CLINICAL RESEARCH ARTICLE

Predictors of mortality among hospitalized children with severe acute malnutrition: a prospective study from Uganda

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BACKGROUND: We determined the predictors of mortality among children admitted with severe acute malnutrition (SAM).
METHODS: This was a prospective study nested in a randomized trial among 6–59-month-old children admitted with SAM. Socio-demographic and medical history data were collected using questionnaires and clinical examination, anthropometry and laboratory tests were performed. They were monitored daily until discharge or death during hospitalization while receiving care according to national guidelines. Predictors of death were assessed using Cox regression.
RESULTS: Of 400 children, 9.8% (n = 39) died during hospitalization. Predictors of mortality included diarrhoea at admission [hazard ratio [HR] 2.19, 95% confidence interval (CI): 1.06; 4.51], lack of appetite [HR 4.50, 95% CI: 1.76; 11.50], suspected sepsis [HR 2.23, 95% CI: 1.18; 4.24] and skin ulcers [HR 4.23, 95% CI: 1.26; 4.17]. Chest indrawing [HR 5.0, 95% CI: 1.53; 16.3], oxygen saturation below 94% [HR 3.92, 95% CI: 1.42; 10.83] and confirmed HIV infection [HR 3.62, 95% CI: 1.69; 7.77] also predicted higher mortality.
CONCLUSION: Infections were major contributors to mortality. This underscores the need for improved prevention and management of these infections among children with severe malnutrition.

INTRODUCTION

Severe acute malnutrition (SAM) continues to be a major cause of morbidity and mortality among children. About 50 million children under 5 years were wasted, of whom 16 million were severely wasted globally in 2014.[1] In Uganda, 5% of children under 5 years are wasted, and 2% have SAM.[2] Moreover, malnutrition directly underlies 45% of deaths among children under 5 years.[3] The Sustainable Development Goal (SDG) 3 seeks to end preventable deaths of newborns and under-5 children by 2030, while SDG 2 targets to end all forms of malnutrition.[4] Since malnutrition is a big contributor of preventable deaths, SDG 2 cannot be realized without understanding and addressing mortality of children who are severely malnourished.[5]

World Health Organization (WHO) recommends outpatient treatment of uncomplicated SAM[6] and studies show that treatment outcome using this approach yields good results.[7,8] On the other hand, in-patient management of SAM involves very sick children who experience high mortality rates. Most studies in developing countries report in-patient mortality rates above 20%.[9–17] This is startling given that clinical management protocols which should be capable of reducing case-fatality rates to 1–5% have been in existence for 30 years.[11,18] The reasons for persistence of high mortality are not clear, but it is hypothesized that adherence to guidelines alone may not be enough to reduce mortality,[14,19] but other factors like lack of resources, training of health workers coupled with high prevalence of HIV and tuberculosis could have a significant role.[18]

Studies have identified diarrhoea as a major risk factor for mortality among SAM children.[12,15,17] Other risk factors include

blood transfusion and intravenous fluids,[14] low-serum leptin,[20] young age, hypothermia, altered mental status, dehydration, anaemia and co-morbidities,[21] as well as oral thrush.[22] HIV infection leads to more medical complications among children with SAM[15,18] and has been found to increase their mortality.[10,13,17,23,24] However, most of these studies were conducted amidst high HIV prevalence. In this era where HIV prevalence has gone down and there is widespread use of antiretroviral treatment, it is important to better understand the predictors of mortality from SAM again so as to refocus efforts to reduce in-patient mortality. We therefore set out to determine the predictors of in-patient mortality among children admitted with SAM in Uganda.

METHODS

Study setting
The study was conducted at the Mwanamugimu Nutritional Unit (MNU), in Mulago National Referral Hospital, Kampala, Uganda. MNU provides in-patient care for children aged 0–13 years with SAM and after hospital discharge, it provides outpatient therapeutic care (OTC) with visits every 2 weeks until nutritional recovery. MNU has a bed capacity of 80 and admits about 120 patients per month. The majority of patients come from within the central region of the country. The HIV prevalence in MNU was 15% and mortality rate was about 20% at the time of data collection.

Study design
This was a prospective cohort study nested in a randomized controlled trial (RCT) investigating the effect of probiotics on

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Predictors of mortality among hospitalized children ...
N Nabukeera-Barungi et al.

