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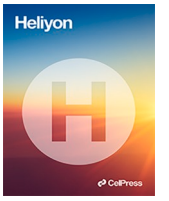

Research article

A retrospective cohort analysis of factors associated with the development of refeeding syndrome in children 0–59 months diagnosed with severe acute malnutrition in a South African setting

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A B S T R A C T

Background: Refeeding syndrome (RFS) is a life-threatening, underdiagnosed, and under-researched complication in treating children with severe acute malnutrition (SAM). This study aimed to determine the incidence and onset of RFS and identify biochemical abnormalities, clinical signs, and complications associated with RFS development in children, 0–59 months, treated with SAM in a South African public hospital setting.
Methods: A retrospective cohort study was performed on hospital medical records of children aged 0–59 months, diagnosed with SAM at Rahima Moosa Mother and Child Hospital, Johannesburg, from 1/10/2014 to 31/12/2018. The onset of RFS among children included in the study was diagnosed based on published criteria for RFS. On admission, children who developed RFS and those who did not were compared concerning biochemistry and clinical signs and symptoms.
Results: A total of 148 medical records were retrieved from the hospital archives. The diagnosis of SAM based on the World Health Organization (WHO) definition was confirmed in 126 children who were then included in the study. The median age of the 126 children (63 % male) with confirmed SAM was 11.2 months (P25:7.0 months; P75:17.0 months). The in-hospital mortality rate was 18.2 %, of which 8.7 % were retrospectively diagnosed as having developed RFS during their recorded hospital stay, despite implementing the WHO treatment guidelines for SAM. A significantly higher percentage of the children who developed RFS presented on admission with hypophosphatemia ($p = 0.015$), hypokalemia ($p = 0.001$), hyponatremia ($p = 0.001$), an international normalized ratio (INR) of above 1.7 ($p = 0.025$), diarrhea ($p = 0.042$), dehydration ($p = 0.029$) and urinary tract infection (UTI) ($p = 0.041$), than those who did not. Children who developed RFS stayed in hospital significantly longer than those who did not (18 vs. 12 days with a p-value of 0.003).
Conclusion: In this population of children with SAM treated in a South African public hospital setting, the presence on hospital admission of low levels of electrolytes, elevated INR, dehydration, diarrhea, and UTI was significantly associated with developing RFS. Recognizing these as possible red flags for developing RFS in children admitted with SAM might contribute to improved outcomes and needs further investigation.

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1. Introduction

Severe acute malnutrition (SAM) is a term used in children under five years of age to indicate severe undernutrition and is diagnosed by the occurrence of either severe wasting i.e. weight-for-length/height < -3 standard deviations (SD) on the World Health Organization (WHO) growth standards; or a mid-upper arm circumference (MUAC) < 11.5 cm in children between 6 and 59 months; and/or the presence of bilateral pitting edema [1]. In 2022, 13.6 million (2.1 %) children under the age of five years suffered from severe wasting worldwide [2]. Of these, 108.8 thousand (0.8 %) were from Southern Africa [2]. Following the WHO management guidelines for SAM may reduce the case fatality rate to below 10 % [3]. However, in 2018 South Africa still had a high case fatality rate of 30.9 % of children under five years dying from SAM [4]. Furthermore, there seems to be a vast difference in mortality rates reported between different provinces in South Africa ranging from 6.5 % to 40.8 % of children under five years dying from SAM, despite following standardized WHO treatment protocols [5,6]. A factor that may affect the outcome of children treated for SAM is that these children are at risk of developing refeeding syndrome (RFS) as a life-threatening complication [7–9].

Since World War II, it has been known that initiating feeds in a starved patient may potentially contribute to their fatality [10]. When feeding is initiated in an individual after starvation, a sudden shift from catabolism to anabolism, and a switch back to carbohydrate metabolism, causes blood glucose and insulin levels to rise and phosphate, potassium, and magnesium shift into the intracellular space [11]. Fluid retention may also increase the extracellular fluid volume [11]. Thus, the syndrome is mainly characterized by a drop in blood phosphate to below-normal levels (hypophosphatemia) within five days of initiating nutritional therapy [3,6]. Clinical symptoms range from mild to severe and may be associated with cardiac arrhythmias, cardiac failure, renal failure, and death [10]. Preventing the onset of RFS in patients treated with SAM may improve outcomes and reduce mortality. However, most RFS studies focus on adults, children with anorexia, and those in intensive care settings. Very little research has focused on RFS in the context of SAM [8,9,12–15] in low-resource settings.

