Risk factors for death in children during inpatient treatment of severe acute malnutrition: a prospective cohort study[1,2]

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ABSTRACT

Background: Children who receive in-hospital treatment of severe acute malnutrition often have high mortality rates, and the reasons are not well understood.

Objective: We assessed risk factors for death in children who were treated for malnutrition in a hospital.

Design: In a prospective observational study of 120 children who were receiving in-hospital treatment of severe acute malnutrition in Uganda with therapeutic formulas F-75 and F-100, we collected data on symptoms, clinical findings, plasma markers of refeeding syndrome (electrolytes and phosphate), and acute phase reactants, and recorded the nutritional therapy given in hospital.

Results: Seventeen children (14%) died. Clinical risk factors for death were the presence of oral thrush (HR: 5.0; 95% CI: 1.6, 15.2), a caretaker-reported severity of illness on a visual analog scale (HR: 1.7; 95% CI: 1.1, 2.6), impaired consciousness (HR: 16.7; 95% CI: 3.1, 90.4), and a capillary refill time >2 s (HR: 3.9; 95% CI: 1.4, 11.3). HIV infection was not associated with mortality (HR: 3.0; 95% CI: 0.7, 12.4), which was most likely due to low power. Biochemical risk factors were a plasma C-reactive protein concentration >15 mg/L on admission and low plasma phosphate that was measured on day 2 (HR: 8.7; 95% CI: 2.5, 30.1), particularly in edematous children. The replacement of F-75 with unfortified rice porridge to ameliorate diarrhea was associated with a higher risk of death, particularly if given during the first 2 d (HR: 5.0; 95% CI: 1.9, 13.3), which was an association that remained after adjustment for potential confounders (HR: 69.5; 95% CI: 7.0, 694.6).

Conclusions: Refeeding syndrome may occur in children who are treated for malnutrition, even with moderately low plasma phosphate, and, in particular, in children with edematous malnutrition. The replacement of F-75 with unfortified rice porridge is associated with increased risk of death, which is possibly mediated by lowering plasma phosphate. The identified clinical risk factors may potentially improve the triage of children with malnutrition. This trial was registered at www.isrctn.com as ISRCTN55092738. *Am J Clin Nutr* 2017;105:494–502.

Keywords: edema, electrolytes, HIV, hypophosphatemia, infections, kwashiorkor, malnutrition, marasmus, mortality, refeeding syndrome

INTRODUCTION

Severe acute malnutrition (SAM)[7] in children is an important health problem that is associated with high mortality (1). Community-based management of SAM with ready-to-use therapeutic foods has improved the treatment of children with uncomplicated SAM, whereas the treatment of children with complications that require inpatient treatment with therapeutic formulas (F-75 and F-100) has not changed much during the past 10–20 y (2, 3).

According to the Sphere Standards, mortality in children who receive inpatient treatment of SAM should be <10% (4), whereas the WHO protocol aims for <5% (5). A method has been developed to predict the risk of mortality in SAM that is based on weight, height, age, and the presence of edema (6). However, many treatment centers have reported mortality rates that are higher than those that have been predicted with the use of this method, which are often ~20–25% (7–10). Suggested reasons for this mortality have been understaffing, substandard management (10, 11), late presentation, a high prevalence of HIV, and complicated and edematous malnutrition (6), but only a few studies have attempted to investigate these explanations.

During refeeding, the transition to an anabolic state causes a high demand of electrolytes as well as a shift of electrolytes from the extracellular space to the intracellular space. These effects can lead to refeeding syndrome, which is characterized by a low concentration of plasma phosphate, thereby potentially leading to respiratory and circulatory failure and even death (12). The

[1] Supported by the University of Copenhagen (Ph.D. grant; to MJHR) and the Augustinus Fonden, Lundbeck Fonden, Brøderende Hartmanns Fond, Arvid Nilssons Fond, Axel Muusfeldts Fond, Aase and Einar Danielsens Fond, and Torkild Steenbecks Legat.

[2] Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://nutrition.org.

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[7] Abbreviations used: CRP, C-reactive protein; CRT, capillary refill time; MNU, Mwanamugimu Nutrition Unit; MUAC, midupper arm circumference; SAM, severe acute malnutrition; VAS, visual analog scale.

Received July 20, 2016. Accepted for publication November 22, 2016.
First published online December 28, 2016; doi: 10.3945/ajcn.116.140822.

current treatment protocol aims to prevent refeeding syndrome by gradually increasing energy intake and by including phosphorous in premixed F-75 and F-100. However, to our knowledge, it has not been investigated whether hypophosphatemia could still be associated with mortality in children who are treated with this treatment protocol.

Diarrhea is common in children with SAM (8). In some cases, diarrhea gets worse when children are fed a milk-based therapeutic formula (13), which is possibly caused by a high osmotic load on an atrophic intestine or by lactose intolerance (14). The WHO protocol is not clear about how to manage this condition, and local practices vary. In our unit, the practice was to replace F-75 or F-100 with rice porridge for a number of days in children with suspected intolerance to the milk-based formula.