93

diarrhoea among children admitted with SAM (ProbiSAM). It was registered at www.isrctn.com (ISRCTN16454889) and described in a recent publication.[25] In addition to standard treatment, all children received either a combination of two probiotics; *Bifidobacterium animalis* subsp. *lactis*, BB-12® and *Lactobacillus rhamnosus*, LGG® (10 billion colony-forming units, at 1:1) or placebo once daily during hospitalization and for an 8–12-week outpatient treatment period. Probiotics did not have an effect on diarrhoea during the in-patient period.[25] In this sub-study, we observed participants to document clinical outcomes regardless of which arm of the RCT they belonged to.

Study participants
Recruitment took place between March 2014 and July 2015. Using the ProbiSAM eligibility criteria, we included 400 children aged 6–59 months admitted with SAM. SAM was defined as mid-upper arm circumference (MUAC) < 11.5 cm or weight-for-height z-scores < −3 SD or bipedal pitting oedema.[26] Parents and caregivers also had to be willing to return for follow-up and provide written informed consent. We excluded children who were in shock, had severe respiratory distress, admission weight <4.0 kg, congenital heart disease, cerebral palsy, obvious structural abnormalities and those who had been admitted with SAM in the preceding 6 months. This exclusion was based on the ProbiSAM study, a RCT in which this study was nested.

Study procedure
Screening of SAM children took place at the paediatrics emergency unit and MNU. After providing written informed consent, a study doctor who was trained in the study methods interviewed all eligible children using a precoded questionnaire. The questionnaire involved taking demographic data and medical history from the parents or caregivers. This was followed by physical examination, making diagnoses and instituting treatment according to the national guidelines.[26] The study doctor also filled out a visual analogue scale ranging between 0 and 10 according to how sick the caregiver thought the child was at admission. Anthropometric measurements were taken by nutritionists. Length was measured using an infant length board (Infant/Child Shorr-Board®, Maryland) and MUAC using a measuring tape, both to the nearest 1 mm. Body weight was measured to the nearest 100 g using a digital scale (Seca 813 Hamburg, Germany). Single body-weight measurements were taken daily, while triple measurements of heights and MUAC were taken once weekly throughout the in-patient period and their average was considered. Z-scores were calculated using the Child Growth Standards of the WHO 2014.[27]

Laboratory tests
The study doctor or nurse drew 4 ml of blood by venipunctures and placed it into 5-ml heparinized vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ). Complete blood counts were analyzed using a Coulter counter. HIV serological testing was done using rapid tests (Determine HIV-1/2 [Abbott Laboratories]), and positive samples were confirmed with HIV 1/2 Stat-Pak Dipstick Assay kit. All children under 18 months who had a positive serology test had an HIV DNA/PCR test done at the hospital's HIV clinic. Plasma was obtained by centrifuging at 1300–2200 × g for 10 min and then stored at −80 °C at MNU until shipped on dry ice to the Department of Nutrition Exercise and Sports, University of Copenhagen, Denmark. Plasma C-reactive protein was measured by a high-sensitivity kit on an ABX Pentra 400 (Horiba, Parc Euromédecine, Rue du Caducée—BP7290, 34184 Montpellier Cedex 4—France).

Thymus measurement
The study paediatricians did ultrasound scans of the thymus gland to measure its size on day 2 of admission. This was done using an ultrasound scanner (SonoScape A6, Guangdong, China) with a paediatric abdominal probe (curved). The sagittal area was obtained with the transducer rotated at 90° to obtain the sagittal scanning plane. After visualizing the image and freezing it, the circumference of the thymus was tracked and the reading of the measurement provided by the computer was recorded. This process was repeated to get a second reading and the average of these two readings was used in the analysis.

