Long-term outcomes of HIV infected, and uninfected children aged 1-59 months following inpatient management of severe acute malnutrition.

by

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Thesis

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South Africa

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11 June 2023

DECLARATION

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university or institution.

MF Bwakura-Dangarembizi

Date: 11 June 2023

DEDICATION

In memory of my big brother

Tapiwanashe Rameck Bwakura

1960 - 2022

ACKNOWLEDGEMENTS

I was honoured to work with 3 committed supervisors, Professor Andy Prendergast (primary), Professor Kusum Nathoo (secondary) and Professor Shane Norris (secondary). Andy was an amazing supervisor whose guidance and mentorship opened a whole new chapter in my life. Prof Nathoo the seasoned and wise clinician would always remind me about “how this would benefit the people”. Shane welcomed me into his unit at Wits University and I will be forever grateful for his guidance.

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The study would not have been possible without the input of amazing research teams in Zambia and Zimbabwe. I will forever be indebted to the children and the families who welcomed me into their spaces and allowed me to be part of their journey.

Andy introduced me to the amazing Zvitambo Institute for Maternal and Child Health Research which has become more than a home. I was accepted by the entire team and spent memorable years with the clinicians and the data and stats team lead by Robert Ntozini (Dr in waiting). Cherlyn, one of the statisticians will always be my “comrade-in-arms”. The “Prendergast Lab group” proved to be a friendly environment of like-minded people whose aim every Friday, was to bring out the best out of a presentation or idea.

My own home, Department of Paediatrics and Child Health at the University of Zimbabwe for allowing me time to conduct the research and the Parirenyatwa and Sally Mugabe Children’s Hospitals who gave me room in their institutions.

Great appreciation goes to my husband, our girls, my mother and siblings for their amazing support. The legacy of the women in our family lives on, thanks to Mbuya Utete.

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THESIS MATERIAL AND CONTRIBUTIONS

I contributed to the conceptualisation of this study together with my supervisors and contributed to the development of the study protocol, manual of operations, standard operating procedures and case record forms. I coordinated the implementation of the study in Zimbabwe and Zambia, study staff training and data collection including anthropometric measurements, daily hospital reviews, and follow up visits. I contributed to the project management, quality control and data management as well as statistical analysis and interpretation of the data presented.

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PUBLICATIONS AND PRESENTATIONS

Part of the work from this thesis was reported and published in peer reviewed scientific journals. Results from the study were also presented in the form of oral and poster presentations at academic and scientific conferences.

Peer Reviewed Publications

Paper 1 (Chapter 3)

Bwakura-Dangarembizi M, Dumbura C, Amadi B, Ngosa D, Majo FD, Nathoo KJ, Mwakamui S, Mutasa K, Chasekwa B, Ntozini R, Kelly P, Prendergast AJ, the HOPE-SAM study team. Risk factors for post discharge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia, *The American Journal of Clinical Nutrition* 2021;113 (3): 665–674

Paper II (Chapter 4)

Bwakura-Dangarembizi M, Dumbura C, Amadi B, Chasekwa B, Ngosa D, Majo FD, Sturgeon JP, Chandwe K, Kapoma C, Bourke CD, Robertson RC, Nathoo KJ, Ntozini R, Norris SA, Kelly P, Prendergast AJ. Recovery of children following hospitalisation for complicated severe acute malnutrition. *Matern Child Nutr*. 2021 Dec 22:e13302. doi: 10.1111/mcn.13302.

Paper III (Chapter 5)

Bwakura-Dangarembizi, M., Dumbura, C., Ngosa, D., Majo, F. D., Piper, J. D., Sturgeon, J. P., Nathoo, K. J., Amadi, B., Norris, S., Chasekwa, B., Ntozini, R., Wells, J. C., Kelly, P., Prendergast, A. J., & HOPE-SAM study team (2022). Fat and lean mass predict time to hospital readmission or mortality in children treated for complicated severe acute malnutrition

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Conference Proceedings

16th Scientific Meeting of the Commonwealth Association of Paediatric Gastroenterology & Nutrition (CAPGAN 2019). Poster Presentation. One year mortality in HIV positive and HIV negative children with complicated severe acute malnutrition.

International Workshop on HIV Pediatrics 2021. Oral presentation. Risk factors for post-discharge mortality following hospitalization for severe acute malnutrition in Zambia and Zimbabwe.

Wellcome Trust - Bloomsbury Centre for Global Health Meeting, March 2022. Oral Presentation. Outcomes of children discharged from hospital following management of Severe Acute Malnutrition.

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ABBREVIATIONS

aHR	adjusted Hazard ratio
BIA	Bioelectrical Impedance Analysis
CRF	Case Record Form
DAG	Direct Acyclic Graph
HAZ	Height-for-age Z-score
HIV	Human Immunodeficiency Virus
Ht	Height
HR	Hazard Ratio
IMAM	Integrated Management of Acute Malnutrition
LMI	Lean Mass Index
MUAC	Mid-upper-arm circumference
OR	Odds Ratio
R	Resistance
R/H	Height-adjusted resistance
SAM	Severe acute malnutrition
TBW	Total Body Water
X_c	Reactance
WAZ	Weight-for-age Z-score
WHZ	Weight-for-height Z-score
WHO	World Health Organisation

GLOSSARY OF TERMS

Bioelectrical impedance analysis: a method of measuring body fat and muscle mass where a small electrical current is passed through the body and the voltage measured to calculate impedance of the body.

Fat free mass: all components of body weight except fat mass

Fat mass: portion of the body weight which comprises fat

Impedance: measure of the opposition to flow of an electrical current as it travels through the body. It is related to the body size and the square of the length of the conductor.

Kwashiorkor: a form of malnutrition characterised by swelling of the extremities

Malnutrition: arises from a deficiency or excess in nutrient intake, imbalance of essential nutrients or impaired nutrient utilisation

Marasmus: a type of malnutrition characterised by severe wasting.

Marasmic-kwashiorkor: a type of severe acute malnutrition characterised by both wasting and oedema.

Moderate acute malnutrition: defined as weight for height Z-score between -2 and -3 or mid-upper-arm circumference 115mm to 125mm

Reactance (X_c): reflects the capacitative losses caused by cell membranes

Ready-to-use therapeutic food: an energy dense, micronutrient paste made using peanuts, sugar, milk powder, oil, vitamins and minerals used for treating severely malnourished children.

Resistance (R): opposition of flow of an electrical current through the body tissues which is inversely related to body water and the electrolyte content of tissues.

Severe acute malnutrition: defined as the presence or oedema of both feet or a low weight for height (below -3 Z scores of the median WHO growth standards or mid-upper arm circumference <115mm) in children below 5 years of age.

Stunting or linear growth failure: defined as height-for-age Z-score below -2 of the WHO growth standards.

Wasting: weight-for-height Z-score below -2 of the WHO growth standards or mid-upper-arm circumference below 125mm.

Z-score: the number of standard deviations a measurement is from the mean value of the reference population

ABSTRACT

Children with complicated severe acute malnutrition (SAM) are at a high risk for mortality and morbidity in the time after hospital discharge, and those with HIV are particularly vulnerable. What is not known is whether this higher risk for poor outcomes in children with HIV has improved in the era of treating all who are infected. The thesis' main aim was to characterize the 52-week outcomes of children aged 1 to 59 months who were hospitalized for complicated SAM and to identify the characteristics present at hospital discharge that were most predictive of these outcomes. The thesis utilised the HOPE SAM study, an observational cohort established in Zimbabwe and Zambia that enrolled children hospitalised for complicated SAM and followed them up for one year after discharge from hospital. The study outcomes were death, morbidity, nutritional recovery and body composition assessed using skinfold thickness and bioelectrical impedance analysis. There were 3 main findings from the thesis; nearly 1 in 10 children treated for SAM died and the risk of dying continued throughout the one year following discharge. Children living with HIV had an almost 4-fold higher mortality compared to those without HIV regardless of whether they were receiving antiretroviral therapy or not; wasted children and those with ongoing SAM had a 2-fold higher mortality compared to those who had oedema on admission; and cerebral palsy was associated with a nearly 6-fold higher mortality risk. Similar risk factors, with the exception of HIV infection and addition of stunting were associated with impaired anthropometric recovery and increased hospital readmission. In this cohort, the time to hospital readmission was correlated with low peripheral fat mass and low lean mass. Overall, this thesis emphasizes the vulnerability of children treated for SAM even after they are released from the hospital and identifies high-risk populations that require focused interventions to enhance outcomes.

PREFACE

My journey to this PhD began with an observation of increased hospitalisation for severe acute malnutrition among children with advanced HIV disease following antiretroviral therapy initiation, followed by a 15-fold increase in 6-month mortality compared with children who had not been hospitalised in the ARROW multicentre clinical trial. Malnutrition underlies nearly half of all deaths in children under 5 years of age, with severe acute malnutrition (SAM) being the most life-threatening form. Infections including HIV underlie most of the deaths from malnutrition.

While great strides have been made in reducing vertical transmission of HIV, and initiation of ART upon making a diagnosis of HIV, late presentation among children living with HIV remains a problem with severe acute malnutrition frequently being the initial presentation to clinical services.

The management of acute malnutrition has evolved over the years and has moved from being completely hospital-based to being predominantly community-based, with hospital management only for children with complicated SAM, which is associated with overt infections and metabolic derangements, using the World Health Organization "Ten Steps to Recovery" guidelines. The main focus has been on reducing in-hospital mortality by managing infections and metabolic instability followed by discharge into community-based centres where ready-to-use therapeutic foods are given until anthropometric recovery.

The just-ended Millennium Development Goals focused on improving child survival with little attention paid to the quality of life post-survival. There is now renewed interest in the contribution to overall child mortality of the post-discharge period in the sustainable development goals.

In my own clinical experience, I observed that a number children were readmitted into hospital and I began asking questions: was it about failure to access ready-to use-therapeutic food at community level, or the fact that children were discharged to the same home environment with poor care practices, and lastly, is anthropometry alone enough to identify the children at highest risk for poor outcomes? I took advantage of my training in epidemiology and with support from my supervisors established a cohort of children hospitalised for complicated SAM in Zimbabwe and Zambia. This cohort would provide data on hospital and post-discharge outcomes (the subject of this thesis) and biological samples that would be used in sub-studies exploring the mechanistic pathways underlying severe acute malnutrition.

The outline of the thesis is shown below

Part 1: Introduction

Chapters 1 and 2 include the background of the study comprising the problem statement and conceptual framework, literature review and methods for the HOPE SAM study within which this thesis work is embedded

Part 2: Empirical Chapters

Chapters 3-5 contain details of the manuscripts published from the study that was undertaken towards this PhD.

1: Risk factors for post discharge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia.

2: Recovery of children following hospitalisation for complicated severe acute malnutrition.

3: Fat and lean mass predict time to hospital readmission or mortality in children treated for complicated severe acute malnutrition in Zimbabwe and Zambia.

Part 3: Integrated Discussion and Conclusion

Chapter 6 comprises an integrated discussion of the thesis, synthesising the main research findings, a review of the strengths and limitations, the relevance and implications of the findings and discusses remaining gaps and proposed future research considerations.

PART 1: INTRODUCTION

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.1 EPIDEMIOLOGY OF CHILDHOOD MALNUTRITION

The World Health Organization describes malnutrition as the cellular imbalance between supply of nutrients and energy and the body's demand for them to ensure growth, maintenance, and specific functions (1). This definition is comparable to a more recent one provided by the American Society for Parenteral and Enteral Nutrition, which defines malnutrition as an imbalance between nutrient intake and requirements that results in cumulative deficits of energy, protein, or micronutrients that may have a negative impact on growth, maintenance, and certain other functions (2). Forty-five percent 45% of all child fatalities are attributed to undernutrition, which includes stunting (low height for age), underweight (low weight for age), and wasting (low weight for height) (3).

Estimates for 2020 place the number of stunted children at 149.2 million (22%) and the number of wasted children at 45.4 million (6.7%); of the wasted children, 14.3 million had severe wasting (4). Whereas 70% of wasted children live in Asia and 27% in sub-Saharan Africa, more than half of all stunted children dwell in Asia and 41% in Africa (4). Although the prevalence of undernutrition has decreased over the past 30 years, low and middle-income countries (LMICs) continue to experience significant levels of it (5-7). All degrees of undernutrition have however been associated with an increased risk of death during childhood, mainly from infectious diseases (8, 9). According to recent research, a large proportion of children under the age of five suffer from both stunting and wasting, which raises their mortality risk in comparison to either condition alone (10). Figure 1 shows the percentage of young children affected by wasting in different regions globally.

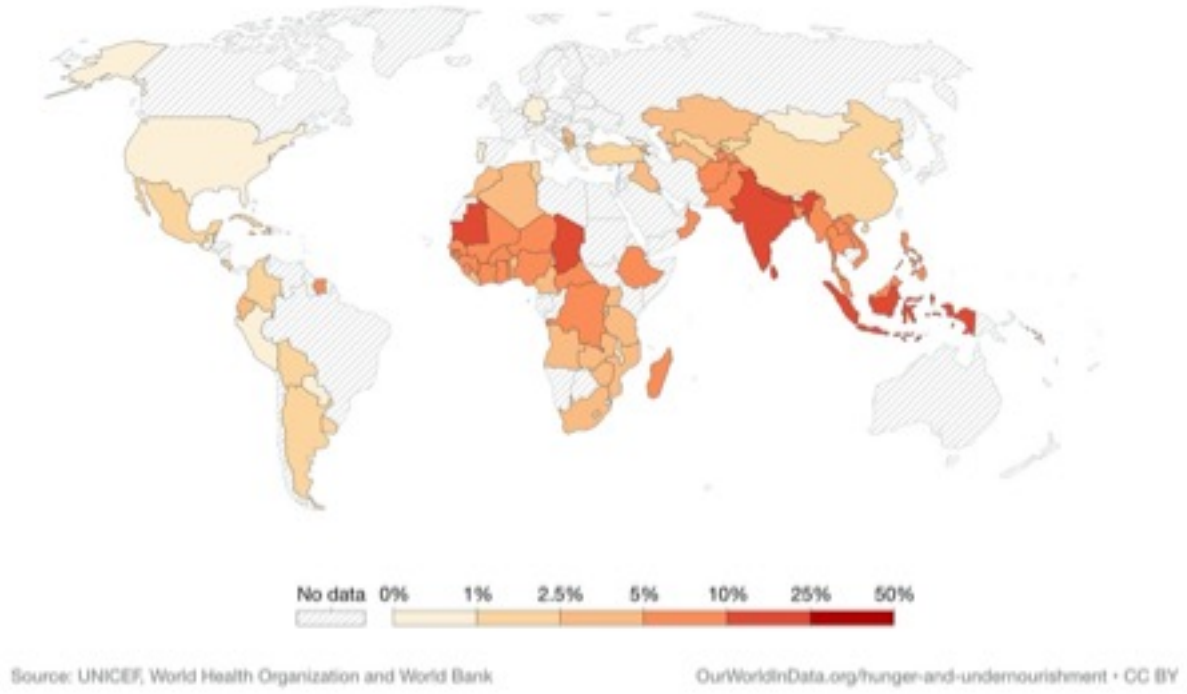


Figure 1: Malnutrition: Share of the children who are wasted, 2020 adapted from https://ourworldindata.org

The underlying causes of malnutrition are multifactorial and are summarised in the "UNICEF Conceptual Framework on the Determinants of Maternal and Child Nutrition", 2020 (11) which builds on the UNICEF 1990 framework (12). While the framework presents malnutrition as undernutrition, overnutrition or micronutrient deficiencies, the underlying causes are similar and they can co-exist in the same child.

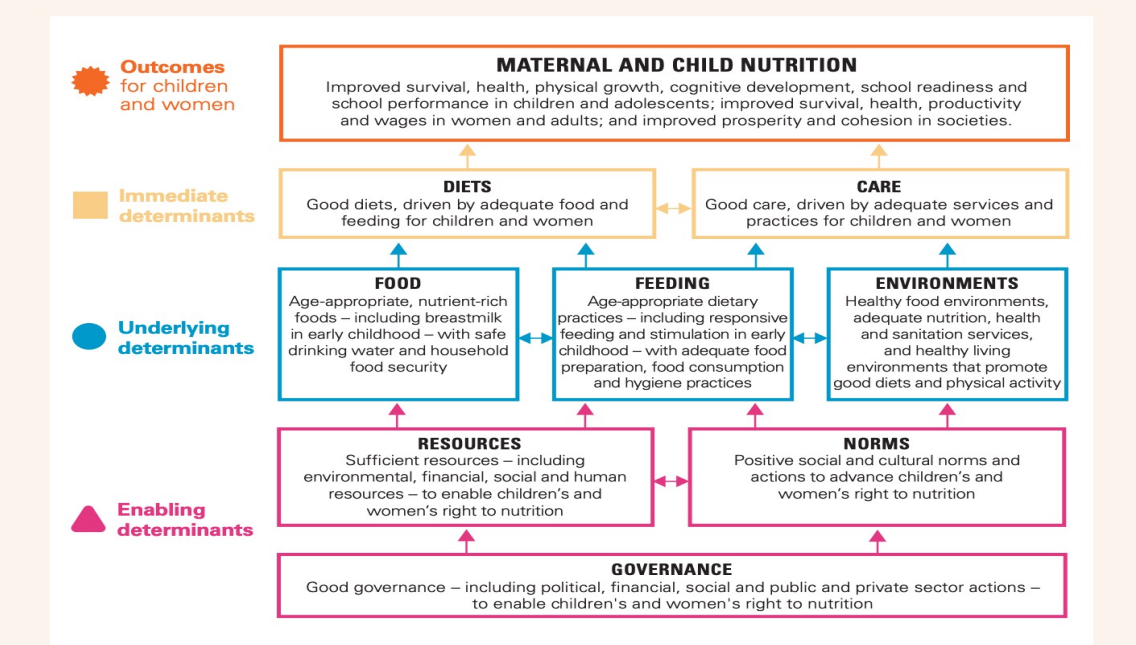


Figure 2: UNICEF Conceptual Framework on the Determinants of Maternal and Child Nutrition, 2020. Adapted from the UNICEF Nutrition Strategy 2020-2030

1.2 CLASSIFICATION OF MALNUTRITION

Malnutrition in children under 5 years of age is generally classified as acute and chronic based on the anthropometric measurements of weight, length/height and mid-upper arm circumference (MUAC). Acute malnutrition includes both wasting and nutritional oedema, although the terms wasting and acute malnutrition tend to be used interchangeably (13). Wasting is commonly viewed as an acute condition resulting from an immediate problem such as an acute illness, reduced food intake or both; however, it can persist for a long time (14). Weight-for-height or mid-upper-arm circumference (MUAC) measurements are used to define wasting in children older than six months. There are currently no standards for MUAC in infants below 6 months of age. Mid-upper arm circumference is a simple measurement that can be obtained by one person and reflects loss of muscle mass and subcutaneous fat (15). While both WHZ and MUAC assess wasting, the cases selected using either measurements

are not the same with children having a low MUAC (<115mm) tending to be younger compared to those with a WHZ <-3 (16). Evidence suggests that MUAC performs better than other anthropometric measurements in identifying children at risk of death (17, 18). Table 1 shows the classification of wasting and stunting into the moderate and severe forms.

Table 1: Classification of wasting and stunting adapted from https://www.ncbi.nlm.nih.gov/books/NBK487900/table/fm.s1.t1/

Measure	**Wasting**	
	Moderate	**Severe**
Weight-for-height Z score (WHZ)	-2 to -3	<-3
Mid-upper-arm circumference (MUAC)	115mm to 125mm	<115mm
	Stunting	
Height-for-age Z score (HAZ)	-2 to -3	<-3

Oedematous malnutrition (previously termed kwashiorkor) occurs more commonly among younger children aged 6 to 29 months of age (19) and is uncommon below 6 months of age. It is an independent criterion for identifying SAM and the main distinguishing characteristic is bilateral nutritional oedema.

Chronic malnutrition is defined by stunting, characterised by poor linear growth (low height-for-age) over long periods often starting in-utero. Stunting arises from ongoing or recurrent malnutrition, which is frequently associated with poverty, poor maternal health and nutrition, recurrent illness, particularly infectious diseases, and/or inadequate infant and young child feeding and care in the early years of life. (20-22).

The classification of malnutrition using anthropometry into acute and chronic may however be an oversimplification as multiple anthropometric deficits can be found in the same child and elevate the risk of dying (23-28). This thesis will concentrate on acute malnutrition.

1.2.1 Severe Acute Malnutrition

SAM is the worst form of undernutrition, affecting nearly 13 million children below 5 years of age every year and leads to 1-2 million deaths annually (5). Most published data on acute childhood malnutrition focuses on severe wasting and there are no reliable estimates of the number of children who have kwashiorkor globally (29) though reports from some parts of sub-Saharan Africa suggest that the oedematous form of acute malnutrition is more prevalent compared to wasting particularly in hospitalised children (30-33). Part of the reason children with oedematous SAM are not captured in cross-sectional surveys is that the condition tends to be transient with the child recovering or dying within a few weeks of onset(29).

The two main clinical phenotypes of SAM; non-oedematous malnutrition (marasmus) and oedematous malnutrition (kwashiorkor and marasmic-kwashiorkor) are shown Picture 1 below. The characteristic features of non-oedematous SAM include depletion of subcutaneous fat stores and muscle tissue while oedematous SAM when fully developed is characterised by oedema, hair and skin changes with hypo- and hyperpigmented lesions that usually start in the buttock area (34). Children with oedematous malnutrition often have abdominal distension with fatty liver and dilated atonic intestines with bacterial overgrowth. They also tend to be apathetic or irritable.

Picture 1: Two forms of severe acute malnutrition, non-oedematous and oedematous malnutrition(35)

1.2.2 Complicated severe acute malnutrition

The presence of medical complications, severe illness, metabolic decompensation and poor appetite are used to classify SAM into the complicated and uncomplicated forms (36). Complicated SAM is managed in an in-patient facility due to the associated high risk of dying . Children who appear clinically well and have a preserved appetite have uncomplicated SAM and are managed as outpatients using therapeutic foods and antibiotics. The rest of this thesis will be focusing on complicated SAM and its outcomes after discharge from hospital.

1.2.3 Body Composition in malnutrition

The anthropometric measurements used to assess nutritional status, diagnose and assess recovery from malnutrition, are only proxies of the physiological and functional deficits underlying malnutrition (37, 38). Body composition describes and quantifies the functional components within the body and can be assessed using various techniques that include skinfold thickness, isotope dilution, bioelectrical impedance analysis, dual-energy x-ray absorptiometry (DXA), air-displacement plethysmography and magnetic resonance imaging (39). For purposes of measurement, there are different body composition models in use with

the simpler two compartment model shown in Figure 3 below, being used more commonly (40, 41). The 2-compartment model comprises fat free mass (FFM) or lean mass, and fat mass (FM) . Body water is the major component of FFM throughout life starting at 80% at birth to approximately 73% during adolescence through to adulthood. If the volume of total body water and the hydration of FFM are known, fat mass can be calculated as the difference between body weight and FFM .

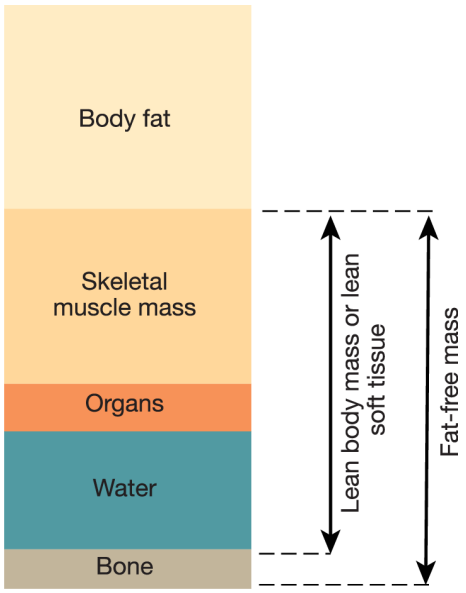


Figure 3: Body composition compartments; differences in the estimation of fat-free mass and lean soft-tissue/lean mass

The gold standard for direct measurement of body composition is isotope dilution using deuterium oxide which when taken orally is largely distributed in body water. After allowing for equilibration, a sample of saliva or urine is collected to measure the amount of deuterium in body water above that naturally present. This is used to directly calculate total body water and derive FFM and FM (42). Dual energy X-Ray Absorptiometry (DXA) measures total body soft tissue composition including bone mineral content in addition to FM and FFM using the three-compartment model . Its main disadvantages are that it requires a dedicated examination room and requires the infant/child to lie still throughout the procedure .

The third technique for determining body composition that was used in this thesis was bioelectrical impedance analysis, which analyses a low electrical current that is passed through the body and measures the impedance (Z) to current follow through various tissues at 5 kHz and 50 kHz. This technique enables an indirect extrapolation of FFM and FM. Impedance is made up of reactance (Xc), which represents the capacitative losses brought on by cell membranes, and resistance (R) to the passage of current. Mostly fluid and electrolyte-containing tissues have high conductivity and thus low impedance, whereas fat and bone have poor conductivity and high impedance (43). Phase angle is a marker of tissue health and is smaller when there is reduced cell integrity and inflammation (44). Using the raw data of impedance (Z50), resistance (R), and reactance (X_c), proxies for FFM/lean mass and lean mass index (LMI) are produced. In epidemiological analysis, the impedance index (Ht^2/Z) exhibits nearly the same behavior as lean mass in the absence of calibration equations since it is significantly correlated with lean mass in any population (45). Skinfold thickness is a simple and inexpensive measure that provide an estimate of regional and total body fatness which correlates well with total body fat mass as assessed by densitometry (46). Considerations for the choice of body composition assessment method to use include accuracy, reliability, condition being studied, cost and ease of use. This study used bioelectrical impedance analysis for approximating FM and FFM and skinfolds thickness (triceps, subscapular and suprailiac) for approximating total body fat.

1.3 PATHOPHYSIOLOGY OF SEVERE ACUTE MALNUTRITION

The underlying causes of SAM are multifactorial with an interplay between infections and inflammation in an environment of socio-political and economic instability (47). Children who live in areas where there is a high burden of infectious diseases including tuberculosis, HIV, diarrhoeal diseases and respiratory tract infections are at risk for malnutrition (21, 48,

49). In the short term, in response to several days of food deprivation, the body uses available fat stores and then breaks down protein in order to maintain essential metabolic processes through gluconeogenesis. Insulin and glucagon regulate the process in the short-term and other hormones including growth hormone and corticosteroids are involved in the long-term catabolism.. The cytokines (tumour necrosis factor and interleukin-1 and 6) released during cachexia, cause anorexia and also have a catabolic effect on skeletal muscle and adipose tissue (50).

The underlying pathogenesis of the oedema in the syndrome of oedematous SAM remains unclear (47), and none of the current hypotheses about the origin of the condition can sufficiently explain its clinical and pathophysiological manifestations (29). However, a number of hypotheses have been proposed to explain the underlying cause of the oedema. The protein deficiency hypothesis, which was predominant in the 1980s, was challenged by later studies that did not show a lower protein intake in children who subsequently developed kwashiorkor from a vulnerable population of 1-3 year olds in Malawi (51). Low albumin as a cause of oedema has been questioned as the oedema resolves without any changes in the plasma albumin concentration (52). Oedematous malnutrition has been described as a condition arising from a maladaptive response to a high carbohydrate diet and infection resulting in increased oxidative stress, oedema, fatty liver and the skin and hair lesions that characterise the condition. More recently, there is evidence linking gut microbiota composition to malnutrition, with decreased species diversity in both the oedematous and non-oedematous forms raising the possibility of developing interventions that support growth of a healthy gut microbiome (29, 53).

Metabolic complications

Severe malnutrition profoundly affects metabolism. Fat loss and muscle wasting characterise wasting while oedematous malnutrition is associated with a maladaptive metabolic response where a high carbohydrate and low protein diet results in glycolysis and protein catabolism (47) which are not able to meet the amino acid response for protein synthesis (54). Oedematous malnutrition is also associated with reduced gluconeogenesis compared to non-oedematous SAM (55). Reduced cardiac output associated with myocardial atrophy has been seen in children with oedematous malnutrition (56). Children with oedematous malnutrition also have a fatty liver which is associated with impaired lipid oxidation in the liver (57). Hypoglycaemia has been associated with reduced lean mass and fat tissue reserves in children with non-oedematous SAM (58). Hyperglycaemia associated with reduced insulin release and impaired glucose clearance has also been described in children with both types of SAM (59). Children with SAM also have low leptin levels, which is a sign of loss of fat tissue (47). Metabolic adjustments that take place during malnutrition associated with infection result in loss of muscle mass and changes in body composition that manifest as wasting and stunting if sustained (60).

1.3.1 Severe Acute Malnutrition and Infections

Malnourished children have an increased frequency of acquiring infectious diseases which tend to be more severe, and result in higher acute and long-term mortality and morbidity from the infection (61). Though there are no estimates of the burden of invasive bacterial infections in malnourished children due to limited diagnostics in areas of high prevalence of SAM , evidence of bacterial infection in severely malnourished children was described from post-mortem findings in the 1960s (62). A clinical and biological characterisation of infections in children hospitalised for complicated SAM in Niger, showed positive blood and urine cultures in 17% and 16% of patients, respectively (63). A similar study in Kampala, Uganda yielded 17.1% bacterial isolates (mainly *Salmonella enteritidis, Salmonella typhimurium,*

Staphylococcus aureus and *Streptococcus pneumoniae*) (32). In this study, the risk of bacteraemia was the same in children living with and without HIV though mortality was higher in those living with HIV (43.5% versus 20.5%). In a study conducted in Kenya among children hospitalised with SAM, nearly half had diarrhoea and mortality was 19% among those with diarrhoea compared to 9% in those who did not have diarrhoea (64). A recent systematic review and meta-analysis of the impact of childhood malnutrition on mortality from pneumonia across LMICs showed a high risk of death in all degrees of underweight with a higher rate of attributable deaths in severely underweight children compared to those who were moderately underweight (65). Compared to children with normal weight, those who were moderately and severely underweight were more likely to die . Hazard ratios for all-cause and disease-specific deaths by degree of wasting in children under 5 years of age are shown in Table 2 (66, 67) .

Table 2 Hazard Ratios of All-Cause and Cause-Specific Deaths, by Degree of Wasting, adapted from

Weight-for-height z-score	All deaths HR (95% CI)	Pneumonia deaths HR (95% CI)	Diarrhea deaths HR (95% CI)	Measles deaths HR (95% CI)	Other infectious deaths HR (95% CI)
<–3	11.6 (9.8, 13.8)	9.7 (6.1, 15.4)	12.3 (9.2, 16.6)	9.6 (5.1, 18.0)	11.2 (5.9, 21.3)
–3 to –2	3.4 (2.9, 4.0)	4.7 (3.1, 7.1)	3.4 (2.5, 4.6)	2.6 (1.3, 5.1)	2.7 (1.4, 5.5)
–2 to <–1	1.6 (1.4, 1.9)	1.9 (1.3, 2.8)	1.6 (1.2, 2.1)	1.0 (0.6, 1.9)	1.7 (1.0, 2.8)
≥–1	1.0	1.0	1.0	1.0	1.0

Sources: Black and others 2013; Olofin and others 2013.
Note: CI = confidence interval; HR = hazard ratio.

Mechanisms underlying the interaction of malnutrition and infection

The cyclical relationship between infection and malnutrition has been recognised for many years with episodes of infection potentiating malnutrition and malnutrition increasing the risk of acquiring infection (68). It has been discovered that environmental pathogen exposure, changed gut microbiota, persistent gut inflammation, loss of the mucosal barrier, and immunological dysbiosis all play a part in the cycle between starvation and infection (Figure

4) (61). Diarrhoea is the clinical manifestation of gut infection but evidence now shows that there is significant gut dysfunction even in the absence of diarrhoea. Environmental enteropathy is a term that describes a small intestinal subclinical disease characterised by gut inflammation and barrier dysfunction, malabsorption, systemic inflammation and subsequent metabolic changes in the absence of diarrhoea. The underlying aetiological factor is believed to be continuous exposure to food and water contaminated with faeces (69). In summary, at the cellular level, malnutrition is characterised by systemic immune activation resulting from acute and chronic infection (70), gut microbial translocation, inflammatory enteropathy (71, 72) and dysregulated immune responses (73).

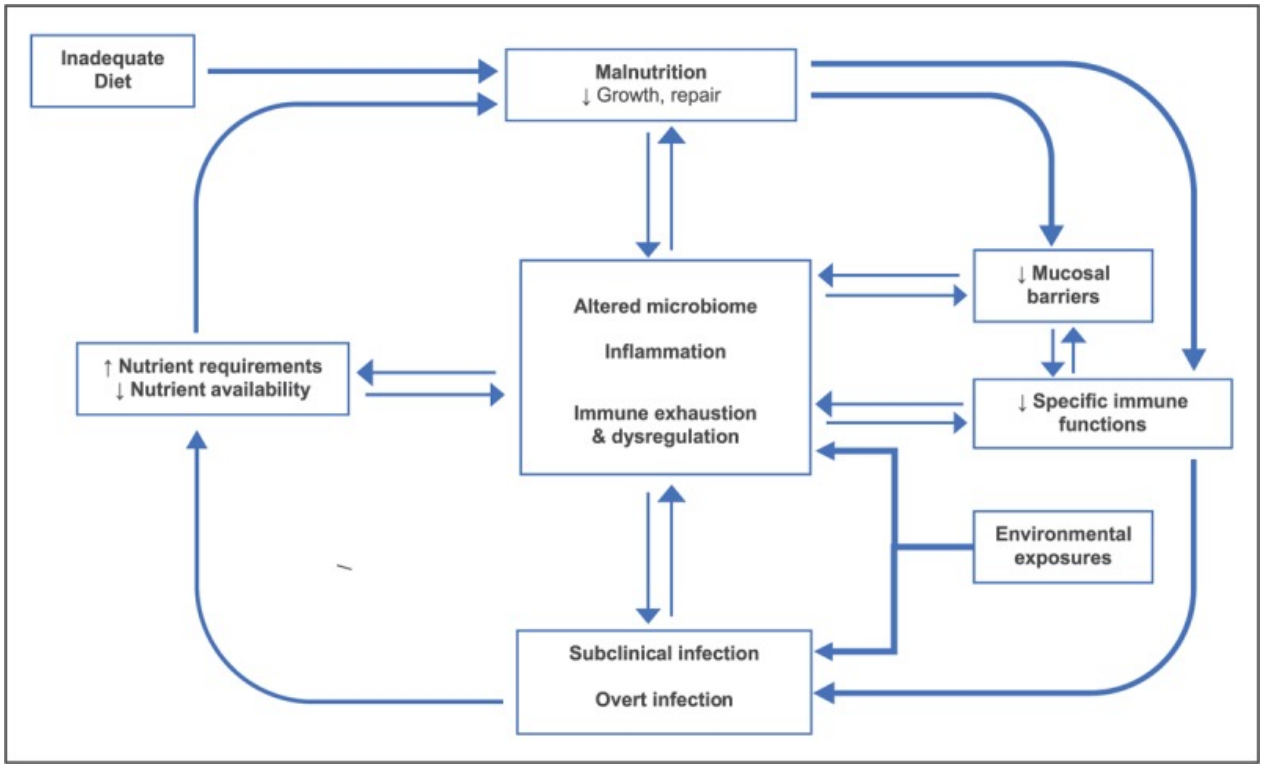


Figure 4: A growing understanding of a 'vicious cycle': interactions between malnutrition, infection and intestinal dysfunction (61)

1.3.2 Severe acute malnutrition and HIV infection

Eastern and Southern Africa continue to experience a high prevalence of both HIV and child

malnutrition (74-76). Although new HIV infections in children have declined (77), a substantial number of infected children present with late disease including severe malnutrition and concurrent bacterial infections due to late diagnosis and delayed antiretroviral therapy (ART) initiation (78, 79). Severely malnourished children living with HIV tend to have the non-oedematous phenotype of SAM even in areas where oedematous SAM is more common (49, 80). The prevalence of stunting and wasting remains high among children living with HIV in the era of universal ART access (76). At the peak of the HIV epidemic, nearly one-third of children hospitalized for SAM in sub-Saharan Africa were HIV-infected (termed HIV-SAM in this thesis) (81). The pathophysiology, clinical presentation, management and outcome of severely malnourished children is significantly affected by HIV (48). Older and younger infants tend to be more affected and the disease is more severe than SAM alone with multiple co-infections including bacterial, viral and parasitic infections that contribute to persistent diarrhoea, pneumonia, tuberculosis (80), skin infections and oral and oropharyngeal candidiasis (82). A study from Zambia on the impact of HIV infection on infectious diseases in children hospitalised for SAM and diarrhoea found no difference of pathogens and similar rates of septicaemia and pulmonary tuberculosis (confirmed on gastric lavage) were similar (49).

Figure 5 shows how HIV compounds the cycle of malnutrition and infection. The HIV inflammatory response contributes to anorexia, oral and oropharyngeal candidiasis reduce food intake, persistent diarrhoea and HIV-related enteropathy cause nutrient loss and the immunosuppression increases vulnerability to more frequent and prolonged infections. In the absence of data in children, WHO has used data from adults to recommend increasing caloric intake by 10% in HIV-infected children who are not symptomatic, by 20-30% in those who have chronic illness and by 50% to 100% in children who are severely malnourished until weight is recovered (83).

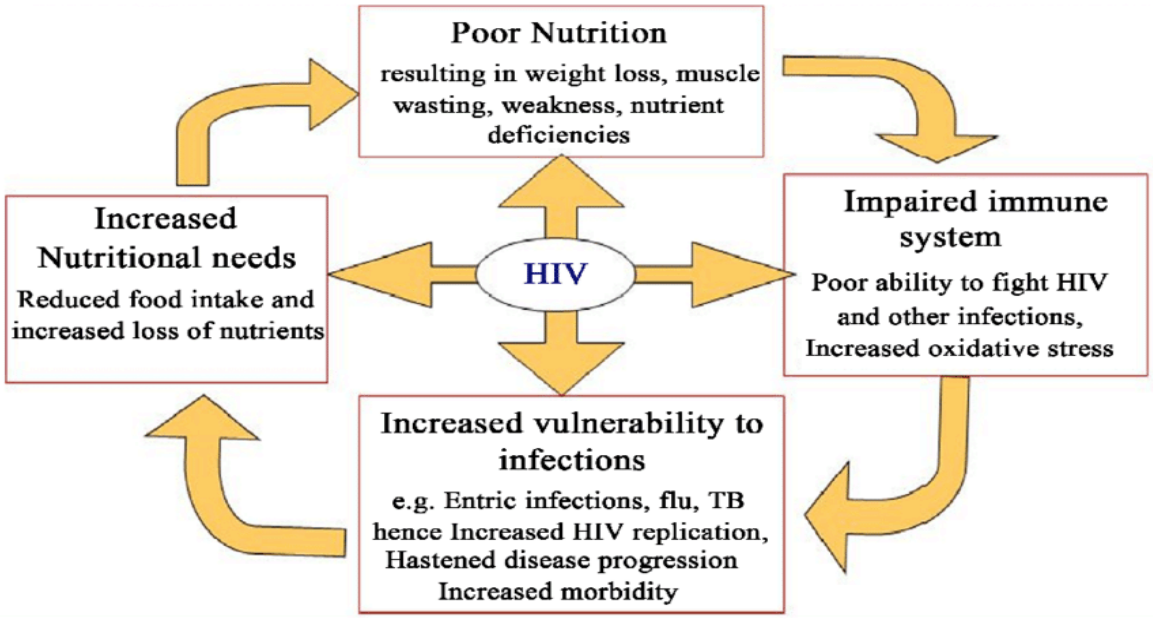


Figure 5: The vicious cycle of malnutrition and HIV *(Source: http://motherchildnutrition.org/nutrition-hiv-aids/nutrition-living-with-hiv-aids/cycle-o f-malnutrition-and-hiv-aids.html).*

1.4 MANAGEMENT OF COMPLICATED SEVERE ACUTE MALNUTRITION

The goals of SAM treatment are to reduce mortality in the short term, establish persistent nutritional recovery, and promote neurocognitive growth (47). The current approach to the management of SAM has evolved over decades and has largely been informed by expert advice, a few observational studies conducted in emergency situations, and only eight randomised controlled trials (47). Figures 6 and 7 illustrate the 10-step plan for in-patient management of difficult SAM as well as the diagnostic and therapeutic methodology for acute malnutrition. Children with complicated SAM receive treatment in in-patient facilities where the main objective is to restore normal physiological function through resuscitation, stabilisation and nutritional rehabilitation based on the WHO ten steps of 2003 which were updated in 2013 (36, 84). WHO developed the 10-management steps for children hospitalised for complicated SAM with the expectation of reducing case fatality rates to less than 10% (85). Adherence to SAM treatment guidelines is variable across facilities and case fatality rates of 10-40% continue to be reported in studies from sub-Saharan Africa (86).