Although the WHO guidelines for treating SAM include progressing feeding slowly, a lack of research in this field makes it difficult to determine whether this approach is optimal for preventing RFS in this vulnerable population [16]. Early work by Patrick (1977) referred to the development of a "recovery syndrome" which resulted in the death of four children with SAM after initiation of high energy feeds. This study carefully described the clinical course of six patients with SAM and offered detailed measurements of leucocyte sodium pump activity as well as concentrations of intracellular potassium and sodium. It also emphasized the value of close monitoring of pulse and respiration, to anticipate cardio-respiratory complications related to the electrolyte shifts [17]. The transition phase of feeding was included in the treatment guidelines for SAM to prevent heart failure and sudden death after research showed the complications and weight loss from diarrhea that occurred after giving large amounts of energy rapidly [1,17,18], although how to optimally transition from the stabilization to the rehabilitation phase has not yet been determined [18,19]. Yet, the overt link between these complications and refeeding syndrome is not clearly stated in the treatment guidelines for SAM, and the electrolyte levels, including phosphate, are not routinely monitored. In the African context, only two published studies thus far have reported RFS incidence in children admitted with SAM [9,15]. Mbethe & Mda reported on 104 children with SAM treated according to the WHO management protocol in a teaching hospital in the Gauteng Province of South Africa [15], while Okinyi studied 160 children with SAM in a Kenyan public hospital after initiating feeding with F-75 [9]. Considering the paucity of data, this study aimed to determine the incidence of RFS and explore associated admission data that might indicate risk factors for the development of RFS in South African children aged 0–59 months diagnosed with SAM and treated according to the WHO treatment guidelines in a public hospital setting.

2. Methods

2.1. Study design, setting, study population and sampling

A retrospective cohort study of retrievable hospital medical records of children aged 0–59 months admitted with SAM to Rahima Moosa Mother and Child Hospital, Coronationville, Johannesburg, South Africa, from 1 October 2014 to 31 December 2018, was conducted. Ethics approval to undertake the study and retrieve retrospective information from archived hospital medical records was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2018/0154/2602), which waived the requirement for informed consent, providing that all information be anonymized. The Gauteng Department of Health and The CEO of Rahima Moosa Mother and Child Hospital granted permission for the study.

A list of children admitted with SAM during the reference period was obtained from the dietetics department's computerized statistical records. The names and hospital numbers were then traced to obtain the hospital medical records from the archives department. The diagnosis of SAM was confirmed by verifying the diagnosis against the WHO criteria [1], namely, weight-for--length/height < -3SD using the WHO z-score tables [20] or a MUAC <11.5 cm and/or the presence of bilateral pitting edema, from the data captured in the medical records. Those participants for whom the diagnosis of SAM could be confirmed (N = 126) were included in the study.

A participant number was allocated to each consecutive file. Each participant's data was linked only to a specific participant number without capturing the name or any identifying information from the file. After data collection, the produced dataset was thus completely anonymized.

2.2. Data collection

Data was extracted and recorded from hospital medical records on standardized forms. Anthropometry (weight, length/height and/