Treatment centers with high mortality often have high rates of edematous malnutrition (7, 8, 10). The pathophysiology of edematous malnutrition is poorly understood, and treatment protocols have recommended largely similar inpatient treatments of children with and without edema (3). An investigation of whether risk factors for death differ in edematous malnutrition and nonedematous malnutrition could help us to understand if the 2 conditions should be treated differently.

The objectives of this study were to compare mortality in children who were hospitalized with SAM with predicted mortality that was based on weight, length, age, and edema and to investigate clinical and laboratory risk factors for in-hospital death. Potentially, this research could improve the triage of children with SAM on admission and suggest areas in which current practice could have room for improvement.

METHODS

Study design

This study was based on data from a prospective observational study in children who were undergoing in-hospital treatment of SAM between October 2012 and February 2013. This trial was registered at www.isrctn.com as ISRCTN55092738.

Study site and standard treatment

The Mwanamugimu Nutrition Unit (MNU) at Mulago Hospital is the main treatment center for children with complicated SAM in Uganda. At the time of the study, children were not routinely screened with appetite tests, and thus, it was not confirmed that all of the children fulfilled the WHO criteria for complicated SAM. However, because of the hospital setting, the general impression was that most children were sick with some kind of complication. Children who were admitted to the unit received standard inpatient treatment according to the Ugandan National Protocol for the Integrated Management of Acute Malnutrition (15), which is based on recommendations of the WHO (5, 16, 17). Children were given therapeutic formulas F-75 and F-100 (Nutriset) and empiric parenteral antibiotics, usually ampicillin and gentamycin. When children were unable to take oral feeds, a nasogastric tube was used. Children with dehydration were rehydrated with an oral rehydration solution for malnourished children (ReSoMal; Nutriset). Intravenous fluids were reserved for children who were in shock or had severe dehydration with persistent vomiting. When children were clinically well and had an appetite and no edema, they were discharged for outpatient treatment with the use of ready-to-use therapeutic food. All biological mothers were offered routine counseling and testing for HIV antibodies according to WHO guidelines (18). If the mother was infected or absent, the child was tested. At the time of the study, it was a common local modification of guidelines to temporarily replace therapeutic diets with rice porridge when children had diarrhea and were suspected of being intolerant to milk-based feeds.

Study size and inclusion and exclusion criteria

A study size of 120 children was anticipated on the basis of power calculations for the main outcome of the study (plasma phosphate) (19). To detect a difference of $\geq$0.5 SDs in plasma phosphate between 2 groups, such as between edematous and nonedematous children, at a 5% significance level and with 80% power, 120 children had to be enrolled in the study. Inclusion criteria were as follows: children were aged 6–59 mo; were admitted to the hospital on weekdays with SAM, which was defined as a weight-for-height z score <-3 with the use of the WHO Growth Standard (16), a midupper arm circumference (MUAC) $<$11.5 cm, or bilateral pitting edema; were living within a distance from the hospital that enabled follow-up visits; and had a caretaker who provided informed consent. Exclusion criteria were as follows: obvious disability, shock, or severe respiratory distress that required resuscitation at admission; previous admissions for SAM in the past 6 mo; a hemoglobin concentration $<$4 g/dL, or weight $<$4.5 kg. For comparison, we extracted data from the unit's logbook on the age, sex, and outcome of admitted children who were not included in the study.

Data collection

Caretakers were interviewed about the children's current symptoms and histories on admission and were asked to evaluate how severe they perceived their children's illnesses on a visual analog scale (VAS) that was scored from 0 to 10 points. A physical examination was performed to assess consciousness, axillary temperature, pulse, respiratory rate, capillary refill time (CRT), liver enlargement, oral thrush, and edema. It was noted whether the child was able to consume all of the first-served therapeutic feed.

Body weight was measured daily with the use of a digital scale to the nearest 100 g. Length was measured to the nearest 1 mm with the use of an infant-length board, and MUAC was measured to the nearest 1 mm with the use of a color-coded measurement tape. Anthropometric z scores were computed according to WHO Growth Standards (20) with the use of the lowest weight recorded during admission (i.e., weight free from edema).

Blood sampling

Blood samples for this study were collected at 2 time points: on admission (if possible before giving the first feed), and again $\sim$48 h later. This time point was chosen because a nadir of plasma phosphate has previously been described $\sim$48 h after the start of refeeding (21). Blood was collected in heparinized evacuated tubes. Plasma was frozen at -20°C for $\leq$2 mo, and concentrations of sodium, potassium, and inorganic phosphate were measured at Ebenezer Ltd. Clinical Laboratory in Kampala (International Organization for Standardization 15189; laboratory no. M0221) with the use of a molybdate ultraviolet method (Cobas Integra 400 Plus; Roche Diagnostics). Lower cutoffs for

normal concentrations of electrolytes were defined as <135 mmol/L for plasma sodium and <3.5 mmol/L for plasma potassium. Hypophosphatemia was defined as having a plasma phosphate concentration <1.6 mmol/L for infants ≤12 mo old and <1.1 mmol/L for older children.