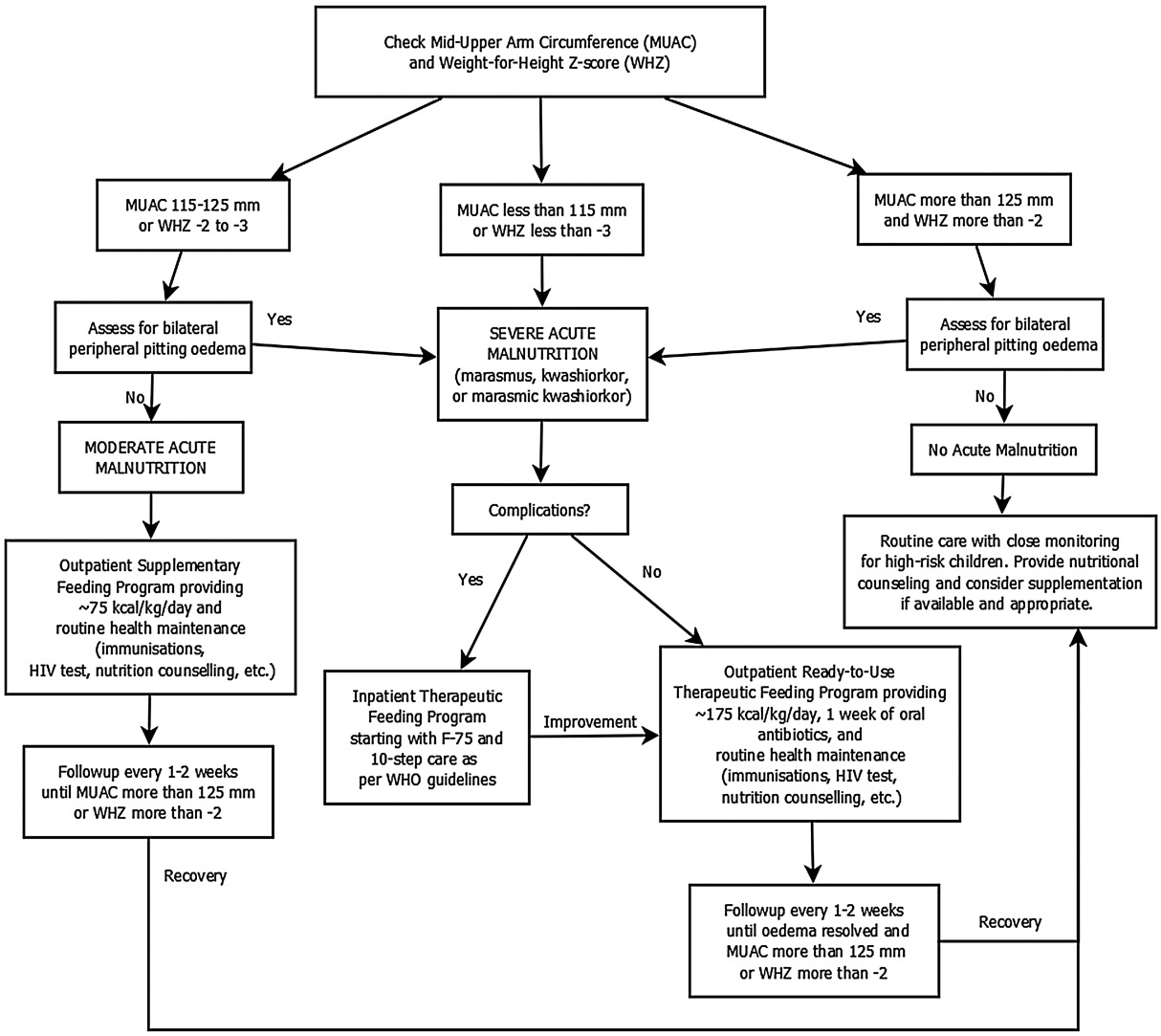


Figure 6: Diagnostic and treatment algorithm for acute malnutrition in children, adapted from reference (87)

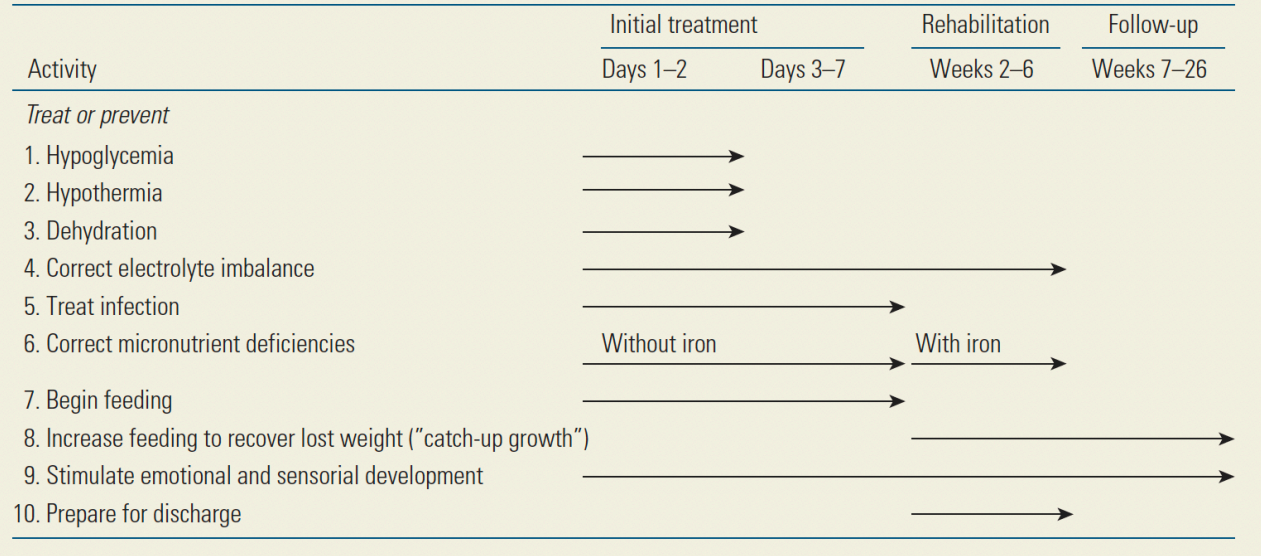


Figure 7: Ten-step in-patient management protocol for severe acute malnutrition, adapted from(84)

The 10-step plan for inpatient management of SAM is divided into three phases; resuscitation, rehabilitation, and follow-up with emotional and sensory stimulation cross-cutting through all phases (88). While these 10-steps are recommended, most of the evidence is not supported by randomised controlled trials (66). Phase one aims to correct the metabolic derangements of hypoglycaemia, hypothermia, dehydration and electrolyte imbalance and treat infection through small frequent feeds, rewarming, broad spectrum antibiotics and appropriate rehydration using intravenous fluids for shock and rehydration solution for malnutrition (ReSoMal) which contains less sodium and more potassium compared to the standard WHO oral rehydration solution (36). The rehabilitation phase continues feeds with a higher calorie formula 100 (F100) or RUTF with continued breastfeeding for breastfed children. During the follow-up phase, parents are urged to feed their children nutrient- and energy-dense foods, keep them active, and attend routine follow-up clinics. Although the treatment regimen is virtually the same, children with severe oedema have a higher risk of mortality during the inpatient phase. The only difference is that starting feed volumes are reduced from 130 ml/kg/day to 100 ml/kg/day (84).

1.4.1 Management of SAM and HIV infection

While there is evidence that severe acute malnutrition in children living with HIV is accompanied by more severe metabolic derangements and multiple pathology, the approach to management is broadly the same as that for children who are not living with HIV (89, 90). The metabolic and nutrient requirements for children living with HIV who have SAM have not been defined, with current evidence suggesting that there is increased metabolic stress and an altered metabolic response (91). Deaths during hospitalisation are nearly four-fold higher among severely malnourished children who are HIV-positive, compared to those who are not infected with HIV (30.4% vs 8.4%), despite use of standardised treatment protocols, and this mortality is not explained by anthropometric parameters alone (89). Mortality in children with HIV/SAM is also compounded by frequent delays in ART initiation. Antiretroviral therapy (ART) is now recommended following a diagnosis of HIV infection in children younger than five years old as its now classified as advanced disease (92). However in severely malnourished children living with HIV, ART initiation is complicated by the complex interplay between the clinical instability and changing physiology related to both HIV and SAM (93). Managing co-infections such as tuberculosis initially present a diagnostic dilemma given the overlapping clinical features, the possibility of drug-drug interactions and the possibility of precipitating the immune reconstitution inflammatory syndrome which has been described in some settings (94). These reasons may result in a significant number of children being discharged from hospital before ART is started (95).

1.4.1.1 ART initiation in children with HIV and SAM

There is no evidence from randomised clinical trials to inform when ART should be initiated in children who are hospitalised for complicated SAM and HIV infection. Current WHO guidelines recommend that ART be started initiation after the initial stabilisation and there are

signs of improvement (36). A retrospective study conducted in Malawi among children managed for uncomplicated SAM in the community, showed that starting ART within 21 days of starting therapeutic feeding resulted in better nutritional recovery (86% vs 60%, P<0.01) compared to starting after 21 days (96). This study did not compare virological or immunological recovery. A few randomised clinical trials have since been done to determine the best time to ART in children with HIV and SAM. In a trial where children, mean age 23.3 months hospitalised for SAM were randomised to receive ART within 14 days of admission or later, weight-for-age and height-for-age Z-score changes were better in the delayed arm at 24 weeks but there were no significant differences in immunological, virological and anthropometric outcomes at 48 weeks of follow up (97). In a Kenyan trial evaluating mortality and safety outcomes among children who initiated ART within 48 hours (urgent) versus 7-14 days (post-stabilisation) of enrolment, at median age 1.9 years, there was no difference in mortality even after adjusting for baseline CD4 counts between the groups at 24 weeks (98). Only 32% of children had malnutrition in this study and it was not set out to answer the question of when ART should be started in severely malnourished children.

1.4.2 In-patient mortality

The current standardised management protocols recommended for children with SAM are based on little high-quality evidence (36), and inpatient mortality reaches up to 30% in many institutions despite implementation (49, 64, 99, 100). However, it is recognised that a number of operational factors limit their implementation, specifically resources to manage unwell children, some of whom need intensive or high dependency care that is not available in most resource-limited settings. Compared to similarly nourished children, those with SAM have a nine-fold higher risk of death (5) with most deaths associated with infectious morbidity such as diarrhoea, acute respiratory infection and gram-negative sepsis (101). Additional factors

include electrolyte imbalance (102) resulting from severe diarrhoea or treatment given as well as co-morbidities (103). In a group of children treated for complicated SAM in a Zambian inpatient institution, more than two-thirds of the children had diarrhoea and over 40% had HIV (99). In-patient mortality among children hospitalized for SAM was 15.7%, according to a recent systematic review and meta-analysis, which also indicated that HIV infection, diarrhoea, pneumonia, shock, lack of appetite, and decreased WHZ were all independent risk factors for death (104).

The epidemiology and outcomes of SAM in the paediatric population were altered by the HIV epidemic (89). In a systematic review and meta-analysis of data from 17 studies, the average seroprevalence of HIV was 29%, and the mortality rate was 30% in HIV infected children as opposed to 8.4% in children without HIV (81). In a 2015 systematic review of causes of hospital admissions among children living with HIV globally, malnutrition/wasting ranked fourth (19%, 95%CI 6-32) among causes of hospitalisation in children after bacterial infections, AIDS-related illnesses, and malaria in the WHO-AFRO region (105).

A study on mortality of children under 5 years admitted to a malnutrition unit in an urban referral hospital in Uganda in 2017, showed a mortality of 25%; HIV infection, bacteraemia and low estimated glomerular filtration rate were all identified as risk factors (106). This mortality is similar to the 24% found in a study by Bachou et al which was conducted in 2003 a pre-ART era when HIV positivity rates were much higher (107). Lower mortality figures have been reported from other settings but most are above the WHO and Sphere targets of 5% and 10%, respectively. A retrospective study from Sudan, where just under 25% of the children had kwashiorkor, reported a mortality of 9.3% (108), and another retrospective study from the Democratic Republic of Congo (DRC) where just over two-thirds had kwashiorkor reported 7.5% mortality (109). The DRC study was retrospective with missing data and a high loss to follow-up which could have underestimated the mortality. Data from the pre-ART era

shows that mortality in children hospitalised for SAM was higher in those who were HIV infected children compared to the uninfected children (110, 111). Despite the substantial improvements in ART access, mortality among malnourished children initiating ART remains higher than among HIV-uninfected children (112). Risk factors for early death in children initiated on ART in Malawi include severe wasting and severe immunodeficiency (113). The DART and ARROW trials which enrolled both adults and children (>/= 4 years) from sub-Saharan African countries also showed a high mortality risk in the first 3 months following ART initiation with infections being the main driver for the deaths and low body mass index and anaemia as associated factors (114).

1.5 POST DISCHARGE MANAGEMENT OF SEVERE ACUTE MALNUTRITION

The WHO's 2013 recommendations for discharging children treated for SAM from an inpatient facility to the community were derived from expert opinion and are based on the following clinical criteria: resolution of medical complications or resolution of oedema, return of appetite, and alertness. Children should be discharged to community-based centres for management of acute malnutrition where they continue to receive nutritional rehabilitation and evaluation for any complications or relapse. Discharge from the outpatient facility is based on anthropometric recovery using the indicator that was used to confirm the diagnosis of SAM as follows:

- WHZ $\geq$ -2 with no oedema for at least 2 weeks,
- MUAC $\geq$125mm with no oedema for at least 2 weeks.

Those who were admitted based on oedema only are discharged using WHZ or MUAC criteria (36). The use of RUTF for community management of acute malnutrition (CMAM) has enabled a great majority of children with SAM to get access to effective treatment (115)

close to where they live. This however depends on functional health care delivery systems where there is efficient linkage of care between the hospitals and community, effective follow-up and monitoring coupled with uninterrupted supply of RUTF. In some settings, when it is deemed that the family will not have any access to community- based nutritional rehabilitation, discharge from hospital is delayed until anthropometric recovery. This has implications on duration of hospitalisation and may not always be feasible. The WHO protocol recommends periodic monitoring to avoid relapse after discharge from treatment programmes, but there is no clear guidance on the definition of relapse, how often the monitoring should be done and by whom (36, 116). The focus of this thesis will be on children discharged from the hospital following treatment of complicated SAM.

1.5.1 Post-discharge mortality

Regardless of the cause for hospitalization, children in sub-Saharan Africa who are discharged from hospitals continue to have a significant risk of mortality and hospital readmission (117, 118). According to a recent systematic review, estimates of the burden of post-discharge death range from 1 to 18 percent and occasionally exceed in-hospital mortality (117). Factors associated with this mortality include young age, malnutrition, previous hospitalisations, pneumonia and HIV infection (119-121). The risk of death tends to be highest in the first few months following hospital discharge (117). While great efforts have been made towards diagnosis and management of acute illness in low-resource settings using management algorithms and treatment guidelines, there has been less focus on post-discharge interventions to improve outcomes.

The ongoing risk of mortality in severely malnourished children is likely multifactorial including biological, social and environmental factors. Infections are the leading cause of death in malnourished children and both innate and adaptive immune system defects are

present (35). Incomplete nutritional and immune recovery may lead to an elevated risk of dying from ongoing chronic infections such as HIV and tuberculosis or nosocomial infections (35, 68, 70). Children return to the same home setting that is marked by poverty, inadequate water and sanitation, inadequate health services, and poor health-seeking behavior, all of which are acknowledged underlying factors of child malnutrition (11) as shown in the conceptual framework in Figure 8 (35).

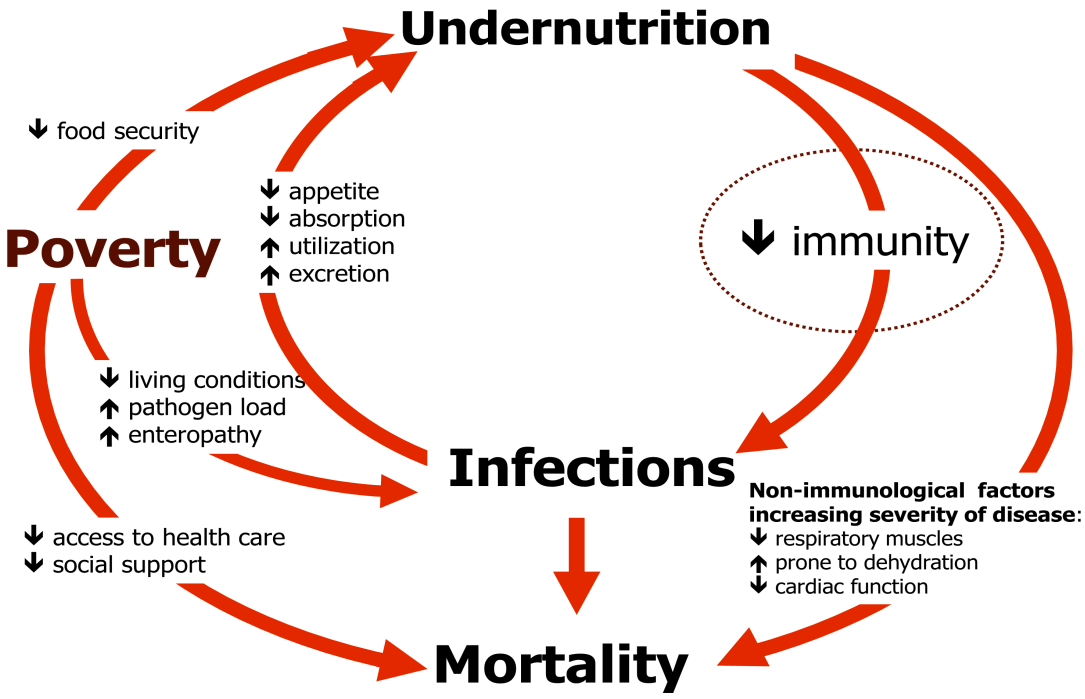


Figure 8: Conceptual framework on the relationship between malnutrition, infections and poverty (35)

There are sparse data on the one year outcomes of children discharged from hospital following treatment of severe acute malnutrition. Most data on acute malnutrition have come from children who are managed in the community for uncomplicated SAM where there are no overt signs of infection or metabolic decompensation. Mortality rates ranging between 0.06% and 10.4% were found in a recent systematic review of outcomes of children discharged from community-based nutritional rehabilitation centres after 6 – 24 months (116). High loss to

follow-up may have reduced the mortality rates in some of the studies (122, 123). Mortality following discharge from hospital is generally highest in the first 3 to 6 months, a time when nutritional recovery may not have been achieved (124, 125). A large prospective study to assess growth and mortality in children discharged from hospital following management of SAM conducted in Malawi in 2006 to 2007, had a post-discharge mortality of 10.4% at one year, with a 4 times higher risk of mortality in HIV-infected compared to uninfected children. Survival was greatest among those who were discharged from community feeding centres as nutritionally cured and clinically stable. High rates of loss to follow-up may have masked the actual rate of mortality (126). Between April 2011 and June 2012, mortality among 405 children with SAM and pneumonia in Bangladesh was 8.7%, which was similar to the 8.6% in-patient mortality (124). In this study, no specific criteria were followed for discharge and there was no nutritional rehabilitation available in the community. Similar rates of inpatient mortality (3.9%) and post-discharge mortality (2.7%) were found among a Gambian cohort of children aged 2-59 months who had been hospitalized for pneumonia, sepsis or meningitis. Mid-upper arm circumference at admission was independently correlated with mortality, which was seven times higher for children with MUACs of 115-130 mm, twenty-four times higher for children with MUACs of 105-114 mm, and forty-four times higher for children with MUACs of 105 mm (127). Similar to other studies, this cohort showed that MUAC performed better than WHZ to identify children at greater risk of dying (17)

1.5.2 Post-discharge morbidity

Children treated for complicated SAM who leave the hospital remain at risk for morbidity from persistent chronic infections or recently acquired infections. A knowledge of the underlying conditions that cause illness and subsequent death and their aetiology would contribute towards the development of strategies to reduce them. One of the outcomes of nutritional rehabilitation is anthropometric recovery. Ngari *et al* conducted a secondary analysis to determine the changes in susceptibility to infections resulting in hospitalisation

and death over a period of 12 months in children who were discharged from hospital following management of SAM and randomised to receive cotrimoxazole or placebo. Improvement in anthropometric (WHZ and MUAC) measurements was associated with a significant reduction in the risk of acquiring illness resulting in hospitalisation and death although the reduction in susceptibility lagged behind anthropometric improvement (128). In a 6-month follow-up study of children aged 6 to 23 months (median age 12 months) discharged from nutritional rehabilitation after treatment for SAM in Dhaka, the most common morbidities included fever (26%), cough (24%) and diarrhoea (20%) (129). While this captures the most vulnerable period for mortality and morbidity, the period of vulnerability may continue beyond 6 months . Another study in Dhaka, Bangladesh where 437 children aged 12-59 months were followed up for 12 months after attaining 80% of weight-for-height, showed a high incidence of diarrhoea (67% of children) and pneumonia (58%); overall, 2.3% of children died at the end of the follow-up period (122). In a prospective cohort study conducted in Ethiopia that tracked SAM-treated infants aged 6-59 months for a year along with matched non-wasted controls, those who were post-SAM had a 40% higher incidence rate ratio of any illness than community controls. The risk for the individual comorbidities (cough, diarrhoea, fever or difficult breathing) was nearly two times in the post-SAM group compared to controls during the 12 months of follow-up (130).

1.5.3 Nutritional recovery and relapse

Children who are discharged from the hospital after receiving treatment for complicated SAM have ongoing vulnerabilities due to incomplete nutritional recovery, ongoing infections, and potential hospital-acquired infections, as well as returning to the same suboptimal socioeconomic environment that may not support optimal recovery and growth (128, 131). A recent systematic review and secondary data analysis documented relapse rates varying between 0% to 37% at different time points following discharge. The main weakness was the inconsistent definitions of relapse. Additionally nearly all the studies reported relapse

following anthropometric recovery(132). A study on post-discharge outcomes for children aged 12-59 months treated for SAM and discharged after reaching 80% of the National Centre for Health Statistics (NCHS) anthropometric targets had a very low relapse rate of 0.6%, defined as oedema or <60% weight-for-height. Some survivor bias could have been introduced by excluding infants below 12 months of age, those who were critically ill, and those who lived far from the research unit in the original study, thus reducing the measured relapse rate(122). A community-based malnutrition program in India identified an association between the length of time following discharge and relapse rates. In the first three months, children were more likely to relapse (9.1%), and this likelihood decreased in the following months (2.1% at six months, and no relapse at 18 months) (133). In Ethiopia, a recent matched cohort study of nutritional status and morbidity in children who had recovered from SAM revealed that post-SAM cases had a 14 times higher risk of acquiring SAM compared to the control group throughout the course of the follow-up period of 12 months. Malnutrition relapse was defined as MAM (MUAC 11.0-12.0cm) and SAM (MUAC 11.0cm or bilateral pedal oedema) at any point throughout the research period (130). Of note is that this study did not use the standard WHO definitions of moderate or severe acute malnutrition.

Most studies of malnutrition relapse assess the risk following management of uncomplicated SAM at community level but children hospitalised for complicated SAM are most at risk. A secondary data analysis was conducted on data from the randomised trial daily cotrimoxazole prophylaxis trial post-discharge for complicated SAM among HIV uninfected Kenyan children (134). The risk of readmission with complicated SAM was 12% in this study and the study did not report on the incidence of uncomplicated SAM not needing hospitalisation(135). There is reason to suspect that relapse of SAM would be higher in the subgroup of children living with HIV infection, given the overlapping and interacting pathology of the two conditions. Hypotheses for the persisting risk of malnutrition relapse in children treated for SAM include the fact that gut bacteria that accompany wasting do not recover to microbiota

maturity during treatment thus affecting nutrient absorption(136), or alternatively, that there exists in the external environment, or even during foetal development, a heightened vulnerability to wasting following an initial episode. Such children would then be vulnerable to seasonal stresses (28).

1.5.4 Body composition during recovery from severe acute malnutrition

More and more research suggests that children's disease progression and health outcomes are significantly influenced by both the amount and distribution of lean mass and body fat (38). Fat and lean mass have utility in predicting clinical outcomes in various conditions including cancer (137, 138), chronic renal disease (139) and sickle cell disease in young people (140). Loss of lean mass has been associated with increased morbidity and poor outcomes in adults with chronic diseases (141-143) and the same has been documented in children (144). Wasting affects both lean and fat mass (145) and assessing these can be used to assess physiological recovery following SAM (146, 147). Loss of fat free mass and a low phase angle is related to mortality in elderly patients and those with chronic diseases including cancer (138). There is growing interest in assessing how malnutrition affects body composition and how this may be used to develop effective interventions to promote survival and long-term quality of life in children(145). A study of survivors of SAM 7 years after discharge from hospital showed reduced lean mass and preserved fat mass in cases compared to controls – a pattern that has potential implications for future metabolic disease(148). A more recent study followed up children hospitalised for SAM before two years of age in Zambia, at 7-12 years to determine anthropometry, body composition (using BIA and Deuterium oxide (D_2O)) and risk factors for chronic disease. Children who had survived SAM had significantly lower suprailiac skinfold and fat-free mass index (FFMI) by D_2O after adjusting for HIV and socioeconomic status (149). An inherent weakness in these follow-up

studies is survivor bias, given the high in-hospital and post-discharge mortality that characterise SAM, especially in areas of high HIV prevalence (78).

Outpatient studies of children receiving RUTF have shown that children gain FFM and, those who recovered from SAM have lower FM compared to community controls (146). A study in the Democratic Republic of Congo that randomised children to receive different types of RUTF assessed body composition using BIA and deuterium oxide isotope dilution, compared with controls. The malnourished children still had FFM deficits compared to controls at the time of anthropometric recovery, with a smaller difference in fat mass (150).

While malnutrition is classified as acute (referring to wasting and nutritional oedema) and chronic (referring to stunting), there is a growing evidence base showing the existence of both wasting and stunting in the same children (151), a condition termed concurrence which is associated with a mortality risk similar to that of severely wasted children (25). In a recent publication, Wells *et al* highlight the temporal links between weight faltering and slowing of linear growth, and argue for the consideration of the spectrum of growth deficits in the identification of children most at risk and the development of preventive interventions(37). Both wasting and stunting are associated with deficits in FM and FFM (152, 153); in fact, some data suggest that all forms of anthropometric deficits appear to adversely impact FM and FFM (154).

1.6 KNOWLEDGE GAPS

After receiving treatment for SAM, there is a demonstrable continuous risk of mortality among children discharged from the hospital. It is vital to identify those at risk and create tailored interventions to enhance their outcomes. Most studies have followed up children after discharge from nutritional rehabilitation units and achieving anthropometric recovery of WHZ

≥ -2, or MUAC ≥ 125mm and resolution of oedema. This misses the most critical period of vulnerability following discharge from hospital, which is characterised by incomplete nutritional and immunological recovery, ongoing chronic and possible nosocomial infections. Children hospitalized for complicated SAM have infectious complications at admission and upon discharge may still have an unresolved infection and be at risk for new infections due to ongoing malnutrition and probable immune dysfunction. Few studies have systematically collected morbidity data, documented hospital readmissions and mortality post-discharge. Additionally, there is need to generate evidence on the outcomes of children hospitalized with HIV and SAM in the era of universal antiretroviral therapy.

The return of appetite and resolution of metabolic disturbances are the main criteria for releasing children from the hospital with complicated SAM; ongoing nutritional deficiencies, subclinical inflammation, and reduced muscle mass, which are not assessed, likely put children at ongoing risk for infectious mortality or morbidity or relapse of malnutrition, are not considered. Additionally, children return to the same home environment which may be characterised by poverty, poor sanitation and suboptimal health-seeking behaviour. Some children experience nutritional recovery after discharge from hospital and remain clinically well, while others have a risk of relapse of SAM, ongoing morbidity and high mortality.

Anthropometry and oedema status currently used to classify, guide management and assess recovery do not estimate physiological or functional convalescence (37, 38). Assessing lean and fat mass in children treated for SAM may complement anthropometric measurements in identifying subgroups of children who are at increased risk for morbidity and mortality, and inform the development of interventions that will improve their outcomes. While some studies have shown that children with HIV-SAM have potential for catch-up anthropometric growth, the addition of body composition may further define the type of tissue they gain and whether this can be used to predict future metabolic disease.

1.7 OVERALL AIM

The overall aim of this thesis is to better understand ~~describe~~ the clinical outcomes of children with and without HIV infection who are hospitalised with complicated SAM, ~~stratified by HIV status~~, over the first year ~~52 weeks~~ post-discharge, and to identify factors at discharge from hospital that best predict these ~~long-term~~ outcomes.

The hypotheses in this thesis are guided by my conceptual framework in Figure 9.

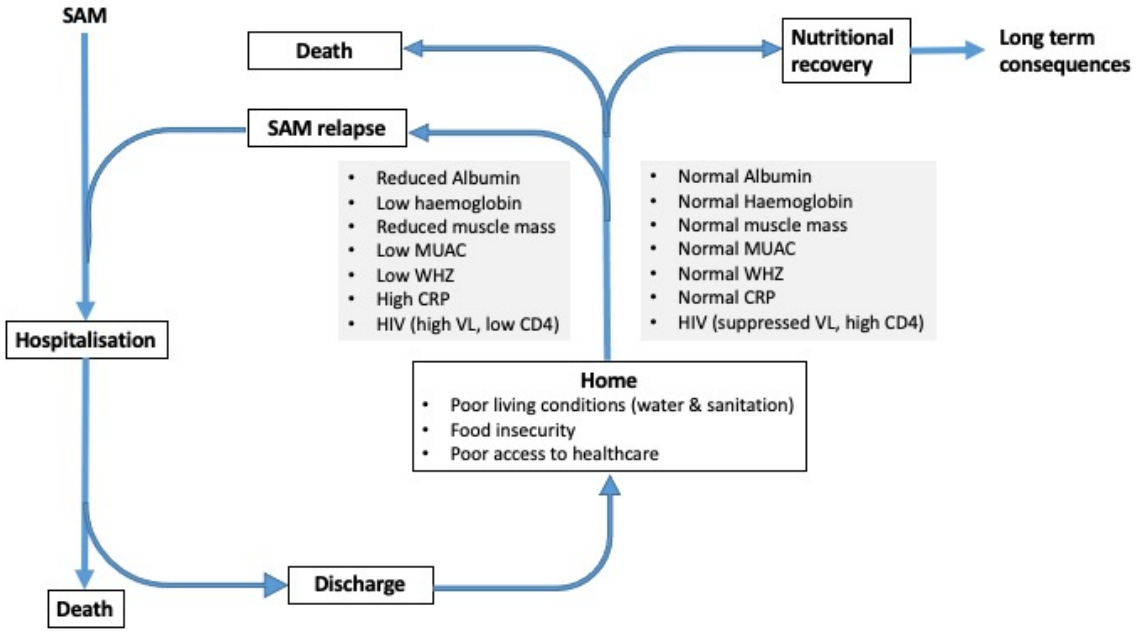


Figure 9: Conceptual framework for the thesis

Children hospitalised with complicated SAM are at high risk for mortality during hospitalisation and are discharged to the same home environment characterised by poor living conditions before complete recovery. This thesis focuses on the child related determinants of their outcome after discharge from hospital.

1.7.1 Research Objectives

Three specific objectives were formulated to address the study aim.

- The first objective (Paper 1 – Chapter 3) was to describe the one-year post discharge mortality in children managed for complicated severe acute malnutrition and determine the risk factors for mortality in Zambia and Zimbabwe.

- The second objective (Paper 2 – Chapter 4) was to describe the recovery of children following hospitalisation for complicated severe acute malnutrition in Zambia and Zimbabwe.
- The third objective (Paper 3 – Chapter 5) was to describe body composition in children one year after discharge from hospital for complicated severe acute malnutrition. Each objective had embedded research questions and hypotheses.

1.7.2 Research Questions and Hypotheses

Research Question 1: What is the one year mortality and associated risk factors in children discharged from hospital following management of severe acute malnutrition?

Hypothesis: Children who have SAM and HIV infection have a higher mortality compared to those with SAM alone.

Research Question 2: What is the pattern of recovery in children discharged from hospital following management of complicated severe acute malnutrition?

Hypotheses:

1. Children living with HIV have earlier and more frequent hospital readmissions, illness episodes and poorer nutritional recovery despite access to antiretroviral therapy, compared to children with SAM alone.
2. A combination of biological and social risk factors predict readmission and nutritional recovery.

Research Question 3: What is the pattern of body composition in children recovering from severe acute malnutrition one-year post-discharge from hospital and the association with time to hospital readmission or death?

Hypothesis: Fat mass measured as skin fold thickness, and lean mass, measured using

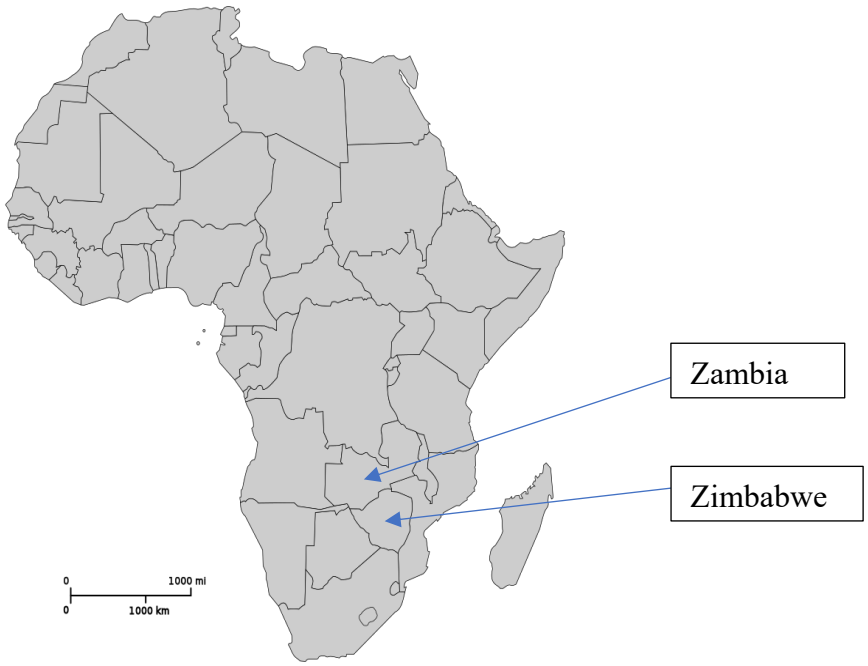
bioelectrical impedance analysis, predicts time to hospital readmission and death in children discharged from hospital after treatment for complicated severe acute malnutrition.

CHAPTER 2: METHODOLOGY

This chapter describes the study setting, study design, data measurement, and management and ethical considerations related to this thesis.

2.1 STUDY SETTING

The work in this thesis is embedded within the Health Outcomes Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM) study. The HOPE-SAM study was a longitudinal observational cohort study of children hospitalized for complicated SAM in tertiary hospitals at two sites in Zimbabwe (Parirenyatwa Hospital and Harare Children's Hospital) and one in Zambia (University Teaching Hospital, Lusaka). In addition to the main aim of this thesis, the HOPE SAM study also sought to better characterise the pathogenesis of SAM through nested laboratory sub-studies evaluating enteropathy, gut microbiota, metabolomics and immune cell function (155).



Picture 2: Map of Africa showing the study countries

At the time of the study, the Demographic and Health Surveys (DHS) for Zambia (156) and Zimbabwe (157) reported undernutrition statistics for children under 5 years of age, as shown in Table ~~2~~3.

Table 3: Demographic and Health Survey undernutrition statistics adapted from (156, 157)

	Stunted	**Wasted**	**Underweight**
Zambia	40%	6%	15%
Zimbabwe	27%	3%	8%

2.2 STUDY PARTICIPANTS

Sample Size

The observational cohort aimed to enrol up to 800 children with complicated SAM. The sample size calculation was based on the primary outcome of mortality. A mortality of 15%, and overall loss to follow-up of 15% would provide 560 evaluable children at 48 weeks, of whom 224 would have HIV-SAM based on an estimated inpatient HIV prevalence of 40% (81). This would provide >80% power to detect absolute differences of 17% in binary outcomes between HIV-positive and HIV-negative children with SAM, and of 0.33 times the standard deviation in continuous outcomes (155).

Participant selection

Caregivers of all children hospitalised with SAM were given information about the study, and children were enrolled as soon as possible after hospitalization. Eligible children were aged below 60 months and hospitalized with SAM, which was defined as weight-for-height Z-score (WHZ) <-3, mid-upper arm circumference (MUAC) <115mm or the presence of bilateral oedema in children above 6 months of age, and WHZ <-3 or nutritional oedema in

those below 6 months, based on WHO criteria (36). Children were admitted if they had medical complications, severe oedema or poor appetite or presented with one or more of the following Integrated Management of Childhood Illness (IMCI) danger signs; unable to drink or breastfeed, vomits everything, has had convulsions or was lethargic or unconscious (36).

Children who had malignancy, died prior to study enrolment or whose caregiver was not willing to learn the child's HIV status were ineligible for study enrolment.

All children with SAM whose caregivers were willing to provide written informed consent and to learn their child's HIV status were offered enrolment. Illiterate caregivers who had understood a verbal explanation of the study provided a thumb print in the presence of a witness. Participant locator information and permission to visit the caregiver/child at home were obtained following the consent to ensure good follow-up rates.

2.3 STUDY PROCEDURES

Study data was collected by the researcher and dedicated study staff. Baseline data on maternal and household characteristics, the child's past medical history and current illness were collected at baseline including anthropometry, The study procedures are summarised in Table 4.

Table 4*: *HOPE SAM Study procedures

Assessment	**Hospitalisation**		**Post-discharge[2]**				
	Baseline	**Discharge[1]**	**2w**	**4w**	**12w**	**24w**	**48w**
Caregiver informed consent to join observational cohort	x						
Summary checklist	x						
Locator information[3]	x						
Baseline data	x						
Daily clinical review	Daily during hospitalisation						
Blood collection (stored)	x	x			x	x	x
HIV testing	x						
CD4 count and viral load (HIV-infected children only)	x				x	x	x
Full blood count	x	x			x	x	x
Anthropometry	x	x	x	x	x	x	x
Skinfold thickness	-	x	x	x	x	x	x
Bioelectrical impedance analysis	x	x	x	x	x	x	x
Discharge data collection	-	x					
Daily morbidity diary			Daily during follow-up period by caregivers				
Follow-up clinic: history, examination, morbidity and mortality data			x	x	x	x	x

[1]The discharge procedures were undertaken on the day of discharge, or as close as possible to that date.

[2]Windows were created around these post-discharge time-points to maximize follow-up for caregivers who miss visits or are unavailable, as follows: 2 weeks (1-3 weeks); 4 weeks (3-5 weeks); 12 weeks (10-14 weeks); 24 weeks (20-28 weeks); 48 weeks (44-52 weeks).

[3]Locator information was updated using the locator form at subsequent visits if caregivers have moved or changed contact details.

2.3.1 Anthropometry measurements

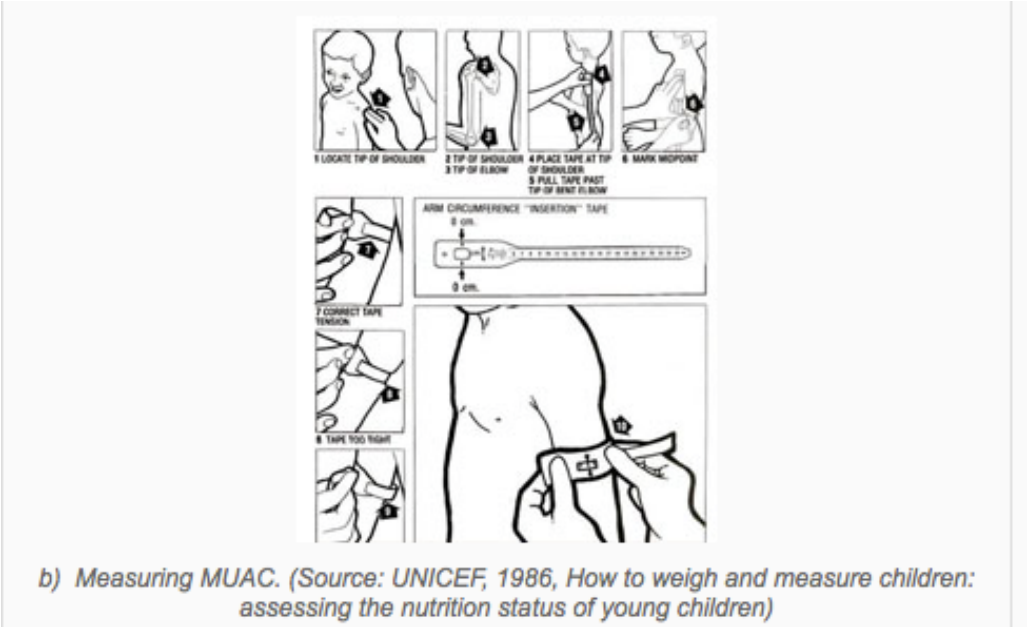
At the time of hospitalization, each child underwent weight, height/length (children <2 years), and MUAC measurement and oedema assessment by the hospital teams. Study nurses who had undergone training and standardization exercises for anthropometric measurements reassessed the children and recorded data onto case record forms.

Weight

Weights for infants and were obtained in triplicate using Seca 376 scales which were calibrated and serviced according to the manufacturer's guidelines to the nearest 0.01kg with the baby undressed. A two-in-one scale was used for children who were unable to stand or those who would not lie still on the baby scale. Young children who were cooperative were weighed on a standing Seca scale to the nearest 0.01kg. Three readings were taken for the weight and recorded on the CRF.