or MUAC), age, gender, ethnicity, country of origin, and clinical symptoms were recorded. Available biochemical values for the first two weeks of hospitalization, as requested by the doctor overseeing the patient, associated with SAM, RFS, or prognosis, were recorded from the hospital medical records. These included blood levels of electrolytes and minerals (phosphorus, potassium, magnesium, calcium, and sodium), indicators of kidney function (urea and creatinine), inflammation and metabolic stress (C-reactive protein (CRP) and albumin), hemoglobin, coagulation (platelets and international normalized ratio (INR), and indicators of liver function (total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and aspartate aminotransaminase (AST). The medical record indicated that blood tests were taken at different intervals for different patients, with no specific protocol being followed. Furthermore, not all patients had repeat blood tests if their initial blood test was normal. Of the 126 participants, 103 participants had phosphate measured on admission. Participants who did not have a baseline and/or a repeated phosphate test were not excluded from the study as these patients may have had phosphate levels measured on subsequent days, especially if they showed clinical signs of RFS. The onset of RFS was retrospectively diagnosed if a drop in phosphate levels of >0.16 mmol/L to a value < 0.65 occurred after feeding was initiated [21]. According to a systematic review [22], no universally accepted definition of RFS existed at the time of the study [10], but the definition by Marik [21] was the most frequently used and, therefore, was chosen for this study.

All clinical signs and medical complications recorded in the medical records that developed after admission were documented.

2.3. Data analysis

Severe wasting was defined as weight-for-length/height < -3 standard deviations (SD) (Z scores) on the World Health Organization (WHO) growth standards [1]. Blood test values were interpreted according to published cut-offs. The sample was stratified into children who developed RFS (the RFS-positive group) and those who did not (the RFS-negative group). Recorded variables were compared between the two groups.

The data from the hospital medical records were captured in Microsoft Excel (2013) and analyzed using SAS® version 9.4, copyright© 2014 (SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.). Medians and interquartile ranges were used to describe numerical data, and frequencies and percentages to describe categorical data. The sample was stratified according to children who developed RFS (RFS-positive group) and those who did not (RFS-negative group). The groups were compared using contingency tables applying the Mann-Whitney U test for numerical data and the Fisher's exact tests, as applicable, for categorical data. A value of $p < 0.050$ was considered statistically significant.

3. Results

According to electronic statistics kept by the Dietetics Department of Rahima Moosa Mother and Child Hospital, 592 children with SAM were admitted during the period under review. Of the 592 children, only 329 (56 %) names and hospital numbers could be traced and only 148 (25 % of the identified total) hospital medical records could be retrieved. The study included 126 children who were diagnosed with SAM retrospectively, of whom 11 (8.7 %) developed RFS after feeding was initiated. Thus, the sample represented 21 % of the children admitted to the hospital with SAM during the review period. The median age of the sample was 11.2 months (P25:7.0

Table 1
Demographic data of the children, stratified according to the development of refeeding syndrome (RFS) (n = 126).

Variables		All (N = 126)		RFS-positive group (n = 11)		RFS-negative group (n = 115)		
Age on admission (months)		N	Median (P25; P75)	n	Median (P25; P75)	n	Median (P25; P75)	p-value[a] for the difference
		126	11.2 (7.0; 17.0)	11	9.4 (8.1; 17.8)	115	12.8 (7.7; 19.7)	0.948
Categorical demographics		**n**	**%**	**n**	**%**	n	**%**	
Gender (n = 126)	Male	79	62.7	7	63.6	72	62.6	1.000
	Female	47	37.3	4	36.4	43	37.4	
Ethnicity (n = 126)	White	0	0.0	0	0.0	0	0.0	1.000
	African	120	95.2	11	100	109	94.8	
	Mixed race	4	3.2	0	0.0	4	3.5	
	Indian	2	1.6	0	0.0	2	1.7	
Nationality (n = 112)	South Africa	72	65.1	5	55.6	67	65.1	0.719
	Zimbabwe	24	20.4	3	33.3	21	20.4	
	Mozambique	8	6.8	1	11.1	7	6.8	
	Malawi	4	3.9	0	0.0	4	3.9	
	Pakistan	1	1.0	0	0.0	1	1.0	
	India	1	1.0	0	0.0	1	1.0	
	Congo, DRC	1	1.0	0	0.0	1	1.0	
	Other	1	1.0	0	0.0	1	1.0	

2The p-value for Nationality corresponds to the "South Africa vs. rest" comparison.
[a] $p < 0.05$ was considered statistically significant (*).

Table 2
Description of cases that developed refeeding syndrome at Rahima Moosa Mother and Child Hospital.