On admission, blood hemoglobin was measured with the use of HemoCue system (Hb 201+; HemoCue). An additional plasma sample was obtained in an evacuated tube containing citrate, frozen at −80°C, and shipped to Denmark on dry ice where C-reactive protein (CRP) and α_1-acid-glycoprotein were measured by using a spectrophotometric method (ABX Pentra 400; Horiba).

Monitoring

Study staff monitored children daily (on weekdays) and recorded weight, the type of feed, whether ReSoMal was given, and whether a nasogastric tube was used. Caretakers were asked about the frequency and consistence of stools during the past 24 h. Diarrhea was defined as ≥3 loose or watery stools/d. If a child died, the date and time was noted. The time to death was calculated as the number of days from admission until death occurred.

Ethical issues

The Makerere University School of Medicine's Research Ethics Committee approved the study, as did the Uganda National Council of Science and Technology. The Danish National Board of Research Ethics gave consultative approval. Caretakers gave written informed consent after oral and written information was provided in English and Luganda. Children included in the study received the same treatment as was received by children who were not included.

Calculating expected mortality

To compare the mortality rate with international standards for the treatment of malnutrition, we estimated the predicted mortality with the use of the method of Prudhon et al. (6) on the basis of weight, length, and the presence of edema.

Statistics

Data were entered in EpiData software (version 3.1; The EpiData Association) and analyzed with the use of Stata software version 12 (StataCorp LP). To compare differences in characteristics between children who died and those who survived, 2-sample *t* tests and a Mann-Whitney rank-sum test (in the case of nonnormally distributed variables) were used. Chi-square or Fisher's exact tests were used to assess differences in proportions. A chi-square goodness-of-fit test was used to evaluate the agreement with the mortality that was predicted according to the Prudhon model.

Risk factors for in-hospital death were analyzed with the use of Cox regression models because children were right censured when they were discharged or left the study for other reasons. Analyses were carried out after adjustment for age (3 age categories of <12, 12–23, and ≥24 mo) and sex. To explore to what extent findings could be explained by potential confounders, further adjustments were made in 4 models for age, sex, edema, MUAC, diarrhea on admission, and caretaker-reported severity of illness on the VAS. Model 1 was also adjusted for HIV status; model 2 was also adjusted for elevated CRP; model 3 was also adjusted for the use of rice porridge in the first 2 d of admission; and model 4 was also adjusted for hypophosphatemia on day 2. For one key variable (the use of rice porridge), further adjustments were made for a wider range of potential confounders including age, sex, edema, MUAC, diarrhea on admission, caretaker-reported severity of illness on the VAS, observed diarrhea in hospital, watery diarrhea, and the use of treatment with ReSoMal. For each factor, we also evaluated an effect modification by edema. For electrolytes on day 2, we investigated the effect modification according to whether rice porridge was given during the first 2 d. Differences were shown graphically with the use of Kaplan-Meyer plots.

RESULTS

Of 395 children who were admitted during the study period, 120 children were included in the study, and 119 children were observed in the unit for ≥1 d (**Figure 1**). Of these children, 45 subjects (38%) were girls (**Table 1**), 76 subjects (64%) had edema, and 104 subjects had their HIV status determined, of whom 20 individuals (19%) were HIV infected (**Table 2**). The primary outcome of the study (i.e., the change in plasma phosphate) and other findings have been reported elsewhere (19, 22–26).

Seventeen children (14%) died during their hospital stay, whereas 16 children (13%) left the hospital before discharge (Figure 1). Of other children in the same age range who were admitted during the study period but were not included in the study, the mortality rate was 21% and was not different from that of included children ($P = 0.13$). The median time before death occurred was 10 d, and only 2 deaths occurred within 48 h of admission. According to the Prudhon model, 9 children of the 119 children who were included in the study were expected to die, thereby corresponding to a mortality rate of 8%, which was significantly less than the rate observed in the study ($P = 0.009$).

Risk factors for inpatient mortality

Age ≥24 mo was associated with higher mortality (Table 2). The HR was 5.7 (95% CI: 1.8, 18.2), which indicated 5.7-times higher risk of death in children aged ≥24 mo compared with children aged 12–23 mo. A low MUAC was the only anthropometric indicator that was associated with mortality with an HR of 0.6 (95% CI: 0.4, 1.0), which indicated that there was a 40% lower mortality risk per centimeter increase in MUAC.

HIV status was determined in 104 children. Of children who died, 5 of 12 children (42%) were HIV infected compared with 15 of 92 children (16%) who survived. Thus, mortality was 8% in HIV-uninfected children, 25% in HIV-infected children, and 33% in the 15 children who were not tested for HIV. However, after adjustment for age and sex, HIV infection was not associated with death (HR: 3.0; 95% CI: 0.7, 12.4). Both breastfeeding and edema were not associated with mortality.