Mid-upper arm circumference

Mid-upper arm circumference was obtained using a non-stretchable UNICEF/WHO tape on the left arm. With the elbow bent at a right angle, the acromion process (shoulder tip) and the olecranon process (elbow tip) were located and the distance between them measured. The length was then divided in half to identify the mid-point which was marked using a washable marker. The MUAC tape was slipped onto the child's hand, up the straightened arm and the reading taken at the midpoint of the upper arm in triplicate.

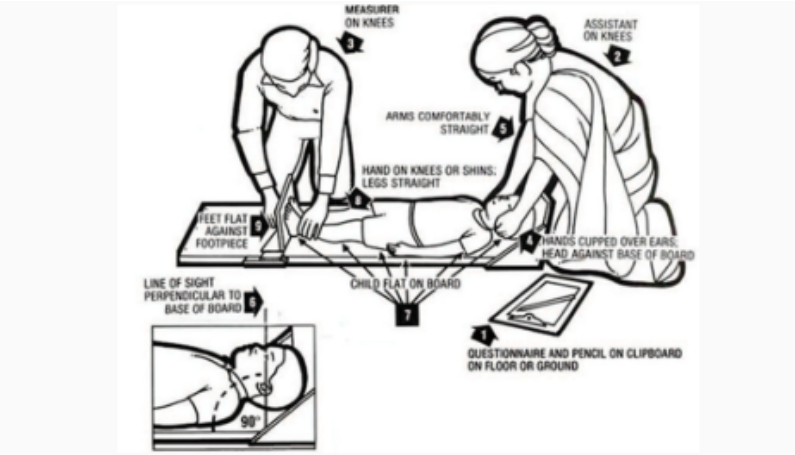


b) Measuring MUAC. (Source: UNICEF, 1986, How to weigh and measure children: assessing the nutrition status of young children)

Picture 3: Measuring MUAC

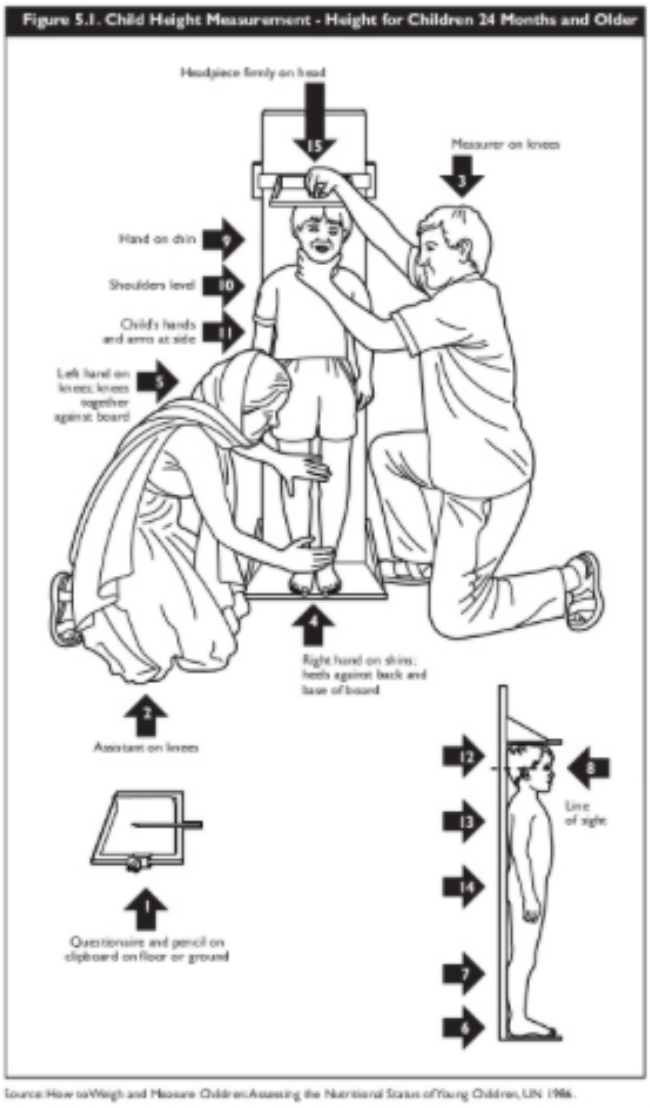
Length/Height

Length was measured using a height measuring board lying on a flat surface for children below the age of 2 years and those above 2 years of age had their standing height measured to the nearest millimetre and three readings obtained.



Measuring length. (Source: UNICEF, 1986, How to weigh and measure children: assessing the nutrition status of young children)

Picture 4: Measuring length



Picture 5: Measuring height

Skinfold thickness

Skinfolds were measured using Holtain calipers with pre-specified positions for calipers and multiple measurements following the standardised procedure by Lohman *et al* (158). The calipers were calibrated and measured zero prior to each clinic. The skinfold site was located and white eye liner pencil used to mark the points to measure. The thumb and forefinger of the left hand was used to elevate a fold of skin and subcutaneous fat about 1cm away from the measurement point and the calipers placed over the skinfold at right angles to the long axis of the fold, approximately halfway between the top of the fold and the body surface. The reading was taken once the dial first slowed to almost a stop. The measurement was recorded to the

nearest 0.2mm and repeated, so that three comparable readings were obtained and recorded on the CRF.

Holtain calipers: Image taken from: http://www.holtain.com

Picture 6: Holtain calipers

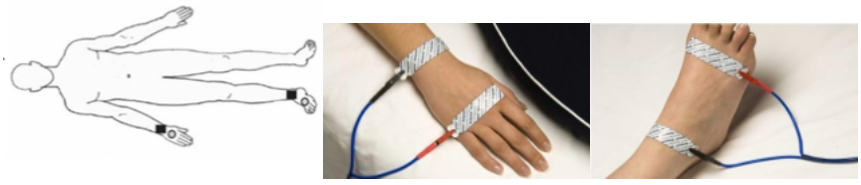
Picture 7: Triceps skinfold measurement

Picture 8: Suprailiac skinfold measurement

Picture 9: Subscapular skinfold measurement

Bioimpedance electrical analysis (BIA)

Body composition was measured by whole-body (wrist-ankle) bio-electrical impedance analysis (BodyStat 1500MD; BodyStat Ltd., Douglas, Isle of Man). The machine was calibrated before use to ensure that the impedance at 50kHz (Z50) reading was between 497 and 503Ohms. Measurements were conducted with the child lying supine, legs slightly apart and arms on the side of the body with palms facing down and not touching the body. Electrodes were placed on the dorsal aspect of the hand and just behind the knuckles and on the dorsal aspect of the foot just behind the toes and on the ankle between the medial and lateral malleoli allowing a minimum distance of 3cm between them to avoid interaction. The machine was switched on for at least a minute before taking the following measurements: Z5 (impedance at 5kHz), Z50 (impedance at 50 kHz), R50 (resistance at 50kHz), Xc50 (reactance at 50kHz) and phase angle. A successful measurement needed to have two recordings whose Z50 reading were 5 or less Ohms apart and repeat measurements were done till two such readings were obtained.



Picture 10: BIA measurement

HIV testing

HIV testing followed the national guidelines of provider initiated testing and counselling. The study offered HIV testing where it had not been done, using a rapid test antibody algorithm for children over 18 months, or HIV DNA PCR for children under 18 months. CD4 percentage and HIV viral load were measured in children who tested positive for HIV.

2.4 HOSPITALISATION

Care during hospitalisation was provided from a dedicated stand-alone unit with facilities for high dependency care at the University Teaching Hospital in Lusaka Zambia and from general paediatric wards in both hospitals in Zimbabwe. Daily data including clinical examination, resolution of acute infections and treatment/nutritional therapy received were collected. Study participants hospitalized more than once during the study period were only enrolled during their first admission. Children with HIV-SAM who were ART-naïve were referred for care.

In-hospital care for the study participants was provided by the hospital teams using country-adapted WHO guidelines for the management of children with severe acute malnutrition (36). Briefly, children went through a stabilisation phase that focused on managing life-threatening complications and feeding using F-75, a low-protein milk-based formula. This was followed by transitioning to the rehabilitation phase when F-100 (a milk formula with a higher protein

and energy content) or RUTF (a lipid-based paste combining milk powder, electrolytes and micronutrients) were gradually introduced while F-75 was reduced. This transition was indicated by the return of appetite. Children were discharged from hospital and transferred to outpatient care when their medical complications and oedema were resolving, and they were judged to be clinically well and alert. Discharge from hospital was not based on anthropometry.

Procedures at hospital discharge

Discharge summaries were written in the participant study clinic notes and also by the hospital team in hand-held notebooks, which the caregivers took with them and used for any subsequent clinic or hospital visits. Anthropometry, including body composition measurements, was done at the time of hospital discharge. Caregivers were given morbidity diaries (Appendix I) and pre-prepared stickers with pictures showing the common childhood illnesses (Appendix J) and shown how to complete the diary. The locator form was updated to ensure accurate residential addresses and contact numbers were on record and caregivers were given appointment cards for follow-up visits which contained the study nurse's contact details. This was in addition to the researcher's contact details which were on the informed consent form, a copy of which was given to the caregiver at the time of study enrolment. The study team checked that caregivers had all medication, RUTF, ART and knew when to return for refills. RUTF was available most of the time during the HOPE SAM study. Whenever there were stock-out of RUTF at hospital or community level, the Zambian site kept the children till they achieved WHZ >-2, or MUAC >125mm or resolution of nutritional oedema (personal communication, Beatrice Amadi). The sites in Zimbabwe did not change the discharge criteria even during RUTF stock-outs and encouraged caregivers to check periodically with their local clinics or the study site.

2.5 POST-DISCHARGE FOLLOW UP

Post-discharge follow up was conducted for 1 year after discharge from hospital in dedicated study clinics at 2, 4, 12, 24 and 48 weeks. Each visit week had a window period to ensure maximal follow-up. At each visit, a history of intercurrent illness including clinic visits or hospitalizations, medication given, and RUTF intake were obtained followed by anthropometric and body composition measurements. The handheld medical records (if available) and the morbidity diary were reviewed, and new diaries and stickers supplied. Nutritional supplements or RUTF were given according to local guidelines, and those who had a relapse of complicated SAM were readmitted into hospital.

A supply of RUTF (usually 2 weeks, depending on availability) was dispended at discharge and caregivers received counselling on how to feed the child. Children were expected to continue RUTF till they achieved moderate acute malnutrition (MAM) status on anthropometry. Frequent stockouts of RUTF were however experienced in Zimbabwe particularly in the urban and peri-urban areas. When RUTF was in stock, it would be discontinued once children attained MAM status, and caregivers were counselled on using locally available food. The practice was different in Zambia, where children with MAM received High Energy Protein Supplement (HEPS) or Corn-Soya Blend and the caregiver was counselled on how to prepare and give HEPS porridge in addition to nutritional counselling on "what to give, how much and how often" according to the Supplementary Feeding Programme for moderately malnourished children (36). Study participants were encouraged to return to the study sites (hospitals) whenever there were RUTF stock-outs in the local clinics but at times the stock-outs also affected the hospitals.

2.6 DATA MANAGEMENT

Data were collected on paper Case Report Forms and double-data entered onto a study specific database. Data were checked for accuracy and completeness. Duplicate and irrelevant

records were removed from the data set. Inconsistencies of sex and date of birth were checked and confirmed using the source CRFs. All anthropometry variables were listed by the participant identifier and week of study and checked for plausibility. Data were explored using descriptive statistics, boxplots, histograms or scatterplots. Outliers were set to missing.

2.7 STATISTICAL METHODS

Analysis was conducted using STATA version 14.0 (StataCorp. College Station, USA). Anthropometric z-scores were calculated using 2006 WHO growth standards.

Study outcomes

The main study outcomes were clinical (mortality, morbidity, relapse of malnutrition) and nutritional (weight, height, MUAC, skin-fold thickness, fat mass and fat free/lean mass by bioimpedance electrical analysis) assessed over 52 weeks of follow-up. The 48 week visit had a window period that was extended to 72 weeks in order to determine the vital status at 1 year. End of study visits occurred at a median of 49.3 (48.1, 51.4) weeks post-discharge, with 21.3% of children seen by 48 weeks and 84.2% of children seen by 52 weeks. End of study visits for all analyses were censored at 52 weeks.

Mortality during hospitalization was captured during the daily study physician visits and, after discharge, through study visits and by telephone and home visits for children who failed to attend study visits. Morbidity during hospitalization was assessed through daily clinical review of the children and any laboratory results. Illnesses that occurred after discharge from hospital were assessed, first, using the daily morbidity diaries, where caregivers were encouraged to record any episodes of illness, second, from caregiver recall and review of handheld medical records at each follow-up visit; and, thirdly, from data collected during hospitalization for children who were readmitted into the study site hospitals during the

follow-up period. Relapse of malnutrition after discharge from hospital was categorized as moderate acute malnutrition, uncomplicated SAM and complicated SAM, according to WHO definitions. Nutritional outcomes were expressed both as continuous variables (attained Z-score and change in Z-score between visits), and as categorical variables (moderate wasting, WHZ<-2; severe wasting, WHZ<-3; stunting, HAZ<-2; severe stunting, HAZ<-3; underweight and WAZ <-2).

Risk factors were evaluated at baseline, hospital discharge and over the period of follow-up for associations with clinical and nutritional outcomes.

Data on potential confounders were collected at enrolment into the study, at discharge and during the follow-up period. These included child feeding practices, household socioeconomic status (defined by household income and cooking method), maternal employment and education, and household factors such as water, sanitation and hygiene practices, availability of electricity, residence (rural, peri-urban or urban) and household size.

2.8 STATISTICAL ANALYSIS

The primary comparison was the clinical and nutritional outcomes of children stratified by HIV status. Specific statistical methods will be discussed in the Empirical chapters. Briefly for the mortality post-discharge, univariable and multivariable Cox regression models were used to identify associations between exposure variables and mortality and Kaplan-Meier curves used to describe the impact of exposures on the mortality. Exposure variables were chosen based on biological plausibility and published literature. Backward elimination with exit p value of 0.1 was used to identify a final main effects model. For the second objective on nutritional recovery, morbidity and readmission; Sankey diagrams were used to visualize the pattern of recovery by nutritional status in the one year after discharge. Ordinal logistic regression with multiple imputation using chained equations to account for missing data was used to model the predictors of moving between nutritional categories. Kaplan-Meir curves

were used to describe time to first hospital readmission. For the third paper on growth and body composition, Lowess plots were used to model changes in body composition and anthropometry over one year. Directed acyclic graphs (DAGs) were used to select the minimum set of covariates to adjust for in the relationship between the exposure and outcomes.

2.9 ETHICS

The HOPE SAM study was approved by the University of Zambia Biomedical Research Ethics Committee (010-02-16), the Medical Research Council of Zimbabwe (MRCZ/A/2044). The work for this PhD was approved by the HREC of the University of Witwatersrand. The ethics committee of Queen Mary University of London provided an advisory review. Written informed consent was obtained from the participants' parents/caregivers.

PART 2: EMPIRICAL CHAPTERS

CHAPTER 3: PAPER 1

POST-DISCHARGE MORTALITY

Bwakura-Dangarembizi M, Dumbura C, Amadi B, Ngosa D, Majo FD, Nathoo KJ, Mwakamui S, Mutasa K, Chasekwa B, Ntozini R, Kelly P, Prendergast AJ, the HOPE-SAM study team. Risk factors for post discharge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia, The American Journal of Clinical Nutrition 2021;113 (3): 665–674

SUMMARY

Children discharged from hospital following management of complicated severe acute malnutrition (SAM) have a high risk of mortality, especially among HIV-positive children. Few studies have examined mortality in the antiretroviral therapy (ART) era. The main objective of this paper was to ascertain 52-week mortality among children discharged from hospital for management of complicated SAM, and to identify independent predictors of mortality. A prospective cohort study whose primary outcome was mortality at 52 weeks after hospital discharge was conducted among children enrolled from three hospitals in Zambia and Zimbabwe between July 2016 and March 2018. Univariable and multivariable Cox regression models were used to identify independent risk factors for death, and to investigate whether HIV modifies these associations.

<u>The main findings are listed below:</u>

- Nearly 10% of children died in the 52 weeks after discharge from hospital.
- HIV infected children had an almost 4-fold higher mortality compared to HIV uninfected children.

- Ongoing SAM at discharge, non-oedematous SAM at hospitalisation and cerebral palsy were independent risk factors for mortality.

3.1 INTRODUCTION

Malnutrition underlies almost 50% of deaths in children below 5 years(5). Severe acute malnutrition (SAM) is characterized by muscle wasting with or without oedema and is classified into complicated and uncomplicated forms to guide clinical management. Children with a preserved appetite who are clinically well have uncomplicated SAM and are managed in the community. Those with poor appetite, severe oedema, medical complications or one or more Integrated Management of Childhood Illness danger signs (inability to drink, vomiting everything, convulsions, lethargic, or unconscious) have complicated SAM and are hospitalized(36). Despite standardized treatment guidelines(84), in-hospital mortality of children with complicated SAM in sub-Saharan Africa remains at 10-40%(89, 126, 159).

Children are discharged from hospital after resolution of complications and return of appetite to continue community-based nutritional rehabilitation. Emerging data suggest that there is high ongoing mortality risk following hospital discharge (160) and discharge from treatment programs(126). A recent systematic review reported mortality rates between 0.6% and 10.4%, 6-24 months after discharge from community-based therapeutic feeding centres following nutritional rehabilitation for uncomplicated SAM (116). Some of these studies had high loss to follow-up, implying that actual mortality may be greater(122, 123). It is likely that children hospitalized for complicated SAM have poorer outcomes than those with

uncomplicated SAM, but there were too few studies to differentiate mortality risk in these groups.

The ongoing risk of post-discharge mortality in children recovering from complicated SAM is likely due to incomplete nutritional and immune recovery, leading to an elevated risk of death from infections(68, 70, 161). In addition, children frequently return to a home environment characterized by poverty, poor water and sanitation, and inadequate health services, which are all recognized underlying determinants of child undernutrition(162). Another major factor underlying mortality in sub-Saharan Africa is concurrent HIV infection(33, 163). HIV has changed the epidemiology, clinical presentation and pathophysiology of SAM(89), resulting in a 3-fold higher risk of death compared to HIV-negative children prior to the availability of ART(81, 89, 164). It remains unclear whether this risk has changed since the introduction of 2013 World Health Organization (WHO) recommendations to treat all HIV-positive children regardless of clinical or immunological disease stage(165).

There is therefore an urgent need to ascertain risk factors for mortality after discharge from hospital with a view to providing additional support to those at highest risk and improving long-term outcomes. This study reports one-year post-discharge mortality in children with complicated SAM and determines the risk factors for mortality. Our hypothesis was that children with HIV and SAM have higher mortality than children with SAM alone, despite availability of ART, and that biological and social risk factors predict post-discharge mortality.

3.2 METHODS

3.2.1 Statistical methods

Baseline variables were compared between HIV-positive and HIV-negative groups using chi-squared or Fisher's exact tests for categorical variables and t-tests for continuous variables. Anthropometric Z-scores were calculated using 2006 WHO growth standards. Univariable and multivariable Cox regression models were used to explore associations between exposure variables and post-discharge mortality. The time at risk was calculated from hospital discharge to 52 weeks, or the date last seen, reported alive or the date of death. Selection of exposure variables was based on biological plausibility and the existing literature(166). All models included (regardless of statistical significance) the following *a priori* variables: age, sex, country, oedema at admission, SAM at discharge and HIV status. SAM at discharge was used as a composite variable since WHZ and MUAC showed collinearity (Supplementary Figure 1).

Backwards elimination with exit p-value 0.1 was undertaken for other risk factors, to produce a final "main effects" model. All available data were included, and no variable was missing for more than 2.5% of the participants. Multivariable fractional polynomials were used to investigate and account for non-linearity of effects of continuous predictors. Interactions between each included risk factor and HIV status were investigated to ascertain whether HIV modified the association between risk factors and mortality. Analyses were conducted using STATA version 14.0 (StataCorp., College Station, USA).

3.3 RESULTS

Seven hundred and fifty-five (755) children hospitalized with SAM were enrolled between 13th July 2016 and 31st March 2018. Five children were subsequently excluded from analysis. Among the 750 eligible children, 2 died and 3 withdrew consent prior to baseline data

collection (Figure 10). Of the 745 children included in the analyses, 37.3%, 32.3% and 30.3% were from Harare Central Hospital, University Teaching Hospital and Parirenyatwa Hospital, respectively.

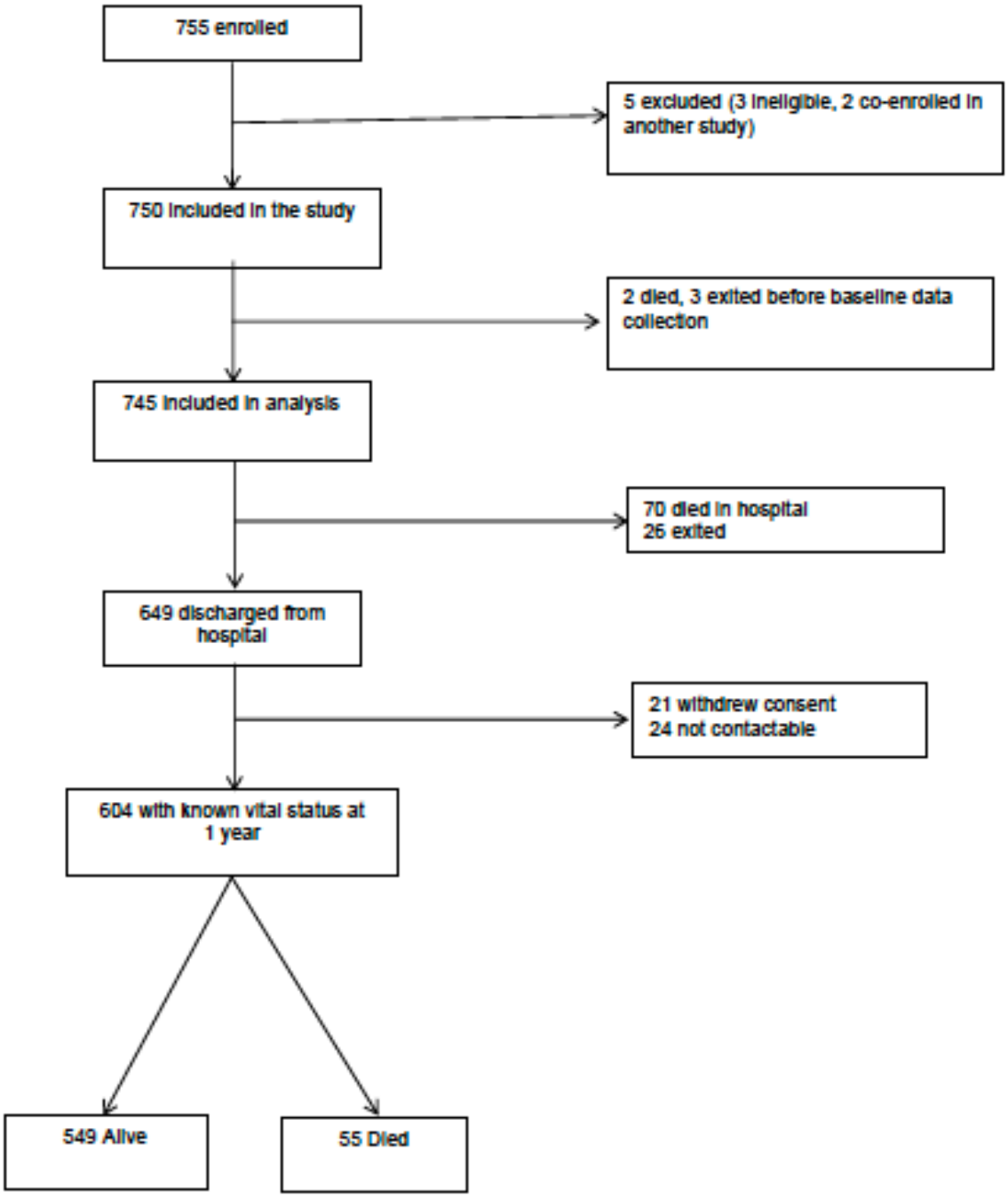


Figure 10 HOPE SAM study flow diagram

3.3.1 Baseline characteristics

Table 45 shows the baseline characteristics of children with SAM, of whom one-fifth were living with HIV. Among those who were not living with HIV, 16.6% were HIV-exposed but uninfected. Just over half of children were male; median age was 17.4 (IQR 12.8, 22.1) months, with 2.7% below 6 months of age. Almost two-thirds of children had oedematous malnutrition. Children living with HIV compared to those who were not living with HIV were significantly older, more wasted, more underweight, more stunted, and less likely to have oedema. A small proportion of children had chronic underlying conditions. Significantly more children with HIV, compared to those who were not living with HIV, were taking antituberculosis medication at admission and just over 40% of children living with HIV were receiving ART.

Table 5: Characteristics of children at hospitalization and discharge

	Admission				Discharge			
	All N=745	**HIV-positive N=162**	**HIV-negative N=583**	**P-value[1]**	**All N=649**	**HIV-positive N=130**	**HIV-negative N=519**	**P-value[1]**
Male	390/745 (52.4%)	82/162 (50.6%)	308/583 (52.8%)	0.62	344/649 (53.0%)	66/130 (50.8%)	278/519 (53.6%)	0.57
Age, months								
median (IQR)	17.4 (12.8, 22.1)	19.3 (13.6, 24.1)	17.1 (12.7, 21.5)	0.002	18.2 (13.6, 22.6)	19.4 (14.3, 24.5)	17.3 (13.2, 21.9)	<0.001
1-5 months	20/745 (2.7%)	4/162 (2.5%)	16/583 (2.7%)	0.07	17/649 (2.6%)	3/130 (2.3%)	14/519 (2.7%)	0.008
6-11 months	131/745 (17.6%)	27/162 (16.7%)	104/583 (17.8%)		89/649 (13.7%)	13/130 (10.0%)	76/519 (14.6%)	
12-23 months	458/745 (61.5%)	90/162 (55.6%)	368/583 (63.2%)		412/649 (63.5%)	74/130 (56.9%)	338/519 (65.2%)	
24-59 months	136/745 (18.3%)	41/162 (25.3%)	95/583 (16.3%)		131/649 (20.2%)	40/130 (30.8%)	91/519 (17.5%)	
Type of SAM at hospitalization								
Oedematous	480/745 (64.4%)	86/162 (53.1%)	394/583 (67.6%)	0.001	53/649 (8.2%)	8/130 (6.2%)	45/519 (8.6%)	0.35
Non-oedematous	265/745 (35.6%)	76/162 (46.9%)	189/583 (32.4%)		596/649 (91.8%)	122/130 (93.8%)	474/519 (91.4%)	
Nutritional status at discharge								
SAM	N/A	N/A	N/A	N/A	285/649 (43.9%)	72/130 (55.4%)	213/519 (41.1%)	0.003

No SAM	N/A	N/A	N/A		364/649 (56.1%)	58/130 (44.6%)	306/519 (59.0%)	
Anthropometry								
WHZ, mean (SD)	-2.9 (1.8)	3.6 (1.8)	-2.7 (1.8)	<0.001	-2.2 (1.5)	-2.4 (1.4)	-2.1 (1.5)	0.05
WAZ, mean (SD)	-3.8 (1.8)	-4.4 (1.5)	-3.6 (1.8)	<0.001	-3.3 (1.6)	-3.7 (1.2)	-3.2 (1.7)	0.002
HAZ, mean (SD)	-3.0 (1.6)	-3.3 (1.3)	-2.9 (1.6)	0.005	-3.1 (1.5)	-3.5 (1.2)	-3.0 (1.6)	0.003
MUAC, mm; mean (SD)	118 (17)	110 (15)	120 (17)	<0.001	123 (16)	117 (14)	124 (16)	<0.001
Chronic underlying conditions								
Cerebral palsy	32/745 (4.3%)	1/162 (0.6%)	31/583 (5.3%)	0.009	30/649 (4.6%)	1/130 (0.8%)	29/519 (5.6%)	0.02
Hydrocephalus	5/745 (0.7%)	0/162 (0.0%)	5/583 (0.9%)	0.24	3/649 (0.5%)	0/130 (0.0%)	3/519 (0.6%)	0.39
Congenital heart disease	14/745 (1.8%)	1/162 (0.6%)	13/583 (2.2%)	0.18	14/649 (2.1%)	1/130 (0.8%)	13/519 (2.5%)	0.22
Cleft palate	4/745 (0.5%)	0/162 (0.0%)	4/583 (0.7%)	0.29	3/649 (0.5%)	0/130 (0.0%)	3/519 (0.6%)	0.39
Medications								
TB medication	24/745 (3.2%)	13/162 (8.0%)	11/583 (1.9%)	<0.001	88/649 (13.6%)	40/130 (30.7%)	48/519 (9.2%)	<0.001
ART medication	N/A	66/162 (40.7%)	N/A	N/A	N/A	66/130 (50.7%)	N/A	N/A
Haemoglobin g/dL;								
median (IQR)[2]	N/A	N/A	N/A	N/A	9.3 (8.2, 10.3)	8.8 (7.7, 9.6)	9.4 (8.3, 10.4)	<0.001
Anaemia[3]								

None (≥ 11g/dL)	N/A	N/A	N/A	N/A	97/621 (15.6%)	13/123 (10.5%)	84/498 (16.9%)	0.02
Mild (10-10.9 g/dL)	N/A	N/A	N/A	N/A	102/621 (16.4%)	12/123 (9.8%)	90/498 (18.1%)	
Moderate (7-9.9 g/dL)	N/A	N/A	N/A	N/A	368/621 (59.3%)	84/123 (68.3%)	284/498 (57.0%)	
Severe (<7 g/dL)	N/A	N/A	N/A	N/A	54/621 (8.7%)	14/123 (11.4%)	40/498 (8.0%)	

Data are n/N (column %) unless stated.

[1]P value comparing HIV-positive and HIV-negative groups.

[2]Haemoglobin was measured at discharge; if no discharge haemoglobin measurement was available, the value closest to discharge was used.

[3]Anaemia was defined according to WHO guidelines (2011)

ART: antiretroviral therapy; HAZ: height-for-age Z-score; IQR: Interquartile range; MUAC: mid-upper arm circumference; N/A: not applicable, WAZ: weight-for-age Z score; WHZ: weight-for-height Z score; SAM: severe acute malnutrition; SD: standard deviation; TB: tuberculosis

Baseline caregiver and household characteristics are shown in Supplementary Table 1. Most children were cared for by their biological mothers. There was no difference in caregiver age by HIV status. Caregivers of children living with HIV were less likely to be married and had fewer years of formal education compared to those who were not living with HIV. Households of children living with HIV compared to those who were not, were more likely to be from peri-urban areas and had poorer sanitation facilities. There were no other significant differences between groups.

3.3.2 Discharge characteristics

The duration of hospitalization was median (IQR) 6 (2, 11) days. Seventy [9.4% (95% confidence interval 7.4, 11.7)] children died in hospital, leading to an incident death rate of 5.4 (95%CI 4.2, 6.8) per 100 child-weeks. Twenty-six children (3.4%) exited during hospitalization, meaning 649 children were followed up post-discharge (Figure 1). At discharge, anthropometry had improved compared to values at hospital admission for WHZ, WAZ and MUAC; almost half of children had ongoing SAM at the time of discharge, as defined by WHO criteria (Table 3). There was a four-fold increase in the number of children discharged on TB treatment compared to admission. Only half of the children living with HIV were discharged on ART; another 44% started ART post-discharge, and 16 (12.3%) never did during follow-up.

3.3.3 Post-discharge mortality

Of the 649 children discharged from hospital, vital status was ascertained for 93.1% at one year (Figure 10). Baseline characteristics of children with and without available vital status were similar (Supplementary Table 2). The median (IQR) follow-up time was 48.4 (39.9, 50.9) weeks. Of the 55 children known to have died, 32 (58.2%, 95%CI 44.1, 71.3) died in

the community and 23 (41.8%, 95%CI 28.7, 55.9) during a subsequent hospital readmission. The median time to death was 16.6 weeks (IQR 9.4, 21.9) but there was evidence of high ongoing mortality risk throughout follow-up (Figure 11). The incident death rate decreased from 0.4 (95%CI 0.2, 1.0) per 100 child-weeks between weeks 0-2 post-discharge, to 0.15 (0.1, 0.2) per 100 child-weeks between weeks 24-48 post-discharge.

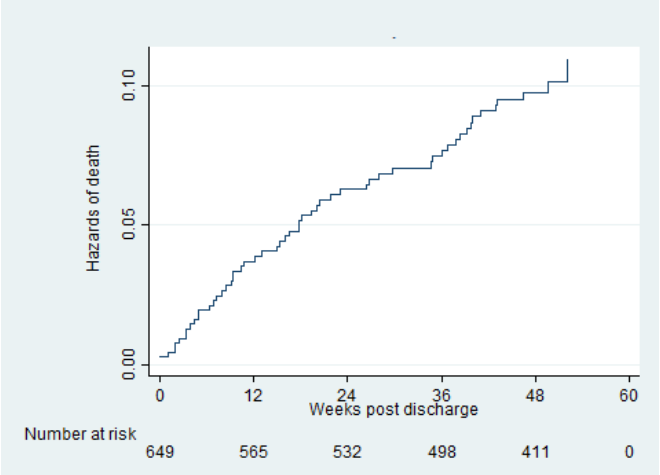


Figure 11: Hazard of death among children discharged after management of complicated severe acute malnutrition

3.3.3.1 Risk factors for mortality

Baseline characteristics of children who were alive at the end of follow-up and those who died are shown in Supplementary Table 3. Children who died were more wasted (mean WHZ -3.4 versus -2.1, P<0.001; mean MUAC 110mm vs. 124mm, P<0.001), underweight (mean WAZ -4.7 vs. -3.2, P<0.001) and stunted (mean HAZ -3.7 vs. -3.0, P=0.002), and had been hospitalized longer than those who survived (median 16 (IQR 8, 21) vs. 12 (7, 14) days, P=0.002). In the final multivariable model (Table ~~5~~6), four factors were significant independent predictors of death: HIV, non-oedematous malnutrition, SAM at discharge and cerebral palsy. Among children living with HIV, mortality was not significantly different according to ART status at the time of discharge (HR 1.09, 95%CI 0.49, 2.45; Supplementary Figure 2).

Children living with HIV compared to those who were not had an almost 4-fold higher mortality, with 20.0% (95%CI 13.5, 27.9) of children living with HIV dying compared to 5.6% (3.8, 7.9) of those who were not living with HIV (adjusted HR 3.83, 95%CI 2.15, 6.82); Figure 12A. Children with non-oedematous compared to oedematous SAM at admission to hospital had twice the mortality risk over the first year post-discharge (aHR 2.23, 95%CI 1.24, 4.01); Figure 12B. Compared to children who did not still have SAM at the time of discharge, those with SAM had over 2-fold higher post-discharge mortality (aHR 2.28, 95%CI 1.22, 4.25); Figure 12C. Children with cerebral palsy had almost 6-fold higher mortality than children without cerebral palsy (aHR 5.60, 95%CI 2.72, 11.50); Figure 12D. Sex, age, duration of hospitalization, primary caregiver and household characteristics were not associated with post-discharge mortality. There was no evidence of interaction between HIV status and SAM at discharge (P=0.33), cerebral palsy (P=0.22) or oedema (P=0.19) in the analyses of post-discharge mortality.

Table 6: Univariable and multivariable analysis of factors associated with post-discharge mortality

	Survived N=594	Died N=55	Unadjusted HR[1] (95%CI)	Adjusted HR[2] (95%CI)	P-value[3]
Child Characteristics					
Country					
Zimbabwe	420 (91.1%)	41 (8.9%)	Reference		
Zambia	174 (92.6%)	14 (7.4%)	0.94 (0.51, 1.72)	0.72 (0.39, 1.35)	0.31
Sex					
Female	275 (90.2%)	30 (9.8%)	Reference		
Male	319 (92.8%)	25 (7.2%)	1.37 (0.81, 2.33)	1.15 (0.67, 1.97)	0.62
Age at discharge, months					
median (IQR)	18.4 (13.6, 22.7)	17.0 (10.1, 22.0)	0.97 (0.94, 1.01)	0.98 (0.94, 1.01)	0.17
HIV status					
HIV-negative	490 (94.4%)	29 (5.6%)	Reference		
HIV-positive	104 (80.0%)	26 (20.0%)	3.69 (2.17, 6.26)	3.83 (2.15, 6.82)	<0.001
Type of SAM at hospitalization					
Oedematous	402 (95.3%)	20 (4.7%)	Reference		
None oedematous	192 (84.6%)	35 (15.4%)	3.45 (1.99, 5.97)	2.23 (1.24, 4.01)	0.007
Nutritional status at discharge					
No SAM	349 (95.9%)	15 (4.1%)	Reference		
SAM	245 (85.9%)	40 (14.1%)	3.69 (2.04, 6.68)	2.28 (1.22, 4.25)	0.010
Chronic underlying conditions[4]					
No cerebral palsy	574/619 (92.7%)	45/619 (7.3%)	Reference		
Cerebral palsy[5]	20/30 (66.7%)	10/30 (33.3%)	5.12 (2.58, 10.16)	5.60 (2.72, 11.50)	<0.001

Data are n (row %) unless stated
[1]Unadjusted Hazard Ratios were estimated using Cox regression analysis.

[2]Adjusted Hazard Ratios were derived from a multivariable fractional polynomial model which contained all other variables in the table.
[3]P value from mfp Cox regression model
[4]Children who had heart disease and cleft palate excluded due to small numbers
[5]One child had both cerebral palsy and hydrocephalus
HAZ: height-for-age Z-score; IQR: Interquartile range; MUAC: mid-upper arm circumference; WAZ: weight-for-age Z score; WHZ: weight-for-height Z score; SAM: severe acute malnutrition; SD: standard deviation; TB: tuberculosis

The following variables were offered up to the backward stepwise regression model; site, country, residence, anaemia, hemoglobin, sex, age at discharge, HIV status, WHZ at discharge, HAZ at discharge, WAZ at discharge, mean MUAC at discharge, oedema at admission, oedema at discharge, SAM at discharge, TB at discharge, cerebral palsy, duration of illness, duration of hospitalization, discharge against medical advice, primary caregiver, maternal age, maternal education, caregiver marital status, caregiver employment, water source, type of toilet, electricity, cooking location. The following variables were retained (P<0.1) by the backward stepwise regression procedure; site, country, residence, age at discharge, oedema at admission, HAZ at discharge, WAZ at discharge, haemoglobin, HIV status, cerebral palsy, primary caregiver, caregiver marital status, caregiver employment, cooking facilities.
These variables were all offered to the final mfp model, except HAZ and WAZ at discharge, which were collinear with SAM at discharge. The Table shows the variables which were either retained by the final mfp model at P<0.05, or which were forced into the model as *a priori* variables (age, sex, country, oedema at admission, SAM at discharge and HIV status.)

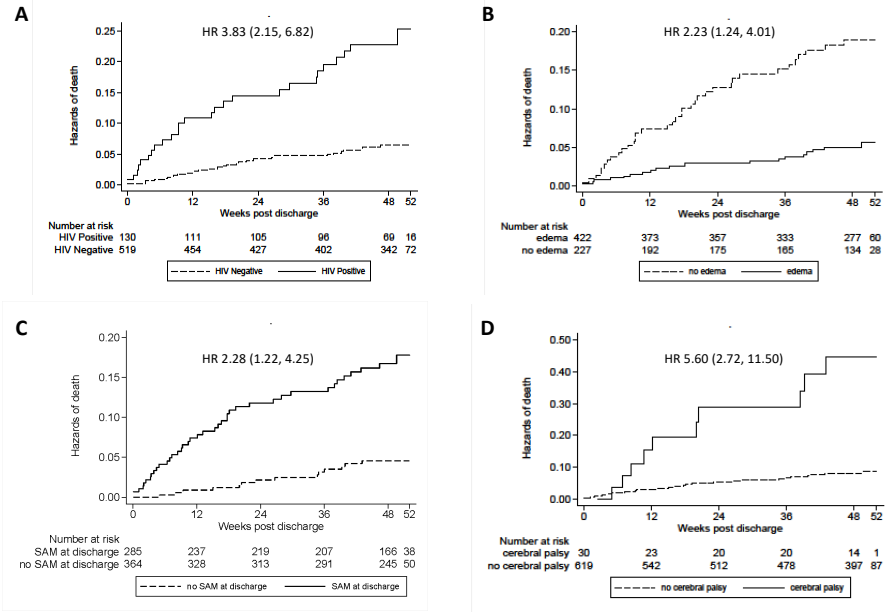


Figure 12: Risk factors for post-discharge mortality.

Kaplan-Meier plots showing the hazard of post-discharge death associated with A HIV status, B oedema at hospitalization, C ongoing SAM at discharge, and D cerebral palsy. Adjusted hazard ratios were derived from a multivariable Cox regression model.