Patient care
Children were treated according to the Uganda national protocol "Integrated Management of Acute Malnutrition"[26] and some aspects of the WHO 2013 guidelines.[6] The in-patient treatment was divided into two phases; phase 1 involved stabilization and transition while phase 2 was rehabilitation. In phase 1, all children were given intravenous antibiotics; gentamycin and ampicillin and those with diarrhoea were given oral rehydration salts *Resomal* depending on the degree of dehydration and only those in shock were rehydrated using intravenous Ringer's lactate together with 10% dextrose. All children received F-75 formula (Nutriset, Malaunay, France) every 2 h at 100–130 ml/kg/day depending on the level of oedema. When medical complications resolved, oedema had subsided to grade 1 or 2 and the child passed the appetite test for ready-to-use therapeutic food (RUTF), they were transitioned to RUTF. During transition, the child started at 50 kcal/kg/day of RUTF and 50 kcal/kg/day of F-75, and this was gradually increased over 2–3 days to 100–135 kcal/kg/day of RUTF alone. Children who could not tolerate RUTF were given F-100 at 100–135 ml/kg/day. Before discharge, the children were introduced to *Kitobero*, a nutritious local dish made of locally available foods. The children were discharged when acute medical conditions had resolved, when they were eating well and clinically well and alert. Upon discharge, the children were given follow-up appointments every second week at the OTC where they continued receiving RUTF until full recovery.

Two study paediatricians reviewed the patients daily for monitoring of clinical progress until discharge. They noted the vital signs, respiratory rate, temperature, chest in-drawing, signs of dehydration and other clinical examination findings. They also made a diagnosis and participated in the treatment. Pneumonia and diarrhoea were diagnosed, classified and treated according to WHO guidelines but suspected sepsis at admission was subjectively diagnosed according to the clinician's judgement. Antibiotics were changed appropriately if there was no improvement in 48 h. All those who had pneumonia clinically and suspected tuberculosis had a chest X-ray taken. Attempts were made to do blood cultures at admission and to repeat if fever persisted or returned. Those who had profuse watery diarrhoea with over 10 motions per day and acidic stools were suspected to have lactose intolerance and were given lactose-free infant formula *Isomil*® (Abbott, Chicago, IL). All children who had a positive HIV serology test were referred for enrolment into HIV care and treatment at the hospital's HIV clinic from where antiretroviral treatment was started as soon as possible for those who were confirmed positive.

Statistical analysis
Data were entered into an Epi-data (version 3.1) database which was designed with appropriate controls and validation checks. Quality assurance was ensured by pre-testing the data-collection tools, training the research assistants and cross-checking all questionnaires for completeness before double data entry. All data analysis was done using STATA version 12 (College Station, TX). Descriptive statistics were used to summarize baseline socio-demographic and clinical characteristics of the children. A chi-square test or t-test was used to study the distribution of mortality among the different predictor variables. To examine if the clinical, laboratory and other variables predicted mortality, Cox proportional hazards regression was used for each predictor separately.
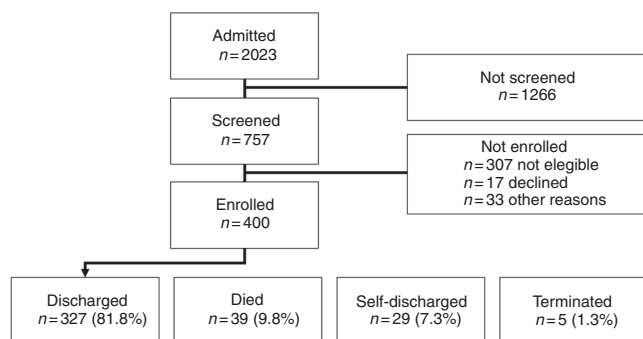
Predictors of mortality among hospitalized children ...
N Nabukeera-Barungi et al.

94

Fig. 1 Flow diagram of study participants

Subsequently, analyses were repeated with adjustment for age and sex. Finally, a multivariate Cox regression model was fitted, including all significant predictors ($P < 0.05$) found in the univariate analyses adjusted for age and sex. A P-value of less than 0.05 was considered as significant and 95% confidence intervals were reported.

Ethical approval
Ethical approval was obtained from the Makerere University School of Medicine Research and Ethics Committee and a consultative approval was given by The National Committee of Health Research Ethics in Denmark. The Uganda National Council of Science and Technology and the Uganda National Drug Authority also approved the study before data collection began. Written informed consent was obtained from all caregivers of the children before recruitment into the study.