Reported symptoms

Diarrhea was reported by caretakers on admission in 11 of 17 children (73%) who died and in 45 of 102 children (46%) who survived ($P = 0.052$). After adjustment for age and sex, reported diarrhea was marginally associated with mortality (HR: 3.1;

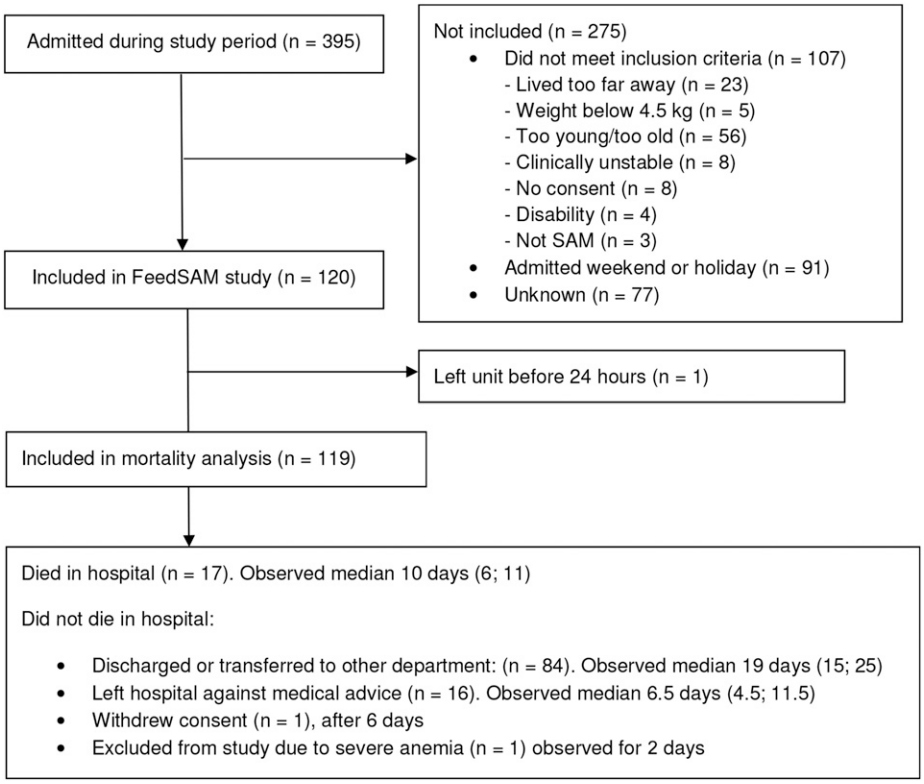

FIGURE 1 Flow diagram showing inclusion and outcome of children in study. Numbers of days are listed as medians (interquartile ranges). FeedSAM, Re-feeding of Children with Severe Acute Malnutrition; SAM, severe acute malnutrition.

95% CI: 0.97, 9.9). The effect size was similar after adjustment for age, sex, MUAC, edema, caretaker-reported severity of illness on the VAS, and HIV status (**Supplemental Table 1**), but the association disappeared when further adjusted for elevated CRP, the use of rice porridge, and hypophosphatemia on day 2. Vomiting, cough, and fever were not risk factors. Caretakers of children who died had evaluated their children as being sicker on the VAS from 0 to 10 points with a 70% increase in mortality risk for each point increase in the VAS.

TABLE 1
Background characteristics of 120 children admitted with severe acute malnutrition

	n[1]	Value
Age, mo	120	15.9 (12.6, 21.9)[2]
Sex, F, % (n)	120	38 (46)
Lived with mother before admission, % (n)	116	75 (87)
Mother and father living together, % (n)	116	53 (62)
Mothers education,[3] % (n)	97	
No school		6 (6)
Primary school		43 (42)
Secondary school		43 (42)
More than secondary school		7 (7)
Household characteristic, % (n)		
Urban or periurban location	103	85 (88)
Occupation, head of household	93	
Unemployed		14 (13)
Agriculture		9 (8)
Domestic service, unskilled manual		25 (23)
Skilled manual, sales and service		39 (36)
Professional, technical, management		14 (13)
Drinking water available on premises	107	20 (21)
Improved, not shared, toilet facility	94	18 (17)
Household owns agricultural land	109	36 (39)
Electricity in household	112	47 (53)

[1] Number of children for whom data were available.
[2] Median (25th, 75th percentiles).
[3] Education attended but not necessarily completed.

Physical examination

Children with oral thrush had higher mortality with an HR of 5.0 (95% CI: 1.6, 15.2). Oral thrush was more frequent in children with HIV; however, when adjusted for HIV infection, oral thrush remained associated with mortality (Supplemental Table 1). More children who died had CRTs >2 s (38% compared with 15%; HR: 3.9; 95% CI: 1.4, 11.3) and impaired consciousness (HR: 16.7; 95% CI: 3.1, 90.4). The ability to complete the first feed, liver enlargement, a respiratory rate <40 or >60 breaths/min, and a high or low axillary temperature were not risk factors for death (data not shown in tables).