3.4 DISCUSSION

Children hospitalized for complicated SAM have high inpatient mortality, but few studies have reported the ongoing risk of death after hospital discharge. In this longitudinal study from a high HIV prevalence setting, we show that almost one-in-ten children died in the year following discharge. Mortality was particularly high among children living with HIV, who had almost 4-fold higher risk of death than those who were not living with HIV, regardless of being on ART. While the incident death rate fell over time following discharge from hospital, the cumulative mortality was almost 10%, which was similar to inpatient mortality during the index admission. We identified three additional independent predictors of mortality: ongoing SAM at the time of discharge, non-oedematous malnutrition and underlying cerebral palsy. The high mortality shown here highlights the long period of vulnerability among children treated for SAM in hospital, particularly in those with HIV infection. Collectively, our data

highlight the urgent need for additional interventions during convalescence to improve long-term outcomes of children with complicated SAM.

We specifically set out to stratify post-discharge mortality by HIV status, because studies conducted in the pre-ART era, or when ART initiation was guided by the degree of immunosuppression, reported higher mortality among children living with HIV compared to those with SAM but not living with HIV(118, 125, 167). Our findings confirm that post-discharge mortality remains almost 4-fold higher in children living with HIV, despite test and treat guidelines recommending ART once a diagnosis of HIV is made. Malnutrition and HIV interact in a vicious cycle driven by shared biological, immunological and socioeconomic factors(168, 169). Malnutrition remains one of the commonest presentations of pediatric HIV infection(33, 170-172), with wasting being a risk factor for mortality even after initiation of ART(94). Chronic inflammation, particularly in children with concurrent HIV and SAM, likely contributes to wasting and has been associated with mortality and hospitalisation(94, 173). Children living with HIV have greater nutritional needs than those who are not living with HIV. WHO recommends that calories should be increased for children living with HIV as follows; by 10% for an asymptomatic child, 20-30% with chronic illness and 50-100% with severe malnutrition, until weight is recovered (83). There are currently no guidelines regarding adjustment to therapeutic feeds for children living with HIV to accommodate additional energy requirements and this was not practiced in our study hospitals. There is uncertainty regarding the optimal timing of ART initiation in children with complicated SAM. Clinicians are often concerned about starting ART in sick children due to potential drug toxicity, immune reconstitution inflammatory syndrome, and poor adherence; however, early ART initiation is safe and feasible (98), and WHO recommends starting ART as soon as possible after stabilization (36). Despite these recommendations, it is striking that only half of the children living with HIV were on treatment at the time of discharge and among those not on ART, one-quarter never started during the subsequent year of follow-up. Mortality did not

differ significantly between children who had started or not started ART at discharge. It was therefore not possible to determine whether inpatient ART initiation would have reduced mortality in this high-risk group, but clearly unnecessary delays arise from onward referral to HIV clinics for ART initiation. Maintaining a continuum of care from hospital discharge into a community-based model offering integrated HIV and nutrition care may improve the outcome of children with these highly interdependent conditions.

Mortality was over 2-fold higher in children with SAM at the time of hospital discharge, compared to those who no longer meet WHO criteria for SAM. Although most children had lost their oedema at the time of discharge, 43.9% had SAM at discharge. Current WHO discharge recommendations from inpatient care are based on resolution of medical and metabolic complications with a view to continuing nutritional rehabilitation as outpatients(36). Data from this cohort confirm the ongoing mortality risk associated with incomplete nutritional recovery. Current treatment protocols do not address underlying causes of malnutrition such as household food insecurity, caregiver wellbeing and suboptimal home environments. We found no associations between death and caregiver or household characteristics in this cohort, but this may reflect the limited range of variables we evaluated. Factors such as maternal mental health, caregiving capabilities and access to healthcare were not evaluated. Nearly 60% of deaths in HOPE-SAM occurred in the community, similar to a Ugandan study of post-discharge mortality in children with acute infections(174). This may reflect the impoverished home environment and poor access to functional health systems. Several prior studies have reported that the highest risk of mortality occurs in the first 3 months post-discharge(119, 125, 127). By contrast, our study showed that the risk of death remained consistent throughout the first year post-discharge. This suggests that if our follow-

up period had been longer than one year, mortality may have been higher, suggesting a much more protracted window of vulnerability than is generally recognised.

Consistent with several other studies(82, 175-178), children living with HIV were less likely to have oedematous SAM compared to those who were not living with HIV, suggesting a degree of immune competence may be required to generate oedema. Nutritional oedema is an acute condition, and children with moderate underlying deficits in weight and height but relatively well-preserved body fat appear to respond well to treatment in the absence of complications(179). Wasting, by contrast, is a more long-term process, and children without oedema in our cohort had lower anthropometric Z-scores. The underlying tissue loss and metabolic dysregulation may require a longer period of recovery, leading to an extended window of vulnerability. Cerebral palsy affected a minority of children but was associated with almost 6-fold higher mortality; one-third of children with cerebral palsy died after discharge from hospital. Many children with cerebral palsy have inherent feeding difficulties and may require more targeted support following hospital discharge.

This is one of the largest longitudinal studies of children hospitalized for complicated SAM to date. We achieved a high ascertainment of vital status one year after discharge through mobile phone contact and home visits among an extremely mobile population. We pre-specified that we would stratify outcomes by HIV status, whereas many studies have not specifically ascertained HIV status among children with SAM(125, 127). Our study has limitations: in particular, we did not have data on several potential risk factors for mortality, including birth weight, gestational age, health-seeking behaviour, adherence to RUTF, and co-infections. Where haemoglobin was not measured at the time of discharge, we used values measured closer to the time of admission. Severe anaemia during hospitalization has been identified as a

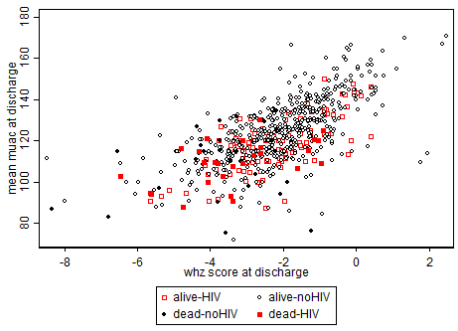
risk factor for post-discharge mortality in sub-Saharan Africa regardless of underlying malnutrition(180, 181); while most children in this cohort were anaemic, less than 10% had severe anaemia, which may have influenced our results. Lastly, our hospital study did not collect data on community-based nutritional rehabilitation post-discharge, which could have influenced mortality.

3.5 CONCLUSION

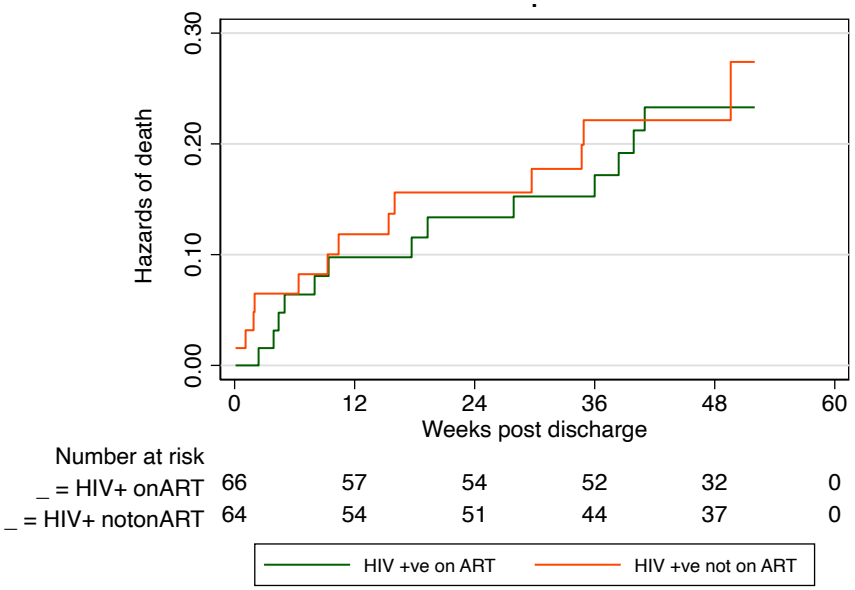
In summary, post-discharge mortality over one year following management of complicated SAM remains unacceptably high, and is similar to inpatient mortality. Overall, one-in-five children managed for complicated SAM died either in hospital or in the community. Mortality was almost four-fold higher among children living with HIV compared to those who were not.. Thus, efforts to eliminate mother-to-child HIV transmission and identify HIV-infected infants early are critical to improving health outcomes. Furthermore, ART-naïve children with complicated SAM should start ART during hospitalization to avoid missing a window of opportunity, and be discharged to a clearly defined and functional continuum of integrated care. ART alone may be insufficient to reduce the excess post-discharge mortality among children with HIV-SAM, and additional intervention strategies should be evaluated. Almost half the children in this study were discharged from hospital with ongoing SAM, and had twice the mortality risk compared to children who no longer met the criteria for SAM following inpatient nutritional rehabilitation. Ensuring that the necessary resources and services for outpatient care are available and accessible is important to bridge this period of vulnerability. We found that children in our setting with non-oedematous SAM and with underlying cerebral palsy are particularly vulnerable and may require more intensive follow-up. Further study into the causes of post-discharge death, and the caregiver and home

environment, may inform a more comprehensive package of care to reduce the unacceptably high burden of post-discharge mortality among children with complicated SAM.

3.6 SUPPLEMENTARY MATERIAL



Supplementary figure 1: Relationship between mean MUAC and WHZ score at discharge



Supplementary figure 2 : Hazards of post-discharge mortality among HIV positive children by ART status

Supplementary Table 1 Baseline Caregiver and Household Characteristics

	All N=745[a]	**HIV-positive N=162**	**HIV-negative N=583**	**P-value[b]**
Primary caregiver				
• Mother	684/727 (94%)	147/156 (94%)	537/571 (94%)	0.90
• Other	43/727 (6%)	9/156 (6%)	34/571 (6%)	
Age, years; median (IQR)	26 (22, 31)	28 (23, 32)	26 (22, 30)	0.07
15-19 years	67/722 (9%)	9/156 (6%)	58/566 (10%)	0.11
20-39 years	625/722 (87%)	143/156 (92%)	482/566 (85%)	
≥40 years	30/722 (4%)	4/156 (2%)	26/566 (5%)	
Marital status				
• Married or stable union	571/727 (73%)	104/156 (67%)	430/571 (75%)	0.03
• Other	156/727 (27%)	52/156 (33%)	141/571 (25%)	
Education, years; median (IQR)	10 (7, 11)	9 (7, 11)	10 (8, 11)	0.03
Employment				
• None	431/723 (60%)	84/156 (54%)	347/567 (61%)	0.08
• skilled	53/723 (7%)	9/156 (6%)	44/567 (8%)	
• unskilled	239/723 (33%)	63/156 (40%)	176/567 (31%)	

Residence				
• Rural	113/739 (15%)	25/161 (16%)	88/578 (15%)	0.02
• Urban	451/739 (61%)	85/161 (53%)	366/578 (63%)	
• Peri-urban	175/739 (24%)	51/161 (31%)	124/578 (22%)	
Drinking water source				
• Improved	689/736 (94%)	153/161 (95%)	536/575 (93%)	0.41
• Unimproved	47/736 (6%)	8/161 (5%)	39/575 (7%)	
Toilet facilities				
• Improved	651/738 (88%)	130/160 (81%)	521/578 (90%)	0.004
• Unimproved	57/738 (8%)	22/160 (14%)	35/578 (6%)	
• None	30/738 (4%)	8/160 (5%)	22/578 (4%)	
Household electricity				
Yes	344/728 (47%)	73/157 (46%)	271/571 (47%)	0.83
Cooking location				
• Indoors	431/727 (59%)	90/158 (57%)	341/569 (60%)	0.80
• Outdoors	145/727 (20%)	33/158 (21%)	112/569 (20%)	
• Both	151/727 (21%)	35/158 (22%)	116/569 (20%)	

Data are n/N (column %) unless stated.

[a]5 children did not have baseline data collected because they died or their caregiver withdrew consent between enrolment and baseline data collection.

[b]P value comparing HIV-positive and HIV-negative groups.

IQR: Interquartile range; SAM: severe acute malnutrition; SD: standard deviation

Supplementary Table 2: Baseline characteristics of children with and without data on one-year vital status

	Vital status known N=604	**Vital status unknown N=45**	**P value[a]**
Child Characteristics			
Gender • Male • Female	 324/604 (54%) 280/604 (46%)	 20/45 (44%) 25/45 (56%)	 0.23
Age at discharge, months; median (IQR)	18.2 (13.6, 22.5)	17.8 (14.2, 26.3)	0.11
• 1-5 months • 6-11 months • 12-23 months • 24-59 months	17/604 (3%) 83/604 (14%) 387/604 (64%) 117/604 (19%)	0/45 (0%) 6/45 (13%) 25/45 (56%) 14/45 (31%)	0.20
Haemoglobin, g/dL; median (IQR)[b]	9.3 (8.1, 10.3)	9.4 (8.4, 10.2)	0.64
Anaemia[c]: • None • Mild • Moderate • Severe	 90/578 (16%) 95/578 (16%) 341/578 (59%) 52/578 (9%)	 7/43 (16%) 7/43 (16%) 27/43 (63%) 2/43 (5%)	 0.81
Nutritional status at discharge • SAM • No SAM	 266/604 (44%) 338/604 (56%)	 19/45 (42%) 26/45 (58%)	 0.81
Anthropometry at discharge			
WHZ, mean (SD)	-2.2 (1.5)	-2.1 (1.5)	0.53
Not wasted Wasted (WHZ<-2) Severely wasted (<-3)	276/604 (46%) 165/604 (27%) 163/604 (27%)	23/45 (52%) 11/45 (24%) 11/45 (24%)	0.78
WAZ, mean (SD)	-3.3 (1.6)	-3.2 (1.7)	0.62

Not underweight Underweight (WAZ -2 to -3) Severely underweight (WAZ <-3)	106/604 (17%) 155/604 (26%) 343/604 (57%)	8/45 (18%) 13/45 (29%) 24/45 (53%)	0.88
HAZ, mean (SD)	-3.1 (1.5)	-3.1 (1.6)	0.87
Not stunted Stunted (HAZ<-2) Severely stunted (HAZ<-3)	134/604 (22%) 168/604 (28%) 302/604 (50%)	11/45 (24%) 14/45 (31%) 20/45 (44%)	0.77
MUAC, mm; mean (SD)	123 (16)	125 (15)	0.23
<115mm 115 to <125mm ≥125mm	184/604 (30%) 258/604 (43%) 162/604 (27%)	12/45 (27%) 21/45 (46%) 12/45 (27%)	0.82
Duration of hospitalization, days; median (IQR)	7 (4, 12)	6 (3, 9)	0.09
HIV status • Positive • Negative	 128/604 (21%) 476/604 (79%)	 2/45 (4%) 43/45 (96%)	 0.007
TB medication at discharge o Yes o No	 84/604 (14%) 520/604 (86%)	 4/45 (9%) 41/45 (81%)	 0.34
Primary caregiver characteristics			
Primary caregiver • Mother • Other	 547/590 (93%) 43/590 (7%)	 42/43 (98%) 1/43 (2%)	 0.22
Age, years; median (IQR)	26 (22, 31)	25 (21, 29)	0.16

Marital status • Married/stable union • Other	 441/589 (75%) 148/589 (25%)	 30/44 (68%) 14/44 (32%)	 0.33
Education, years; median (IQR)	10 (8, 11)	10 (7, 11)	0.84
Employment • None • Skilled • Unskilled	 346/586 (60%) 45/586 (7%) 195/586 (33%)	 27/44 (61%) 1/44 (2%) 16/44 (37%)	 0.60
Household Characteristics			
Residence • Rural • Urban • Peri-urban	 94/602 (16%) 378/602 (63%) 130/602 (22%)	 5/43 (12%) 26/43 (60%) 12/43 (28%)	 0.56
Drinking water source • Improved • Unimproved	 559/597 (94%) 38/597 (6%)	 40/44 (91%) 4/44 (9%)	 0.48
Toilet facilities • Improved • Unimproved • None	 533/600 (89%) 46/600 (7%) 21/600 (4%)	 35/43 (81%) 5/43 (12%) 3/43 (7%)	 0.31
Electricity in the home • Yes • No	 310/590 (53%) 280/590 (47%)	 29/44 (66%) 15/44 (34%)	 0.09

Data are n/N (column %) unless stated.
[a]P value comparing vital status known and vital status unknown groups.
[b]Haemoglobin was measured at discharge; if no discharge haemoglobin measurement was available, the value closest to discharge was used.
[c]Anaemia was defined according to WHO guidelines (2011) as: none $\geq$ 11g/dL, mild 10-10.9 g/dL, moderate 7-9.9 g/dL, and severe <7 g/dL.
IQR: Interquartile range; SAM: severe acute malnutrition; WHZ: weight-for-height Z score; SD: standard deviation; WAZ: weight-for-age Z score; HAZ: height-for-age Z-score; MUAC: mid-upper arm circumference; TB: tuberculosis

Supplementary Table 3: Characteristics of children who died and survived post-discharge

	Survived N=594	**Died N=55**
Child Characteristics		
Age at discharge, months; median (IQR)	18.4 (13.6, 22.7)	17.0 (10.1, 22.0)
• 1-5 months	12/17 (71%)	5/17 (29%)
• 6-11 months	79/89 (89%)	10/89 (11%)
• 12-23 months	382/412 (93%)	30/412 (7%)
• 24-59 months	121/131 (92%)	10/131 (8%)
Haemoglobin, g/dL; median (IQR)	9.3 (8.2, 10.3)	9.4 (8.1, 10.3)
Anaemia		
• None	90/97 (93%)	7/97 (7%)
• Mild	89/102 (87%)	13/102 (13%)
• Moderate	344/368 (93%)	24/368 (7%)
• Severe	44/54 (81%)	10/54 (19%)
Nutritional status at discharge		
• SAM	245/285 (86%)	40/285 (14%)
• No SAM	349/364 (96%)	15/364 (4%)
Anthropometry at discharge		
WHZ; mean (SD)	-2.1 (1.4)	-3.4 (1.5)
Not wasted (WHZ>-2)	291/299 (97%)	8/299 (3%)
Moderately wasted (WHZ -2 to -3)	163/176 (93%)	13/176 (7%)
Severely wasted (WHZ <-3)	140/174 (80%)	34/174 (20%)
WAZ; mean (SD)	-3.2 (1.5)	-4.7 (1.7)
Not underweight (WAZ>-2)	113/114 (99%)	1/114 (1%)
Underweight (WAZ -2 to -3)	164/168 (98%)	4/168 (2%)
Severely underweight (WAZ <-3)	317/367 (86%)	50/367 (14%)
HAZ; mean (SD)	-3.0 (1.5)	-3.7 (1.6)
Not stunted (HAZ >-2)	139/145 (96%)	6/145 (4%)
Stunted (HAZ -2 to -3)	165/182 (91%)	17/182 (9%)
Severely stunted (HAZ<-3)	290/322 (90%)	32/322 (10%)
MUAC, mm; mean (SD)	124 (15)	110 (14)
>125mm	160/174 (92%)	14/174 (8%)
125mm to 115mm	270/279 (97%)	9/279 (3%)
<115mm	164/196 (84%)	32/196 (16%)
Duration of hospitalization, days; median (IQR)	12 (7, 14)	16 (8, 21)
TB medication at discharge		
○ Yes	74/88 (84%)	14/88 (16%)
○ No	520/561 (93%)	41/561 (7%)
Primary caregiver characteristics		

Primary caregiver		
• Mother	536/590 (91%)	54/590 (9%)
• Other	42/43 (98%)	1/43 (2%)
Age, years; median (IQR)	26 (22, 31)	28 (23, 34)
Marital status		
• Married/stable union	430/471 (91%)	41/471 (9%)
• Other	148/162 (91%)	14/162 (9%)
Education, years; median (IQR)	10 (8, 11)	10 (7, 11)
Employment		
• None	344/373 (92%)	29/373 (8%)
• skilled	38/46 (83%)	8/46 (17%)
• unskilled	193/211 (91%)	18/211 (9%)
Household Characteristics		
Residence		
• Rural	91/99 (92%)	8/99 (8%)
• Urban	368/404 (91%)	36/404 (9%)
• Peri-urban	131/142 (92%)	11/142 (8%)
Drinking water source		
• Improved	548/599 (91%)	51/599 (9%)
• Unimproved	38/42 (90%)	4/42 (10%)
Toilet facilities		
• Improved	519/568 (91%)	49/568 (9%)
• Unimproved	46/51 (90%)	5/51 (10%)
• None	23/24 (96%)	1/24 (4%)
Electricity in the home		
• Yes	311/339 (92%)	28/339 (8%)
• No	272/295 (91%)	23/295 (8%)

Data are n (row %) unless stated
IQR: Interquartile range; SAM: severe acute malnutrition WHZ: weight-for-height Z score; SD: standard deviation; WAZ: weight-for-age Z score; HAZ: height-for-age Z-score; MUAC: mid-upper arm circumference

CHAPTER 4: PAPER II

RECOVERY FOLLOWING HOSPITALISATION FOR SAM

Bwakura-Dangarembizi M, Dumbura C, Amadi B, Chasekwa B, Ngosa D, Majo FD, Sturgeon JP, Chandwe K, Kapoma C, Bourke CD, Robertson RC, Nathoo KJ, Ntozini R, Norris SA, Kelly P, Prendergast AJ. Recovery of children following hospitalisation for complicated severe acute malnutrition. Matern Child Nutr. 2021 Dec 22:e13302. doi: 10.1111/mcn.13302.

SUMMARY

Nutritional recovery and hospital readmission following inpatient management of complicated severe acute malnutrition (SAM) are poorly characterized. We aimed to ascertain patterns and factors associated with hospital readmission, nutritional recovery and morbidity, in children discharged from hospital following management of complicated SAM in Zambia and Zimbabwe over 52-weeks post-hospitalization. Multivariable Fine-Gray subdistribution hazard model, with death and loss to follow-up as competing risks, was used to identify factors associated with hospital readmission; negative binomial regression to assess time to hospitalisation; and ordinal logistic regression to model factors associated with nutritional recovery.

The main findings are listed below:

- One-in-six children managed for SAM were readmitted into hospital over the first year after discharge and one-in-eight remained undernourished by 52 weeks of follow-up
- Non-oedematous SAM, ongoing SAM at the time of discharge and underlying cerebral palsy were independent risk factors for hospital readmission and poor nutritional recovery

- Low HAZ was a risk factor for hospital readmission and poor nutritional recovery

4.1 Introduction

Severe acute malnutrition (SAM) is defined by the presence of bilateral nutritional oedema, severe wasting (weight for height Z-score (WHZ) <−3), and/or mid-upper arm circumference (MUAC) <115 mm, and is associated with a high risk of death, mainly from infections(182). An estimated 16.4 million children below 5 years of age were affected by SAM globally in 2017 (183). The vicious cycle of malnutrition and infection is well recognized, and often leads to clinical complications (169, 182). Complicated SAM, which is characterized by clinical instability and lack of appetite, is managed in inpatient facilities where medical complications and acute infections are treated (36). The goals of managing SAM are to prevent short-term morbidity and mortality, achieve sustained nutritional recovery, and support long-term neurocognitive development (47). Discharge from hospital to continue outpatient therapeutic feeding is based on return of appetite and resolution of medical complications rather than improvements in anthropometry. Subsequent discharge from outpatient treatment programs occurs when there is adequate nutritional recovery (defined as WHZ >-2, or MUAC >125mm and/or resolution of oedema for 2 weeks) (36).

Following discharge from in-patient treatment for complicated SAM, children have persistent vulnerabilities, leading to an ongoing high mortality risk (131). Contributing factors include immune impairment, chronic infections such as TB and HIV, and a return to the same poor social environment (128). Data from the Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM) cohort in Zimbabwe and Zambia showed that 43.9% of children had ongoing SAM (by WHO criteria) at the time of discharge from hospital and these children had a more than two-fold increased risk of dying in the first year post-discharge, compared to children who had anthropometric recovery at discharge. Children with

HIV infection had 3-fold higher mortality than children with SAM alone, and this mortality risk persisted despite antiretroviral therapy (ART). Non-oedematous SAM and cerebral palsy were additional risk factors for post-discharge mortality in this cohort(184) .

Achieving good short-term and long-term health outcomes after treatment of SAM is challenging, especially in poorly resourced settings with fragile health systems (117, 122, 132). Few studies have systematically mapped patterns of nutritional recovery and morbidity after discharge from hospital following management of complicated SAM. Understanding the factors associated with nutritional recovery and hospital readmission would help identify the most vulnerable children at the time of discharge, and may inform additional interventions to improve outcomes. Here, we present further data from the HOPE-SAM cohort, in which children were followed for one year after hospital discharge following management of complicated SAM. Our hypotheses were, first, that HIV-positive compared to HIV-negative children with SAM have earlier and more frequent hospital readmissions, more illness episodes and poorer nutritional recovery, despite availability of ART; and, second, that a combination of biological and social risk factors predict readmission and nutritional recovery.

4.2 METHODS

4.2.1 Statistical analysis

4.2.1.1 Time to first hospital readmission

Fine-Gray sub distribution hazard models were used to estimate the hazard ratios for hospital readmission, with death and loss to follow-up as competing risks. Cox proportional hazards model was used as a sensitivity analysis, assuming no competing risks. Cumulative incidence curves were used to describe time to first hospital readmission. Selection of exposure

variables was based on biological plausibility and included the following: country, residence, sex, age, oedema at hospitalization, HIV status, duration of hospitalization, stunting, HAZ, cerebral palsy, haemoglobin, premature cessation of breastfeeding, SAM at discharge, tuberculosis at discharge, caregiver education, caregiver marital status and toilet type. Strength of association with time to first hospital readmission was initially assessed using univariable analyses. Variables significant at P<0.25 (tuberculosis at discharge, premature cessation of breastfeeding [defined as stopping breastfeeding before 12 months of age], duration of hospitalization, HAZ at discharge, toilet type) were included in a multivariable competing risks regression model together with a set of pre-specified variables that were forced to remain in the model: age, sex, country, oedema on admission, SAM at discharge, cerebral palsy and HIV status. Variables with p <0.05 in the final model were deemed associated factors.

4.2.1.2 Incident rate of hospital readmissions

Negative binomial regression models which account for overdispersion, were used to estimate the incidence rate of readmissions. Risk factors for readmission were identified using the same approach as for time to first hospital readmission.

4.2.1.3 Morbidity analysis

The following morbidity outcomes were assessed at each study visit by caregiver recall: fever, diarrhoea, respiratory symptoms (defined as cough or difficult breathing), poor appetite and weight loss. The period prevalence of illness episodes was estimated as the proportion of children with any caregiver-reported symptom in the two weeks preceding each visit, stratified by HIV status.

4.2.1.4 Nutritional recovery

Nutritional status was assessed at five time points post-discharge using regression models with WHZ and MUAC as outcomes. Ordinal logistic regression was used to identify factors

associated with nutritional recovery, defined as moving from a lower to a higher nutritional category (i.e. from SAM to either MAM or adequately-nourished and from MAM to adequately-nourished). Exposure variables were chosen in the same way as those for hospitalization.

4.3 RESULTS

A total of 755 children with SAM were enrolled between 13th July 2016 and 31st March 2018; Supplementary Figure 1 summarises their enrolment and follow-up. Five children were excluded due to co-enrolment in other studies or ineligibility. Among 750 eligible children, 2 died and 3 withdrew consent prior to baseline data collection, leaving 745 children in the study. Seventy children died during their initial hospitalization and 26 exited the study before discharge, leaving 649 children who were discharged from hospital and included in these analyses. Fifty-five children died and 21 withdrew consent during post-discharge follow-up. Post-discharge follow-up at each scheduled study visit ranged between 72.8% and 78.2% (Supplementary Figure 3).

4.3.1 Discharge characteristics

Child, caregiver and household characteristics are shown in Table ~~6~~7. The median age of children at discharge from hospital was 18.2 months (IQR 13.6, 22.6), with 53% males. Twenty percent (20%) of children were living with HIV infection. Sixty-five percent of children had oedematous malnutrition on admission to hospital and 78% were stunted (HAZ<-2). Children living with HIV infection compared to those who were not, were significantly older, more wasted, underweight and stunted, and more likely to have had previous SAM or persistent diarrhoea; they were also hospitalized for longer, were more anaemic and were more likely to be discharged on TB medication. Only 25% of the cohort

were breastfeeding at the time of hospital discharge; 31.4% had stopped before 12 months of age (at median 8 months; IQR 6, 9). Nearly all (93.2%) children were cared for by their biological mother, who had median 11 years of education (IQR 10, 11).

Table 7: Child, Caregiver and Household characteristics at hospital discharge

	All N=649	HIV-positive N=130	HIV-negative N=519	P-value[a]
Country				
• Zambia	188/649 (29.0%)	56/130 (43.1%)	132/519 (25.4%)	<0.001
• Zimbabwe	461/649 (71.0%)	74/130 (56.9%)	387/519 (74.6%)	
Age, months; median (IQR)	18.2 (13.6, 22.6)	20.0.(14.5, 24.9)	17.5 (13.4, 22.1)	<0.001
Male	344/649 (53.0%)	66/130 (50.8%)	278/519 (53.6%)	0.57
Oedematous SAM at hospitalization	422/649 (65.0%)	67/130 (51.5%)	355/519 (68.4%)	<0.001
Stunted (HAZ <-2)	504/649 (77.7%)	117/130 (90.0%)	387/519 (74.6%)	<0.001
Anthropometry				
WHZ, mean (SD)	-2.2 (1.5)	-2.4 (1.4)	-2.1 (1.5)	0.05
WAZ, mean (SD)	-3.3 (1.6)	-3.7 (1.2)	-3.2 (1.7)	0.002
HAZ, mean (SD)	-3.1 (1.5)	-3.5 (1.2)	-3.0 (1.6)	0.003
MUAC, cm; mean (SD)	12.3 (1.6)	11.7 (1.4)	12.4 (1.6)	<0.001
Past history				
• Complicated SAM	92/638 (14.4%)	30/129 (23.3%)	62/509 (12.2%)	0.001
• Uncomplicated SAM	124/622 (19.9%)	40/124 (32.3%)	84/498 (16.9%)	<0.001
• Persistent diarrhoea (past 14days)	352/649 (54.2%)	84/130 (64.6%)	268/519 (51.6%)	0.008
Breastfeeding				
• Currently breastfeeding	165/649 (25.4%)	30/130 (23.1%)	135/519 (26.0%)	0.49
• Premature breastfeeding cessation (<12months of age)	162/516 (31.4%)	29/105 (27.6%)	133/411 (32.4%)	0.35
• Duration of breastfeeding, months; median (IQR)	8 (6, 9)	8 (6, 9)	8 (6, 9)	0.90
Duration of hospitalization, days; median (IQR)	7 (4, 12)	10 (6, 17)	7 (4, 11)	<0.001
Haemoglobin, g/dL; median (IQR)[b]	9.3 (8.2, 10.3)	8.8 (7.7, 9.6)	9.4 (8.3, 10.4)	<0.001

Chronic underlying conditions				
• Cerebral palsy	30/649 (4.6%)	1/130 (0.8%)	29/519 (5.6%)	0.02
• Hydrocephalus	3/649 (0.5%)	0/130 (0%)	3/519 (0.6%)	0.39
• Congenital heart disease	14/649 (2.2%)	1/130 (0.8%)	13/519 (2.5%)	0.22
Medications at discharge				
• TB medication	88/649 (13.6%)	40/130 (30.8%)	48/519 (9.2%)	<0.001
• ART medication	N/A	66/130 (50.8%)	N/A	N/A
Primary caregiver characteristics				
Relationship to the child				
• Mother	590/633 (93.2%)	116/125 (92.8%)	474/508 (93.3%)	0.84
• Mother's age, years; median (IQR)	26 (22, 30)	28 (23, 32)	26 (22, 31)	0.19
Caregiver marital status				
• Married/stable union	471/633 (74.4%)	88/125 (70.4%)	383/508 (75.4%)	0.25
Caregiver education, years; median (IQR)	10 (8,11)	10 (8, 11)	9 (7, 11)	0.01
Caregiver Employment				
• None	373/630 (59.2%)	67/125 (53.6%)	306/505 (60.6%)	0.07
• Skilled	46/630 (7.3%)	6/125 (4.8%)	40/505 (7.9%)	
• Unskilled	211/630 (33.5%)	52/125 (41.6%)	159/505 (31.5%)	
Household characteristics				
Place of residence	99/645 (15.3%)	20/130 (15.4%)	79/515 (15.3%)	0.02
• Rural	404/645 (62.6%)	70/130 (53.8%)	102/515 (19.8%)	
• Urban	142/645 (22.0%)	40/130 (30.7%)	334/515 (64.9%)	
• Peri-urban				
Household drinking water source				
• Improved	599/641 (93.4%)	123/130 (94.6%)	476/511 (93.2%)	0.54
Household toilet facilities				
• Improved	568/643 (88.3%)	105/129 (81.4%)	463/514 (90.1%)	0.01
• Unimproved	51/643 (7.9%)	18/129 (14.0%)	33/514 (6.4%)	
• None	24/643 (3.7%)	6/129 (4.7%)	18/514 (3.5%)	
Household electricity				
• Yes	295/634 (46.5%)	55/126 (43.7%)	240/508 (47.2%)	0.47

Data are n/N (column %) unless otherwise stated.
[a]P value comparing HIV-positive and HIV-negative groups at discharge.
Haemoglobin was measured at discharge; if no discharge haemoglobin measurement was available, the value measured at the time point closest to discharge was used.
ART: antiretroviral therapy; HAZ: height-for-age Z-score; IQR: Interquartile range; MUAC: mid-upper arm circumference; SAM: severe acute malnutrition; WAZ: weight-for-age Z score; WHZ: weight-for-height Z score; SD: standard deviation; TB: tuberculosis, N/A : Not applicable

Seventy-one (10.9%) of children discharged from hospital never attended a subsequent follow-up visit; these children had significantly younger mothers than those attending at least one follow-up visit (median 23 versus 27 years, P<0.001) and were less likely to be on TB medication (5.6% versus 14.5%, P=0.04) but were otherwise similar to the follow-up cohort (Supplementary Table 4).

4.3.2 Rates of hospital readmission

Supplementary Table 5 shows the unadjusted and adjusted incident rate ratios for hospital readmission for each explanatory variable. Among the 89 children who were readmitted to hospital, 25 (28.1%) were admitted more than once and 13/89 (14.6%) died. We found two factors to be independently associated with readmission incidence: non-oedematous SAM and HAZ. Children with non-oedematous SAM had a 65% increased readmission rate compared to those with oedematous SAM (aIRR 1.65, 95% CI 1.05, 2.61). Better linear growth was associated with a lower rate of readmission: for every unit increase in HAZ there was a 19% lower rate of hospital readmission (aIRR 0.81, 95%CI 0.71, 0.94). There was some evidence of lower readmission rate for children in Zambia versus Zimbabwe (aIRR 0.62, 95%CI 0.37, 1.05), and higher readmission rate among children with cerebral palsy (aIRR 2.02, 95%CI 0.89, 4.59). No other factors predicted hospital readmission rate.

4.3.3 Time to first hospitalization

Of the 649 children discharged from hospital, data on readmission were available for 578 (89%). Of these, 89 (15.4%; 95%CI 12.7, 18.6) were readmitted through week 52, with 52.8% of admissions occurring in the first 12 weeks after discharge (Figure 13A). Time to readmission did not differ significantly between children living with HIV and those who were not (Figure 13B).

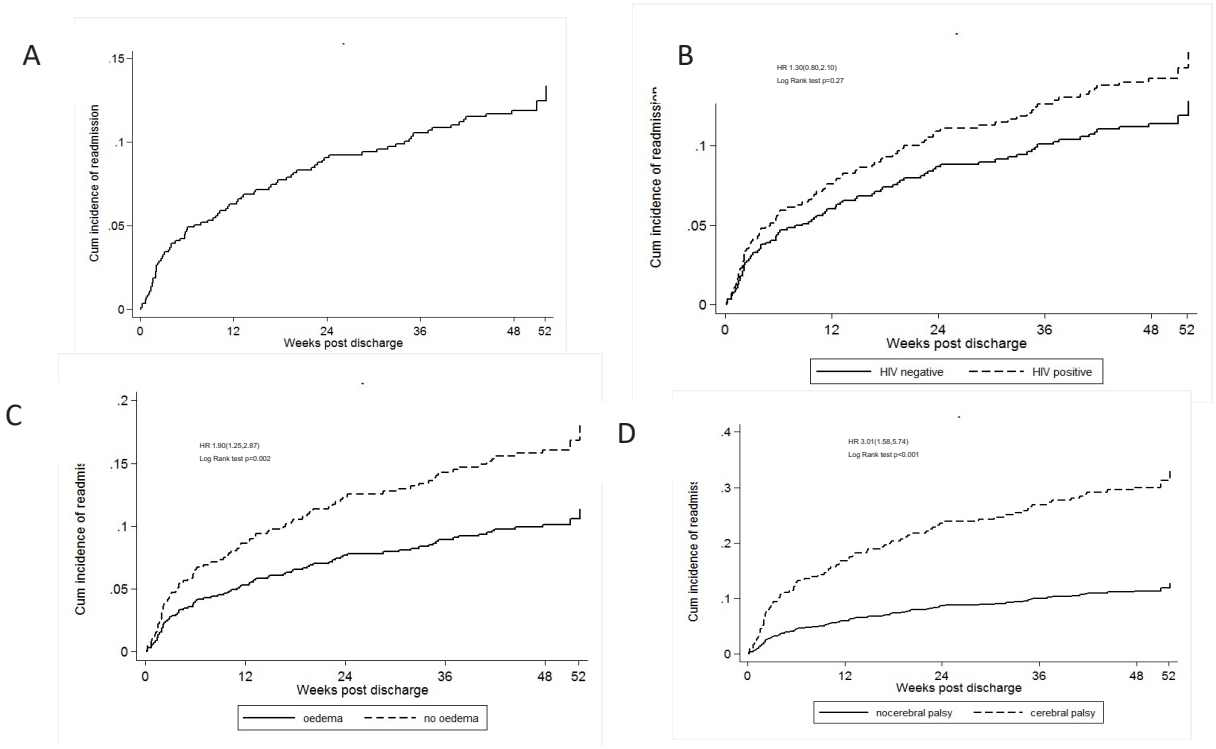


Figure 13: Cumulative incidence readmission among children discharged from hospital after treatment for complicated SAM.

Curves showing cumulative incidence of readmission (death and loss to follow up as competing risks) post-discharge and log rank test p value. A: overall cumulative incidence of readmission; B: cumulative incidence of readmission by child HIV status; C: cumulative incidence of readmission among children with oedematous versus non-oedematous SAM at the time of initial hospitalization; D: cumulative incidence of readmission in children with cerebral palsy versus those without cerebral palsy. Univariable sub hazard ratios and log rank test p values were used to compare the differences in time to readmission between groups. Adjusted sub hazard ratios are shown in Table 11.

Four factors were independently associated with time to first hospital readmission, using both the Fine-Gray hazard model which accounted for death and loss to follow up as competing risks, and the Cox proportional hazards model (Table ~~7~~8) . Non-oedematous compared to oedematous SAM was associated with a 64% increased sub hazard of readmission (aSHR 1.64, 95%CI 1.03, 2.64; Figure 13C). Unit increases in HAZ were associated with an 18% lower sub hazard of readmission (aSHR 0.82, 95%CI 0.71, 0.95); this association remained even after adjusting for WHZ (data not shown). Children with cerebral palsy were three times more likely to be readmitted (aSHR 2.96, 95%CI 1.56, 5.61; Figure 13D). Finally, there was evidence that children enrolled in Zambia had a longer time period to hospital readmission compared to those enrolled in Zimbabwe (aSHR 0.52, 95%CI 0.28, 0.97).

Table 8: Factors associated with time to readmission

	Never hospitalized N=560 (%)	**Hospitalized** N=89(%)	**Cox proportional hazards model for time to readmission**	**P value**	**Competing risk regression model time to readmission** aSHR (95% CI)	**p value**
Country • Zimbabwe • Zambia	392/461 (85.0%) 168/188 (89.4%)	69/461 (15.0%) 20/188 (10.6%)	Reference 0.60 (0.35, 1.01)	0.06	Reference 0.52 (0.28, 0.97)	0.04
Sex • Male • Female	289/344 (84.0%) 271/305 (88.9%)	55/344 (16.0%) 34/305 (11.1%)	Reference 0.75 (0.48, 1.17)	0.20	Reference 0.70 (0.45, 1.11)	0.13
Age at discharge (mo), median (IQR)	18.4 (13.8, 22.5)	17.2 (11.8, 23.4)	0.98 (0.96, 1.01)	0.23	0.99 (0.95, 1.02)	0.36
HIV status • Negative • Positive	452/519 (87.1%) 108/130 (83.1%)	67/519 (12.9%) 22/130 (16.9%)	Reference 1.37 (0.81, 2.32)	0.24	Reference 1.27 (0.72, 2.25)	0.41
Type of SAM at hospitalization • Oedematous • Non-oedematous	377/422 (89.3%) 183/227 (80.6%)	45/422 (10.7%) 44/227 (19.4%)	Reference 1.63 (1.04, 2.55)	0.03	Reference 1.64 (1.03, 2.64)	0.04
Nutritional status at discharge • No SAM • SAM	325/364 (89.3%) 235/285 (82.5%)	39/364 (10.7%) 50/285 (17.5%)	Reference 1.21 (0.77, 1.90)	0.41	Reference 1.14 (0.72, 1.81)	0.58
Discharge HAZ, mean (SD)	-3.0 (1.5)	-3.7 (1.7)	0.81 (0.70, 0.93)	0.002	0.82 (0.71, 0.95)	0.007
Chronic underlying conditions • **No cerebral palsy** • **Cerebral palsy**	540/619 (87.2%) 20/30 (66.7%)	79/619 (12.8%) 10/30 (33.3%)	Reference 3.06 (1.54, 6.08)	0.001	Reference 2.96 (1.56, 5.61)	0.001

Data are n (row %) unless stated

Univariable analysis was carried out to determine strength of association of each of the seventeen variables; country, residence, sex, age, oedema at hospitalization, HIV status, duration of hospitalization, stunting, HAZ, cerebral palsy, haemoglobin, premature cessation of breastfeeding, SAM at discharge, tuberculosis at discharge, caregiver education, caregiver marital status and toilet type with incidence of readmission using a cut-off of $P < 0.25$.