RESULTS
During the study period, 757 SAM children were screened and 400 were enrolled (Fig. 1). The mean age was 17 ± 8.5 months and there were more boys (57.5%) than girls (Table 1). Diarrhoea was diagnosed in 61.0%, oedema in 65.8% and 17.0% had pneumonia. At the time of enrolment, none of them had hypothermia, but 13.5% ($n = 53$) had a documented fever with axillary temperature of $\geq 37.5\,°C$. At admission, 1.3% ($n = 5$) were diagnosed with malaria using blood smears. Comparison of weight-for-length z-scores, MUAC, diarrhoea, HIV and sickness severity VAS by gender showed that they were evenly distributed between boys and girls ($P > 0.05$). Of the 324 mothers who were tested for HIV, 33.6% tested HIV positive (Table 2). Among the 400 SAM children, 11.7% ($n = 43$) of 367 who were tested had confirmed HIV. In addition, 19.6% ($n = 72$) were HIV exposed either by having a positive mother, or for children below 18 months by having a positive serology test, but negative HIV DNA-PCR test. Overall, 16.8% (50/298) had severe anaemia (Hb below 7 g/dl). Blood cultures were done among 196 children and only 6.1% ($n = 12$) were positive after 7 days.

Mortality
Of the 400 children enrolled, 9.8% (39/400) died during in-patient therapeutic care (ITC), 81.8% (327/400) improved and were discharged from hospital to OTC, 7.3% (29/400) were lost to follow-up during ITC and 1.3% (5/400) were terminated from the study. Twenty-six percent ($n = 10/39$) of the deaths occurred in the first 48 h of admission, and 46.2% ($n = 18$) died in the first 7 days. The mean duration of hospitalization was 18.1 ± 9.2 days. The median time to death was 8 days (range 1–21). The mean age for those who died was 17 months. The mortality rate was the highest among those who were HIV infected; 25.6% (11/43) compared to 7.9% (17/215) among the HIV-negative children [HR 3.62, 95% CI: 1.69; 7.77] (Table 3). Of the HIV-infected children, 33%

Table 1. Baseline demographic and clinical characteristics of 400 children admitted with severe acute malnutrition

Female sex	170	42.5%
Age (months)	17	±8.5
Clinical features		
Anthropometry		
Weight (kg)	6.95	±1.85
Height/length (cm)	71.2	±6.2
Mid-upper arm circumference (cm)	11.6	±1.5
Weight-for-length (Z)	−2.6	±1.5
Height/length-for-age (Z)	−3.1	±1.4
Clinical history		
Fever	211	52.8%
Cough	262	65.5%
Lack of appetite	240	60.0%
Weight loss	259	64.8%
Severity of sickness VAS[a]	6	±1.9
Sick for >2 weeks	260	65.0%
Physical examination		
Oedema	263	65.8%
Temperature ≥37.5 °C	53	13.5%
Tachypnoea[b]	58	14.7%
Chest indrawing	7	1.8%
Oxygen saturation <94% ($n = 187$)	25	13.5%
Skin ulcers	8	2.0%
Oral thrush	84	21%
Diagnosis		
Diarrhoea	244	61.0%
Pneumonia	68	17.0%
Suspected septicaemia	96	24.0%
HIV status ($n = 367$)		
Positive	43	11.7%
Exposed, negative	72	19.6%
Negative	253	68.7%
Blood tests		
Serum C-reactive protein (mg/L) ($n = 352$)		
<5	54	15.3%
5–10	80	22.7%
>10	218	61.9%
Leucocyte counts (10^9/L) ($n = 296$)	12.6	±6.6
Lymphocytes	6.2	±2.9
Neutrophils	5.0	±5.0
Haemoglobin (g/dl)	8.8	±2.2

Data are number and % or mean ± standard deviation. For some categorical variables, numbers do not add up due to missing data
[a] Evaluated by the child's caregiver on a visual analogue scale from 0 to 10
[b] Respiratory rate ≥ 50 breaths/min for those below 12 months and ≥40 breaths/min for those ≥12 months

(14/43) were receiving antiretroviral therapy (ART) at admission but 19 of the remaining children started on ART by the hospital's HIV clinic during admission. Mortality among the ones who were taking ART at admission was 1/14 (7%) compared to 6/19 (32%) among those who started ART after admission. Of the 11 HIV-infected children who died in the study, 4 died before starting ART, 6 died after starting ART in hospital and only 1 who was on ART at admission died.

Predictors of mortality among hospitalized children ...
N Nabukeera-Barungi et al.