Blood biochemistry

On admission, the only biochemical variable that differed between children who died and those who survived was the plasma CRP concentration with medians (25th, 75th percentiles) of 26.8 mg/L (19.0, 71.4 mg/L) in children who died and 15.9 mg/L (6.1, 32.7 mg/L) in survivors (data not shown in tables). A plasma CRP concentration >15 mg/L was associated with higher mortality (HR: 12.6; 95% CI: 1.6, 100.1).

On admission, plasma phosphate concentrations did not differ between children who died and those who survived. However, on day 2, plasma phosphate concentrations were lower in children

TABLE 2
Risk factors for death in 119 children admitted with severe acute malnutrition

	n[1]	Died (n = 17)	Survived (n = 102)	P	HR (95% CI)[2]	P
Sex, F, % (n)	119	29 (5)	39 (40)	0.66	0.7 (0.2, 2.0)	0.46
Age, mo, % (n)	119			0.009		
6–11		29 (5)	20 (20)		3.3 (0.9, 11.5)	0.07
12–23		29 (5)	66 (67)		Reference	
24–59		41 (7)	15 (16)		5.7 (1.8, 18.2)	0.003
Anthropometric data						
Weight-for-length z score[3]	119	−3.8 ± 1.5[4]	−3.3 ± 1.3	0.14	0.7 (0.5, 1.1)	0.16
Midupper arm circumference, cm	118	10.9 ± 1.3	11.6 ± 1.3	0.03	0.6 (0.4, 1.0)	0.04
Clinical data, % (n)						
HIV infected	104	42 (5)	16 (15)	0.051	3.0 (0.7, 12.4)	0.14
Currently breastfeeding	111	6 (1)	19 (18)	0.30	0.3 (0.0, 2.3)	0.24
Edema present	119	65 (11)	64 (65)	0.94	1.0 (0.4, 2.9)	0.98
Reported symptoms						
Diarrhea	112	73 (11)	46 (45)	0.052	3.1 (0.97, 9.9)	0.06
Fever	112	20 (3)	43 (42)	0.09	0.3 (0.1, 1.2)	0.09
Severity of illness[5]	110	8.2 ± 1.5	6.8 ± 1.9	0.009	1.7 (1.1, 2.6)	0.01
Oral thrush present	97	47 (7)	21 (17)	0.049	5.0 (1.6, 15.2)	0.005
Vital signs, % (n)						
Capillary refill time >2 s	112	38 (6)	15 (14)	0.04	3.9 (1.4, 11.3)	0.01
Impaired consciousness	117	13 (2)	2 (2)	0.09	16.7 (3.1, 90.4)	0.001
Biochemical data[6]						
Admission						
Hemoglobin, g/dL	111	8.9 ± 2.3	9.1 ± 2.3	0.85	0.9 (0.8, 1.2)	0.55
C-reactive protein concentration >15 mg/L	82	92 (12)	52 (36)	0.01	12.6 (1.6, 100.1)	0.02
α_1-Acid glycoprotein, g/L	82	2.39 ± 0.64	2.40 ± 0.75	0.96	1.1 (0.5, 2.3)	0.85
Sodium concentration <135 mmol/L)	114	20 (3)	22 (22)	1.00	0.9 (0.2, 3.6)	0.90
Potassium concentration <3.5 mmol/L)	114	20 (3)	10 (10)	0.38	2.9 (0.8, 10.5)	0.10
Hypophosphatemia[7]	114	81 (13)	59 (58)	0.10	2.8 (0.8, 10.7)	0.12
Electrolytes, day 2						
Sodium concentration <135 mmol/L	94	25 (3)	24 (20)	1.00	1.0 (0.3, 3.7)	0.96
Potassium concentration <3.5 mmol/L	94	8 (1)	1 (1)	0.24	2.1 (0.3, 18.5)	0.49
Hypophosphatemia[7]	94	58 (7)	13 (11)	0.001	8.7 (2.5, 30.1)	0.001
Observation and treatment in stabilization phase						
Diarrhea	114	65 (11)	49 (48)	0.24	1.5 (0.6, 4.1)	0.41
Nasogastric tube used	115	41 (7)	22 (22)	0.10	1.8 (0.7, 4.9)	0.27
Oral rehydration solution[8] given	114	35 (6)	14 (14)	0.08	2.7 (1.0, 7.4)	0.050
Oral rehydration solution[8] given, first 2 d	114	18 (3)	12 (12)	0.70	1.5 (0.4,5.2)	0.62
Rice porridge given	114	65 (11)	32 (31)	0.01	3.4 (1.3, 9.4)	0.02
Rice porridge given, first 2 d	114	59 (10)	20 (19)	0.002	5.0 (1.9, 13.3)	0.001