The 5 variables that were significant at $p < 0.25$ (duration of hospitalization, HAZ, premature cessation of breastfeeding, toilet type and TB at discharge) and the 7 a priori variables (country, sex, age at discharge, HIV status, baseline oedema, SAM at discharge and cerebral palsy) were offered up to the multivariable model. The table shows the adjusted hazards (cox regression model) and adjusted sub-hazard ratios obtained from the final model where death and loss to follow up were treated as a competing risks. Duration of hospitalization, premature cessation of breastfeeding, TB at discharge and toilet type were not retained in the final model.

IQR: Interquartile range; SAM: severe acute malnutrition, SD: standard deviation; HAZ: height-for-age Z-score; TB: tuberculosis

aSHR: adjusted sub-hazard ratio from competing risks model (treating death and loss to follow up before readmission as competing risks

4.4.4 Morbidity

Nearly half (48.8%) of children had at least one caregiver-reported symptom of ill-health within 4 weeks of discharge, with a gradual decline at later follow-up visits. Fever and respiratory illnesses were the most commonly reported symptoms overall; both declined markedly between 24 and 52 weeks. There were more caregiver-reported symptoms in children living with HIV versus those who were not [63.9% (95%CI 53.7%, 73.0%) versus 44.7% (39.6%, 49.9%); P=0.001] at week 4, driven particularly by differences in weight loss and appetite, but groups were otherwise similar during follow-up. There was a significant interaction between HIV status and reported weight loss [OR 0.71(0.57,0.90) p=0.004] as well as diarrhoea, [OR 0.83(0.70,0.99) p=0.036] over time.

4.3.5 Nutritional Recovery

Nutritional status over the follow-up period is shown in Figure 14. At the time of hospital discharge, 43.9% (95%CI 40.1, 47.8) of children had SAM, 27.6% (24.3, 31.2) had MAM and 28.5% (25.2, 32.1) were well-nourished. The proportion of children with SAM declined to 22.4% (95%CI 18.9, 26.4) by week 4, 12.4% (9.6, 15.8) by week 12, 11.9% (9.2, 15.2) by week 24, and 4.5% (2.9, 6.8) by week 52 Overall, 28.8% (95% CI 24.8, 33.2) and 12.1% (9.4, 15.5) of children were still undernourished (i.e. WHZ<-2; i.e. SAM or MAM) 24 and 52 weeks after discharge from hospital, respectively. While the proportion with nutritional recovery at 52 weeks was similar between children living with and without HIV (88.6% versus 87.8%, respectively), children living with HIV had a generally slower recovery rate following hospital discharge (Supplementary Figure 4). There was a significant difference in the proportion of children classified as SAM, MAM and adequately-nourished between the 2 groups of children at week 2 (P=0.003) and week 4 (P=0.02), but no significant difference between the groups from week 12 onwards.

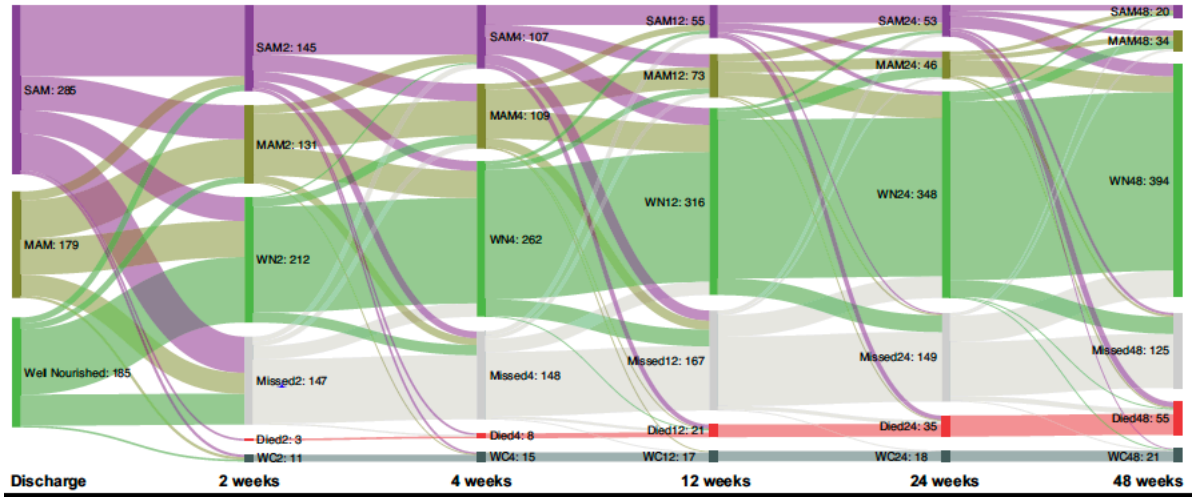


Figure 14 Patterns of nutritional recovery among all children discharged from hospital after treatment for complicated SAM.

Sankey diagrams showing the pattern of nutritional recovery between hospital discharge and 52 weeks post-discharge. Nutritional status was assessed at every study visit and classified as severe acute malnutrition (SAM), moderate acute malnutrition (MAM) or adequately-nourished (AN). The purple colour represents SAM, yellow MAM, and green AN. Children who withdrew consent were classified as (WC) and those who missed visits but turned up later were classified as missed.

Supplementary Table 6 shows the regression model of nutritional recovery using WHZ and MUAC as outcome factors and 15 shows the trend in mean WHZ and MUAC over the period of follow-up. Females compared to males had better recovery by WHZ, while males had a better recovery when MUAC was used. Young age at discharge (<12 months) was associated with poor recovery throughout the period of follow-up compared to older children. Children living with HIV compared to those who were not had a faster recovery in WHZ compared to MUAC. Children who had non-oedematous SAM at hospitalisation recovered at a slower rate than those who had oedema; similarly, children with ongoing SAM at discharge recovered more slowly than those who did not have SAM at discharge. Recovery of children with cerebral palsy remained poor through the period of follow up.

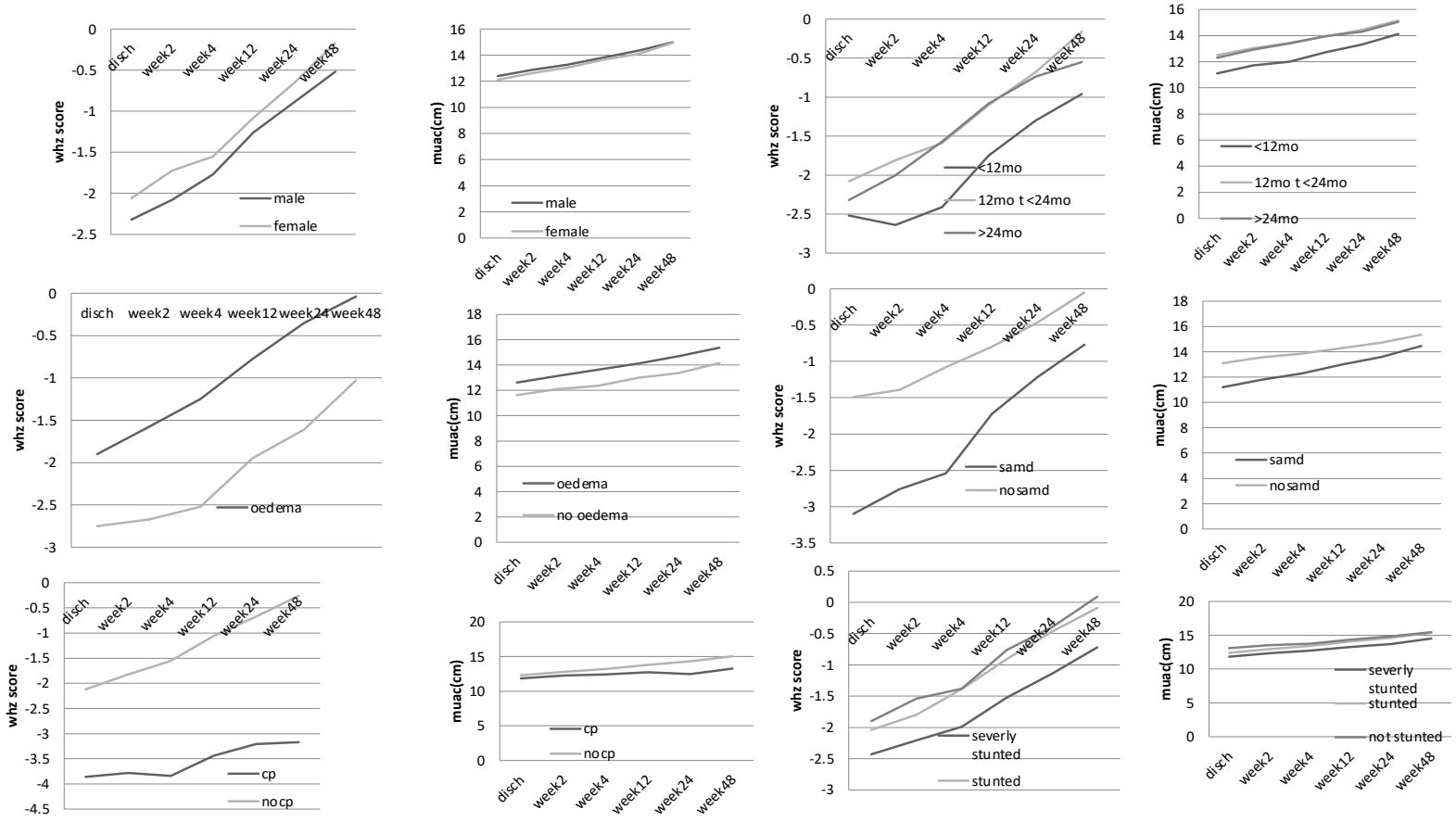


Figure 15: Mean WHZ and MUAC trend over the follow up time

Graphs showing mean change in WHZ and MUAC over the period of follow up for the following variables; sex, age, baseline oedema, SAM at discharge, cerebral palsy and stunt

Six independent factors were associated with moving from a lower to a higher nutritional status in the multivariable ordinal logistic regression model (Supplementary Table 7). Two factors (age at discharge and HIV status) were associated with early recovery (at weeks 2 and 4 only), while four factors (non-oedematous SAM at hospitalization, ongoing SAM at discharge, cerebral palsy and HAZ) were consistently associated with recovery throughout the follow-up period. Every one month increase in age was associated with a 4% higher odds (aOR 1.04, 95%CI 1.01, 1.06) of moving from a lower to a higher nutritional status at 4 weeks, while HIV was associated with a 41% lower odds (aOR 0.59, 95%CI 0.36, 0.97) of moving to a higher nutritional status. Children with non-oedematous compared to oedematous SAM had 71% lower odds (aOR 0.29, 95%CI 0.19, 0.44) of moving from a lower to a higher nutritional status at week 4. Children with ongoing SAM at hospital discharge had 86% lower odds (aOR 0.14, 95%CI 0.09, 0.21) and children with cerebral palsy had a 84% lower odds (aOR 0.16, 95%CI 0.06, 0.40) of moving to a higher nutritional status by week 4. Finally, in this cohort where 78% of the children were stunted, every unit increase in HAZ was associated with a 40% increased odds of moving from a lower to a higher nutritional status (aOR 1.40, 95%CI 1.20, 1.61) by week 4. Effect size estimates for the four consistent risk factors remained similar throughout follow-up, except for the association between SAM at discharge and nutritional recovery, which attenuated over time (Supplementary Table 7). Sex, being on TB medication, premature cessation of breastfeeding, and household toilet type were not significantly associated with nutritional recovery at any time-point.

4.4 DISCUSSION

Children discharged from hospital after management of complicated SAM continue to be at high risk for illness, hospital readmission and poor nutritional recovery. In this longitudinal study of children followed up after hospital discharge for SAM at three sites in southern Africa, one-in-six were readmitted into hospital over the first year post-discharge. Children had frequent illness episodes, and one-in-eight children remained undernourished by 52 weeks post-discharge. Four consistent risk factors for hospital readmission and nutritional recovery over the one year of follow up were identified: non-oedematous SAM at hospitalization, ongoing SAM at discharge, discharge HAZ and underlying cerebral palsy. Contrary to the initial hypothesis, and despite the previous finding that it is a predictor of post-discharge mortality(184), HIV was not associated with time to hospital readmission. However, HIV infection and young age at discharge were associated with poor nutritional recovery assessed using WHZ or MUAC. Overall, these data define clear vulnerable population groups among children recovering from complicated SAM, and identify risk factors that are congruent with the previous analysis of post-discharge mortality risk in the same cohort(184). Children with non-oedematous SAM, stunting and disability in particular need to be considered for targeted convalescent care after discharge from hospital following complicated SAM. Infants below 12 months of age should be particularly prioritised for care during the period of post-discharge convalescence, given their slower recovery compared to older children.

WHO guidelines recommend that complicated SAM should be managed in hospital, followed by referral to a community-based nutritional rehabilitation facility (36, 88). Adherence to this model of care depends on functional health systems and access to resources. The period from hospital discharge to nutritional recovery is fraught with vulnerabilities from ongoing undernutrition, unresolved infections, hospital-acquired infections, perturbed physiological

pathways and ongoing immune impairment(128). Children discharged from hospital in sub-Saharan Africa following SAM have a particularly high risk of mortality and hospital readmission(135), with several comorbidities (including HIV) being recognized risk factors in previous studies (117, 174). Interestingly, HIV infection was not a risk factor for readmission in this cohort, though it was one of the major risk factors we previously identified for post-discharge mortality(184). It is possible that the higher death rate among children living with HIV, almost half of which occurred in the community, proportionately reduced the number of readmissions in this group. Alternatively, children living with HIV may be protected from readmission (but not mortality) by cotrimoxazole prophylaxis, since hospitalization in children with malnutrition is usually triggered by infections (185, 186). By contrast, cotrimoxazole prophylaxis did not reduce mortality or hospital readmissions in HIV-uninfected children discharged from hospital following complicated SAM in Kenya(134). Low HAZ is an indicator of poor linear growth and was an independent risk factor for hospital readmission. Diagnosis of SAM does not take into account stunting (HAZ<-2), which reflects chronic malnutrition associated with multiple causes such as poverty, food insecurity, repeated infections, and intrauterine growth restriction (24). There is increasing evidence that children with concurrent wasting and stunting are at greater risk for both mortality and morbidity (24, 27, 37). This increased risk is hypothesized to be mediated through decreased muscle mass and fat mass (seen in both wasting and stunting) resulting in low levels of the hormone leptin, which has a key role in both innate and adaptive immunity (60). The observation that HAZ is associated with hospital readmission supports the need to better understand the pathophysiology of stunting in children with SAM. The observation that children enrolled in Zambia had a longer time to first hospital readmission compared to children enrolled in Zimbabwe, may be a result of continued nutritional support once children were categorized with moderate acute malnutrition, which was not the practice in Zimbabwe.

This study reports the pattern of illness during follow-up after complicated SAM. Consistent with other studies, fever, respiratory illness and diarrhoea were the most commonly reported symptoms post-discharge (122, 129). The pattern of morbidity in children treated for SAM therefore reflects the typical infectious disease burden seen in LMICs. This cohort showed a sharp decline in reported symptoms after 24 weeks of follow-up, suggesting that the first six months following discharge is a critical time for comorbidities. The high prevalence of illness during these first few months highlights the need for continued surveillance and interventions to prevent and treat infections after discharge. It has long been proposed that a cycle exists whereby malnutrition impairs immunity, thereby increasing host susceptibility to infection, which in turn intensifies the severity of malnutrition (61, 169, 187, 188). This is a hypothesis which is being explored using biological specimens collected from HOPE-SAM participants(155) . The effect of antimicrobials in children recovering from complicated SAM requires further study, especially since they may have additional benefits for weight gain and nutritional recovery(189). For example, an ongoing study among children with uncomplicated SAM in Burkina Faso is providing azithromycin as an adjunct to standard outpatient treatment (ClinicalTrials.gov Identifier: NCT03568643).

At the time of hospital discharge, 44% of children had ongoing SAM. Most studies on nutritional recovery evaluate children after discharge from community-based therapeutic feeding centres, thus missing the immediate post-discharge period(122, 190). Even then, there is no standard definition of relapse following treatment of SAM from existing studies due to different follow-up periods, treatment protocols and inconsistent reporting of point prevalence, cumulative prevalence and incidence rates (132). This analysis showed that 6 months after discharge from hospital, 22% of children had not achieved nutritional recovery (here defined as improvement in anthropometry from SAM to either MAM or adequately-nourished, or from MAM to adequately-nourished). One-year after discharge, 12% of children

still had MAM or SAM. Consistent with the observation that ongoing SAM at discharge was a predictor of poor nutritional recovery, a study of Ethiopian children with MAM who did not receive supplementary feeds, showed that the most wasted children at baseline had the lowest chance of recovering after 28 weeks of follow-up (191). Previous studies have found a strong association between poor linear growth and nutritional recovery in children with MAM and SAM(24, 192). Management of SAM is the same regardless of whether or not children are stunted. However, children who have both SAM and stunting may need additional interventions as the overlapping effects of stunting and wasting compound the risk of poor outcomes (24, 27, 193).

This analysis showed that HIV infection slowed nutritional recovery in the early weeks following hospital discharge; at weeks 2 and 4 post-discharge children living with HIV had a lower odds of nutritional recovery, but this effect was not seen from week 12 onwards. Overall these findings are similar to a study by Fergusson *et al* (167) from Malawi, where nutritional recovery 4 months after discharge from hospital was similar at for both children living with and without HIV infection Unlike the children in the HOPE SAM cohort (in whom 28.5% had a WHZ >-2 at discharge), children in the Malawi cohort were discharged after attaining a WHZ of 85% (equivalent to WHZ ≥-1). The odds of nutritional recovery were extremely poor in children with cerebral palsy. Children with disability are at risk for poor nutritional status, especially if they have severe gross motor impairment and oropharyngeal dysfunction, leading to reduced food intake, increased nutrient loss, additional nutrient requirements and significantly increased energy expenditure (194). In the analysis models where MUAC and WHZ were used as continuous variables, young age at discharge, non-oedematous SAM at the time of initial hospitalization, SAM at discharge and cerebral palsy were associated with poor nutritional recovery throughout the period of follow-up. This indicates that the public health approach which uses cut-offs for nutritional status may miss

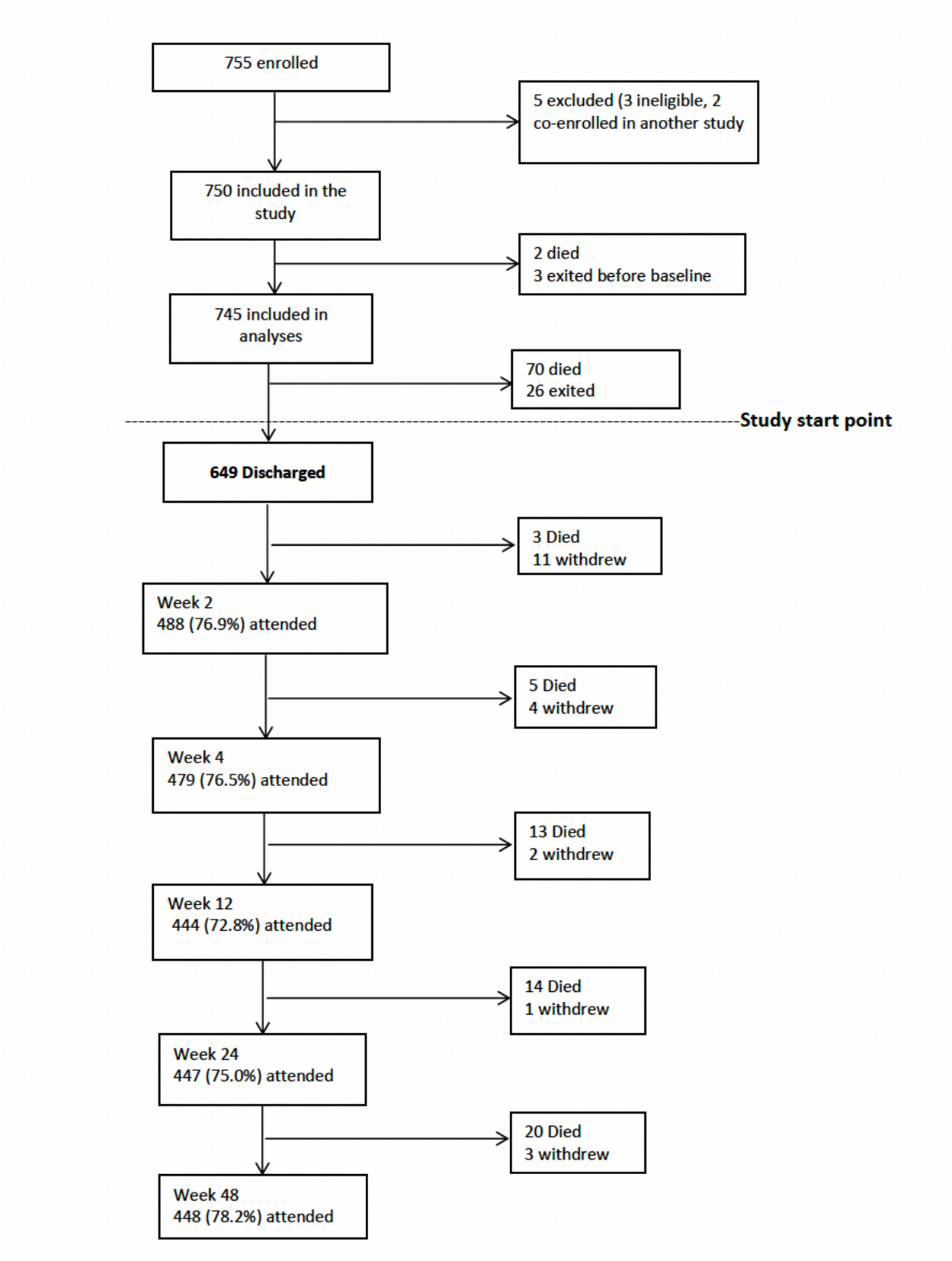
children who have poor nutritional recovery. Children living with HIV compared to those who were not, had a slower recovery up to 4 weeks post-discharge. Taken together, these data provide clear evidence that a proportion of children do not achieve nutritional recovery one year after discharge from hospital, with severe wasting, disability and stunting as key risk factors. These findings support what Stobaugh described as “different trajectories of recovery”, suggesting that uniform outpatient management for all children recovering from SAM may not ensure sustainable recovery (24). The existing approach of giving nutritional rehabilitation may be insufficient to promote full and lasting recovery in all children. Future studies need to evaluate whether enhanced convalescent care and/or adjunctive therapies improve outcomes for the children most vulnerable to relapse and readmission.

This study has strengths and limitations. Relatively high rates of follow-up among this highly mobile and vulnerable population compared to other studies was achieved, through phone calls, text messages, free study clinics and home visits. However, anthropometry and morbidity data were not collected on 15.8% of the study population at 52 weeks which could have biased the findings. Where there were missing risk factors for analysis, imputation led to no major changes in the inferences obtained. Reliance on caregiver-reported data for children who were hospitalized at non-study sites, may have underestimated the proportion of children readmitted into hospital. A major limitation was that nutritional rehabilitation provided in the community was not documented. Information collected on the home environment may have failed to capture key factors associated with clinical outcomes such as feeding practices, household food security and caregiver health-seeking behaviour. An in-depth social science study of the same population is underway to address this issue. Relapse of malnutrition may have been underestimated as events were only captured during study visits. For example, it is well known that nutritional oedema can be transient and mild cases could have resolved between study visits(19).

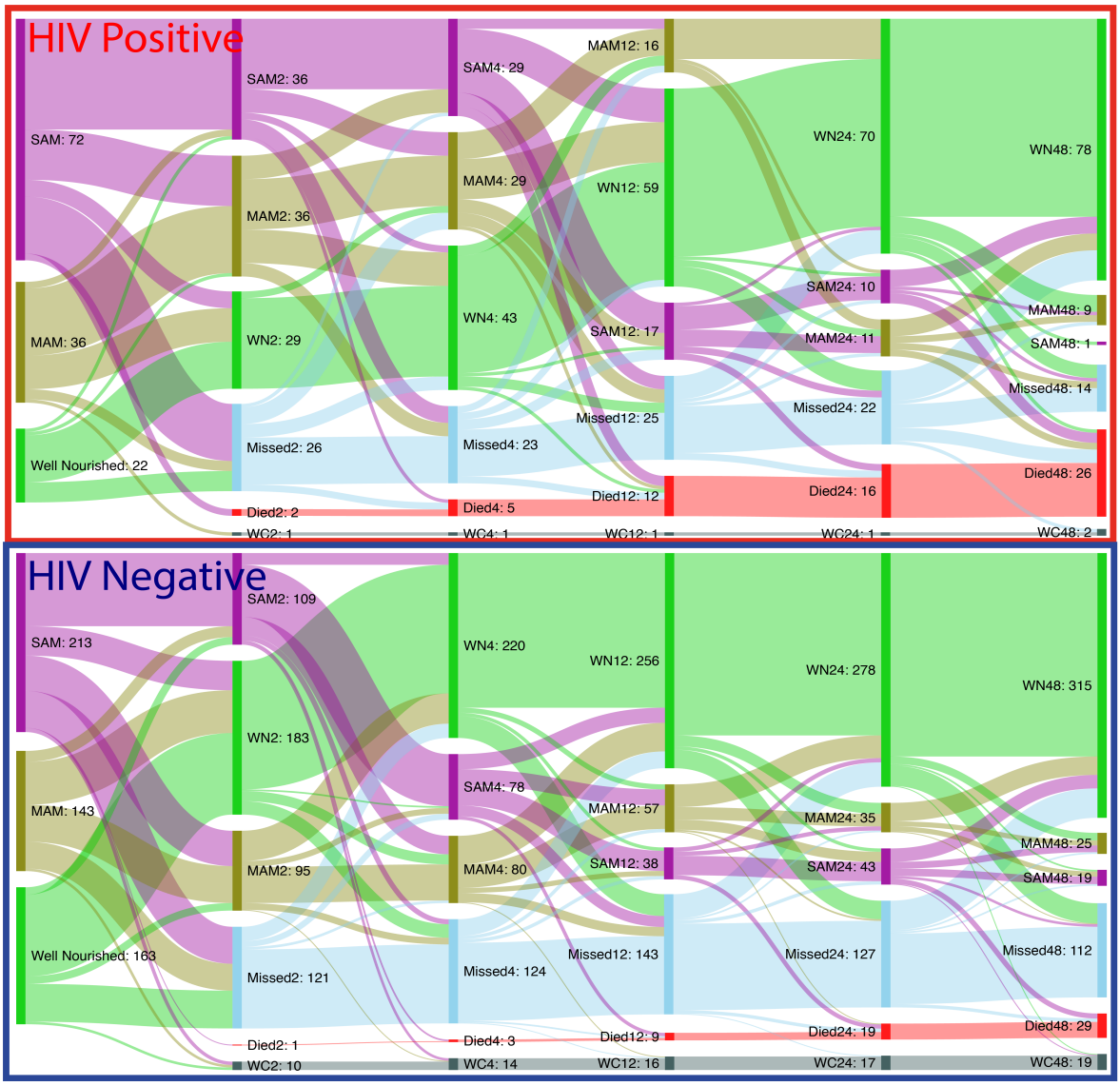
4.5 CONCLUSION

Few longitudinal studies have defined morbidity and nutritional recovery of children discharged from hospital for complicated SAM. Here, high rates of hospital readmission and caregiver-reported illness in the first 6 months after discharge, and failure to achieve nutritional recovery by one year post-discharge in 12% of the cohort. The current analysis, together with the previous findings on mortality in the same cohort, identify a small number of consistent risk factors for adverse outcomes following discharge from hospital: HIV, non-oedematous SAM, cerebral palsy and ongoing SAM at the time of discharge(184). The current classification of malnutrition into acute and chronic and subsequent approach to management ignores the contribution of poor linear growth to the poor outcomes in children who are both wasted and stunted namely relapse of malnutrition and associated morbidity(24). HAZ should be considered in identifying severely malnourished children who are at risk for poorer outcomes. Prioritizing these high-risk groups for more intensive follow-up may be beneficial. Providing additional and holistic convalescent care for all children discharged from hospital following SAM may contribute to improving long-term outcomes of this vulnerable population.

4.6 SUPPLEMENTARY MATERIAL



Supplementary Figure 3: Follow up study flow diagram



Supplementary Figure 4 Patterns of nutritional recovery by HIV status

Sankey diagrams showing the pattern of nutritional recovery between hospital discharge and 52 weeks post-discharge. Nutritional status was assessed at every study visit and classified as severe acute malnutrition (SAM), moderate acute malnutrition (MAM) or adequately-nourished (AN). The purple colour represents SAM, yellow MAM, and green AN. Children who withdrew consent were classified as (WC) and those who missed visits but turned up later were classified as missed.

Supplementary Table 4: Admission characteristics of children who did not attend any visit and those who attended at least one visit

	Last seen at discharge N=71	**Attended at least one visit N=578**	**P-value[a]**
Country • **Zambia** • **Zimbabwe**	19/71 (26.8%) 52/71 (73.2%)	169/578 (29.2%) 409/578 (70.8%)	0.66
Male	31/71 (43.7%)	313/578 (54.2%)	0.10
Age, months; median (IQR)	18.6 (14.4, 22)	18.0 (13.5, 22.7)	0.94
HIV status • **Positive**	10/71 (14.1%)	120/578 (20.8%)	0.19
Previous history • **Complicated SAM** • **Uncomplicated SAM** • **Persistent diarrhoea past 2 weeks**	 10/70 (14.3%) 13/69 (18.8%) 15/62 (24.2%)	 82/568 (14.4%) 111/589 (20.1%) 108/528 (20.5%)	 0.97 0.81 0.49
Currently breastfeeding	14/71 (19.7%)	114/572 (19.9%)	0.97
Premature breastfeeding cessation <12mo	13/57 (22.3%)	149/458 (32.5%)	0.14
• **Duration of breastfeeding mo; median (IQR)**	9 (9, 9)	8 (5, 9)	0.10
Type of SAM at admission • Oedematous	52/71 (73.2%)	370/578 (64.0%)	0.12
Nutritional status at discharge • SAM at discharge	29/71 (40.9%)	256/578 (44.3%)	0.58
Anthropometry			
WHZ, mean (SD)	-1.95 (1.3)	-2.23 (1.5)	0.13
WAZ, mean (SD)	-3.10 (1.5)	-3.36 (1.6)	0.19
HAZ, mean (SD)	-3.01 (1.4)	-3.11 (1.6)	0.60
MUAC, cm; mean (SD)	12.5 (1.8)	12.2 (1.6)	0.26
Stunting at discharge • Yes	55/71(77.5%)	449/578 (77.7%)	0.97
Duration of hospitalisation, days; median (IQR)	6 (4, 10)	7 (4, 13)	0.14

Chronic underlying conditions			
• Cerebral palsy	1/71 (1.4%)	29/578 (5.0%)	0.17
• Hydrocephalus	0/71 (0.0%)	3/578 (0.5%)	0.54
• Congenital heart disease	1/71 (1.4%)	13/578 (2.3%)	0.65
Medications at discharge			
• TB medication	4/71 (5.6%)	84/578 (14.5%)	0.04
• ART medication(HIV positive only)	5/10 (50.0%)	61/120 (50.8%)	0.96
Haemoglobin, g/dL; median (IQR)[b]	9.2 (8.4, 10.6)	9.3 (8.2, 10.3)	0.56
Primary caregiver			
• Mother	68/69 (98.6%)	522/564 (92.6%)	0.06
Age, years; median (IQR)	23 (21, 28)	27 (23, 31)	<0.001
Marital status			
• Married/stable union	51/69 (73.9%)	420/564 (74.5%)	0.92
Education, years; median (IQR)	9 (7, 11)	10 (8, 11)	0.66
Employment			
• None	37/69 (53.6%)	336/562 (59.8%)	0.49
• skilled	7/69 (10.1%)	39/562 (6.9%)	
• unskilled	25/69 (36.2%)	186/562 (33.1%)	
Residence			
• Rural	9/70 (12.9%)	90/575 (15.7%)	0.66
• Urban	43/70 (61.4%)	361/575 (62.8%)	
• Peri-urban	18/70 (25.7%)	124/575 (21.6%)	
Drinking water source			
• Improved	66/70 (94.3%)	533/571 (93.4%)	0.76
Toilet facilities			
• Improved	62/69 (89.9%)	506/574 (88.2%)	0.90
• Unimproved	5/69 (7.3%)	46/574 (8.0%)	
• None	2/69 (2.9%)	22/574 (3.8%)	
Household electricity			
• Yes	33/66 (50.0%)	262/568 (46.1%)	0.55

Data are n (column %) unless stated. [a] p value comparing those who never attended a visit post discharge and those who attended one or more visits.
Chi squared test was used to compare categorical variables and t test was used to compare continuous variables.

HAZ: height-for-age Z-score; IQR: Interquartile range, SAM: severe acute malnutrition, SD: standard deviation; TB: tuberculosis

Supplementary Table 5: Incident rate ratios for hospital readmission over 52 weeks of follow-up

	N	Readmission rate per 100 child-weeks (95%CI)	Unadjusted IRR (95%CI)	P value	Adjusted IRR (95%CI)	P-value
Country						
• Zimbabwe	461	0.45 (0.35, 0.57)	Reference	0.28	Reference	0.08
• Zambia	188	0.33 (0.21, 0.51)	0.75 (0.45, 1.25)		0.62 (0.37, 1.05)	
Sex						
• Male	344	0.48 (0.37, 0.63)	Reference	0.10	Reference	0.11
• Female	305	0.34 (0.24, 0.48)	0.69 (0.44, 1.07)		0.69 (0.44, 1.08)	
Age at discharge (mo), median (IQR)	-	-	0.98 (0.95, 1.01)	0.12	0.98 (0.95, 1.01)	0.12
HIV status						
• HIV-positive	130	0.53 (0.35, 0.80)	1.17 (0.69, 2.00)	0.56	1.22 (0.71, 2.11)	0.47
• HIV-negative	519	0.39 (0.30, 0.49)	Reference		Reference	
Type of SAM at hospitalization						
• Non-oedematous	227	0.63 (0.47, 0.83)	2.09 (1.35, 3.23)	0.001	1.65 (1.05, 2.61)	0.03
• Oedematous	422	0.31 (0.23, 0.42)	Reference		Reference	
Discharge Anthropometry	-	-	0.75 (0.65, 0.86)	<0.001	0.81 (0.71, 0.94)	0.005
• HAZ						
Nutritional status at discharge						
• SAM	285	0.57 (0.43, 0.75)	1.96 (1.26. 3.04)	0.003	1.33 (0.84, 2.11)	0.23
• No SAM	364	0.31 (0.23, 0.42)	Reference		Reference	
Cerebral palsy						
• Yes	30	1.33 (0.72, 2.47)	2.31 (1.00, 5.35)	0.05	2.02 (0.89, 4.59)	0.09
• No	619	0.38 (0.31, 0.48)	Reference		Reference	

Univariable and multivariable negative binomial models were used to calculate the incidence rate ratio (IRR) for readmission through 52 weeks. Univariable analysis was carried out to determine strength of association of each of the seventeen variables; country, residence, sex, age, oedema at hospitalization, HIV status, duration of hospitalization, stunting, HAZ, cerebral palsy, haemoglobin, premature cessation of breastfeeding, SAM at discharge, tuberculosis at discharge, caregiver education, caregiver marital status and toilet type with incidence of readmission using a cut-off of $P < 0.25$.

The three variables that were significant at $P < 0.25$ (duration of hospitalization, HAZ, and TB at discharge) and 7 variables selected for inclusion *a priori* on the basis of their known association with post-discharge mortality (country, sex, age at discharge, HIV status, baseline oedema, SAM at discharge and cerebral palsy) were offered up to the final multivariable model. The table shows the 8 variables that were retained in the final multivariable model. TB at discharge and duration of hospitalization were not retained in the final model

Supplementary Table 6: Regression model of nutritional recovery using WHZ and MUAC

	Week 2		**Week 4**		**Week 12**		**Week 24**		**Week 48- 52**	
	WHZ	**MUAC**	**WHZ**	**MUAC**	**WHZ**	**MUAC**	**WHZ**	**MUAC**	**WHZ**	**MUAC**
	Coef (95% CI)	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**	**Coef (95% CI)**
Country: Zambia	0.34(0.08,0.60)	0.18(-0.06,0.42)	0.21(-0.06,0.47)	-0.01(-0.27,0.26)	-0.07(-0.35,0.20)	0.26(0.54,0.02)	0.19(-0.09,0.47)	-0.10(-0.39,0.20)	0.15(-0.15,0.44)	-0.52(-0.80,-0.23)
Female	0.32(0.09,0.54)	-0.30(-0.52,-0.09)	0.24(0.01,0.46)	-0.26(-0.49,-0.04)	0.15(-0.08,0.38)	-0.26(-0.49,-0.03)	0.23 (-0.01,0.47)	-0.31(-0.56,0.05)	0.20(-0.03,0.44)	-0.16(-0.41,0.08)
Age at discharge (mo) *Age categories <12mo 12mo-<24mo >24mo	0.02(0.01,0.03) Ref 0.72(0.31,1.14) 0.84(0.37,1.32)	0.03(0.02,0.04) Ref 0.67(0.36,0.99) 0.86(0.48,1.23)	0.02(0.01,0.04) Ref 0.50(0.12,0.89) 0.83(0.38,1.27)	0.04(0.03,0.05) Ref 0.85(0.51,1.18) 1.18(0,78,1.59)	0.02(0.00,0.03) Ref 0.40(0.03,0..76) 0.62(0.19,1.05)	0.04(0.02,0.05) Ref 0.75(0.40,1.10) 1.10(0.68,1.52)	0.01(-0.00,0.03) Ref 0.30(-0.07,0.66) 0.52(0.08,0.96)	0.03(0.01,0.04) Ref 0.75(0.37,1.13) 0.98(0.52,1.44)	0.00(-0.02,0.01) Ref 0.48(0.13,0.83) 0.30(-0.14,0.74)	0.02(0.00,0.04) Ref 0.72(0.35,1.09) 0.86(0.39.1.32)
HIV positive	-0.11(-0.41,0.18)	-0.33(-0.61,-0.04)	-0.19 (-0.49,0.11)	-0.37(-0.68,-0.07)	0.10(-0.21,0.40)	-0.36(-0.66,-0.60)	0.07(-0.25,0.39)	-0.29(-0.63,-0.05)	0.59(0.28,0.91)	0.19(-0.14,0.52)
No oedema at hospitalization	-0.82 (-1.07,0.58)	-0.48(-0.71,-0.25)	-0.92 (-1.1,-0.68)	-0.67(-0.91,-0.42)	-0.92 -1.17,-0.67)	-0.65(-0.90,-0.40)	-1.08(-1.34,-0.82)	-0.96(-1.22,-0.67)	-0.90(-1.16,-0.64)	-0.89(-1.16,-0.62)
SAM at discharge	-1.13 (-1.37,0.90)	-1.28-1.51,-1.06)	-1.17(-1.40,-0.94)	-1.10(-1.33,-0.87)	-0.67 (-0.91-0.43)	-0.84(-1.08,-0.60)	-0.46(-0.71,-0.21)	0.64(-0.91,-0.38)	-0.42(-0.66,-0.17)	-0.51(-0.77,-0.26)
Discharge HAZ *HAZ categories HAZ>=-2 HAZ -3 to <-2 HAZ <-3	0.15 (0.06,0.23) Ref -0.43(-0.75,-0.12) -0.49(-0.79,-0.19)	0.33(0.25,0.40) Ref -0.78(-1.08,-0.46) -0.96(-1.24,-0.68)	0.13(0.04,0.21) Ref -0.17(-0.48,0.14) -0.34(-0.62,-0.04)	0.30(0.22,0.37) Ref -0.50(-0.93,-0.17) -0.80(-1.11,-0.51)	0.17(0.08,0.26) Ref -0.28(-0.60,0.05) -0.49(-0.79,-0.19)	0.32(0.24,-.40) Ref -0.36(-0.70,-0.02) -0.80(-1.11,-0.49)	0.18(0.10,0.27) Ref -0.16(-0.50,0.18) -0.51(-0.82,-0.19)	0.35(0.26,0.43) Ref -0.30(-0.67,0.07) -0.89(-1.23,-0.55)	0.20(0.11,0.28) Ref -0.27(-0.60,0.06) -0.57(-0.87,-0.26)	0.29(0.21,0.38) Ref -0.22(-0.57,0.13) -0.79(-1.11,-0.47)

Cerebral palsy	-1.58 (-2.08,1.08)	-0.25(-0.73,0.23)	-1.84(-2.34,-1.34)	-0.69(-1.22,-0.15)	-1.95(-2.48,-1.41)	-0.69(-1.22,-0.15)	-2.20(2.80,-1.60)	-1.46(-2.08,-0.84)	-2.35(-2.99,-1.71)	-1.34(-2.01,-0.67)

Coefficients of nutritional recovery were estimated using a regression model with WHZ and MUAC as continuous outcomes.
Univariable analysis was carried out to determine strength of association of each of the seventeen variables; country, residence, sex, age, oedema at hospitalization, HIV status, duration of hospitalization, stunting, HAZ, cerebral palsy, haemoglobin, premature cessation of breastfeeding, SAM at discharge, tuberculosis at discharge, caregiver education, caregiver marital status and toilet type with incidence of readmission using a cut-off of $P < 0.25$.