95

Table 2. Social characteristics and treatment of 400 children admitted with severe acute malnutrition		
Breastfed		
Currently	54	13.9%
Never	11	2.8%
Previously	324	83.3%
Treatment before admission		
Modern medicine	341	93.4%
Traditional medicine	182	50.1%
Treatment at admission		
Resomal	239	59.8%
Treatment during admission		
Lactose-free milk	43	10.9%
Social characteristics		
Sibling died	71	18.3%
Mother lives with child	326	81.7%
Mother's education[a]		
≤Primary	211	54.8%
Post primary	153	39.7%
Mother's marital status[b]		
Married/cohabiting	212	54.8%
Never married	63	16.3%
Separated/widow	97	25.1%
Mother's HIV status		
Positive	109	33.6%
Negative	215	66.4%
Primary caregiver		
Stays home	222	57.7%
Works with child	77	20.0%
Works away from child	86	22.3%

Data are number and %
[a,b] Numbers do not add up to 100% due to missing data

The children who died had no post-mortem to confirm the causes of death and yet most of them had more than one diagnosis. However, the attending study paediatricians described the most likely causes of death as follows: 30.7%[12] severe pneumonia, 25.7%[10] septicaemia, 23.1%[9] shock due to diarrhoea and dehydration, 12.8%[5] tuberculosis, 5.1%[2] severe anaemia and 2.6%[1] aspiration pneumonia.

Predictors of mortality
Cox regression automatically eliminated two children from the analysis because they left the hospital before 24 h elapsed. Correlates of mortality from the age-adjusted and sex-adjusted Cox regression analysis included female sex [HR 1.97, 95% CI: 1.04; 3.73], diarrhoea [HR 2.19, 95% CI: 1.06; 4.51], lack of appetite [HR 4.50, 95% CI: 1.76; 11.50], suspected septicaemia [HR 2.23, 95% CI: 1.18; 4.24] and skin ulcers [HR 4.23, 95% CI: 1.26; 4.17] (Table 3). Low oxygen saturation was also a positive predictor of mortality [HR 3.92, 95% CI: 1.42; 10.83]. Similarly, tachypnoea was associated with a two-fold increase in mortality [HR 2.16, 95% CI: 1.07; 4.36]. Chest in-drawing was present in only seven children at admission but it predicted a fivefold increase in mortality [HR 5.0, 95% CI: 1.53; 16.3]. HIV-positive children were 3.6 times more likely to die compared to HIV-negative ones [HR 3.62, 95% CI: 1.69; 7.77]. Similarly, the risk of mortality increased with increasing neutrophil counts [HR 1.07, 95% CI: 1.01; 1.12]. Altogether, 43 children were given lactose-free milk at any time during admission and this did

not predict mortality [HR 0.68, 95% CI: 0.28; 1.66]. We also found that none of the social factors were predictors of mortality.

In the multivariate model, lack of appetite, oxygen saturation below 94%, diarrhoea and HIV status remained as independent predictors of mortality as shown in Table 3. However, the number of observations in the final multivariate model is only 128, due to missing values mainly for oxygen saturation and neutrophil count and HIV status.

DISCUSSION
Our main finding is that the predictors of mortality included diarrhoea, HIV infection, suspected septicaemia and signs of severe pneumonia at admission.

Confirmed HIV-positive children were 3.6 times more likely to die. Similarly, Bartz et al. found higher mortality among the HIV seropositive (33.3%) than seronegative SAM children (5.4%).[20] In a systematic review and meta-analysis by Fergusson et al. involving 17 studies, confirmed HIV-infected children were significantly more likely to die than HIV-uninfected children with SAM (30.4 vs. 8.4%; $P < 0.001$).[23] This is in line with what other studies also found.[24,28,29] Given that only one (7%) of those on ART at admission died compared to 38% of those who were not on ART, this underscores the need for early initiation of ART among children with HIV in order to improve survival.[30]

Over 60% of the children presented with diarrhoea at admission as reported by other studies.[11,17,21] Diarrhoea predicted a two-fold increase in mortality as previously reported.[12,15,17,31] Although having a diagnosis of pneumonia was not a predictor of mortality in our study, signs of pneumonia like tachypnoea, chest indrawing and hypoxia predicted mortality. This is similar to two studies conducted in Bangladesh which found higher mortality among children with hypoxaemia and those with danger signs of severe pneumonia.[32,33] Even though the diagnosis of septicaemia was subjective and depended on the admitting clinician's clinical judgement and not on a set criterion, those with suspected sepsis had a two-fold higher mortality. Related to sepsis, neutrophil counts positively predicted mortality. This is similar to a case-control study in Bangladesh in 2011 which found that the presence of clinical septicaemia had 11.7 times the odds of death.[34]