Cases that developed RFS	Nr of days after admission RFS was detected	Phosphate value (mmol/L)		
		Baseline	Level on day of RFS diagnosis	Drop in phosphate level
1	4	0.60	0.44	0.16
2	6	0.69	0.46	0.23
3	10	0.90	0.59	0.31
4	3	0.70	0.53	0.17
5	3	1.16	0.65	0.51
6	6	1.03	0.47	0.56
7	9	1.20	0.59	0.61
8	4	0.90	0.31	0.59
9	5	1.03	0.35	0.68
10	13	2.37	0.63	1.74
11	9	2.49	0.62	1.78

Table 3
Anthropometry, duration of hospitalization and mortality rate stratified according to the development of refeeding syndrome (RFS).

Variables	All (N = 126)			RFS-positive group (n = 11)			RFS-negative group (n-115)			p-value[a] for the difference
	n	Median	P25;P75	n	Median	P25;P75	n	Median	P25;P75	
Weight on admission (kg)	126	6.3	5.3;7.3	11	5.6	4.7;7.3	115	6.4	5.3; 7.3	0.450
Weight on admission of group with no bilateral pitting edema	74	5.9	4.9; 7.0	4	4.7	4.4; 5.4	70	5.9	5.0; 7.0	0.2731
Length/height on admission (cm)	121	69.0	65.0; 77.0	10	67.5	62.0; 70.0	111	69.0	65.0; 77.5	0.460
MUAC on admission (cm)	60	11.1	10.4; 12.5	4	11.2	10.3; 12.7	56	11.1	10.4; 12.5	0.953
Duration of hospitalization (days)	125	12.0	8; 17	11	18.0	15; 27	114	12.0	7; 16	0.003*
Weight on discharge (kg)	105	7.1	6.1; 8.3	9	6.9	6.0; 7.6	96	7.1	6.4; 8.3	0.749
Weight change between admission and discharge in group with no bilateral pitting edema	74	0.7	0.3; 1.0	3[b]	1.0	0.9; 1.0	61[b]	0.6	0.2; 9.3	0.1158
Time to death (days)	19	9.0	2.1;15.0	2	14	9.0; 19.0	17	7.0	2.0; 15.0	0.286

[a] $p < 0.05$ was considered statistically significant (*).
[b] Discharge weight were not recorded in the files for all the participants.

months; P75:17.0 months). Most children were male (62.7 %), and most were of African descent (95.2 %) and from South Africa (64.3 %) and Zimbabwe (21.4 %). The demographical data did not differ significantly between the two groups (Table 1). Table 2 indicates when the children with SAM developed RFS, as well as the drop in phosphate levels from baseline.

The anthropometry, length of hospital stay and mortality are summarized in Table 3. MUAC was recorded for fewer than half of the children (n = 60; 47.6 %) and did not differ between RFS positive and negative groups. On admission, bilateral pitting edema was present in 7 (63.6%) of patients in the RFS positive group and 45 (39.1%) of patients in the RFS negative group. In the group without bilateral edema on admission, only 4 children experienced slight weight loss (minimum 0.1 kg, maximum 0.8 kg) during hospital stay, while the rest picked up weight (minimum 0.04 kg, maximum 2.2 kg). The median weight gain was <1 kg in the group overall, and there was no significant difference in the weight on admission or weight gain between the RSF-positive and RSF-negative groups.

The median duration of hospitalization was 12 days (P25:8 days; P75:17 days). The median stay in hospital was significantly longer for the RFS-positive group than for the RFS-negative group (18 vs. 12 days; p = 0.003).

Nineteen (19) children (mortality rate = 15.1 %) died in the hospital, and the median time to death was nine days (see Table 3). However, the mortality rates did not differ significantly between the RFS positive (n = 2; 18.2 %) and the RFS negative groups (n = 17, 14.8 %), and there was no significant difference between the time to death between the groups.

