching our referral centre. Our findings confirm the narrow window for life-saving interventions for a sick child presenting to a healthcare facility.

Our study had several limitations. There is a possible selection bias as mean time from admission to initial assessment was 11.1 h with a median of 13.0 h, potentially missing severely ill children who died very soon after admission. Our study was conducted in a consultant referral hospital, limiting generalisability to other healthcare facilities. Although we demonstrated IMCI criteria performed well in predicting inpatient death, they were not developed for this purpose. Having a control group in a high malaria transmission setting would have strengthened our study. A larger number of children in the ≥60-month age group would have made our study more comprehensive and robust. Although a large number of potential predictors of inpatient death were examined, we used a Bonferroni correction to mitigate the effect of multiple comparisons.[40]

In an area of low malaria transmission, IMCI clinical signs and syndromes helped to identify children at risk for adverse outcomes and are valuable regardless of local malaria epidemiology. Since no participant who died in our study had malaria, IMCI signs predicted outcomes for severe non-malarial illnesses. Although malaria was often clinically diagnosed, few were confirmed positive by malaria smear. Inappropriate focus on malaria in a low transmission setting may delay recognition and management of severe non-malarial illnesses. As areas of low malaria transmission are likely to expand,[8] identifying clinical danger signs and improving algorithms to rapidly triage a child according to risk of death in these settings may further reduce child mortality.

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What is already known on this topic

- The majority of child mortality studies in sub-Saharan Africa have been performed in high malaria transmission areas.
- Successful malaria control programmes suggest a growing proportion of sick children will be managed in areas where malaria is uncommon.
- Most inpatient child deaths occur shortly after admission, underscoring the importance of rapid triage to prevent adverse outcomes.

What this study adds

- Most Integrated Management of Childhood Illness criteria performed well for predicting inpatient child mortality in an area where malaria is uncommon.
- Clinical evaluation rapidly identified patients likely to have poor outcomes even though they did not reliably identify subsequent laboratory diagnoses.

Table 1

Bivariable analysis of demographic and clinical characteristics by hospital outcome among febrile paediatric admissions in northern Tanzania, 2007–8

		Hospital outcome			
Characteristic*	**Overall (%) (n=466)**	**Alive (%) (n=432)**	**Dead (%) (n=34)**	**OR (95% CI)**	**p Value**
Coma[e]	11/460 (2)	3/426 (1)	8/34 (24)	43.4 (10.9 to 173)	<0.001
Blantyre coma score <5	29/460 (6)	14/426 (3)	15/34 (44)	23.2 (9.8 to 55.0)	<0.001
Unable to sit aged >9 months	53/323 (2)	4/349 (1)	5/24 (21)	22.7 (5.6 to 91.5)	<0.001
Central cyanosis[e]	5/462 (1)	2/428 (0.5)	3/34 (9)	20.6 (3.3 to 128)	0.003
Deep breathing	7/466 (2)	3/432 (0.7)	4/34 (12)	19.0 (4.1 to 89.1)	<0.001
Capillary refill >3 s[e]	16/466 (3)	10/432 (2)	6/34 (18)	9.0 (3.0 to 26.7)	<0.001
Unable to breastfeed/drink	41/464 (9)	28/430 (7)	13/34 (38)	8.9 (4.0 to 19.6)	<0.001
Stiff neck	26/461 (6)	18/427 (4)	8/34 (24)	7.0 (2.8 to 17.6)	<0.001
Bulging fontanelle	10/445 (2)	7/415 (2)	3/30 (10)	6.5 (1.6 to 26.5)	0.024
History of difficulty breathing	179/464 (39)	153/430 (36)	26/34 (76)	5.9 (2.6 to 12.3)	<0.001
Severe anaemia	41/458 (9)	31/424 (7)	10/34 (29)	5.3 (2.3 to 12.0)	<0.001
Lethargy[p]	87/465 (19)	70/431 (16)	17/34 (50)	5.2 (2.5 to 10.6)	<0.001
Visible severe wasting[p]	45/460 (10)	35/427 (8)	10/33 (30)	4.9 (2.2 to 11.1)	<0.001
Skin pinch >2 s	29/464 (6)	22/430 (5)	7/34 (21)	4.8 (1.9 to 12.3)	0.003
Abnormal breath sounds	204/456 (45)	179/423 (42)	25/33 (76)	4.3 (1.9 to 9.7)	<0.001
Signs of respiratory difficulty[p]	145/462 (31)	124/428 (29)	21/34 (62)	4.0 (1.9 to 8.2)	<0.001
Fever >7 days	121/458 (26)	103/425 (24)	18/33 (55)	3.8 (1.8 to 7.7)	<0.001
Generalised lymphadenopathy[†]	49/457 (11)	40/424 (9)	9/33 (27)	3.6 (1.6 to 8.3)	0.005
Oral candidiasis	40/459 (9)	33/427 (8)	7/32 (22)	3.4 (1.4 to 8.3)	0.015
Convulsions in past 48 h	67/461 (15)	57/428 (13)	10/33 (30)	2.8 (1.3 to 6.3)	0.017
Anticonvulsant in past 6 h	40/225 (18)	32/202 (16)	8/23 (35)	2.8 (1.1 to 7.2)	0.040
Referral from other inpatient facility	177/463 (38)	157/429 (37)	20/34 (59)	2.5 (1.2 to 5.0)	0.010
Weight-for-age z score, median	−0.79	−0.75	−1.89		0.014
Median days ill prior to admission	4	4	9.5		0.004