[1] Number of children for whom data were available.
[2] Analyzed with the use of Cox regression with adjustment for age and sex.
[3] Calculated with the use of the lowest weight recorded during admission to obtain weight that was free from edema.
[4] Mean ± SD (all such values).
[5] Evaluated by the child's caretaker on a visual analog scale from 0 to 10 points.
[6] All values, except for hemoglobin, were measured in plasma.
[7] Hypophosphatemia was defined as having a plasma phosphate concentration <1.6 mmol/L for infants ≤12 mo of age and <1.1 mmol/L for older children.
[8] ReSoMal (Nutriset).

who died (mean ± SD: 1.13 ± 0.28 mmol/L in children who died compared with 1.53 ± 0.37 mmol/L in survivors; $P = 0.001$) (data not shown in tables), and hypophosphatemia on day 2 was associated with 8.7-fold higher risk of dying (95% CI: 2.5, 30.1) (**Figure 2**). Similarly, more children who died experienced a decrease in plasma phosphate from admission to day 2 than did those who survived (36% compared with 5%, respectively; $P = 0.007$) (data not shown in tables). Hypophosphatemia remained associated with mortality in most of the adjusted models (Supplemental Table 1).

Treatment and observations during stabilization

Children who died had their F-75 substituted with rice porridge more frequently (65% compared with 32% in children who survived) at some point during the stabilization phase, and this practice was associated with mortality (HR: 3.4; 95% CI: 1.3, 9.4).

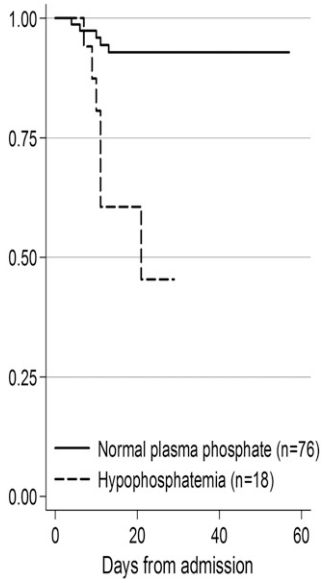

FIGURE 2 Survival plots of children with hypophosphatemia and with normal plasma phosphate on day 2 (HR: 8.7; 95% CI: 2.5, 30.1).

In particular, feeding rice porridge during the first 2 d had an HR of 5.0 (95% CI: 1.9, 13.3) (**Figure 3**), which was an association that remained after adjustment for potential confounders (Supplemental Table 1) and also after more extensive adjustments for observed diarrhea, watery diarrhea, oral rehydration therapy, HIV status, and severity of illness according to the caretaker (HR: 69.5; 95% CI: 7.0, 694.6) (data not shown in tables). However, when further adjusted for hypophosphatemia on day 2, this association became nonsignificant (HR: 9.4; 95% CI: 1.0, 89.0) (Supplemental Table 1). An interaction was seen with rice-porridge use during the first 2 d, and hypophosphatemia on day 2 ($P < 0.001$), which indicated that hypophosphatemia was only associated with death in children who were given rice porridge during the preceding days (HR: 22.7; 95% CI: 2.1, 246.7) but not in children who were only fed F-75.

Observed diarrhea during stabilization was not associated with mortality and neither was watery diarrhea, observed fever, or the use of a nasogastric tube (data not shown in tables). ReSoMal that was given in the stabilization phase was a marginally significant risk factor for death (HR: 2.7; 95% CI: 1.0, 7.4), but the association disappeared after adjustment for rice-porridge use during the same period (HR: 2.2; 95% CI: 0.7, 7.2) (Supplemental Table 1).

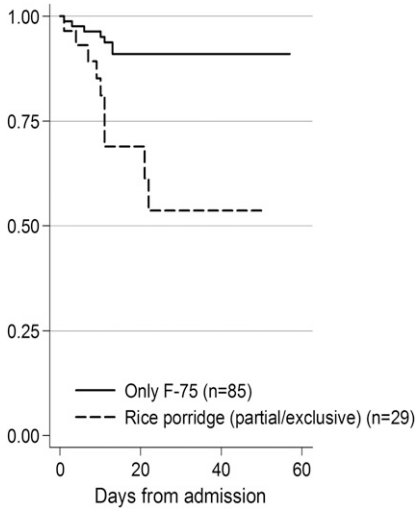

FIGURE 3 Survival plots according to whether rice porridge was given during the first 2 d (HR: 5.0; 95% CI: 1.9, 13.3).

Mortality risk factors in edematous and nonedematous children

An interaction was shown between edema and plasma phosphate on day 2. Hypophosphatemia was only a risk factor in edematous children (P-interaction = 0.01) (**Supplemental Table 2**, **Figure 4**). As previously reported, edematous children had lower plasma phosphate (19). Whereas >50% of edematous children with hypophosphatemia on day 2 died, all but 1 of 48 edematous children with normal plasma phosphate survived. Nonedematous children had similar mortality with and without hypophosphatemia on day 2.