Table 4 summarizes the abnormal biochemical findings, showing that on admission, a significantly larger percentage of children in the RFS-positive group presented with hypophosphatemia (p = 0.015) and hypokalemia (0.001), hyponatremia (p = 0.001), and elevated INR (p = 0.025) than in the RFS negative group. Additionally, the serum phosphate levels of the 19 children who died in hospital (median: 1.25 mmol/L; P25:0.90 mmol/L; P75: 1.50 mmol/L) were lower than those who survived (median: 1.40 mmol/L; P25:1.1 mmol/L; P75: 1.70 mmol/L) but the difference was not statistically significant (p = 0.259).

Table 5 summarizes the clinical signs and symptoms recorded on admission. Complications on admission were very common. A significantly higher percentage of children who developed RFS presented with diarrhea (p = 0.042), dehydration (p = 0.029), and urinary tract infection (UTI) (p = 0.041) on admission than those that did not. The RFS positive group included fewer children who were human immunodeficiency virus (HIV) exposed (had a negative PCR test but whose mother was positive) than the RFS negative group but the difference was not quite significant (p = 0.054). As mentioned before, SAM with bilateral pitting edema was present in 7 (63.6 %) and 45 (39.1 %) of the RFS positive and RFSnegative groups, respectively) on admission, however, this finding was not statistically significant (p = 0.200).

Table 4
Abnormal biochemical findings on admission (n = 126).

Classification	Diagnostic criteria for classification		RFS-positive group (n = 11)		RFS-negative group (n = 115)		p-value[c]
			(n) [a]	n [b] %	(n)[a]	n [b] %	
Hypophosphatemia (n = 100)	<1 year	<1.3 mmol/L	(10)	6	(90)	19	0.015*
	1–16 years	<0.9 mmol/L		60.0 %		21.1 %	
Hypokalemia (n = 112)	Pediatric (0–14 years)	<3.5 mmol/L	(10)	9	(102)	37	0.001*
				90.0 %		36.3 %	
Hypomagnesaemia (n = 1)	Pediatric (0–14 years)	<0.6 mmol/L	(10)	0	(91)	2	1.000
				0.0 %		2.2 %	
Hypocalcemia (n = 101)	<4 weeks	<2.0 mmol/L	(10)	6	(91)	59	0.741
	4 weeks–16 years	<2.2 mmol/L		60.0 %		64.8 %	
Hyponatremia (n = 113)	Pediatric (0–14 years)	<133 mmol/L	(10)	7	(103)	19	0.001*
				70.0 %		18.4 %	
Hypoalbuminemia (n = 103)	<4 weeks	<25 g/L	(10)	9	(93)	68	0.445
	4 weeks–1 year	<30 g/L		90.0 %		73.1 %	
	1–16 years	<35 g/L					
Elevated CRP[d] (n = 104)	Pediatric (0–14 years)	>15 mg/L	(9)	6	(95)	54	0.730
				66.7 %		56.8 %	
Elevated urea (n = 113)	0–12 months	>5.5 mmol/L	(10)	3	(103)	25	0.707
	1–16 years	>6.5 mmol/L		30.0 %		24.3 %	
Elevated creatinine (n = 112)	Neonate (<28 days)	>75 μmol/L	(10)	4	(102)	30	0.488
	1 month–4 years	>39 μmol/L		40.0 %		29.4 %	
Elevated bilirubin (n = 81)	14 days–16 years	>21 μmol/L	(9)	1	(72)	6	0.576
				11.1 %		8.3 %	
Elevated ALP[e] (n = 83)	Neonate (<28 days)	>391 IU/L	(9)	2	(74)	3	0.089
	Infant (28 days–1 year)	>425 IU/		22.2 %		4.1 %	
	1–14 years	>308 IU/L					
Elevated GGT[f] (n = 81)	Pediatric (0–14 years)	>40 IU/L	(9)	8	(72)	40	0.075
				88.9 %		55.6 %	
Elevated ALT[g] (n = 82)	0–12 months	>41 IU/L	(9)	6	(73)	37	0.487
	1–2 years	>28 IU/L		66.7 %		50.7 %	
	3–6 years	>29 IU/L					
Elevated AST[h] (n = 82)	Neonate (<28 days)	>92 IU/L	(9)	4	(73)	35	1.000
	1–14 years	>60 IU/L		44.4 %		48.0 %	
Anemia (n = 101)	6–59 months	<11 g/dl	(10)	7	(91)	69	0.706
				70.0 %		75.8 %	
Thrombocytopenia (n = 99)	Pediatric (0–14 years)	<150 ($\times 10^3$/μl)	(10)	1	(89)	10	1.000
				10.0 %		11.2 %	
Elevated INR[i] (n = 52)	Pediatric (0–14 years)	>1.7	(8)	5	(44)	9	0.025*
				62.5 %		20.5 %	