The 5 variables that were significant at $p < 0.25$ (duration of hospitalization, HAZ, premature cessation of breastfeeding, toilet type and TB at discharge) and the 7 a priori variables (country, sex, age at discharge, HIV status, baseline oedema, SAM at discharge and cerebral palsy) were offered up to the regression model.
The table shows the adjusted coefficients obtained from the final model at each time-point.

SAM: severe acute malnutrition, HAZ: height-for-age Z-score; TB: tuberculosis; WHZ: weight-for-height Z-score, MUAC: mid-upper-arm circumference

Supplementary Table 7 Ordinal Logistic regression model of nutritional recovery

	Week 2		Week 4		Week 12		Week 24		Week 52	
	Odds of nutritional recovery Adjusted OR (95%CI)	**P value**	**Odds of nutritional recovery Adjusted OR (95%CI)**	**P value**	**Odds of nutritional recovery Adjusted OR (95%CI)**	**P value**	**Odds of nutritional recovery Adjusted OR (95%CI)**	**P value**	**Odds of nutritional recovery Adjusted OR (95%CI)**	**P value**
Country • Zimbabwe • Zambia	Reference 1.50 (1.00, 2.25)	0.05	Reference 1.18 (0.76, 1.82)	0.47	Reference 0.86 (0.50, 1.46)	0.56	Reference 1.87 (1.04, 3.36)	0.04	Reference 1.29 (0.60, 2.77)	0.52
Sex • Male • Female	Reference 1.11 (0.76, 1.64)	0.57	Reference 1.05 (0.70, 1.57)	0.83	Reference 1.09 (0.68, 1.75)	0.73	Reference 1.12 (0.68, 1.84)	0.65	Reference 1.99 (1.00, 3.40)	0.05
Age at discharge	1.03 (1.01, 1.05)	0.01	1.04 (1.01, 1.06)	0.003	1.01 (0.99, 1.03)	0.34	1.00 (0.98, 1.04)	0.55	1.00 (0.97, 1.04)	0.84
HIV status • HIV-negative • HIV-positive	Reference 0.60 (0.37, 0.96)	0.03	Reference 0.59 (0.36, 0.97)	0.04	Reference 0.76 (0.43, 1.35)	0.36	Reference 1.04 (0.56, 1.94)	0.89	Reference 1.33 (0.57, 3.10)	0.51
Type of SAM at hospitalization • oedematous • Non-oedematous	Reference 0.36 (0.24, 0.54)	<0.001	Reference 0.29 (0.19, 0.44)	<0.001	Reference 0.27 (0.16, 0.43)	<0.001	Reference 0.31 (0.18, 0.51)	<0.001	Reference 0.20 (0.10, 0.41)	<0.001
Nutritional status at discharge • No SAM • SAM	Reference 0.13 (0.09, 0.20)	<0.001	Reference 0.14 (0.09, 0.21)	<0.001	Reference 0.21 (0.13, 0.35)	<0.001	Reference 0.42 (0.25, 0.70)	0.001	Reference 0.34 (0.17, 0.70)	0.003
Discharge HAZ	1.47 (1.28, 1.70)	<0.001	1.40 (1.21, 1.61)	<0.001	1.50 (1.26, 1.79)	<0.001	1.26 (1.07, 1.49)	0.006	1.56 (1.23, 2.00)	<0.001
Chronic underlying conditions • No cerebral palsy • Cerebral palsy	Reference 0.17 (0.07, 0.43)	<0.001	Reference 0.16 (0.06, 0.40)	<0.001	Reference 0.08 (0.03, 0.22)	<0.001	Reference 0.10 (0.04, 0.27)	<0.001	Reference 0.02 (0.01, 0.06)	<0.001

Adjusted odds ratios of nutritional recovery were estimated using an ordinal logistic regression model
Univariable analysis was carried out to determine strength of association of each of the seventeen variables; country, residence, sex, age, oedema at hospitalization, HIV status, duration of hospitalization, stunting, HAZ, cerebral palsy, haemoglobin, premature cessation of breastfeeding, SAM at discharge, tuberculosis at discharge, caregiver education, caregiver marital status and toilet type with incidence of readmission using a cut-off of $P < 0.25$.

The 5 variables that were significant at p <0.25 (duration of hospitalization, HAZ, premature cessation of breastfeeding, toilet type and TB at discharge) and the 7 a priori variables (country, sex, age at discharge, HIV status, baseline oedema, SAM at discharge and cerebral palsy) were offered up to the mfp model.
The table shows the adjusted hazard ratios obtained from the final model at each time-point. Duration of hospitalization, premature cessation of breastfeeding, TB at discharge and toilet type were not retained in the final model at any time-point.
SAM: severe acute malnutrition, HAZ: height-for-age Z-score; TB: tuberculosis

CHAPTER 5: PAPER III

BODY COMPOSITION FOLLOWING HOSPITALISATION FOR SAM

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SUMMARY

HIV and severe wasting were found to be associated with post-discharge mortality and hospital readmission among children with complicated severe acute malnutrition (SAM); for reasons that are not clear. Skinfold thicknesses and bioelectrical impedance analysis (BIA) were used to assess body composition in a cohort of children who had been managed for complicated SAM to investigate whether fat and lean mass were independent predictors of time to death or readmission.

The main findings are listed below:

- Low lean and peripheral fat mass at discharge from hospital were independently associated with death/time to readmission.
- Children living with HIV infection compared to those who were not had lower gains in both fat and lean mass.
- Children who had non-oedematous compared to oedematous SAM at hospitalisation had lower mean changes in total fat mass and lean mass measured using impedance index.

- A cluster of children who had the lowest lean and total fat mass, the highest degree of wasting and stunting, the highest proportion who were living with HIV and had ongoing SAM at hospital discharge, had a nearly 3-fold increased odds of mortality or hospital readmission after adjusting for age.

5.1 INTRODUCTION

Malnutrition remains a global health challenge contributing to nearly 50% of all deaths in children below the age of 5 years (5) . Severe acute malnutrition (SAM), defined as a weight-for-height Z-score (WHZ) <-3, mid-upper arm circumference (MUAC) <115mm, and/or bilateral nutritional oedema, has particularly high mortality when associated with clinical complications requiring hospitalisation. SAM is classified into oedematous and non-oedematous forms and treatment success is defined by a target WHZ, MUAC or resolution of oedema, depending on the criteria initially used for classification (36) . Children hospitalized for complicated SAM remain at high risk for mortality in the year following hospital discharge. A recent publication from the HOPE SAM cohort showed that non-oedematous SAM, ongoing SAM at the time of discharge, cerebral palsy and HIV infection were independent predictors of mortality (184).

None of the anthropometric measures used to define SAM estimate the restoration of associated physiological and functional deficits (37, 38) . Body composition, measured as fat mass (FM) and lean mass (LM), has been shown to predict clinical outcomes in conditions such as cancer (137, 138) , chronic kidney disease (139) and sickle cell disease in children and adolescents (140). Lean mass comprises skeletal muscle, the skeleton, soft lean tissues and vital organs, while fat mass is distributed into central and peripheral fat stores (195, 196). Loss of lean mass has been associated with decreased survival, worse clinical outcomes, increased rate of infections, complications, duration of hospitalisation and prolonged recovery in adults with chronic diseases (141-143) and similar data are emerging for children (144).

Interest in measuring body composition in undernourished children and exploring the long-term consequences for the development of non-communicable diseases has increased over the past few decades as mortality from SAM falls and children survive into adulthood (197). Wasting is associated with deficits in both lean and fat mass (145) and body composition can be used to evaluate physiological recovery following SAM (146, 147). However, there are few published data on the relationship between body composition and mortality, readmission and growth recovery in children managed for SAM. Assessing body composition may improve our understanding of underlying mechanistic pathways, recovery of physiological function and how to optimise clinical outcomes (38).

Body composition was measured longitudinally in a cohort of children over 52 weeks after discharge from hospital in Zambia and Zimbabwe following management of complicated SAM. The hypothesis being tested was that low lean and fat mass would identify children most at risk of death or hospital readmission following hospital discharge for complicated SAM, and that body composition differences by HIV and oedema status may partly explain the differential long-term outcomes between children (184, 198).

5.2 METHODS

In addition to the standard anthropometry, body composition using bioelectrical impedance analysis and skinfold thicknesses were done at admission, discharge and throughout the follow up period except on admission when skinfolds were not taken. Children were censored at the earliest last known alive date or at week 52 after discharge. As children could be readmitted over the one year of follow up, the follow up time points were determined from the date of initial hospital discharge. The following variables were chosen based on biological plausibility and published literature: lean mass index (LMI), impedance index (II) and phase

angle (PA), sum of skin folds (triceps, suprailiac and subscapular. Models were adjusted for factors based on biological plausibility together with some apriori variables (age at discharge, sex and country)

5.2.1 Statistical analysis

All the body composition variables were converted to internal z-scores for the analysis. Directed acyclic graphs (DAGs) constructed using DAGitty version 3.0 were used to select the minimum set of covariates for adjustment for each of the outcomes. (Supplementary Figure 5)

5.2.1.1 Survival Analysis

The primary outcome for this analysis was a composite of mortality or time to first hospital readmission. Cox proportional hazards models were used to estimate hazard ratios of death or hospital readmission with body composition variables as exposures, after adjusting for the following minimum set of covariates obtained from the DAG: age at discharge, sex, HAZ and WHZ at discharge, HIV status, oedema at hospitalisation, and maternal employment

To compare the longitudinal BIA and skinfold thickness z-scores between children with and without oedema at hospitalisation and those with and without HIV infection, mixed effects models were run with HIV or oedema as fixed effects and participant identifiers as the random effect. In order to address the third objective which sought to identify groups of children sharing common discharge body composition and anthropometric characteristics which had been shown to be risk factors for mortality, hierarchical clustering was used. Logistic regression and linear regression were used for categorical and continuous variables respectively to compare time to the composite outcome of time to readmission or death.

5.2.1.2 Longitudinal changes in body composition

All available data from participant discharge to study discontinuation were summarised. Non-overlapping visit windows were used and the measurement closest to the study visit week was used for analyses. Mixed effects models were used to compare longitudinal skinfolds z-scores and BIA data converted to internal z-scores between children with and without HIV infection and between children with and without oedema at initial hospitalisation, using HIV or oedema as fixed effects and participant identifier as the random effect. The minimum covariate set for HIV status as an exposure were birthweight, sex, age at discharge, oedema at initial hospitalisation, HAZ and WHZ at discharge, hospital readmission, toilet type and maternal employment. The minimum covariate set for oedema as an exposure were birthweight, HIV status, age at discharge, hospital readmission, maternal employment and toilet type. Coefficients and confidence intervals obtained from the univariable and multivariable mixed effects models were interpreted. Margins plots were used to show the change in body composition by HIV status and baseline oedema status over 52 weeks of follow-up.

5.2.1.3 Clustering analysis

Hierarchical clustering was conducted to identify groups of children sharing common characteristics based on discharge body composition variables and anthropometric factors previously associated with mortality in the same cohort (oedema status at initial hospitalisation, HAZ and WHZ at discharge) (184). The number of clusters was identified using the Calinski-Harabasz stopping rule. Comparison of characteristics and outcomes of children across groups was made using logistic regression for categorical variables and linear regression for continuous variables.

Direct acyclic graphs (DAGs) (Supplementary Figure 5) constructed using DAGitty version 3.0 (www.dagitty.net) were used to select the minimum set of covariates

requiring adjustment for the causal relationships between HIV status and oedema status at initial hospitalization with body composition, and between body composition and the composite outcome of death or hospital readmission. The minimum covariate set for HIV status as an exposure and body composition as an outcome (A) were birthweight, sex, age, oedema at initial hospitalisation, HAZ and WHZ at discharge, hospital readmission, toilet type and maternal employment. The minimum covariate set for oedema as an exposure and body composition as an outcome (B) were birthweight, HIV status, age , hospital readmission, maternal employment and toilet type. The minimum adjustment set for the relationship between body composition and death or hospital readmission (C) included age, sex, WHZ and HAZ at discharge, HIV status, oedema at initial hospitalisation and maternal employment.

5.3 RESULTS

5.3.1 Study Enrolment

Of the 649 children who were discharged from hospital after treatment of SAM, 45 left before any measurements were done, leaving 604 children with discharge measurements (Supplementary Figure 6). Complete BIA and skinfolds data were collected in 334 and 563 children, respectively. Following data cleaning and removal of implausible values, 284 (47%) children contributed complete BIA data and 546 (90.4%) skinfolds measurements at hospital discharge.

5.3.2 Baseline Characteristics

Baseline characteristics of the children with and without discharge BIA measurements were broadly similar, except for small differences in country, caregiver employment, and anthropometry: children with missing data had a marginally lower WHZ, but higher HAZ than those with available BIA data, and no differences in WAZ or MUAC (Supplementary Table 8)

5.3.3 Discharge Characteristics

Having previously shown that post-discharge mortality is higher in children living with HIV compared to those without HIV and in children with non-oedematous compared to oedematous SAM(184), discharge characteristics were stratified by HIV and oedema status. At discharge, children living with HIV compared to those who were not were significantly older, and were more likely to have non-oedematous SAM at admission and ongoing SAM at discharge. Anthropometry (WAZ, HAZ and MUAC), sum of skinfolds, impedance and lean mass indices were significantly lower in children living with HIV infection compared to those who were not living with HIV children at the time of hospital discharge. Children with oedematous SAM were significantly older, less likely to be living with HIV, and less likely to have ongoing SAM at the time of hospital discharge compared to those with non-oedematous SAM. Children with non-oedematous SAM were more stunted and had significantly less fat and lean mass than children with oedematous SAM (Table ~~8~~9).

Table 9: Discharge anthropometry and body composition

	All N= 604	HIV-positive N=121	HIV-negative N=483	P-value[a]	Oedema at Baseline N=391	No oedema at baseline N=213	P value[b]
Male	322/604 (53.3%)	60/121 (49.6%)	262/483 (54.2%)	0.36	208/391 (53.2%)	114/213 (53.5%)	0.94
Age, months; median (IQR)	18.0 (13.6, 22.8)	20.2 (15.4, 26.0)	17.5 (13.4, 22.1)	<0.001	19.3 (14.8, 23.3)	15.7 (11.2, 21.2)	<0.001
Oedema at hospitalisation	391/604 (64.7%)	63/121 (52.1%)	328/483 (67.9%)	0.001	n/a	n/a	n/a
HIV-positive	n/a	n/a	n/a		63/391 (16.1%)	58/213 (27.2%)	0.001
SAM at discharge	264/604 (43.7%)	66/121 (54.6%)	198/483 (41.0%)	0.007	146/391 (37.3%)	118/213 (55.4%)	<0.001
Anthropometry at discharge							
WHZ, mean (SD)	-2.2 (1.5)	-2.4 (1.4)	-2.1 (1.5)	0.09	-1.9 (1.4)	-2.7 (1.4)	<0.001
WAZ, mean (SD)	-3.3 (1.6)	-3.7 (1.2)	-3.2 (1.7)	0.006	-3.0 (1.5)	-4.0 (1.5)	<0.001
HAZ, mean (SD)	-3.1 (1.5)	-3.4 (1.2)	-3.0 (1.6)	0.007	-2.9 (1.5)	-3.4 (1.6)	<0.001
MUAC, mm; mean (SD)	123.0 (15.7)	116.9 (13.5)	124.6 (15.9)	<0.001	126.5 (15.6)	116.5 (13.8)	<0.001
MUAC z-score (SD)	-2.4 (1.61)	-3.16 (1.40)	-2.23 (1.61)	<0.001	-2.10 (1.61)	-3.00 (1.45)	<0.001
Body composition at discharge							
Triceps skinfolds, mm, mean (SD)	6.65 (2.35)	5.54 (1.59)	6.94 (2.43)	<0.001	6.98 (2.54)	6.01 (1.78)	<0.001
Triceps skinfolds z-score, mean (SD)	-1.19 (1.69)	-2.02 (1.45)	-0.97 (1.68)	<0.001	-0.93 (1.71)	-1.69 (1.52)	<0.001
Subscapular skinfolds, mm, mean (SD)	5.21 (1.97)	4.46 (1.70)	5.35 (2.00)	<0.001	5.36 (2.18)	4.92 (1.43)	0.01
Subscapular skinfolds z-score, mean (SD)	-1.49 (2.02)	-2.10 (2.02)	-1.34 (1.99)	<0.001	-1.34 (2.13)	-1.79 (1.76)	0.01
Suprailiac skinfolds, mm, mean (SD)	4.48 (2.00)	3.63 (1.70)	4.70 (2.02)	<0.001	4.65 (2.07)	4.16 (1.82)	0.006
Suprailiac skinfolds z-score, mean (SD)	0.002 (1.00)	0.11 (1.01)	-0.42 (0.85)	<0.001	0.08 (1.03)	-0.16 (0.92)	0.007
Sum of skinfolds, mm, mean (SD)	16.39 (5.07)	14.10 (4.29)	17.02 (5.07)	<0.001	17.04 (5.35)	15.10 (4.18)	<0.001
Sum of skinfolds z-score, mean (SD)	0.008 (1.00)	-0.47 (0.84)	0.13 (1.00)	<0.001	0.14 (1.05)	-0.24 (0.82)	<0.001
Impedance index, cm^2/Ω; mean (SD)	0.63 (0.19)	0.59 (0.17)	0.64 (0.20)	0.07	0.67 (0.18)	0.56 (0.19)	<0.001
Impedance index z-score, mean (SD)	0.01 (1.00)	-0.20 (0.90)	0.06 (1.02)	0.07	0.22 (0.95)	-0.37 (0.98)	<0.001
Lean mass index, 1/ Ω; mean (SD)	11.73 (2.43)	10.97 (2.12)	11.92 (2.47)	0.008	11.96 (2.32)	11.30 (2.56)	0.03
Lean mass index z -score, mean (SD	0.009 (-0.11)	-0.30 (0.88)	0.09 (1.02)	0.008	0.10 (0.96)	-0.17 (1.06)	0.03
Phase angle	3.26 (1.27)	3.31 (1.34)	3.25 (1.26)	0.77	3.23 (1.26)	3.33 (1.30)	0.54
Phase angle z-score	0.001 (-0.11)	0.04 (1.05)	-0.01 (1.00)	0.77	-0.03 (1.00)	0.05 (1.02)	0.54

Data are n/total (column %) unless otherwise stated. 1/ Z (Ω) was used as a proxy for lean mass index. HAZ, height-for-age z-score; IQR, interquartile range; MUAC, mid-upper-arm circumference; SAM, severe acute malnutrition; SD, standard deviation; WAZ, weight-for-age z-score, [a]P value comparing HIV-positive and HIV-negative groups, [b]P value comparing children with and without oedema at initial hospitalisation

5.3.4 Associations between discharge body composition and time to death or hospital readmission

In the adjusted Cox regression model (Table 910), both lean and peripheral fat mass were independently associated with mortality or readmission into hospital. Each z-score increase in lean mass index and impedance index, was associated with a 33% (aHR 0.67, 95%CI 0.47, 0.98) and 48% (aHR 0.52, 95%CI 0.30, 0.90) reduction in hazard of death or hospital readmission. Each z-score increase in triceps skinfold was associated with a 17% (aHR 0.83, 95%CI 0.71, 0.96) reduction in death or readmission. By contrast, subscapular and suprailiac skinfolds, and phase angle were not associated with death or time to readmission.

Table 10: Cox regression model of discharge body composition factors associated with time to death or readmission

	N	Unadjusted HR(95%CI)	P-value	Adjusted HR* (95%CI)	P-value
Bioimpedance electrical analysis					
• Lean mass index Z-score,	N=284	0.53 (0.37, 0.75)	0.002	0.62 (0.41, 0.94)	0.02
• Impedance index Z-score	N=286	0.48 (0.33, 0.71)	<0.001	0.48 (0.24, 0.83)	0.01
• Phase angle Z-score	N=296	1.0 3(0.79,1.36)	0.84	1.07 (0.81,1.43)	0.63
Skin folds					
• Triceps skinfold Z-score	N= 557	0.72 (0.63,0.83)	<0.001	0.77 (0.64, 0.91)	0.002
• Subscapular skinfold Z-score	N= 550	0.86 (0.76, 0.97)	0.01	0.89 (0.79, 1.02)	0.09
• Suprailiac skinfold Z-score	N= 563	0.75 (0.58, 0.97)	0.03	0.90 (0.68, 1.19)	0.46
• Sum of skinfolds Z-score	N= 551	0.63 (0.47, 0.83)	0.001	0.69 (0.49, 0.98)	0.04

*Multivariable models included a minimum adjustment set identified from a directed acyclic graph: age at discharge, sex, baseline oedema, WHZ , HAZ, HIV status, and maternal employment

Interaction of each body composition variable by HIV and oedema status was tested and there was evidence of interaction between LMI and oedema status only. Stratified analysis showed that among children with oedema, each unit increase in LMI was associated with a 61% (aHR 0.39, 95%CI 0.20, 0.75) reduction in the hazards of death or readmission; by contrast, there was no association between LMI and death/readmission in children without oedema. In summary, lean mass and peripheral fat mass were independently associated with hospital readmission. When the components of the composite variable were analysed

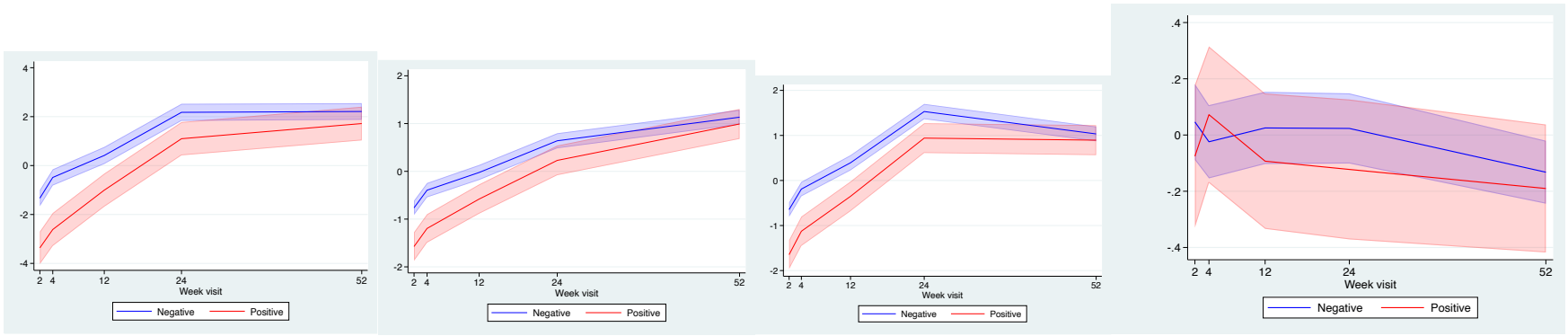
separately, readmission and not death was significantly associated with low lean mass and peripheral fat mass (Supplementary Tables 9 and 10).

5.3.5 Body composition over 52 weeks of follow-up

Figure 16 shows the change in skinfolds (representing fat mass) and impedance index (representing lean mass) over time stratified by HIV status and oedema status. Individual trajectories are shown as spaghetti plots in Supplementary Figure 7. Over the 52 weeks of follow-up, all children showed a general increase in fat and lean mass. Triceps skinfolds (a measure of peripheral fat) increased throughout the period of follow-up; subscapular skinfolds (a measure of central fat) increased up to 24 weeks followed by a decline; and sum of skinfolds (a marker of total fat) increased up to 24 weeks, then plateaued.

By HIV status

A. Total skinfolds Z-score **B. Triceps skinfolds Z-score** **C. Subscapular skinfolds Z-score** **D. Impedance index Z-score**



By baseline oedema status

E.Total skinfolds Z-score **F. Triceps skinfolds Z-score** **G. Subscapular skinfolds Z-score** **H. Impedance index Z-score**

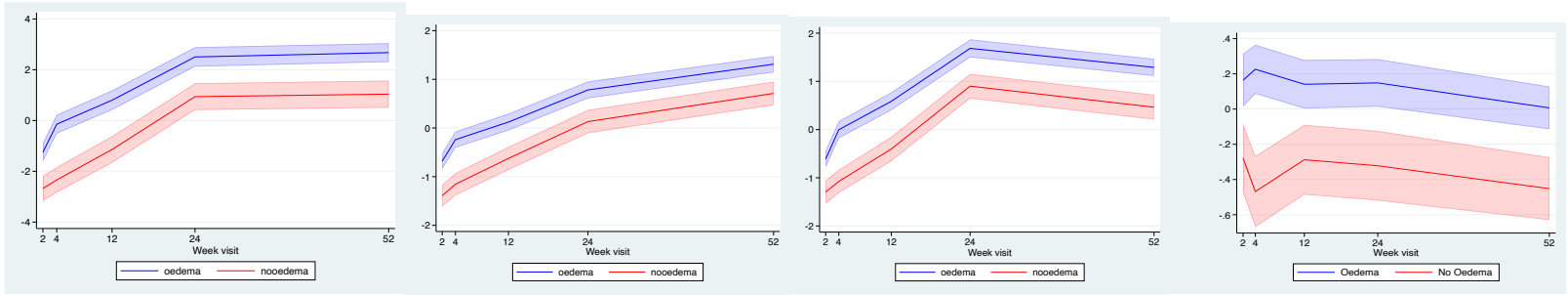


Figure 16: Change in body composition over 52 weeks of follow-up stratified by HIV status and baseline oedema status

Margins plots of change in body composition over 52 weeks of follow-up stratified by HIV status and oedema status at initial hospitalisation.

5.3.6 Association between anthropometry and body composition with baseline oedema and HIV status

Table ~~10~~11 shows the univariable and multivariable mixed effects analysis of the association between HIV and baseline oedema status, with anthropometry and body composition during follow-up. HIV-positive compared to HIV-negative children had lower gains in anthropometry, fat mass and lean mass over 52 weeks. Mean changes in MUAC (-0.44cm, (95% CI -0.62, -0.25)) and HAZ (-0.32 z-score (95% CI -0.60,-0.04)) were lower in HIV-positive compared to HIV-negative children. Fat mass gains were lower in HIV-positive compared to HIV-negative children: -1.49 z-scores (95%CI 2.01, -0.97) for total fat mass, -0.66 z-scores (95%CI -0.91, -0.41) for central fat mass, and -0.60 z-scores (95% CI -083, -0.37) for peripheral fat mass. Change in lean mass measured by impedance index was also lower in HIV-positive compared to HIV-negative children (-0.13 (95%CI -0.24, -0.01) over 52 weeks.

Compared to children with oedema at the time of initial hospitalisation, mean changes in MUAC, WHZ and WAZ were significantly lower in children with non-oedematous SAM, while HAZ was not different between groups. Both fat and lean mass were significantly lower in children without oedema: -1.47 z-score (95% CI -1.97, -0.97) for total fat mass and -0.23 z-scores (95%CI -0.36, -0.09) for impedance index z-score.

Taken together, whilst children showed overall gains in lean and fat mass and anthropometry during 52 weeks of follow-up, changes were significantly lower for HIV-positive children and for those with non-oedematous malnutrition.

Table 11: Univariable and multivariable mixed effects analysis of body composition, and anthropometry over 52 weeks of follow-up

Variable	HIV-positive versus HIV-negative		Non-oedematous versus oedematous	
	Unadjusted Coefficient (95% CI) P value	**Adjusted Coefficient (95% CI) P value**	**Unadjusted Coefficient (95% CI) P value**	**Adjusted Coefficient (95% CI) P value**
Mid-upper arm circumference, cm	-0.81 (-1.07, -0.54) <0.001	-0.44 (-0.62, -0.25) <0.001	-1.09 (-1.30, -0.88) <0.001	-0.76 (-0.98, -0.54) <0001
MUAC Z-score	-0.79 (-1.05,-0.53) <0.001	-0.44 (-0.62,-0.25) <0.001	-1.02 (-1.23, -0.81) <0.001	-0.70 (-0.92,-0.48) <0.001
Weight-for-height Z-score	-0.25 (-0.51, 0.01) 0.06	-0.11 (-0.05, 0.27) 0.18	-1.07 (-1.27, -0.87) <0.001	-0.89 (-1.10, -0.67) <0.001
Height-for-age Z-score	-0.39 (-0.67, -0.12) 0.005	-0.32 (-0.60, -0.04) 0.03	-0.51 (-0.74, -0.28) <0.001	-0.19 (-0.44, 0.05) 0.12
Weight-for-age Z-score	-0.45 (-0.78, -0.15 0.004	-0.04 (-0.11, -0.18) 0.63	-1.14 (-1.38, -0.90) <0.001	-0.77 (-1.01, -0.52) <0.001
Triceps skinfold Z-score	-0.86 (-1.11,-0.62) <0.001	-0.60 (-0.83, -0.37) <0.001	-0.85 (-1.07, -0.64) <0.001	-0.63 (-0.85, -0.41) <0.001
Subscapular skinfold Z-score	-0.93 (-1.19, -0.67) <0.001	-0.66 (-0.91, -0.41) <0.001	-0.91 (-1.13, -0.69) <0.001	-0.73 (-1.00, -0.45) <0.001
Suprailiac skinfold Z-score	-0.34 (-0.48, -0.20) <0.001	-0.30 (-0.45, -0.15) <0.001	-0.22 (-0.34, -0.11) <0.001	-0.11 (-0.24, 0.02) 0.09
Total skinfolds Z-score	-2.08 (-2.64, -1.52) <0.001	-1.49 (-2.01, -0.97) <0.001	-1.95 (-2.42, -1.48) <0.001	-1.47 (-1.97, -0.97) <0.001
Lean mass index Z-score	-0.21(-0.37, -0.06) 0.007	-0.11 (-0.27, 0.04) 0.16	-0.27 (-0.40, -0.14) <0.001	-0.23 (-0.37, -0.08) 0.002
Impedance index Z-score,	-0.31 (-0.46, -0.16) <0.001	-0.13 (-0.24, -0.01) 0.04	-0.37 (-0.50, -0.24) <0.001	-0.23 (-0.36, -0.09) 0.002
Phase angle Z-score	0.01 (-0.15,0.13) 0.90	-0.001 (-0.15,0.15) 1.0	-0.08 (-0.04,0.20) 0.21	0.08 (-0.06,0.21) 0.25

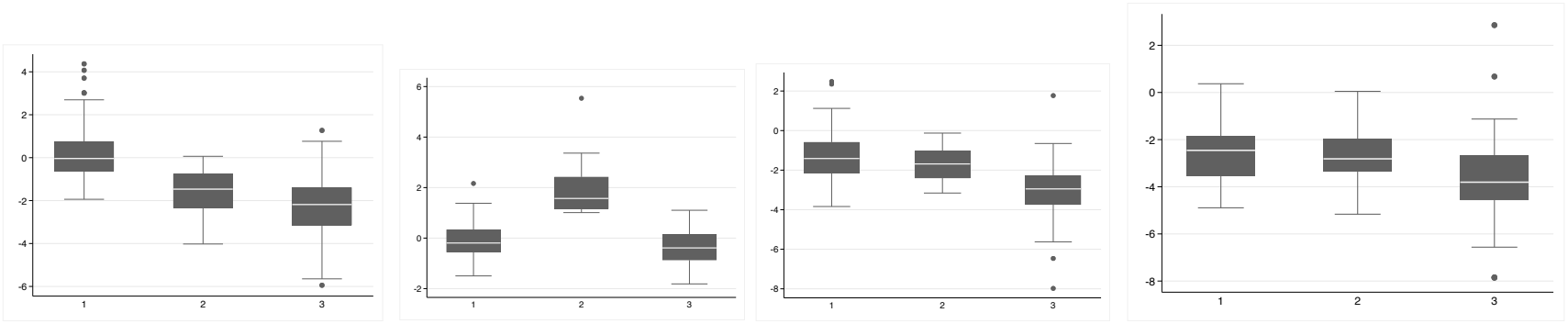
All values are mean differences (95% CI) from a multivariable mixed effects model, with HIV or oedema as fixed effects and participant identifier as the random effect. Adjustment set for HIV status: sex, birthweight, age at discharge, oedema at hospitalisation, HAZ, WHZ, maternal employment, toilet type and hospital readmission. Adjustment set for oedema status: birthweight, age at discharge, HIV status, hospital readmission, toilet type and maternal employment status

5.3.7 Clustering analysis

Hierarchical clustering based on body composition and anthropometry identified three groups of children at the time of hospital discharge, group 1 (n=110, 40.7%), group 2 (n=24, 8.9%) and group 3 (n=136, 50.4%), whose characteristics were strongly associated with time to readmission or death (Figure 17; Supplementary Figure 8). Group 1 children had the highest proportion of oedema at hospitalisation (85.5%), the highest fat mass and the lowest HIV infection rates. Group 2 had the highest lean mass compared to the other groups. Group 3 had the lowest fat and lean mass, WHZ and HAZ, the highest proportion of HIV-positive children (32.4%) and ongoing SAM at the time of hospital discharge (66.2%) compared to group 2 and 3.

While group 1 had the highest fat mass and group 2 had the highest lean mass, the two groups had similar weight-for-height Z-score, height-for-age Z-score, rates of HIV positivity and SAM at discharge and the odds of death or death or readmission were similar between groups. Overall, compared to group 1, children in group 3 had a 2.7-fold increased odds of death or readmission to hospital (aOR 2.7 (95%CI 1.3, 5.4) after adjusting for age (Supplementary Table 11)

Triceps skinfolds z-score **B. Lean mass index z-score** **C. Weight-for-height Z-score** **D. Height-for-age Z-score**



E. Baseline oedema **F. HIV status** **G. SAM at discharge** **H. Died/readmitted**

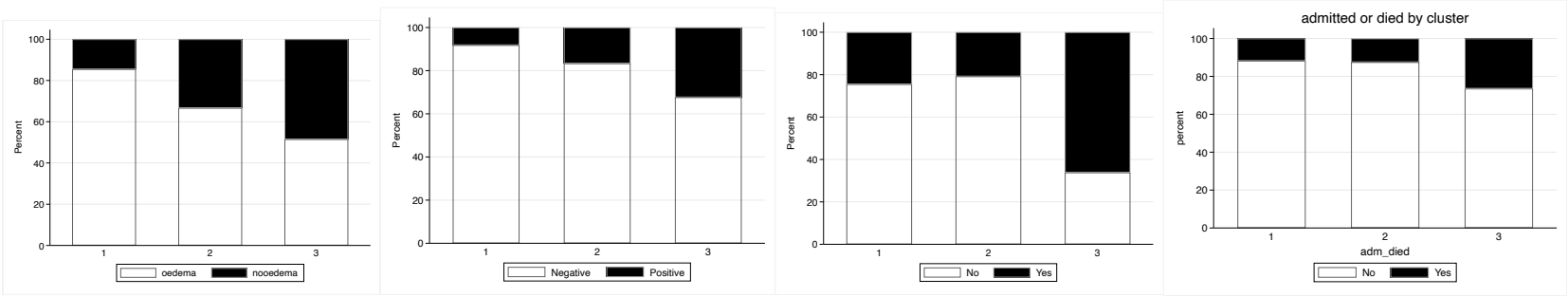


Figure 17: Characteristics of subgroups of children at discharge: *Three groups were identified by hierarchical clustering; (Group 1 n=110, Group 2 n=24 and Group 3 n=136). The group characteristics are shown as proportions for each variable associated with poor outcomes (A. Triceps skinfolds z-score, B. Lean mass index z-score, C. WHZ, D. HAZ, E. baseline oedema, F. HIV status, G. SAM at discharge and H. composite outcome of died/readmitted)*

5.4 DISCUSSION

In this cohort of children treated for complicated SAM and discharged from three hospitals in southern Africa, body composition, in addition to anthropometry, is an important determinant of mortality or hospital readmission in the year following hospital discharge. Specifically, low lean and peripheral fat mass (measured using BIA and skinfolds) were independently associated with the composite outcome of death or readmission. Furthermore, a distinct phenotypic group of children at the highest risk for mortality and hospital readmission were characterised by particularly low WHZ, HAZ, lean and fat mass, high prevalence of HIV infection and ongoing SAM at the time of discharge. Collectively, these findings highlight the importance of considering body composition in the assessment of nutritional recovery and risk stratification of children with SAM in order to optimise post-discharge outcomes.

The most important clinical outcomes in the year post-discharge from hospital are readmission or death. Results from this study show that greater peripheral fat and lean mass were associated with reduced time to readmission or death. Clinical studies in adults have shown that higher muscle mass is a major determinant of survival independent of body mass index (60). Children have a lower muscle mass in relation to body weight compared to adults, and those with complicated SAM stand to suffer more from the acute muscle wasting resulting from food insufficiency, infection and inflammation. Early studies on nutritional status and muscle mass showed that muscle mass was an important determinant of survival(199), but few studies have evaluated lean mass in children with SAM. These findings confirm that greater lean mass at discharge from hospital is associated with reduced mortality or hospital readmission, regardless of HIV status, although the relationship between lean mass and clinical outcomes appeared to be confined to children with oedema. Only higher triceps skinfold was associated with mortality or readmission , suggesting that the pattern of fat loss

or preservation is important (145). Fat is used as a metabolic fuel during periods of food deprivation and this is reflected in peripheral fat loss. During complicated SAM, which is characterised by infection and inflammation, leptin from central fat stores plays a role in stimulating the immune system through lymphopoiesis(200), and upregulation of the innate and adaptive immune response(201). Advances in the measurement of fat and lean mass in malnourished children is set to provide more insight into monitoring growth and development, disease progression and response to treatment(140).

Data from the HOPE SAM cohort previously showed that oedematous SAM accounted for nearly two-thirds of children hospitalised for complicated SAM , and that those with no oedema had twice the mortality risk one year post-discharge(184). Children with non-oedematous SAM had slower anthropometric recovery and gained less fat and lean mass over the year following hospital discharge. Children hospitalised with oedema tend to recover anthropometric parameters faster than wasted children whose condition is more likely to have been longstanding. Change in lean mass was significantly lower in children with non-oedematous SAM suggesting that they take longer to recover from the insult of infection, inflammation and food deprivation. Results for phase angle were null, indicating that it is the gross amount of lean tissue, rather than more subtle markers of membrane quality, that is important for survival.

There are sparse data(145, 202) on body composition in children recovering from complicated severe acute malnutrition. In this longitudinal study of under-five children in Zambia and Zimbabwe, both fat and lean mass were significantly lower in children living with HIV compared to those who were not living with HIV at the time of hospital discharge. Weight loss in persons living with HIV affects both lean and fat tissue and remains a significant

problem even in the era of combination antiretroviral therapy (203). While there was a general increase in fat over one year of follow-up, the mean changes in regional and total fat were significantly lower in children living with HIV compared to those not living with HIV. These findings differ from a study on nutritional recovery among HIV-positive and HIV-negative children with SAM from Malawi which showed similar improvements in triceps (peripheral fat) and subscapular (central fat) skinfolds over four months of follow-up (167). The difference between studies may be because the Malawi study enrolled children with uncomplicated SAM, whereas HOPE SAM enrolled children discharged from hospital after management of complicated SAM. The additional burden of infection, inflammation and metabolic derangements in children with complicated SAM are likely to exert additional nutrient demands during the recovery period, and may fundamentally alter body composition parameters. Studies have shown that the additional metabolic demands for amino acids to support the generation of acute phase proteins and an adaptive immune response exerts a catabolic effect, particularly on skeletal muscle (47, 60), resulting in loss of lean mass.

Three phenotypic groups were defined based on anthropometry and body composition, that had differences in mortality or readmission one year after discharge from hospital. The group with the worst anthropometry, body composition markers, ongoing SAM and highest HIV infection rates had the highest odds of death or readmission compared to the other two groups. The similar odds of death or readmission among groups 1 and 2 whose main difference was fat mass and lean mass suggest that for a similar weight-for-height and height-for-age, the amount of lean or fat mass are associated with survival. This may suggest that there are different pathways to survival involving the preservation of fat and lean mass, respectively. The current classification of malnutrition that is based on body size may not have any link with the physiological changes that contribute to the poor outcomes in these children.

Children with complicated SAM have disrupted metabolic, organ and immunological function, and consideration should be given to using more physiological measures for risk stratification and development of interventions that restore healthy function.