A plasma CRP concentration >15 mg/L was also a greater risk factor in edematous children than in nonedematous children because all edematous children who died had plasma CRP concentrations >15 mg/L (P-interaction < 0.047).

DISCUSSION

The mortality rate of 14% was above the acceptable rates according to the WHO and the Sphere Standards, which aim for mortality rates of <5% and <10%, respectively. The mortality rate also exceeded the 8% expected mortality that was predicted by weight, length, and the rate of edema (6). However, these standards have been criticized for not being applicable in settings with high rates of HIV and complicated malnutrition (7, 27). The mortality rate of 8% in HIV-negative children was similar to the predicted mortality.

Clinical observations

We identified low MUAC, caretaker-reported disease severity, oral thrush, a CRT >2 s, and impaired consciousness as risk factors and reported diarrhea as a marginally significant risk factor. With limited resources, these factors can be assessed on admission and used to prioritize high-risk children. Low MUAC (7, 28, 29), diarrhea (8, 9), and impaired consciousness (9, 28, 30) have previously been associated with mortality in children with SAM. Two previous studies reported a CRT >2 s as a risk factor (9, 28). Although current WHO guidelines consider a CRT >3 s a danger sign (31), these results suggest that a CRT from 2 to 3 s may also be a warning sign.

To our knowledge, a VAS has not been used before to report the severity of illness in children with SAM. The scale had simple pictograms of faces that were similar to those used on a scale to assess pain. The association with mortality suggests that a VAS could be useful to evaluate disease severity and could be considered in clinical work and research. The association also emphasizes that parental concern should be taken seriously in the triage of sick children.

Risk factors related to treatment

Although plasma CRP and plasma phosphate will usually not be measured in low-income settings, these risk factors may suggest areas in which treatment could be improved.

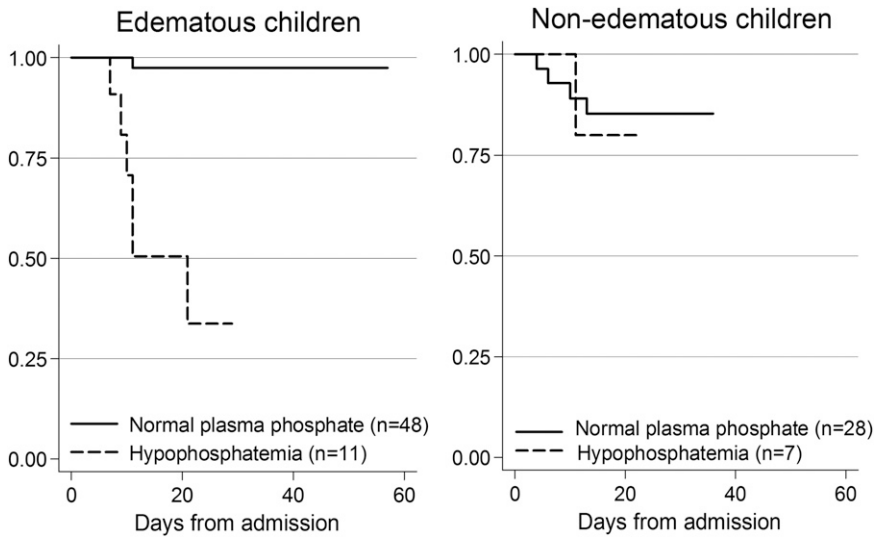

FIGURE 4 Survival plots of edematous and nonedematous children by hypophosphatemia on day 2. In edematous children the HR for hypophosphatemia was 41.3 (95% CI: 4.7, 362.0); in nonedematous children, the HR for hypophosphatemia was 0.9 (95% CI: 0.6, 12.9) (*P*-interaction = 0.047).

High plasma CRP was a risk factor for death as previously reported (32), thereby reflecting that infections often play a role in the deaths of children with SAM perhaps because of an immunodeficiency of malnutrition (33). In line with this outcome, bacteremia has been shown to be a risk factor (9, 28, 30, 34, 35), which emphasizes that improved management of infections in children with SAM is urgently needed.

Although HIV infection was not significantly associated with mortality, mortality rates of 25% in HIV infected children and 8% in uninfected children resembled rates that were reported in a meta-analysis (27). However, we may have had too little power to detect any significant difference in mortality.

In contrast with HIV status, oral thrush was associated with higher mortality as reported previously (30). This association was more common in HIV-infected children and was a possible marker of immunosuppression. However, oral thrush remained associated with mortality when controlling for HIV status, which suggested that the degree of immunosuppression may be more important than HIV infection per se or that other factors than HIV could cause immunosuppression.