[a] Number of children in the group with available values.
[b] number of children in the group with abnormal values.
[c] $p < 0.050$ was considered statistically significant (*).
[d] CRP (C-reactive protein).
[e] ALP (alkaline phosphatase).
[f] GGT (gamma-glutamyl transferase).
[g] ALT (alanine aminotransferase).
[h] AST (aspartate aminotransaminase).
[i] INR (international normalized ratio).

4. Discussion

This retrospective study among children with SAM treated in a South African public hospital setting recorded an incidence of RFS of 8.7 % (11 children). Children who developed RFS were found to be significantly more likely to present with hypophosphatemia, hypokalemia, hyponatremia, dehydration, coagulopathy, and UTI on admission and stayed in the hospital for significantly longer than children who did not develop RFS. Five children developed RFS within five days of hospitalization, which supports evidence from the literature of RFS occurring within five days after initiating feeds as one of the main characteristics of the syndrome [7,10] The remaining children developed RFS from day 6 to day 13. Possible reasons for the delayed onset of RFS are the late placement of nasogastric tubes for feeding, changes in the type of feeds, and late transitioning in sick patients. Mbethe and Mda [15] reported an incidence of 15 % in a teaching hospital in Gauteng, South Africa, and Okinyi [9] reported 21 % in a Kenyan hospital. However, the different definitions that were used to define the onset of hypophosphatemia in these three studies complicate comparisons. To effectively study associated risk factors and outcomes of RFS in the context of SAM, a universally accepted definition for hypophosphatemia to indicate the onset of RFS, which is currently lacking [7,10], needs to be developed.

In agreement with the findings of Mbethe and Mda [15], hypophosphatemia was significantly ($p = 0.035$) associated with RFS in

Table 5
Clinical signs and medical complications on admission.

Clinical signs and medical complications	Total group (N = 126)		RFS-positive group (n = 11)		RFS-negative group (n = 115)		p-value [a]
	N	%	n	%	n	%	
Vomiting	59 (N = 126)	46.8 %	7 (n = 11)	63.6 %	52 (n= 115)	45.2 %	0.345
Diarrhea	66 (N = 126)	52.4 %	9 (n= 11)	81.8 %	57 (n= 115)	49.6 %	0.042*
AGE[b]	67 (N = 126)	53.2 %	8 (n= 11)	72.7 %	59 (n= 115)	51.3 %	0.216
Dehydration	62 (N = 126)	49.2 %	9 (n= 11)	81.8 %	53 (n= 115)	46.1 %	0.029*
Bilateral pitting edema	52 (N = 126)	41.3 %	7 (n= 11)	63.6 %	45 (n= 115)	39.1 %	0.200
Dermatosis	39 (N = 126)	31.0 %	5 (n= 11)	45.5 %	34 (n = 115)	29.6 %	0.314
Hypoglycemia (<3 mmol/L)	13 (N = 125)	10.4 %	3 (n= 11)	27.3 %	10 (n = 114)	8.8 %	0.089
Hyperglycemia (>7 mmol/L)	41 (N = 125)	32.8 %	4 (n= 11)	36.4 %	37 (n = 114)	32.5 %	0.749
Hypothermia	2 (N = 126)	1.6 %	1 (n= 11)	9.1 %	1 (n = 115)	0.9 %	0.168
Pneumonia	46 (N = 126)	36.5 %	4 (n= 11)	36.4 %	42 (n = 115)	36.5 %	1.000
Respiratory complications[c]	54 (N = 126)	42.9 %	6 (n= 11)	54.6 %	48 (n= 115)	41.7 %	0.528
Sepsis	22 (N = 126)	17.5 %	4 (n = 11)	36.4 %	18 (n= 115)	15.7 %	0.100
Septic shock	7 (N = 126)	5.6 %	1 (n= 11)	9.1 %	6 (n= 115)	5.2 %	0.481
Loss of appetite	76 (N = 126)	60.3 %	8 (n= 11)	72.7 %	68 (n= 115)	59.1 %	0.524
Hepatomegaly	47 (N = 126)	37.3 %	6 (n= 11)	54.6 %	41 (n= 115)	35.7 %	0.327
Oral thrush	25 (N = 126)	19.8 %	1 (n= 11)	9 0.1 %	24 (n= 115)	20.9 %	0.692
HIV [d] infection	23 (N = 126)	18.3 %	0 (n = 11)	–	23 (n = 115)	20.0 %	0.213
HIV [d] exposed	63 (N = 126)	50.0 %	2 (n = 11)	18.2 %	61 (n= 115)	53.0 %	0.054
Tuberculosis	17 (N = 126)	13.5 %	1 (n= 11)	9.1 %	16 (n= 115)	13.9	1.000
UTI [e]	25 (N = 126)	19.8 %	5 (n= 11)	45.5 %	20 (n= 115)	17.4	0.041*
Nasogastric tube feeding	28 (N = 126)	22.2 %	4 (n= 11)	36.4 %	24 (n= 115)	20.9 %	0.260