Our finding of higher mortality among females was surprising since records at the MNU show that boys die more than girls (personal communication). The possibility of this being due to gender differences in health-seeking behaviour is unlikely since no studies have reported this practice in Uganda. In addition, admission data show that the sickness severity was similar between boys and girls. Generally, most published articles have not found gender differences in mortality among SAM children. Since this association disappeared in the multivariate model, it shows that female sex depended on other variables. Children with lack of appetite experienced over four-fold higher risk of mortality probably because anorexia points towards more severe illness. Similarly, a study in Niger found anorexia to be an independent predictor of mortality in a large-scale nutrition program.[35] We also found that skin ulcers, which denote a severe form of dermatosis, predicted a four-fold increase in the risk of death as reported by other studies.[36,37] Although anthropometry, especially MUAC has been found to predict mortality,[22,29] it was not a predictor in our study.

In the multivariate model, female sex, tachypnoea, suspected septicaemia and high neutrophil counts fell out as predictors of mortality, implying that these predictors were mostly explained by the remaining predictors. Only lack of appetite, oxygen saturation below 94%, diarrhoea and HIV status remained independent predictors of mortality. However, there are some limitations of the multivariate model; first of all, it only includes 128 children and 11 deaths and not all 400 children and 39 deaths. Therefore, we

Predictors of mortality among hospitalized children …
N Nabukeera-Barungi et al.

96

Table 3. Predictors of mortality among 400 children with severe acute malnutrition

	Survival status[a]		P	N	Age and sex adjusted	P	Multivariate analysis[c]	P
	Died (n = 39)	Survived (n = 361)			Hazard ratio (95% CI)[b]		Hazard ratio (95% CI)[b]	
Female sex	23 (59)	147 (41)	0.03	398	1.97 (1.04; 3.73)	0.04	1.07 (0.27; 4.16)	0.93
Age (months)	16.7 ± 6.4	17.0 ± 8.7	0.83	398	1.00 (0.96; 1.04)	0.97		
History								
Fever	25 (64)	186 (52)	0.14	397	1.60 (0.83; 3.07)	0.16		
Weight loss	31 (80)	228 (64)	0.06	391	2.08 (0.94; 4.57)	0.07		
Severity of sickness VAS[d]	6.4 ± 2.0	6.0 ± 1.9	0.23	397	1.08 (0.92; 1.27)	0.37		
Lack of appetite	34 (87)	206 (57)	<0.001	397	4.50 (1.76; 11.50)	0.002	3.28 (0.59; 18.20)	0.17
Breastfed				389				
Previously	24 (71)	300 (85)	0.11		–	–		
Never	2 (6)	9 (3)			2.00 (0.47; 8.51)	0.35		
Currently	8 (24)	46 (13)			1.93 (0.84; 4.45)	0.12		
Physical examination								
Mid-upper arm circumference (cm)	11.1 ± 1.4	11.6 ± 1.5	0.08	388	0.82 (0.64; 1.06)	0.12		
Oedema	24 (62)	240 (67)	0.54	397	0.79 (0.40; 1.52)	0.48		
Oral thrush	11 (28)	73 (20)	0.25	397	1.31 (0.65; 2.63)	0.45		
Tachypnoea[e]	11 (28.2)	47 (13.2)	0.01	383	2.16 (1.07; 4.36)	0.03	0.99 (0.93; 1.07)	0.88
Chest indrawing	3 (8)	4 (1)	0.003	398	5.00 (1.53; 16.3)	0.01		
Oxygen saturation <94%	6 (37.5)	19 (11.1)	0.003	185	3.92 (1.42; 10.83)	0.01	11.11 (1.60; 61.68)	0.01
Skin ulcers	3 (8)	5 (1)	0.01	398	4.23 (1.26; 4.17)	0.02		
Diagnosis								
Diarrhoea	29 (74)	215 (60)	0.08	397	2.19 (1.06; 4.51)	0.03	3.51 (0.49; 24.93)	0.21
Pneumonia	11 (28)	57 (16)	0.05	398	1.84 (0.91; 3.72)	0.09		
Suspected septicaemia	16 (41)	80 (22)	0.01	396	2.23 (1.18; 4.24)	0.01	0.32 (0.04; 2.24)	0.20
HIV status				367				
Positive	11 (31)	32 (10)			3.62 (1.69; 7.77)	0.001	2.25 (0.45; 11.27)	0.42
Exposed, negative	7 (20)	65 (20)			1.42 (0.59; 3.43)	0.44	2.86 (0.53; 15.40)	0.24
Negative	17 (49)	235 (71)	0.001		–	–		
Plasma C-reactive protein (mg/L)				352				
<5	2 (7)	78 (24)	0.09		–	–		
5–10	5 (17)	49 (15)			3.94 (0.76; 20.41)	0.10		
>10	23 (77)	195 (61)			4.00 (0.94; 17.02)	0.06		
Leukocyte count (10^3/ml)				296				
Neutrophils	7.7 ± 8.2	4.8 ± 4.5	0.01		1.07 (1.01; 1.12)	0.01	1.02 (0.87; 1.20)	0.82
Lymphocytes	6.4 ± 4.6	6.2 ± 2.8	0.74		1.03 (0.90; 1.18)	0.71		
Haemoglobin (g/dl)	8.73 ± 3.6	8.79 ± 2.0	0.90	296	0.99 (0.83; 1.17)	0.88		
Thymus size (cm^2)	1.13 ± 0.8	1.06 ± 0.4	0.45	388	1.31 (0.71; 2.41)	0.38		