Diarrhea, rice porridge, and refeeding syndrome

Low plasma phosphate on day 2 was a risk factor for death, as was similarly reported in studies from Malawi (36) and Kenya (21), whereas a study from Bangladesh did not associate hypophosphatemia with mortality (37). Previously, a phosphate nadir was identified during the first 2 d of refeeding (21, 36), but this effect was shown in studies in which children were fed locally prepared (not premixed) F-75 without added phosphorous. As previously reported, we did not see any obvious phosphate nadir because mean plasma phosphate increased throughout treatment (19). However, in 8 children, plasma phosphate dropped from admission to day 2, and 50% of these children died. Day 2 after refeeding was also when low plasma phosphate was associated with mortality, thereby suggesting that the plasma phosphate response to treatment is more important than the concentration at admission.

Low plasma phosphate may be a manifestation of refeeding syndrome, which can occur during the transition to an anabolic state when blood insulin rises, phosphate requirements increase, and phosphate and electrolytes are driven into cells, thereby potentially resulting in circulatory failure or even death (12, 38). Usually symptoms are thought to occur only when plasma phosphate concentrations are $<$0.3 mmol/L (38). We did not measure this severe hypophosphatemia; however, plasma phosphate that was just below normal concentrations was associated with mortality, but only in edematous children, perhaps because plasma phosphate was generally lower with edema. One study that did not show an association between hypophosphatemia and mortality in SAM was from Bangladesh where edematous malnutrition is less common (37).

Mortality was associated with the substitution of F-75 with rice porridge, particularly if this was done during the first 2 d of treatment. Rice porridge was probably given to the sickest children with the most severe diarrhea, which possibly caused confounding by indication. However, the association remained after controlling for potential confounders that are related to severity of illness or to diarrhea, which suggested that rice porridge or a lack of F-75 had an effect that was not only caused by confounding.

As previously reported, children who were given rice porridge had lower plasma phosphate on day 2 but not at admission (19). The rice porridge that was used was made from unfortified white rice flour and water. Its main source of energy (89%) was carbohydrate, it contained virtually no fat, and it had a low content of minerals such as phosphorous, potassium, and zinc (19). It is plausible that rice porridge, despite its lower energy content, could have caused a greater insulin rise than was the case with F-75 and, consequently, because of its effect on plasma phosphate, could have caused higher mortality. This possibility was supported by the observation that the use of rice porridge was not associated with mortality after controlling for plasma phosphate on day 2, and the interaction with rice porridge and hypophosphatemia indicated that low plasma phosphate was only associated with mortality in children who were fed rice porridge.

Rice porridge is not part of established treatment guidelines for SAM, and its use was stopped in the MNU shortly after the completion of our study. The rice porridge was given to ameliorate diarrhea, which is a major problem in children admitted to the MNU on the basis of studies that reported the use of a rice-based oral rehydration solution to reduce stool output in diarrhea (39, 40). The use of rice porridge in the MNU had not previously been linked to mortality, perhaps because many deaths occurred several days after it was given.

Limitations to this observational study include a relatively low sample size with limited power. Second, multiple testing may have caused false-positive findings, which would mean that some associations may have been chance findings. Our findings are mainly hypothesis generating, and more studies are needed to confirm our results. Third, our study only informed us about deaths that occurred in the hospital. Children who left the hospital prematurely may have died at home. However, with the use of Cox regression, children were only given weight in the analysis during the time they were observed. Fourth, by excluding children who required resuscitation on admission, we likely missed some early deaths. Therefore, this study may particularly inform us about deaths that occur after the first days of admission. Finally, because appetite tests were not routinely done, we could not be sure that all children fulfilled the WHO criteria for complicated SAM. However, most children were sick on admission, and we believe that few children would have been eligible for outpatient treatment.

In conclusion, despite these limitations, our results emphasize that nutritional therapy is as important as other medical treatment when managing children with SAM and serves as a warning against guideline modifications outside of carefully monitored clinical trials in these vulnerable patients. Future studies should assess if hypophosphatemia on day 2 is associated with mortality in populations who are only fed F-75 and if treatment outcomes can be improved by increasing the phosphorous content of the therapeutic diet, or by reducing carbohydrate, to make the transition to anabolism more gradual.

We thank Elizabeth Kiboneka, who is head of the MNU, for facilitating the study and providing supervision and guidance; Anne-Louise Hother Nielsen for assisting with the data analysis; Sofine Heilskov, Amira Catharina Khatar Sørensen, and Kia Hee Schultz for data collection; Vivian Julia Anker for laboratory analyses; and Julian Eyotaru, Loice Atuhaire, Susan Awori, Justine Naggayi, and Joseph Mbabazi for data collection and skilled care of our patients.

The authors' responsibilities were as follows—MJHR: wrote the first draft of the paper; MJHR, EB-I, HN, and CGM: conducted the research; MJHR, HN, and HF: designed the research; MJHR and CR: performed the statistical analysis; and all authors: read and revised the manuscript and read and approved the final manuscript as submitted. The funding sources had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. None of the authors reported a conflict of interest related to the study.

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