[a] $p < 0.050$ was considered statistically significant.
[b] AGE (acute gastroenteritis).
[c] dyspnea/respiratory distress, respiratory failure, ventilatory dependency.
[d] HIV (human immunodeficiency virus).
[e] UTI (urinary tract infection).

this study. Notably, the serum phosphate levels were taken on admission before feeds had been initiated. Therefore, low phosphate might be a prognostic marker for developing RFS. Moreover, several studies have found that low admission phosphate levels are associated with an increased risk of dying [18,23]. Thus, phosphate assessment is indicated in all patients with SAM to allow for proper supplementation [23,24]. Notably, the current study used the definition of RFS given by Marik [18], which was derived from repeated measurements of plasma phosphate in patients in an intensive care unit from a high-income country. However, serial blood tests to detect a dropping serum phosphate may not be feasible in many settings where SAM is rife. The incomplete data on plasma phosphate recorded in the medical files in the current setting attests to this problem and suggests that serum phosphate may be less suitable for point of care interpretation and decision in resource poor environments. Therefore, it would be critically important to also identify other risk factors (red flags) for RFS that could be more suitable in these contexts.

In this study, 46 (41 %) children with SAM presented with hypokalemia and 26 (23 %) with hyponatremia on admission. According to previous studies, hyponatremia and hypokalemia are common electrolyte disturbances in malnourished children, made worse by diarrhea, vomiting, and dehydration [25,26]. In addition, hypokalemia and hypomagnesemia frequently occur in children with SAM because of muscle loss and kidney dysfunction due to reductive adaptations during starvation [27]. Diarrhea [15,18] and dehydration [24] are also commonly associated with RFS or hypophosphatemia. In this study, about half of the children presented with diarrhea and/or dehydration on admission, and children who developed RFS during their hospital stay presented with a significantly higher presence of diarrhea ($p = 0.042$), dehydration ($p = 0.029$), hypokalemia ($p < 0.001$) and hyponatremia ($p = 0.004$) on admission than those who did not. Notably, the WHO guidelines recommend the careful monitoring of pulse and respiratory rate as these electrolyte shifts may trigger cardiac and respiratory decompensation, leading to intravascular fluid overload and subsequent diarrhea and collapse. However, in the current study, the retrieved medical files did not report pulse and respiratory rate in enough detail to allow meaningful data capture and analysis.