[a] Data are number (%), mean (±standard deviation) and N = number of observations in Cox regression
[b] 95% confidence interval
[c] Number of observations involved were 128, of which 11 were deaths
[d] Visual analogue scale
[e] Respiratory rate ≥50/min < 12 months, ≥40/min ≥ 12 months

cannot rule out some bias in the results. Also, due to missing data, it was not possible to include chest indrawing and skin ulcers in the multivariate analyses.

Our mortality rate was lower than two recent studies in the same unit which found a mortality rate of 14 and 12.2% 2 and 3 years before our study, respectively.[20,22] This could be a result of being part of a randomized trial in which the children received very close monitoring both day and night, with extensive involvement of the study paediatricians and nutritionists in their management. In addition, we eliminated those who were in shock, unconscious and with severe respiratory distress at admission, all of which have been found to increase the risk of death.[16,21,32] We also excluded children who were below 6 months, those below 4.0 kg of body weight and those with cerebral palsy and congenital abnormalities who could potentially increase the mortality. Furthermore, we had a lower HIV prevalence than previous studies in the same unit; 11 vs. 24–30%.[14,20] On the other hand, despite adherence to the WHO guidelines and use of better-qualified health workers, our mortality did not reach the WHO acceptable hospital mortality rate of <5%[38] but attained the Sphere Standards in which mortality among children receiving in-patient treatment of SAM should be <10%.[39] It has been

Predictors of mortality among hospitalized children ...
N Nabukeera-Barungi et al.

97

suggested that in sub-Saharan Africa, severe comorbidity, especially in the context of overloaded, demotivated, eroded and under-resourced child health services makes it impossible to attain the WHO standard.[40] Our study was carried out in a resource-constrained setting with very sick children, understaffing and high patient load.

The strengths of this study included the prospective design which allowed us to collect data regarding predictors at admission without being biased by knowledge of the outcome, and the low loss-to-follow-up. One limitation of our study is that our eligibility criteria excluded some of the very ill children, thus decreasing the validity of our findings. Despite this, the study provides important lessons about predictors of mortality and the possibility of reduction in mortality among SAM children. In addition, post-mortem analyses were not performed; therefore, there is no certainty about the causes of death.

CONCLUSIONS
HIV infection, diarrhoea, suspected sepsis, severe dermatosis, anorexia and severe pneumonia were predictors of mortality among hospitalized children with SAM. Prevention of HIV among children, as well as early diagnosis and initiation of ART should be emphasized. There is a need to improve the diagnosis and treatment of infections and optimize nutritional rehabilitation in children with SAM.

AUTHOR CONTRIBUTIONS
B.G. and H.F. were involved in acquisition of funds and conception of the study. N.N. B., B.G. and H.F. designed the study. H.N., B.L., N.N.B. and B.G. were responsible for designing study tools, data collection, entry and cleaning. N.N.B. did the data analysis, and all authors contributed to data interpretation. N.N.B. drafted the manuscript, and all authors critically revised and approved it.

ADDITIONAL INFORMATION
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98

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