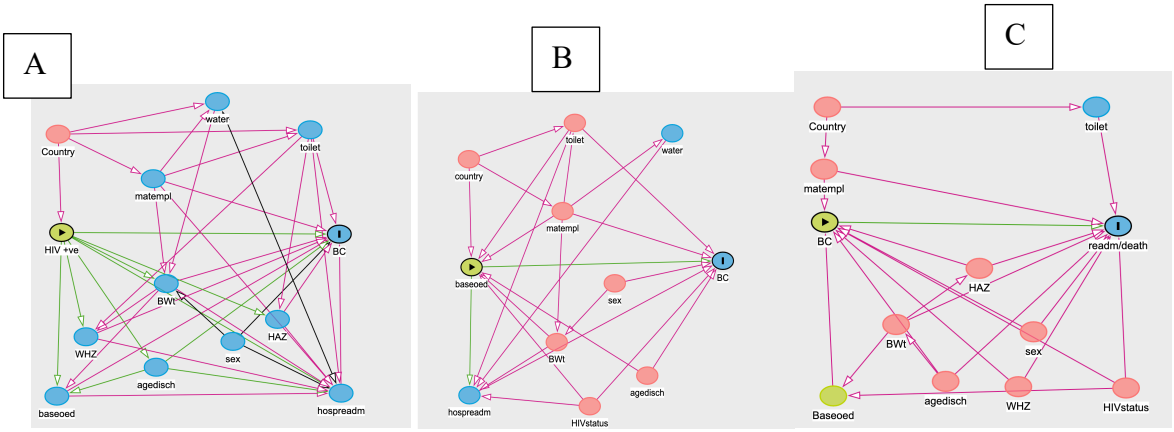
The main strength of this study is that it was large cohort that was followed longitudinally from hospital discharge to 52 weeks, in a setting of high HIV prevalence, and used rarely-deployed techniques to measure body composition at the time of discharge. The high outcome ascertainment for death and readmission due to close follow-up of this cohort strengthens the inferences regarding body composition and clinical outcomes. Limitations of this study include the inability to obtain bioelectrical impedance data on more than half of participants. While BIA is a non-invasive and technically straightforward assessment of body composition, it requires cooperation from the child who must be relaxed and still; this was not always easy, particularly at the time of discharge from hospital. Nevertheless, the sample of children with BIA measurements had similar discharge characteristics to those without measurements, and their rates of mortality and readmission were similar. The BIA method is not able to determine the exact fat mass and fat-free mass which requires isotope calibration against a reference standard; however, the proxy markers of impedance index and lean mass index provided robust relative measures of lean mass that behave similarly to calibrated values in epidemiological analyses.

5.5 CONCLUSION

In summary, this analysis showed that body composition (in particular lean mass and peripheral fat) at the time of hospital discharge are important determinants of mortality and hospital readmission in children managed for complicated SAM. In this cohort, anthropometry and body composition identified specific groups of children with poor outcomes over the year following discharge from hospital. Body composition measurements

reflect the physiological changes accompanying response to treatment and recovery. Screening children prior to discharge using BIA and triceps skinfold measurement may be additional tools to identify children at risk who need more targeted interventions to improve their outcomes. Complicated SAM is characterised by multiple deranged metabolic, immune and hormonal pathways. There is therefore need for interventions that address the inflammatory state that characterises complicated SAM during the convalescent period using therapeutic foods that reduce metabolic stress, modulate inflammation and increase nutrient bioavailability, to improve fat and lean mass recovery, particularly in the highest risk children with severe wasting and HIV infection.

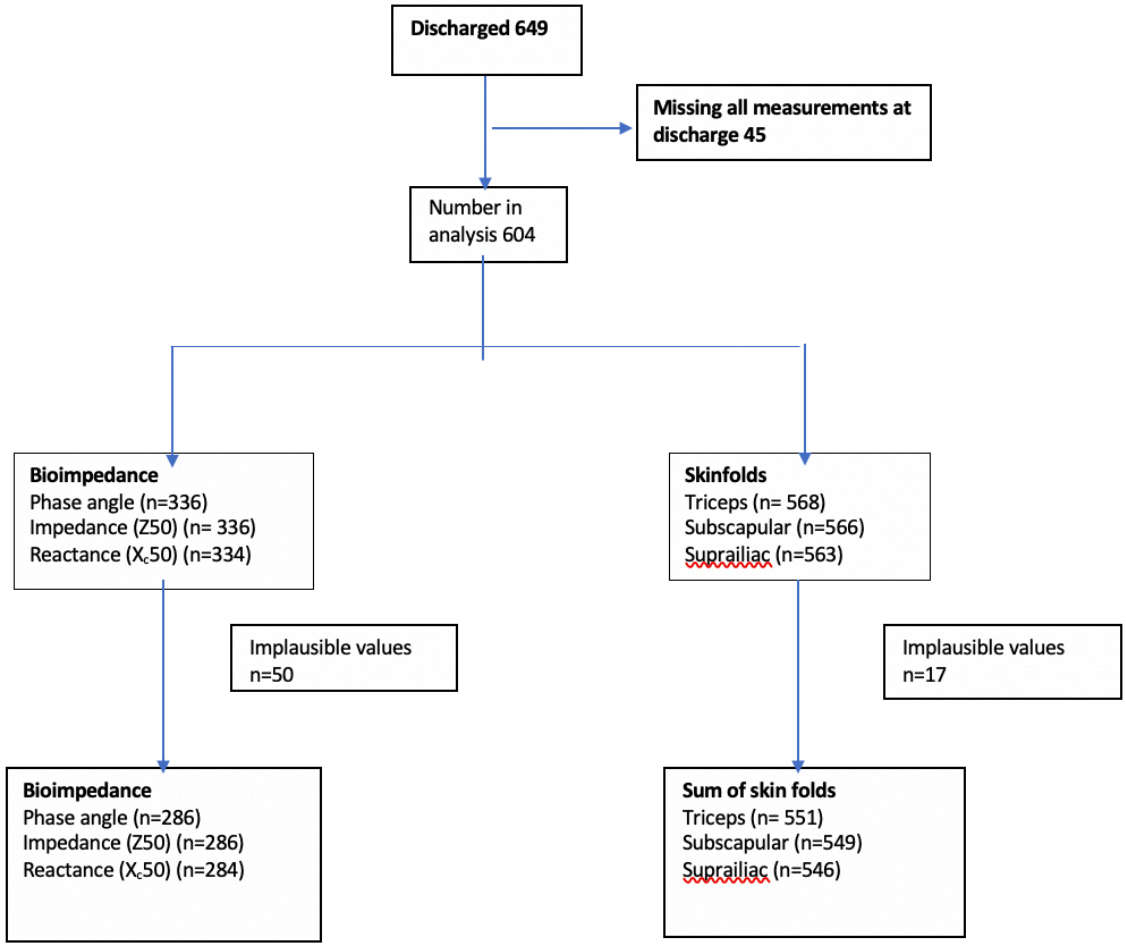
5.6 SUPPLEMENTARY MATERIAL



Supplementary Fig 5: Direct Acyclic Graphs

DAGs to identify confounding variables requiring adjustment for the causal relationship between HIV status and oedema at hospitalisation with body composition, and body composition with the composite outcome of death and readmission.

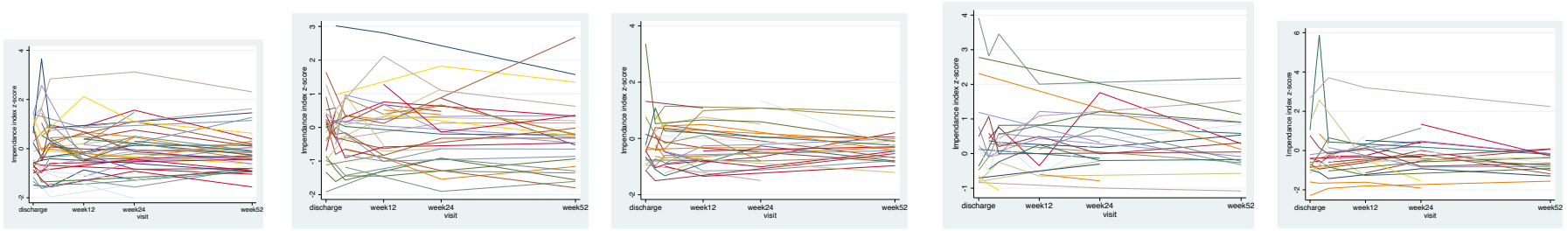
Minimum adjustment set by (A) HIV status: Birth weight, HAZ at discharge, WHZ at discharge, age, baseline oedema, hospital readmission, maternal employment, sex, toilet, by (B) Baseline oedema status: Birth weight, age, HIV status, hospital readmission, maternal employment and toilet type, by (C) Body composition: age, sex, WHZ at discharge, HAZ at discharge, HIV status, baseline oedema , maternal employment



Supplementary Figure 6: Body composition flow diagram

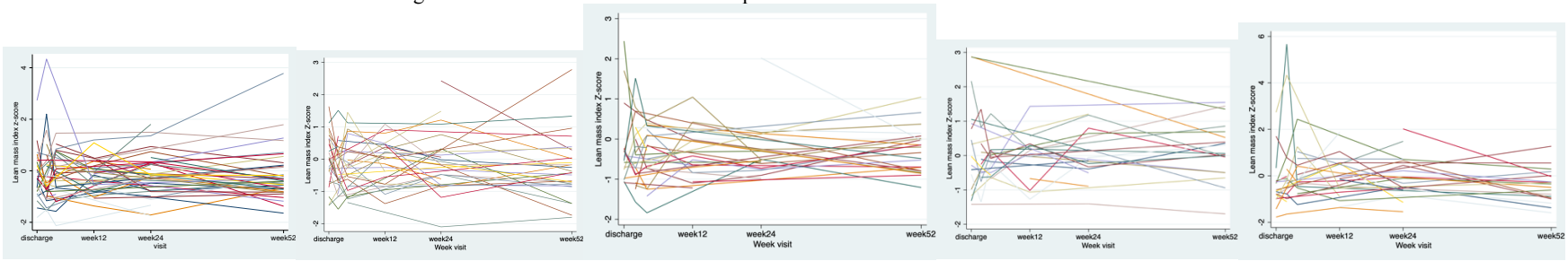
a. Impedance index Z-score

*All children HIV negative HIV positive Oedema at baseline No oedema at baseline



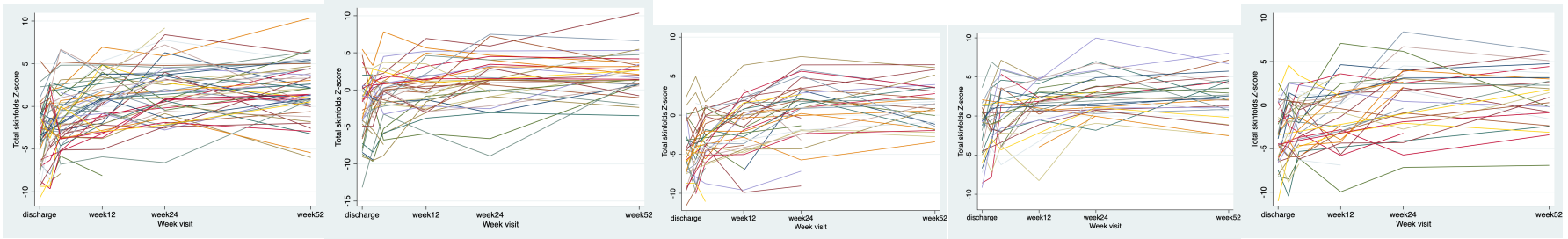
b. Lean mass index Z-score

*All children HIV negative HIV positive Oedema at baseline No oedema at baseline



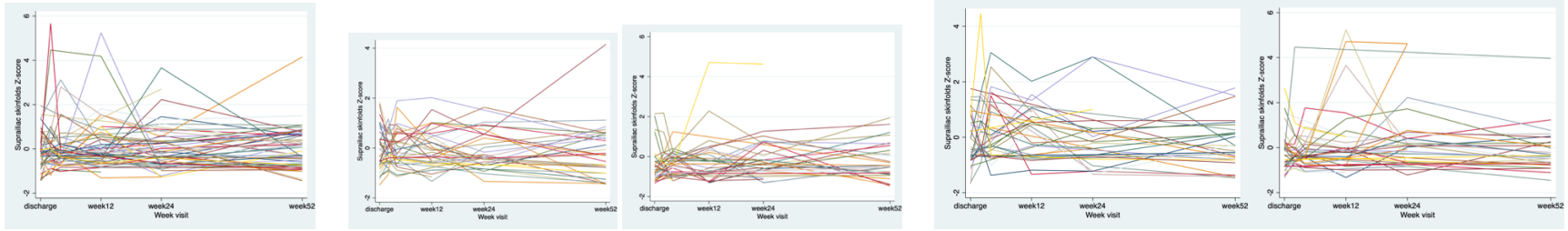
c. Total skinfolds Z-score

*All children HIV negative HIV positive Oedema at baseline No oedema at baseline



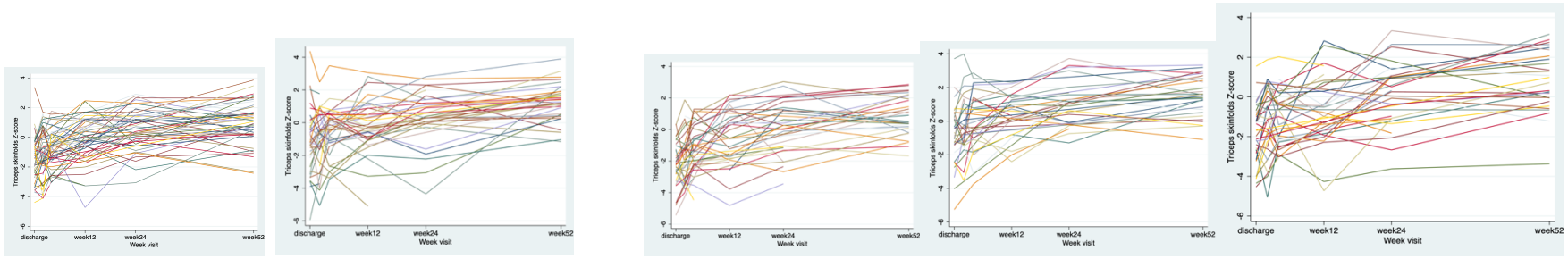
d. Suprailiac Z-score

*All children HIV negative HIV positive Oedema at baseline No oedema at baseline



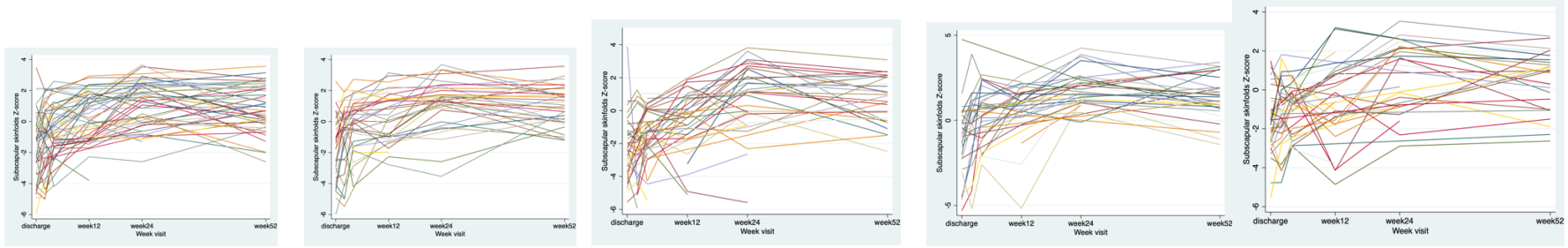
e. Triceps Z-score

*All children HIV negative HIV positive Oedema at baseline No oedema at baseline



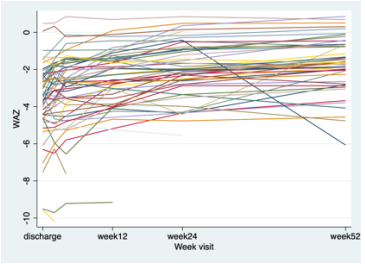
f. Subscapular Z-score

*All children HIV negative HIV positive Oedema at baseline No oedema at baseline

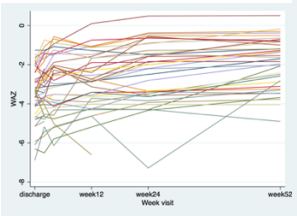


g. Weight for age Z-score

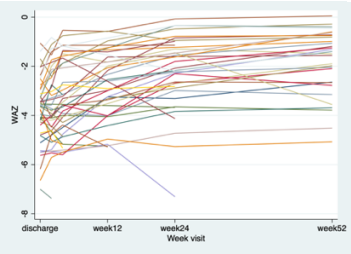
*All children



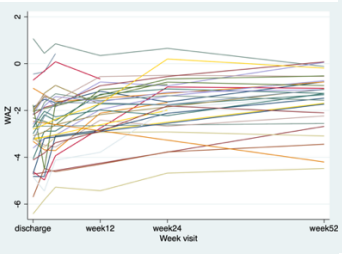
HIV negative



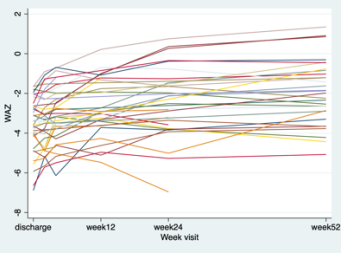
HIV positive



Oedema at baseline

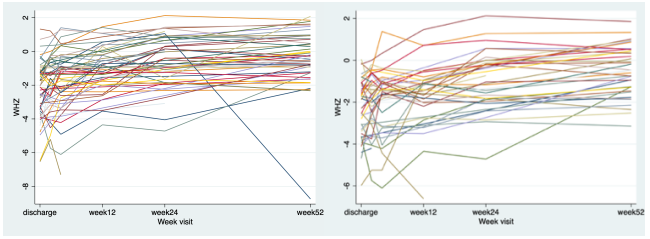


No oedema at baseline



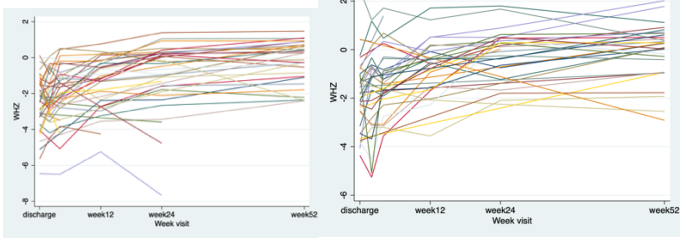
h. Weight for height Z-score

*All children



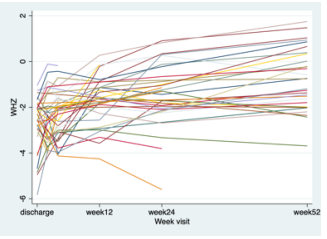
HIV negative

HIV positive



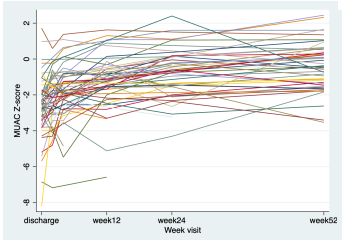
Oedema at baseline

No oedema at baseline

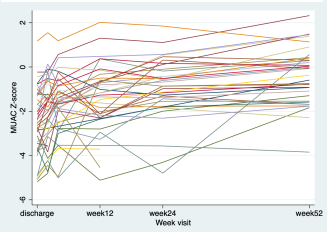


i. MUAC Z-score

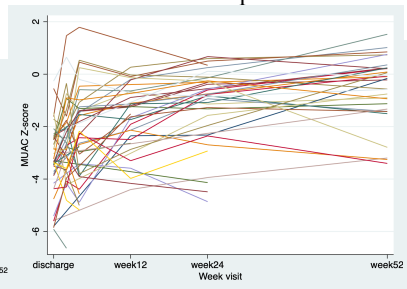
*All children



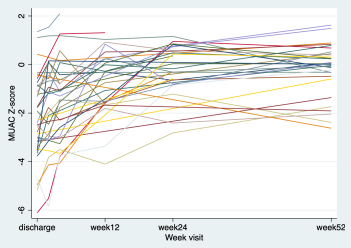
HIV negative



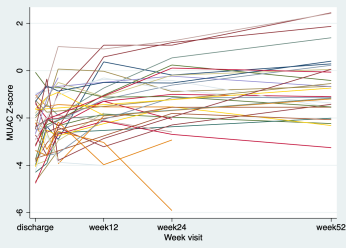
HIV positive



Oedema at baseline

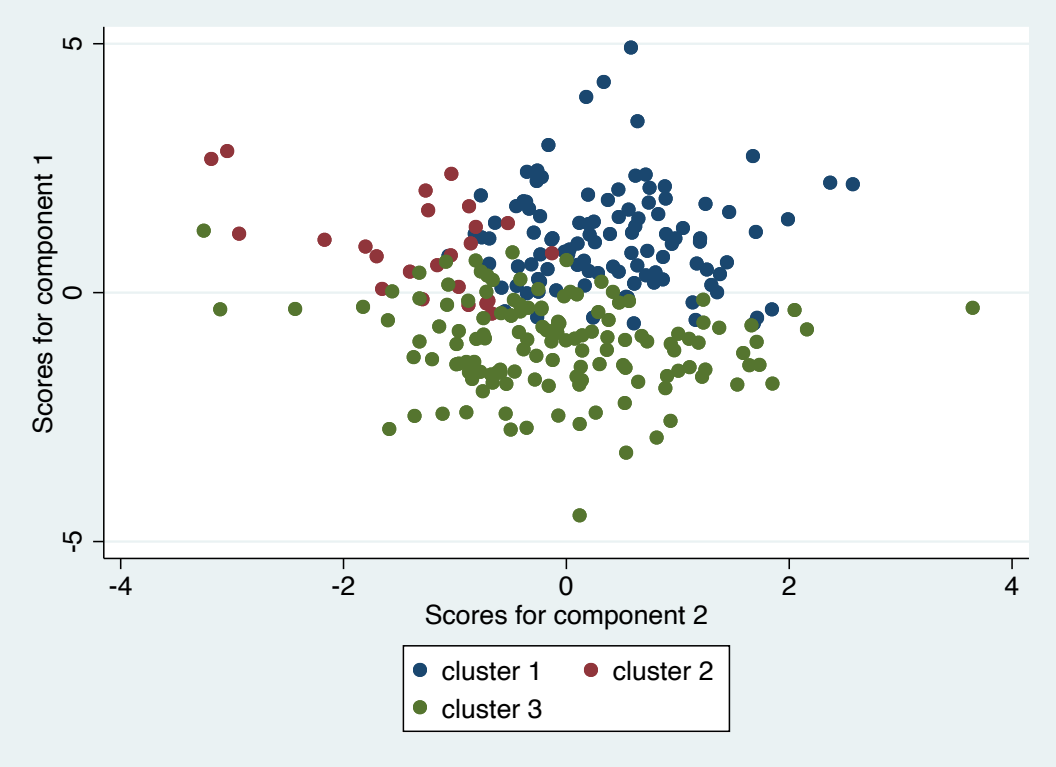


No oedema at baseline



Supplementary Figure 7: Individual trajectories of body composition and anthropometry over 52 weeks of follow up stratified by HIV status and oedema at initial hospitalisation

Lowess plots were used to model the changes in body composition and anthropometric variables over the 52 weeks of follow up stratified by HIV status and oedema status at the time of hospitalization. A randomly selected sample of 10% was selected for each variable for the HIV negative and no oedema at baseline due to a large sample. Random samples of 40% and 30% were chosen for the HIV positive and those without oedema because of fewer number



Supplementary Figure 8: Subgroups of children at discharge identified by anthropometry and body composition variable

Supplementary Table 8: Discharge characteristics of children with and without bioimpedance electrical analysis data

	No bioimpedance analysis data N=321	With available bioimpedance analysis data N=283	P-value
Country			
• **Zambia**	111/321 (34.6%)	74/283 (26.2%)	0.03
• **Zimbabwe**	210/321 (65.4%)	209/283 (73.8%)	
Male	164/321 (51.1%)	158/283 (55.8%)	0.24
Age, months; median (IQR)	18 (13, 22)	19 (14, 24)	0.09
HIV status			
• Positive	63/321 (19.6%)	58/283 (20.5%)	0.79
• Negative	258/321 (80.4%)	225/283 (79.5%)	
Previous history			
• Complicated SAM	43/317 (13.6%)	47/277 (17.0%)	0.39
• Uncomplicated SAM	62/315 (19.7%)	55/277 (19.9%)	0.84
• Persistent diarrhoea	63/295 (21.4%)	52/261 (19.9%)	0.66
• Diarrhoea past 2 weeks	177/321(55.1%)	149/283(52.7%)	0.54
Currently breastfeeding	67/319 (21.0%)	51/280 (18.2%)	0.39
Premature breastfeeding cessation <12mo	90/320 (28.1%)	72/281 (25.6%)	0.47
*Duration of breastfeeding (months); median (IQR)	14 (9, 18)	14 (9, 18)	0.81
Oedematous SAM at hospitalisation	208/321 (64.8%)	183/283 (64.7%)	0.97
SAM at discharge	135/321 (42.1%)	129/283 (45.6%)	0.38
Anthropometry			
WHZ, mean (SD)	-2.21 (1.45)	-2.18 (1.48)	0.80
WAZ, mean (SD)	-3.27 (1.52)	-3.41 (1.66)	0.28
HAZ, mean (SD)	-2.96 (1.50)	-3.23 (1.57)	0.03
MUAC, cm; mean (SD)	12.25 (1.60)	12.35 (1.54)	0.47
Duration of hospitalisation; median (IQR)	10 (7, 14)	10 (8, 15)	0.79
Chronic underlying conditions			
• Cerebral palsy	12/321 (3.7%)	15/283 (5.3%)	0.46
• Hydrocephalus	2/321 (0.6%)	1/282 (0.4%)	0.64
• Congenital heart disease	5/321 (1.6%)	7/282 (2.5%)	0.420.46
Medications at discharge			0.19
• TB medication	41/321 (12.8%)	42/282 (14.9%)	
• ART medication	29/63 (46.0%)	33/57 (57.9%)	
Primary caregiver			
• Mother	291/315 (92.4%)	256/274 (93.4%)	0.62
• Age, years; median (IQR)	26 (22, 31)	27 (22, 31)	0.73
• Married/stable union	232/315 (73.7%)	202/274 (73.7%)	0.98
• Education, years; median (IQR)	10 (7, 11)	10 (8, 11)	0.30
Employment			
• None			

• skilled	171/314 (54.5%)	174/273 (63.7%)	0.03
• unskilled	30/314 (9.6%)	12/273 (4.4%)	
Residence	112/314 (35.7%)	87/273 (31.9%)	
• Rural			
• Urban	45/319 (14.1%)	48/282 (17.0%)	0.48
• Peri-urban	195/319 (61.1%)	173/282(61.4%)	
	79/319 (24.8%)	61/282 (21.6%)	
Drinking water source			
• Improved	298/315 (94.6%)	261/282 (92.6%)	0.31
Toilet facilities			
• Improved	280/318 (88.1%)	248/281 (88.3%)	0.09
• Unimproved	31/318 (9.8%)	19/281 (6.8%)	
• None	7/318 (2.2%)	14/28 (5.0%)	
Household electricity	150/311 (48.2%)	129/279 (46.2%)	0.63

Data are presented as n/N (column percentages) unless otherwise indicated

Supplementary Table 9: Cox regression model of discharge body composition factors associated with time to readmission

	N	Unadjusted HR (95%CI)	P-value	Adjusted HR* (95%CI)	P-value
Bioimpedance analysis					
• Lean mass index Z-score,	N=284	0.53 (0.37, 0.75)	0.002	0.62 (0.41, 0.94)	0.02
• Impedance index Z-score	N=286	0.48 (0.33, 0.71)	<0.001	0.48 (0.24, 0.83)	0.01
• Phase angle Z-score	N=296	1.0 3(0.79,1.36)	0.84	1.07 (0.81,1.43)	0.63
Skin folds					
• Triceps skinfold Z-score	N= 557	0.72 (0.63,0.83)	<0.001	0.77 (0.64, 0.91)	0.002
• Subscapular skinfold Z-score	N= 550	0.86 (0.76, 0.97)	0.01	0.89 (0.79, 1.02)	0.09
• Suprailiac skinfold Z-score	N= 563	0.75 (0.58, 0.97)	0.03	0.90 (0.68, 1.19)	0.46
• Sum of skinfolds Z-score	N= 551	0.63 (0.47, 0.83)	0.001	0.69 (0.49, 0.98)	0.04

Supplementary Table 10: Cox regression model of discharge body composition factors associated with time to death

	N	Unadjusted HR (95%CI)	P-value	Adjusted HR* (95%CI)	P-value
Bioimpedance analysis					
• Lean mass index Z-score	N=284	0.60 (0.32, 1.02)	0.06	1.01 (0.56, 1.83)	0.97
• Impedance index Z-score	N=286	0.33 (0.18, 0.60)	<0.001	0.74 (0.25, 2.18)	0.58
• Phase angle Z-score	N=298	0.98 (0.64, 1.49)	0.92	0.91 (0.58, 1.41)	0.66
Skin folds					
• Triceps skinfold Z-score	N=557	0.68 (0.56, 0.82)	<0.001	1.02 (0.80, 1.31)	0.86
• Subscapular skinfold Z-score	N=550	0.88 (0.75, 1.03)	0.12	1.08 (0.93, 1.26)	0.31
• Suprailiac skinfold Z-score	N=563	0.49 (0.32,0.73)	<0.001	0.81 (0.53, 1.24)	0.34
• Sum of skinfolds Z-score	N=551	0.57 (0.39, 0.85)	0.006	1.30 (0.85, 2.00)	0.23

*Multivariable models included a minimum adjustment set identified from a directed acyclic graph: age at discharge, sex, baseline oedema, WHZ , HAZ, HIV status, and maternal employment.

Supplementary Table 11: Regression analysis showing mean differences and odds ratios between groups using group 1 as reference

	Group 1 (n=110) **40.7%** **Mean (SD)** **N (%)**	**Group 2 (n= 24)** **8.9%** **Mean (SD)** **N (%)**	**Group 3 (n=136)** **50.4%** **Mean (SD)** **N (%)**	**OR or *mean difference** **Group 1 vs 2** **(95% CI) P value[b]**	**OR or *mean difference** **Group 1 vs 3** **(95% CI) P value[a]**
Factors contributing to clustering					
Mean difference					
• *Lean mass index z-score	-0.07 (0.65)	1.95 (1.02)	-0.36 (0.67)	2.02 (1.71, 2.33); <0.001	-0.28 (-0.46, -0.10); 0.002
• *Impedance index z-score	0.17 (0.80)	1.30 (1.10)	-0.33 (0.89)	1.13 (0.74, 1.52); <0.001	-0.50 (-0.73, -0.28); <0.001
• *Sum of skinfolds Z-score	0.79 (0.94)	-0.05 (0.70)	-0.61 (0.64)	-0.85 (-1.19, -0.50); <0.001	-1.40 (-1.60, -1.20); <0.001
• *Triceps skinfolds Z-score	0.20 (1.22)	-1.60 (1.12)	-2.23 (1.28)	-1.79 (-2.35, -1.24); <0.001	-2.43 (-2.75, -2.12); <0.001
• *Discharge WHZ	-1.26 (1.13)	-1.72 (0.81)	-2.98 (1.20)	-0.47 (0.97, 0.04); 0.07	-1.72 (-2.01, -1.44); <0.001
• *Discharge HAZ	-2.56 (1.21)	-2.74 (1.24)	-3.74 (1.56)	-0.18 (-0.80, 0.44); 0.57	-1.18 (-1.53, -0.82); <0.001
Odds ratio					
Baseline oedema	94 (85.5)	16 (66.7)	70 (51.5)	2.94 (1.08, 8.00); 0.04	5.54 (3.00, 10.38); <0.001
Baseline factors not contributing to clustering					
Odds ratio					
• Male	58 (52.7)	17 (70.8)	78 (57.4)	0.81 (0.45, 1.46); 0.48	1.22 (0.62, 2.41); 0.56
Country					
• Zambia	17 (15.5)	10 (41.7)	39 (28.7)	-0.79 (-1.42, -0.15); 0.02	0.57 (-0.32, 1.47); 0.21
• Zimbabwe	93 (84.6)	14 (58.3)	97 (71.3)	Ref	Ref
HIV-positive	9 (8.2)	4 (16.7)	44 (32.4)	2.24 (0.63, 8.01); 0.21	5.37 (2.48, 11.60); <0.001

SAM at discharge	27 (24.6)	5 (20.8)	90 (66.2)	0.81 (0.28, 2.37); 0.70	6.01 (3.4, 10.54); <0.001
Currently breastfeeding	14 (14.9)	20 (17.1)	6 (11.1)	0.58 (0.272, 1.25); 0.17	0.51 (0.20, 1.31); 0.16
Diarrhoea previous 2 weeks	79 (71.8)	18 (75.0)	95 (69.9)	0.77 (0.41, 1.46); 0.43	1.77 (0.78, 4.00); 0.17
Maternal HIV status (positive)	26 (23.6)	12 (50.0)	64 (47.1)	2.54 (1.03, 6.28); 0.04	2.87 (1.68, 4.90); <0.001
Household factors					
Household electricity	46 (41.8)	15 (62.5)	61 (46.2)	2.32 (0.93, 5.76); 0.07	1.20 (0.72, 2.00); 0.49
Peri-urban/Urban	95 (86.4)	18 (75.0)	109 (80.7)	0.04 (-0.45, 0.63); 0.88	2.07 (0.73, 5.89); 0.17
Rural	15 (13.6)	6 (25.0)	26 (19.3)	Ref	Ref
Toilet					
• None/unimproved	14 (10.1)	12 (10.9)	1 (4.2)	-0.05 (-0.86, 0.77); 0.91	1.00 (-1.09, 3.06); 0.35
• Improved	120 (89.6)	98 (89.1)	23 (95.8)	Ref	Ref
Outcome					
• Died or readmitted	13 (11.8)	3 (12.5)	36 (26.5)	1.07 (0.23, 4.08); 0.93	2.69 (1.34, 5.4); 0.005
• Died	2 (1.8)	1 (4.2)	14 (10.3)	2.35 (0.20, 27.9); 0.49	6.20 (1.38, 27.9); 0.02
• Readmitted	13(11.8)	2 (8.3)	25 (18.4)	0.68 (0.14, 3.22); 0.63	1.68 (0.82, 3.46); 0.16
Mean difference					
Age at discharge median (IQR)	19.75 (15.0, 23.5)	15.5 (13.0, 19.4)	18.5 (13.0, 24.1)	-0.50 (-2.35, 1.36); 0.60	-0.15 (-2.35, 2.00); 0.89
*Maternal age median(IQR)	26.5 (22, 30)	23.5 (20, 29)	27.0(23., 32.)	-0.87 (-2.58, 0.85); 0.32	-1.61 (-3.72, 0.50); 0.13

Data are mean values (standard deviations) for continuous variables or N.(%) for categorical variables, [a] P value showing difference between group 1 and 2, [b] P value showing difference between group 1 and 3. Variables included in the clustering: LMI, sum of skinfolds Z-score, triceps Z-score, WHZ and HAZ (at discharge) and baseline oedema at hospitalisation

Part 3: Integrated Discussion and Conclusion

CHAPTER 6: INTEGRATED DISCUSSION AND CONCLUSION

This chapter consolidates findings from the empirical chapters with regards to the main objectives of this thesis. The main themes that emerged from the analyses are identified and discussed. The conceptual framework is revisited and considered in light of the results obtained. The implications of the findings from this thesis are considered and recommendations for future research made. The chapter ends with reflections on the strengths and limitations of this thesis.

6.1 KEY FINDINGS

This thesis aimed to provide insights into the clinical outcomes of children one year after discharge from hospital for treatment of complicated SAM, stratified by HIV status, and identify factors that predicted these outcomes. A longitudinal cohort study was designed to follow up children under 5 years of age who were discharged from hospital after treatment of complicated SAM over a period of one year. Three objectives were put forward to answer the main aim of the study and the summarised findings are presented in Table ~~11~~12.

Table 12: Consolidated study findings

Chapter	Objective, Research question, and Hypothesis	Key findings
3	**Objective 1:** To describe the one-year post discharge mortality in children managed for complicated severe acute malnutrition and determine the risk factors for mortality in Zambia and Zimbabwe. **Research question 1** What is the one year mortality and associated factors in children discharged from hospital following management of severe acute malnutrition? **Hypothesis:** Children who have SAM and HIV infection have a higher mortality compared to those with SAM alone and a combination of	• Overall the results showed that post-discharge mortality over one year was unacceptably high with one in five children dying in hospital or in the community. • Mortality was sustained throughout the one-year of follow up with the highest incidence in the first 16 weeks after discharge. • Four independent risk factors for mortality were identified • Children living with HIV had an almost 4-fold higher risk of dying compared to those who were not living with HIV, regardless of being on ART o Half of the children living with HIV were not initiated on ART at the time of discharge from hospital and a quarter of them were still not on ART at the end of the follow-up period

	biological and social risk factors predict mortality	• Children who had ongoing SAM at the time of hospital discharge had a more than 2-fold increased risk of dying compared to those who had anthropometric recovery. • Non-oedematous compared to oedematous SAM was associated with more that 2-fold increased risk of mortality • Children with cerebral palsy had an almost 6-fold higher mortality compared to those without cerebral palsy. • Post-discharge interventions that target children managed for complicated SAM, particularly those at highest risk of dying, should considered. The findings from this thesis confirmed the hypothesis that children with SAM and HIV infection are at a higher risk for dying compared to those with SAM but are not HIV infected. The study was not able to compare mortality based on biological risk factors that included C-reactive protein as a marker of inflammation, CD4% and HIV viral loads as markers

		of immune restoration and viral suppression for those children who were living with HIV infection.
4	**Objective 2:** To describe the recovery of children in the one year following hospitalisation for complicated SAM in Zambia and Zimbabwe. **Research question 2** What is the pattern of recovery in children discharged from hospital following management of complicated SAM? **Hypothesis** Children living with HIV have earlier and more frequent illness episodes, hospital readmissions, and poorer nutritional recovery despite access to antiretroviral therapy, compared to children with SAM alone and a combination of biological and social risk factors	• On-in-six children discharged from hospital were readmitted over the one year period of follow-up • Children with non-oedematous SAM had a 65% increased rate of all cause hospital readmission compared to children with oedematous SAM. • Low HAZ was independently associated with incidence of all-cause hospital readmission. • Children with cerebral palsy were three times more likely to be readmitted into hospital compared to children without cerebral palsy • Caregiver reported symptoms were frequently reported within the first 4 weeks of discharge from hospital followed by a decline. Nearly half of all children had one caregiver-reported symptom of ill-health in the first 4 weeks after hospital discharge. • Children living with HIV had more caregiver-reported symptoms compared to those who were not living with HIV at week 4.

	predict readmission and nutritional recovery	• Low HAZ, an indicator of poor linear growth was a significant risk factor for hospital readmission even though it is not currently considered in the classification and management of children with SAM. • There was evidence of nutritional recovery by anthropometry over the period of follow-up, though 22% and 12% of children remained undernourished at 6 and 12 months, respectively • Six independent factors were associated with moving from a lower to a higher nutritional state. • Increase in age and being HIV uninfected were associated with early recovery (week 2 and 4) • Children living with HIV showed a slower recovery path compared to those who were not living with HIV. • Four factors, non-oedematous SAM at initial hospitalisation, ongoing SAM at discharge, low HAZ and cerebral palsy, were associated with lower nutritional recovery throughout the period of follow-up • Existing public sector nutritional rehabilitation programs do not promote full and lasting recovery in

		children discharged from hospital for treatment of SAM with children following different recovery patterns and those with cerebral palsy not showing evidence of nutritional recovery. While the results from this thesis showed that nutritional recovery was slower and poorer in HIV infected children, there was no association with more frequent hospital readmissions and a higher frequency of reported illnesses.
5	**Objective 3** To describe body composition in children one year after discharge from hospital for complicated severe acute malnutrition. **Research question 3** What is the pattern of body composition in children recovering from severe acute malnutrition one-year post-discharge from hospital and the association with time to hospital readmission or	• Overall, children treated for complicated SAM showed gains in lean and total fat mass though the changes were significantly lower for children living with HIV and those who had non-oedematous SAM. o Triceps skinfolds, a measure of peripheral fat increased throughout the period of follow up o Subscapular skinfolds, a measure of central fat increased up to week 24 then declined o The sum of skinfolds, a measure of total fat, increased up to 24 weeks then plateaued

	death. **Hypothesis**: Fat mass measured as skin fold thickness, and lean mass, measured using bioelectrical impedance analysis, predict time to hospital readmission and death in children discharged from hospital after treatment for complicated severe acute malnutrition.	• Low lean mass and peripheral fat mass at hospital discharge were independently associated with mortality or time to hospital readmission. ○ On further analysis, only readmission and not mortality was significantly associated with low lean mass and low peripheral fat mass. • Children living with HIV compared to those who were not, had lower gains in total fat mass measured by skinfold thickness. • Children with non-oedematous compared to those with oedematous SAM had lower mean changes in total fat mass measured as sum of skinfolds and lean mass measured using impedance index • A cluster of children who had the lowest lean and total fat mass, the highest degree of wasting and stunting, the highest proportion who were living with HIV and had ongoing SAM at hospital discharge, had a nearly 3-fold increased odds of mortality or hospital readmission after adjusting for age.