Coagulopathy has not been described as a risk factor for RFS. De Maayer and Saloojee found that having a prolonged clotting time (INR >1.7) conferred the highest risk of death among children with SAM [28]. In this study, a significantly higher percentage of children in the RFS-positive group presented with an INR >1.7 on admission than the children in the RFS-negative group ($p = 0.049$), which might reflect the severity of SAM. However, the association between prolonged INR and RFS also reflects liver synthetic function rather than coagulopathy *per se*, thus further research is required to clarify issue further research is required.

Other clinical features commonly associated with RFS or hypophosphatemia are edema [15,18,24] and dermatosis [13,24], which also commonly occur in children with SAM [1]. In this study, 41 % of the children presented with edema on admission. However, although the prevalence of edema was higher in the RFS-positive group than in the RFS-negative group (63.6 % vs. 40 %), the difference did not reach statistical significance. Similarly, the prevalence of dermatosis, reported in 31 % of the children, was not significantly different between the two groups.

Urinary tract infection was present in 19.8 % of children on admission and was significantly more prevalent ($p = 0.041$) in the

group that developed RFS than in those that did not. Children with SAM are more vulnerable to infections due to their lowered immune system [29]. Urinary tract infections are common in malnourished children, especially those with a more severe form of malnutrition [29,30]. Furthermore, Mandla et al. found UTI to be a significant risk factor for mortality in children admitted with SAM [5].

In the Kenyan study [3], the prevalence of RFS was significantly associated with HIV infection (but not with dehydration status), while HIV infection was found in a South African study to be associated with an increased risk of death in children with SAM and RFS [28]. The current study in which 18.3 % of the children were HIV positive and 50 % HIV exposed did not confirm the association with RFS.

In 2018, the reported mortality rate of children under the age of five years with SAM in South Africa was 30.9 % [4]. Furthermore, varying mortality rates have been reported in children under five years with SAM in South African public hospital settings, ranging from 6.5 % to 40.8 % [5,6]. Mbethe and Mda [15] reported a mortality rate of 9.5 % and noted that most of the children in their study who died had developed RFS. The overall mortality rate in this study was 15.1 %. A higher percentage (18.2 %) of children died in the RFS-positive group compared in the RFS-negative group (14.5 %). However, this may not be a true representation of the study population as 91.7 % (n = 24) of hospital medical records of children who demised could be obtained, compared to only 37.7 % (n = 124) of hospital medical records for those who were discharged from hospital, indicating retrieval bias. The true mortality in both groups might thus be lower. The only other South African study on RFS in children with SAM reported that 6 % of children who developed RFS died [15]. RFS also resulted in a significantly longer duration of hospitalization (18 vs. 12 days, $p = 0.003$), which is similar to observations in older adults [31].

A limitation of this study was the difficulty in obtaining medical records from the hospital archives thus producing a small sample size. Furthermore, as discussed, retrieval bias was suspected in relation to the medical records of children with SAM who died during their hospital stay. The study also relied on the information recorded in the hospital medical records and records completed by others. Thus, there was no way of knowing if measurement errors such as inaccurate weighing, measuring of length/height, and MUAC had been made by medical personnel on admission or if errors or omittances occurred when the data was originally captured in the hospital medical records. Nevertheless, the sample size and findings compare well with similar studies in Africa [5,11] which demonstrates the necessity for more research in this field to be able to make further conclusions and suggestions for improvement.

5. Conclusion and recommendations

The incidence of RFS is difficult to determine owing to the lack of a standardised definition. Furthermore, children with SAM are at an Increased risk of developing RFS, which is a life-threatening condition. In this study, the development of RFS in children admitted with SAM was significantly associated with the presence of low levels of phosphorus, potassium and sodium, elevated INR, dehydration, diarrhea, and UTI on admission.

As children with SAM are already at risk of death, being able to identify children who are more likely to develop RFS can lead to better management of this sub-group of children with SAM, and improve clinical outcomes. More research is undoubtedly needed to determine risk factors for the development of RFS in children with SAM to be able to assess the current protocols for possible improvement.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Natalie Heydenrych: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tim De Maayer:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Mariette Nel:** Software, Formal analysis, Conceptualization. **Louise van den Berg:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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