Values represent numerator and denominator unless stated otherwise.

[*] Characteristics evaluated but not associated with hospital outcome include: age, sex, mother's education less than standard 7, median kilometres to hospital, antimicrobials in past 48 h, antimalarials in past 48 h, fever in past 48 h, diarrhoea ≥3 times in past 24 h, diarrhoea for >14 days, history of bloody diarrhoea, vomiting ≥3 times in past 24 h, history of vomiting everything, history of cough, sunken eyes, jaundice, severe pallor, stridor, hepatomegaly, splenomegaly, pitting oedema bilaterally, severe acute malnutrition, mid-upper arm circumference <115 mm, hypoglycaemia, HIV-infected, malaria film positive and bacteremia (blood culture positive).

[†] Defined as lymph node(s) >1 cm in >2 areas.

[e] WHO emergency sign.

[p] WHO priority sign.

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Table 2

Bivariable analysis of Integrated Management of Childhood Illness (IMCI)-defined clinical syndromes and hospital outcome in paediatric febrile admissions aged ≥2 to <60 months in northern Tanzania, 2007–8

		Hospital outcome			
IMCI clinical syndrome	**Overall (%) (n=387)**	**Alive (%) (n=358)**	**Dead (%) (n=29)**	**OR (95% CI)**	**p Value**
Pneumonia					
Very severe	97/375 (26)	77/346 (22)	20/29 (69)	7.8 (3.4 to 17.7)	<0.001
Severe	68/289 (24)	64/280 (23)	4/9 (44)	2.7 (0.7 to 10.4)	0.222
Non-severe	54/222 (24)	51/217 (24)	3/5 (60)	4.9 (0.8 to 30.0)	0.094
Any type of pneumonia	218/378 (58)	191/349 (55)	27/29 (93)	11.2 (2.6 to 47.7)	<0.001
Meningitis					
≥2 predictors	70/379 (18)	53/351 (15)	17/28 (60)	8.7 (3.9 to 19.6)	<0.001
≥3 predictors	25/384 (7)	12/355 (3)	13/29 (45)	23.2 (9.2 to 58.9)	<0.001
≥4 predictors	9/383 (2)	5/357 (1)	4/26 (15)	12.8 (3.2 to 51.1)	0.002
Severe dehydration	53/383 (14)	40/354 (11)	13/29 (45)	6.4 (2.9 to 14.2)	<0.001
General danger signs					
≥1 sign	143/380 (38)	122/351 (35)	21/29 (72)	4.9 (2.1 to 11.5)	<0.001
≥2 signs	45/383 (12)	30/354 (8)	15/29 (52)	11.6 (5.1 to 26.2)	<0.001
≥3 signs	11/384 (3)	6/356 (2)	5/28 (18)	12.7 (3.6 to 44.7)	<0.001
Septicaemia	117/378 (31)	101/349 (29)	16/29 (55)	3.0 (1.4 to 6.5)	0.003
Typhoid fever	35/384 (9)	26/356 (7)	9/28 (32)	6.0 (2.5 to 14.6)	<0.001
Malaria					
Non-severe	3/383 (1)	3/354 (1)	0/29 (0)	Undefined	1.00
Severe *					
≥3 predictors	11/372 (3)	6/348 (2)	5/24 (21)	15.0 (4.2 to 53.6)	<0.001
≥4 predictors	4/386 (1)	2/357 (1)	2/29 (7)	13.1 (1.8 to 97.0)	0.030

Values represent numerator and denominator unless stated otherwise.

* No patients exhibited ≥5 severe malaria predictors.