		• The evidence suggests that the increased risk of mortality and hospital readmission may be mediated through underlying body composition, which may not be captured using routine anthropometry. • Targeted interventions that increase lean and peripheral fat mass should be considered in the post-discharge care of children treated for SAM Results from the thesis confirmed the hypothesis that lean mass and peripheral fat mass at the time of discharge from hospital were independently associated with hospital readmission. They were however not associated with death.

6.2 EMERGING THEMES

Three main themes emerged from the results obtained in this thesis: first the classification of severe acute malnutrition using anthropometry and the presence or absence of oedema; secondly, the comorbidities associated with severe acute malnutrition; and lastly, the importance of convalescence following discharge from hospital.

6.2.1 Classification of severe acute malnutrition

Malnutrition is currently classified using anthropometry and the presence of oedema because of its programmatic simplicity, but this phenotypic definition does not indicate the underlying cause or nutritional deficit. Additionally, the approach to nutritional rehabilitation is the same whether or not there is predominantly wasting or oedema.

a. Oedematous versus non-oedematous SAM

The clear finding from this thesis was that non-oedematous SAM was associated with higher mortality, hospital readmission and morbidity after discharge from hospital. Unpublished data from the HOPE SAM cohort showed that children with oedematous SAM were at higher risk of dying compared to those with no oedema during hospitalisation, while children with oedema who survived hospitalisation did better after hospital discharge. Oedematous SAM has been described as a maladaptive response to food deprivation and infection, which may result in a higher immediate mortality and better recovery once the acute period has settled. Children with non-oedematous SAM have less lean mass, as was shown in the Chapter 5 of the thesis, and may need a longer period of convalescence compared to those who had oedema on admission. Given the different pathophysiological pathways of oedematous and non-oedematous SAM, consideration should be given to managing them differently. Ongoing research into the pathophysiology of oedematous SAM will inform the appropriate interventions that can target underlying pathways.

b. Wasting and Stunting (WaSt)

As discussed in Chapter 1 under the epidemiology of malnutrition, the classification into acute and chronic malnutrition is based on anthropometric measurements. While wasting is associated with a high risk of death, recent evidence shows that all degrees of undernutrition (wasting, underweight and stunting) are associated with an increased risk of death, and children with both wasting and stunting have a higher mortality compared to those with wasting alone. Seventy-eight percent of children enrolled into HOPE SAM had concurrent stunting and yet this was not considered in the classification or approach to management using the current guidelines. A recent systematic review conducted on the relationship between wasting and stunting concluded that wasting and stunting are driven by common factors and there is need to develop an integrated policy, financing and programmatic approaches to the prevention and treatment of childhood malnutrition(23). Data from body composition obtained in this thesis, showed that children who are wasted have low fat mass and lean mass which is a reflection of both tissue and functional loss. In the short term, it will be important to identify children with concurrent wasting and stunting as a high risk group and prioritise interventions for them.

c. Body composition

Findings from this thesis showed that while all children treated for SAM gained lean and fat mass during the follow-up period, those living with HIV and with non-oedematous SAM had lower mean changes in fat mass. Those who had non-oedematous SAM also had lower mean changes in lean mass. Low discharge lean and peripheral fat mass were independently associated with shorter time to hospital readmission. The role of body composition as a prognostic tool needs to be considered for children recovering from SAM. The severe wasting that characterises SAM may also be a result of sarcopenia. Sarcopenia, characterised by low skeletal muscle mass and low muscle strength or low physical function, is a prevalent health problem in adults, and is associated with an increased risk of morbidity, immobility and mortality(204, 205). There is increasing interest for research into

sarcopenia among the paediatric population, though there are currently no standard definitions, particularly in the younger age-groups where there is no simple method to assess muscle function (206). There is no literature on sarcopenia in association with complicated SAM, but a review published on paediatric sarcopenia, showed an association with increased duration of hospitalisation and fungal infection risk in children being managed for leukaemia(206) as well as post-colectomy complications in children with ulcerative colitis(207). The risk factors for muscle loss identified in adults (protein imbalance, increased inflammation, increased catabolism and insulin resistance) are similar to the pathophysiological consequences of severe wasting(205). Specific interventions to target these processes such as vitamin D, nutritional supplements (including branched chain amino acids), and resistance exercises have produced positive results in sarcopenic Asian adults(205) and their role in children suffering from sarcopenia should be considered.

6.2.2 Comorbidities

Complicated SAM is characterised by altered metabolism and infectious comorbidities resulting from the immunodeficiency caused by the undernutrition. The simplistic approach to severe malnutrition in low-resource settings, as primarily a nutritional disorder that is complicated by infection, and treatment that focuses on nutritional rehabilitation and anthropometric recovery as the endpoint may need to be reconsidered. There is need to consider moving to an aetiology-based classification of complicated SAM that will guide treatment. In this thesis, two main comorbidities, HIV and cerebral palsy, were associated with an increased risk of death and hospital readmission (for cerebral palsy). HIV remains an important cause of morbidity in spite of universal ART and increased coverage of PMTCT services. HIV infection increases caloric requirements even during the asymptomatic period and there is more demand with onset of other infections. While current guidelines classify HIV infection in children under

5 years as severe disease requiring immediate ART initiation, bottlenecks remain in the pathway to successful ART initiation, including missed opportunities for PMTCT, late infant diagnosis, and delay in ART initiation when children present to hospital with SAM or other infections. Nearly half of the children in this study had not initiated ART at the time of hospital discharge and 12% were not on ART even at the end of follow-up. There should be a deliberate effort to initiate children on life saving ART before hospital discharge, and ensure retention in care by providing integrated services for both malnutrition and HIV. Post-discharge mortality in this thesis was nearly 6-fold higher for children with cerebral palsy, compared to children without cerebral palsy. The current WHO guidelines for management of severe acute malnutrition do not specifically address the specific feeding difficulties of children living with disabilities. A continuum of integrated comprehensive care that addresses all child health issues including growth monitoring, provision of care and support for children living with HIV and other disabilities, would assist with retention in care.

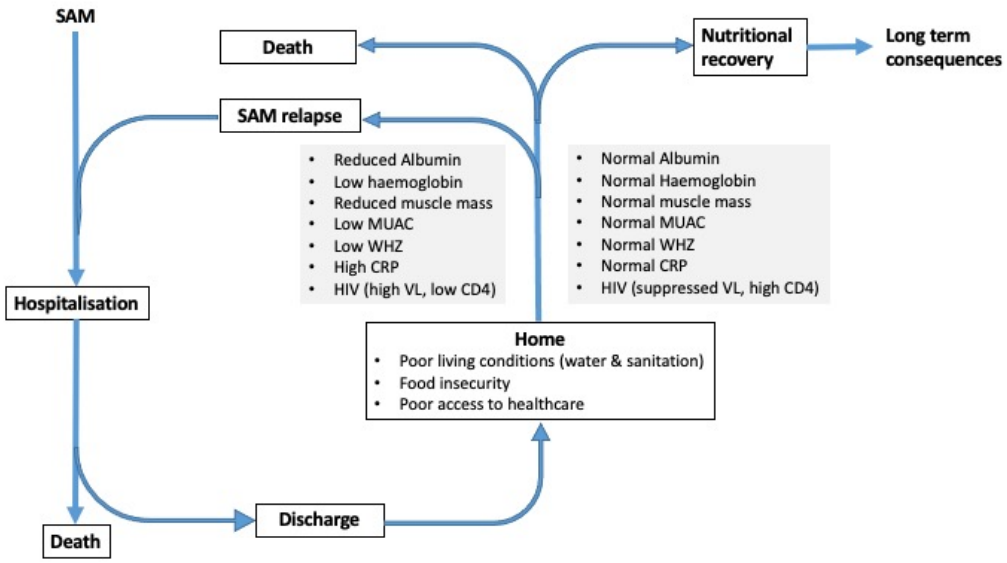
6.2.3 Convalescence

This thesis highlighted the continued vulnerability faced by children managed for complicated SAM in the one year following discharge from hospital. There is currently no structured convalescence for this group of children, whose recovery may take longer compared to well-nourished children. The anthropometric basis used for assessing recovery completely ignores the underlying cause of the malnutrition. In particular, complicated SAM selects the sickest children who may have underlying diagnoses that may be contributing to their undernutrition such as cerebral palsy, heart disease, gastrointestinal disorders interfering with nutrient digestion and absorption, and other congenital abnormalities in addition to infection. Assuming that a period of nutritional rehabilitation will restore all the metabolic, immunologic and physical perturbations may be a simplistic way of approaching care of these children. Some children have severe anthropometric deficits and may not improve to reach the cut-off points of being well-nourished or may not improve as long as the underlying condition

is ongoing. Some may need a longer period of nutritional rehabilitation and currently there is no evidence base to guide the duration of nutritional rehabilitation. This thesis showed that complicated SAM is ~~not~~ a heterogenous condition, and that children follow different patterns of recovery. There is no evidence to inform the standard definition of malnutrition relapse for children discharged from in-patient facilities who have clear ongoing risks of morbidity and mortality. Studies conducted in different settings have shown varying relapse rates due to the lack of standardisation of the definition of relapse. There may be need to consider rate of recovery for children at highest risk instead of using universal anthropometric cut offs.

6.3 CONCEPTUAL FRAMEWORK

This section reflects upon the conceptual framework presented at the beginning of the thesis and shown below, upon which this work is based.



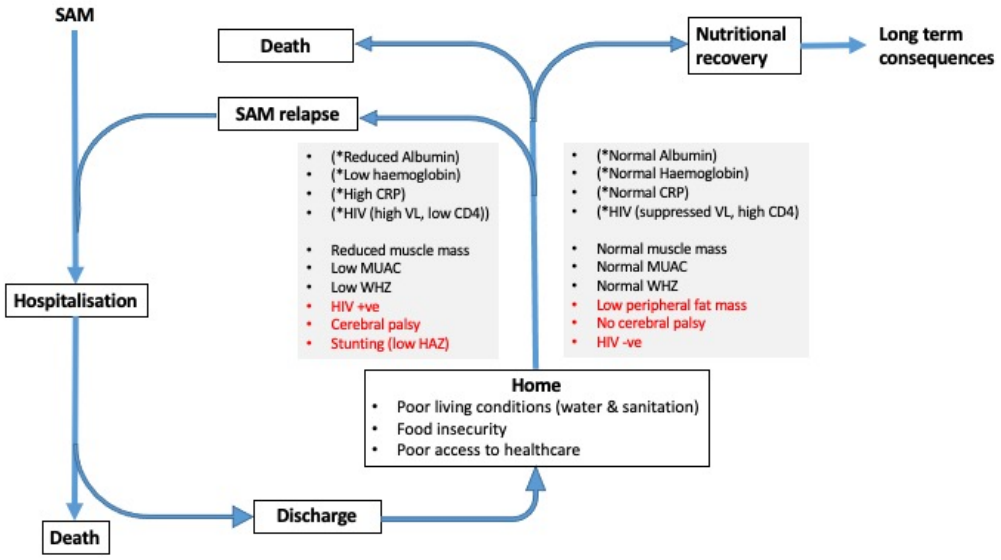


Figure 18: Revised Conceptual framework.

*The variables in red font are additions based on the findings from the thesis. *Variables were not studied in this thesis but remain important*

The findings from the thesis confirmed that HIV infection, wasting measured by MUAC or WHZ were associated with a higher post discharge mortality, morbidity and slower nutritional recovery and low muscle mass was associated with hospital readmission. Empirical data from this thesis identified additional risk factors for poor outcomes which are shown in red in the revised conceptual framework. Children with cerebral palsy were at risk for both death and hospital readmission, while stunting was associated with hospital readmission and poor nutritional recovery. Low peripheral fat mass was significantly associated with hospital readmission.

While there was evidence of ongoing morbidity from caregiver reports as well as hospital readmission, this thesis did not focus on C-reactive protein as a marker of inflammation. HIV infection in children was confirmed as a risk factor for mortality and morbidity (in the first few weeks after hospital discharge). The study was not able to compare clinical outcomes based on CD4% and HIV viral loads as markers of immune restoration and viral suppression

respectively for children who were living with HIV infection and were receiving ART. HIV infection worsens the vicious cycle of infection and malnutrition and future studies should determine the association between nutritional recovery in children receiving ART and HIV viral suppression.

An assessment of the body's physiological function at hospital discharge using body composition, and deeper phenotyping of other organ systems, may identify the children at highest risk for hospital readmission or death. Children are largely discharged back into the same home environments characterised by poverty. Additional work to define the role of the socioeconomic environment; including the home conditions, caregiver capabilities and access to services for children may inform the development of a more comprehensive post discharge package of care.

6.4 IMPLICATIONS

This thesis provides empiric evidence for the persistent vulnerabilities of severely malnourished children following hospital-based management of the acute condition.

6.4.1 Practice

Groups of children who are at higher risk for mortality, morbidity, poor nutritional recovery and readmission into hospital were defined and this should contributes to the development of interventions that will improve post-discharge outcomes. Post-discharge follow up of children should be targeted in order to address the needs of the groups most at risk and optimise their outcomes. Antiretroviral therapy initiation following stabilisation should be prioritised in children living with HIV given the vicious cycle of interaction between HIV and undernutrition. Ultimately, optimising efforts to prevent

vertical transmission of HIV by ensuring that all women are aware of their status, initiate and remain on suppressive ART and the infants access early infant diagnosis and treatment will reduce the prevalence of children presenting with advanced HIV disease. Lastly, a continuum of care that supports families from hospital to the community where HIV and nutrition care for the child are integrated could also improve outcomes of this vulnerable children and encourage them to remain engaged in care.

6.4.2 Policy

A 2-fold higher risk of dying was seen in children who had ongoing SAM at hospital discharge compared to children who did not have ongoing SAM. In-patient management of complicated SAM focuses on correcting the medical complications and treating acute infections after which children are transferred to continue nutritional rehabilitation in the community where they are monitored for nutritional recovery and malnutrition relapse based on anthropometry. The four components that define CMAM including community outreach, outpatient care for children with uncomplicated SAM, in-patient care for those with complicated SAM and services for children with MAM requires a robust system that operates within the broader context of providing a comprehensive child care package. A good referral pathway from the hospital to the community and back as well as access to therapeutic and supplementary food are essential for the majority of children who leave hospital with ongoing SAM. In addition to instructing caregivers on the immediate causes of childhood undernutrition, there is also need to empower them to address the underlying causes of undernutrition related to household food security, care and feeding practices and the household environment. Empowered caregivers will be more likely to identify ill health and seek help before the illness deteriorates. While WHO recommends that in the absence of a community based program, children should be discharged when they achieve anthropometric recovery, there are challenges associated with this approach. Longer

duration of hospitalisation places the children at risk for developing hospital acquired infections and there are also opportunity costs for caregivers.

An additional policy issue relates to monitoring children after discharge from hospital and identifying relapse of malnutrition. There is need for clear policy that defines relapse of malnutrition and when such a diagnosis is made. The work done in this thesis showed that children follow different recovery paths such that some had not reached anthropometric recovery one year after discharge from hospital.

Children who had cerebral palsy (CP) had a nearly 6-fold higher risk of dying post-discharge due to physiological and socioeconomic factors that lead to feeding difficulties(208). Globally, an estimated 8.1 million children (1.2%) under 5 years of age have cerebral palsy with the prevalence being highest in Africa (1.6%)(209). Results from this thesis add to the body of evidence that this group of children is vulnerable to developing malnutrition and having poor outcomes following discharge from hospital. In spite of this, the WHO and country IMAM guidelines do not address the specific physical needs of these children. There is a clear need to develop guidance on the management of SAM and disability including the type of therapeutic food given how response to nutritional rehabilitation should be monitored. Most children with cerebral palsy have swallowing difficulties and may find it difficult to take the recommended ready-to-use therapeutic food paste.

Children with concurrent anthropometric deficits such as wasting and stunting are at greater risk for both mortality and morbidity compared to wasting or stunting separately. There is need to include stunting in the risk stratification of children with SAM.

6.4.3 Future Research

Two-thirds of severe acute malnutrition in southern Africa is the oedematous form and there is need to continue research into its pathophysiology as this will help inform an evidence-based approach to management.

Mortality from complicated SAM results from infectious illness and chronic inflammation as well as disruption of metabolic and other physiological pathways (70). The current treatment approaches for complicated SAM are focused on acute infections and nutritional rehabilitation with less emphasis on recovery of immune function which may lag behind nutritional recovery.

There is need to define and characterise the co-morbidities that are responsible for the high post-discharge mortality in children with SAM. In particular, the immune dysfunction, gut dysfunction (inflammation, permeability and altered structure and function), and HIV viral suppression and immune recovery.

The role of stunting in what has been defined as "acute" malnutrition also needs further exploration given the apparent overlap of the syndromes of wasting and stunting and their contribution to a higher risk of mortality.

In terms of interventions to improve post-discharge outcomes, there is need to develop a holistic package of care that addresses immune recovery, gut recovery, appropriately formulated nutrition for the damaged gut, and a psychosocial package that addresses the neurodevelopment of the child recovering from SAM as well as the caregiver's mental health and capabilities.

6.5 LIMITATIONS

One of the main limitations of this thesis is that data on some potential risk factors for mortality and morbidity were not collected, in particular birth weight, gestational age and other underlying factors such as socioeconomic variables. Second, children were discharged from

hospital to continue outpatient therapeutic feeding but data on access to and how much RUTF each child consumed was not obtained. It is also known that families share RUTF or other supplementary foods within the household, and how much the malnourished child consumes is often not clear. Third, the study had set out to collect data on immune restoration (T-cell profile) and HIV viral load in children living with HIV, but there was a significant amount of missing data which could have biased the results. A number of factors could have affected the rates or relapse of malnutrition including loss to follow-up that affected the completeness of data on anthropometry. Additionally, reliance on caregiver-reported symptoms may have underestimated the proportion of children having illnesses and hospitalisation during the period of follow-up. Episodes of relapse of malnutrition, particularly oedematous SAM which can be mild and transient, could have been missed as this depended on caregiver reports and evaluation during study visits. Lastly, body composition was assessed using bioelectrical impedance analysis which does not assess the exact fat and fat-free mass. BIA data were also missing on more than half of the children though there was no difference in the outcome of death or readmission on sensitivity analysis.

6.6 CONCLUSION

Children with non-oedematous SAM and those living with HIV are at particular longer-term risk following management of SAM, and consequently, these children require a longer and more holistic convalescent period.

7. REFERENCES

References

1. de Onís M, Monteiro C, Akré J, Glugston G. The worldwide magnitude of protein-energy malnutrition: an overview from the WHO Global Database on Child Growth. Bulletin of the World Health Organization. 1993;71(6):703-12.
2. Mehta N M, Corkins M R, Lyman B, Malone A, Goday P S, Carney L N, et al. Defining Pediatric Malnutrition: A Paradigm Shift Toward Etiology-Related Definitions. International Journal of Parenteral and Enteral Nutrition. 2013;37(4):460-81.
3. World Health Organisation. Malnutrition. In: Organisation WH, editor. Geneva2021.
4. United Nations Children's Fund (UNICEF) tWHO, International Bank for Reconstruction and Development/The World Bank Group,. Levels and trends in child malnutrition: key findings of the 2021 edition of the joint child malnutrition estimates. New York: United Nations Children's Fund; 2021.
5. Black R E, Victora C G, Walker S P, Bhutta Z A, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382:427–51.
6. Olofin I, McDonald CM, Ezzati M, Flaxman S, Black RE, Fawzi WW, et al. Associations of Suboptimal Growth with All-Cause and Cause-Specific Mortality in Children under Five Years: A Pooled Analysis of Ten Prospective Studies. Plos One. 2013;8(5).
7. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet. 2013;382(9890):417-25.
8. Pelletier DL, Rfongilo EA, Schroeder DG, JP. H. The effects of malnutrition on child mortality in developing countries. Bull World Health Organ. 1995;73(4):443-8.
9. Caulfield LE, de Onis M, Blössner M, RE. B. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. American J ournal of Clinical Nutrition. 2004;80:193-8.
10. Victora CG, Christian P, Vidaletti LP, Gatica-Domínguez G, Menon P, Black RE. Revisiting maternal and child undernutrition in low-income and middle-income countries: variable progress towards an unfinished agenda. The Lancet

. 2021;397 (10282):1388–99. .
11. United Nations Children's Fund. Nutrition for every child: UNICEF Nutrition Strategy 2020-2030. New York, USA; 2020.
12. United Nations Children's F. Strategy for improved nutrition of children and women in developing countries. The Indian Journal of Pediatrics. 1991;58(1):13-24.
13. Frison S, Checchi F, Kerac M. Omitting edema measurement: how much acute malnutrition are we missing? The American journal of clinical nutrition. 2015;102(5):1176-81.
14. Emergency Nutrition Network. Aetiology of Wasting. New York, USA; 2018.
15. Gibson RS. Principles of Nutritional Assessment. New York: Oxford University Press, Inc; 2005.
16. World Health Organisation, Fund. UNCs. WHO child growth standards and the identification of severe acute malnutrition in infants and children. Geneva; 2009.
17. Briend A, Maire B, Fontaine O, M. G. Mid-upper arm circumference and weight-for-height to identify high-risk malnourished under-five children. Maternal and Child Nutrition. 2012;8(1):130-3.
18. Berkley J A, Mwangi I, Griffiths K, Ahmed I, Mithwani S, English M, et al. Assessment of Severe Acute Malnutrition Among Hospitalized Children in Rural Kenya, comparison of Weight for Height and Mid Upper Arm Circumference. Journal of American Medical Association. 2005;294(5):591-7.
19. Alvarez JL, Dent N, Browne L, Myatt M, Briend A. Putting Child Kwashiorkor on the map. 2016.

20. Owor Maxensia, Tumwine James, Joyce. K. Socio-economic risk factors for severe protein energy malnutrition among children in Mulago Hospital, Kampala. East African medical journal. 2000;77:471-5.
21. Saloojee H, De Maayer T, Garenne ML, K. K. What's new? Investigating risk factors for severe childhood malnutrition in a high HIV prevalence South African setting. Scandinavian Journal of Public Health Suppl 2007;69:96-106.
22. Smith LE. Convergence and Divergence in Statistical and Programmatic Approaches to Address Child Stunting and Wasting. The Journal of Nutrition. 2018;148(6):823-4.
23. Thurstans S, Sessions N, Dolan C, Sadler K, Cichon B, Isanaka S, et al. The relationship between wasting and stunting in young children: A systematic review. Maternal & child nutrition. 2021;18(1):e13246.
24. Stobaugh H, Rogers BL, Rosenberg IH, Webb P, Maleta KM, Manary M J, et al. Children with Poor Linear Growth Are at Risk for Repeated Relapse to Wasting after Recovery from Moderate Acute Malnutrition. The Journal of Nutrition. 2018;148(6):974-9.
25. Khara T, Mwangome M, Ngari M, Dolan C. Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6-59 months from 84 countries. Maternal & child nutrition. 2018;14(2):e12516-e.
26. Myatt M, Khara T, Schoenbuchner S, Pietzsch S, Dolan C, Lelijveld N, et al. Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. . Archives of Public Health. 2018;76(28).
27. McDonald CM, Olofin I, Flaxman S, Fawzi WW, Spiegelman D, Caufield LE, et al. The effect of multiple anthropometric deficits on child mortality: Meta-analysis of individual data in 10 prospective studies from developing countries. American Journal of Clinical Nutrition. 2013;97(4).
28. Schoenbuchner SM, Dolan C, Mwangome M, Hall A, Richard SA, Wells JC, et al. The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016. The American journal of clinical nutrition. 2019;110(2):498-507.
29. Briend A. Kwashiorkor: still an enigma- the search must go on. 2014.
30. Ndekha MJ. Kwashiorkor and severe acute malnutrition in childhood. The Lancet. 2008;371(9626):1748.
31. Courtright P, Canner J. The distribution of kwashiorkor in the southern region of Malawi. Annals of Tropical Paediatrics. 1995;15(3):221-6.
32. Bachou H, Tylleskär T, Kaddu-Mulindwa DH, Tumwine JK. Bacteraemia among severely malnourished children infected and uninfected with the human immunodeficiency virus-1 in Kampala, Uganda. BMC Infectious Diseases. 2006;6(1):160.
33. Chimhuya S, Kambarami RA, H. M. The levels of malnutrition and risk factors for mortality at Harare Central Hospital-Zimbabwe: an observational study. Central Africa Journal of Medicine. 2007;53:30-4.
34. Grover Z, Ee L. Protein Energy Malnutrition. Pediatric Clinics of North America. 2009;56:1055-68.
35. Rytter M J H, Kolte L, Briend A, Friis H, Christensen VB. The immune system in children with malnutrition--a systematic review. PLoS ONE. 2014;9(8).
36. World Health Organisation. Guideline: Updates on the management of severe acute malnutrition in infants and children. Guidelines. Geneva; 2013.
37. Wells JCK, Briend A, Boyd EM, Berkely JA , Hall A, Isanaka S, et al. Beyond wasted and stunted—a major shift to fight child undernutrition. The Lancet Child & Adolescent Health. 2019;3:831-4.
38. Renault S, Kangas S, Dailey-Chwalibóg T, Salpéteur C. “ Moving beyond anthropometry : Conducting BIA to measure body composition of acutely malnourished children : lessons from operational research ”. . France: Action Against Hunger 2018.
39. International Atomic Energy Agency. Body composition assessment from birth to two years of age.

. Vienna, Austria2013.

40. Carrero J, Johansen K, Lindholm B, Stenvinkel P, Cuppari L, Avesani C. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney International. 2016;90.
41. Holmes CJ, Racette SB. The Utility of Body Composition Assessment in Nutrition and Clinical Practice: An Overview of Current Methodology. Nutrients. 2021;13(8):2493.
42. Mupere E, Mukisa J, Turyagyenda L, Aber P, Uebelhoer LS, Bourdon C, et al. Implementation of a field study of body composition among infants and young children in sub-Saharan Africa2019 01/07/2019 00:00:00; (60):[52 p.]. Available from: https://www.ennonline.net/fex/60/bodycompositionafrica.
43. Brantlov S, Jødal L, Lange A, Rittig S, Ward LC. Standardisation of bioelectrical impedance analysis for the estimation of body composition in healthy paediatric populations: a systematic review. . Journal of Medical Engineering & Technology 2017.
44. Barrea L, Muscogiuri G, Pugliese G, Laudisio D, de Alteriis G, Graziadio C, et al. Phase Angle as an Easy Diagnostic Tool of Meta-Inflammation for the Nutritionist. Nutrients. 2021;13(5):1446.
45. Wells JCK, Williams JE, Fewtrell M, Singhal A, Lucas A, Cole TJ. A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. International Journal of Obesity. 2007;31(3):507-14.
46. Westsrate JA, P. D. Body compostion in children: proposal for a method for calculating body fat percentage from total body density or skinfold-thickness measurements. American Journal of Clinical Nutrition. 1989;50:1104-15.
47. Bhutta ZA, Berkley J A, Bandsma RHJ, Kerac M, Trehan I, A. B. Severe childhood malnutrition. Nature Reviews Disease Primers. 2017;3.
48. Trehan I , O'Hare BA, Phiri A, GT. H. Challenges in the Management of HIV-Infected Malnourished Children in Sub-Saharan Africa. AIDS Research and Treatment. 2012.
49. Amadi Beatrice, Kelly Paul, Mwiya Mwiya, Mulwazi Elvin, Sianongo Sandie, Changwe Francis, et al. Intestinal and Systemic Infection, HIV, and Mortality in Zambian Children With Persistent Diarrhea and Malnutrition. Journal of Pediatric Gastroenterology and Nutrition. 2001;32(5).
50. Mak RH, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein-energy wasting in children with chronic kidney disease. . Pediatric nephrology 2012;27(2):173-81.
51. Lin CA, Boslaugh S, Ciliberto HM, Maleta K, Ashorn P, Briend A, et al. A prospective assessment of food and nutrient intake in a population of Malawian children at risk for kwashiorkor. Journal of pediatric gastroenterology and nutrition. 2007;44(4):487-93.
52. Golden MH, Golden BE, AA. J. Albumin and nutritional oedema. Lancet. 1980;18160(8160):114-6.
53. Iddrisu I, Monteagudo-Mera, A. P, C., , Pyle S, Shahzad M, Andrews S, et al. Malnutrition and Gut Microbiota in Children. . Nutrients. 2021;13(8).
54. Whitehead RG, GA. A. Pathophysiological factors of importance in protein-calorie malnutrition. . British Medical Bulletin 1972;28(1):72-9.
55. Bandsma RH, Mendel M, Spoelstra MN, Reijngoud DJ, Boer T, Stellaard F, et al. Mechanisms behind decreased endogenous glucose production in malnourished children. . Pediatric Research 2010;68(5):423-8.
56. Bergman JW, Human DG, De Moor MM, JM. S. Effect of kwashiorkor on the cardiovascular system. Archives of Diseases in Childhood. 1988;63(11):1359-62.
57. Badaloo AV, Forrester T, Reid M, Jahoor F. Lipid kinetic differences between children with kwashiorkor and those with marasmus. The American journal of clinical nutrition. 2006;83(6):1283-8.
58. Ledger E, Harawa PP, Daniel AI, Candler T, Prentice AM, RHJ. B. Dysglycemia in Children with Severe Acute Malnutrition: A Systematic Review and Meta-Analysis. Advances in Nutrition. 2021;12(3):959-68.
59. Spoelstra MN, Mari A, Mendel M, Senga E, van Rheenen P, van Dijk TH, et al. Kwashiorkor and marasmus are both associated with impaired glucose clearance related to pancreatic β-cell dysfunction. Metabolism. 2012;61(9):1224-30.
60. Briend A, Khara T, Dolan C. Wasting and stunting—similarities and differences: Policy and programmatic implications. Food and Nutrition Bulletin. 2015;36(1):S15-23.
61. Walson JL, Berkley J A. The impact of malnutrition on childhood infections. Current Opinion in Infectious Diseases. 2018;31:231-6.

62. Phillips I, B. W. Acute bacterial infection in kwashiorkor and marasmus. British Medical Journal. 1968;1(5589):407-9.
63. Page A-L, de Rekeneire N, Sayadi S, Aberrane S, Janssens A-C, Rieux C, et al. Infections in children admitted with complicated severe acute malnutrition in Niger. Plos One. 2013;8(7).
64. Maitland K, Berkley J A, Shebbe M, Peshu N, English M, Newton C R J C. Children with Severe Malnutrition: Can Those at Highest Risk of Death Be Identified with the WHO Protocol? Plos One. 2006;3(12).
65. Kirolos A, Blacow RM, Parajuli A, Welton NJ, Khanna A, Allen SJ, et al. The impact of childhood malnutrition on mortality from pneumonia: a systematic review and network meta-analysis. BMJ Global Health. 2021;6(11):e007411.
66. Black R, Laxminarayan R, Temmerman M, Walker N. Reproductive, Maternal, Newborn, and Child Health. . Washington, DC: World Bank; 2016.
67. Lenters L, Wazny K, ZA. B. Management of Severe and Moderate Acute Malnutrition in Children.Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities. In: Black RE, Laxminarayan R, Temmerman M ea, editors. Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, Third Edition 2. Washington DC: The International Bank for Reconstruction and Development / The World Bank; 2016.
68. Jones K D, Thitiri J, Ngari M, A BJ. Childhood malnutrition: Toward an understanding of infections, inflammation, and antimicrobials. Food and Nutrition Bulletin. 2014;35(2).
69. Watanabe K, A. PJW. Environmental Enteropathy: Elusive but Significant Subclinical Abnormalities in Developing Countries. EBioMedicine. 2016;10:25-32.
70. Bourke CD, Berkley J A, Prendergast AJ. Immune Dysfunction as a Cause and Consequence of Malnutrition. Trends in Immunology. 2016;37(6):386-9.
71. Prendergast AJ, Kelly P. Enteropathies in the developing world: neglected effects on global health. American Journal of Tropical Medicine and Hygiene. 2012;86.
72. Guerrant RL, DeBoer MD, Moore SR, Scharf RJ, Lima AAM. The impoverished gut--a triple burden of diarrhoea, stunting and chronic disease. Nature Reviews Gastroenterology Hepatology. 2013;10(4):220-9.
73. Prendergast AJ, Kelly P. Interactions between intestinal pathogens, enteropathy and malnutrition in developing countries. Current Opinion in Infectious Diseases. 2016;29(3):229-36.
74. Poda GG, Hsu C-Y, Chao JCJ. Malnutrition is associated with HIV infection in children less than 5 years in Bobo-Dioulasso City, Burkina Faso: A case-control study. Medicine (Baltimore). 2017;96(21):e7019-e.
75. Koethe JR, Heimburger DC. Nutritional aspects of HIV-associated wasting in sub-Saharan Africa. The American journal of clinical nutrition. 2010;91(4):1138S-42S.
76. Nigussie J, Girma B, Molla A, Mareg M, Mihretu E. Under-nutrition and associated factors among children infected with human immunodeficiency virus in sub-Saharan Africa: a systematic review and meta-analysis. Archives of Public Health. 2022;80(1):19.
77. World Health Organisation. Global guidance on criteria and processes for validation: Elimination of Mother-to-Child transmission of HIV and Syphilis. Geneva: World Health Organization; 2017 2017.
78. Munthali T, Jacobs C, Sitali L, Dambe R, Michelo C. Mortality and morbidity patterns in under-five children with severe acute malnutrition (SAM) in Zambia: a five-year retrospective review of hospital-based records (2009–2013). Archives of Public Health. 2015;73(23).
79. Preidis G A, McCollum E D, Mwansambo C, Kazembe P K, Schutze G E, Kline M W. Pneumonia and Malnutrition are Highly Predictive of Mortality among African Children Hospitalized with Human Immunodeficiency Virus Infection or Exposure in the Era of Antiretroviral Therapy. Journal of Pediatrics. 2011;159(3):484-9.
80. De Maayer T, Saloojee H. Clinical outcomes of severe malnutrition in a high tuberculosis and HIV setting. Archives of disease in childhood. 2011;96(6):560-4.
81. Fergusson P, Tomkins A. HIV prevalence and mortality among children undergoing treatment for severe acute malnutrition in sub-Saharan Africa: a systematic review and meta-analysis. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009;103(6):541-8.
82. Kessler L, Daley H, Malenga G, Graham S. The impact of HIV infection on the clinical presentation of severe malnutrition in children at QECH. Malawi Med J 2001;13(3):30-3.

83. World Health Organisation. Guidelines for an Integrated Approach to the Nutritional care of HIV-infected children (6 months-14 years) https://www.who.int/nutrition/publications/hivaids/9789241597524/en/; 2009.
84. Ashworth A, Khanum S, Jackson A, C. S. Guidelines for the treatment of severely malnourished children. Geneva, Switzerland: WHO; 2003.
85. World Health Organisation. Pocket book of Hospital Care for Children

Guidelines for the management of common childhood Illnesses. Organisation WH, editor. Geneva: World Health Organisation; 2013.
86. Tickell KD, DM. D. Inpatient management of children with severe acute malnutrition: a review of WHO guidelines

. Bull World Health Organ. 2016;94:642-51.
87. Trehan I, Manary MJ. Management of severe acute malnutrition in low-income and middle-income countries. Archives of Diseases in Childhood. 2015;100:283-7.
88. World Health Organisation G. Management of severe malnutrition : a manual for physicians and other senior health workers. 1999.
89. Heikens GT, Bunn J, Amadi A, Manary M, Chhagan M, Berkley JA, et al. Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence. Lancet. 2008;371:1305-7.
90. Rose AM, Hall CS, Martinez-Alier N. Aetiology and management of malnutrition in HIV-positive children. Archives of Diseases in Childhood. 2014;99(6):546-51.
91. Gonzales GB, Njunge JM, Gichuki BM, Wen B, Potani I, Voskuijl W, et al. Plasma proteomics reveals markers of metabolic stress in HIV infected children with severe acute malnutrition. Scientific Reports. 2020;10(1):11235.
92. World Health Organisation. WHO Guidelines Approved by the Guidelines Review Committee. Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy. Geneva2017.
93. Manary M, Trehan I. Systematic review of the care of HIV-infected children with severe acute malnutrition. World Health Organisation; 2012.
94. Prendergast A, Bwakura-Dangarembizi MF, Cook AD, Bakeera-Kitaka S, Natukunda E, Nahirya Ntegee P, et al. Hospitalization for severe malnutrition among HIV-infected children starting antiretroviral therapy. AIDS. 2011;25:951-6.
95. Braitstein P, Songok J, Vreeman RC, Wools-Kaloustian KK, Koskei P, Walusuna L, et al. "Wamepotea" (they have become lost): outcomes of HIV-positive and HIV-exposed children lost to follow-up from a large HIV treatment program in western Kenya. Journal of acquired immune deficiency syndromes 2011;57(3):e40-6.
96. Kim MH, Cox C, Dave A, Draper HR, Kabue M, Schutze GE, et al. Prompt initiation of ART With therapeutic food is associated with improved outcomes in HIV-infected Malawian children with malnutrition.

. Journal of Acquired Immune Deficiency Syndrome. 2012;59(2):173-6.
97. Archary M, Sartorius B, La Russa P, Sibaya T, Healy M, Bobat RA. Effect of the Timing of Antiretroviral Treatment Initiation on Outcomes in Children Living With Human Immunodeficiency Virus Admitted With Severe Acute Malnutrition. J Pediatric Infect Dis Soc. 2021;10(3):259-66.
98. Njuguna IN, Cranmer LM, Otieno VO, Mugo C, Okinyi HM, Benki-Nugent S, et al. Urgent versus post-stabilisation antiretroviral treatment in hospitalised HIV-infected children in Kenya (PUSH): a randomised controlled trial. Lancet HIV. 2018;5:e12-e22.
99. Irena A H, Mwambazi M, Mulenga V. Diarrhea is a Major killer of Children with Severe Acute Malnutrition Admitted to Inpatient Set-up in Lusaka, Zambia. Nutrition Journal. 2011;10.
100. Talbert A, Thuo N, Karisa J, Chesaro C, Ohuma E, Ignas J, et al. Diarrhoea Complicating Severe Acute Malnutrition in Kenyan Children: A Prospective Descriptive Study of Risk Factors and Outcome. PLoS ONE. 2012;7(6).
101. Collins S, Dent N, Binns P, Bahwere P, Sadler K, Hallam A. Management of severe acute malnutrition in children. Lancet. 2006;368:1992-2000.

102. Rytter MJH, Babirekere-Iriso E, Namusoke H, Christensen VB, Michaelsen KM, Mortensen CG, et al. Risk factors for death in children during inpatient treatment of severe acute malnutrition: A prospective cohort study. American Journal of Clinical Nutrition. 2017;105:495=502.
103. Harris C, Mills R, Seager E, Blackstock S, Hiwa T, Pumphrey J, et al. Paediatric deaths in a tertiary government hospital setting, Malawi. Paediatrics and International Child Health. 2019;39(4):240-8.
104. Karunaratne Radhini, Sturgeon Jonathan P, Patel Rajvi, Prendergast Andrew J. Predictors of inpatient mortality among children hospitalized for severe acute malnutrition: a systematic review and meta-analysis. The American journal of clinical nutrition. 2020;112(4):1069-79.
105. Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. The Lancet HIV. 2015;2(10):e438-e44.
106. Nalwanga D, Musiime V, Kizito S, Kiggundu JB, Batte A, Musoke P, et al. Mortality among children under five years admitted for routine care of severe acute malnutrition: a prospective cohort study from Kampala, Uganda. BMC Pediatrics. 2020;20(1).
107. Bachou H, Tumwine JK, Mwadime RKN, Tylleskar T. Risk factors in hospital deaths in severely malnourished children in Kampala, Uganda. BMC Pediatr. 2006;6(7).
108. Kanan S, Swar M. Prevalence and outcome of severe malnutrition in children less than five-year-old in Omdurman Paediatric Hospital, Sudan. Sudan Journal of Paediatrics. 2016;16(1):23-30.
109. Kambale R, Ngaboyeka G, Ntagazibwa J, Bisimwa M, Kasole L, Habiyambere V, et al. Severe acute malnutrition in children admitted in an Intensive Therapeutic and Feeding Centre of South Kivu, Eastern Democratic Republic of Congo: Why do our patients die? PLoS One. 2020;15(7):e0236022.
110. Fergusson P, Tomkins A, M. K. Improving survival of children with severe acute malnutrition in HIV-prevalent settings. . International Health. 2009;1(1):10-6.
111. Bahwere P, Piwoz E, Joshua M, Sadler K, Grobler-Tanner CH, Guerrero S, et al. Uptake of HIV testing and outcomes within a Community-based Therapeutic Care (CTC) programme to treat Severe Acute Malnutrition in Malawi: a descriptive study. BMC Infectious Diseases. 2008; 106(8).
112. Muenchhoff M, Healy M, Singh R, Roider J, Groll A, Kindra C, et al. Malnutrition in HIV-Infected Children Is an Indicator of Severe Disease with an Impaired Response to Antiretroviral Therapy. AIDS Research and Human Retroviruses. 2018;34(1):46-55.
113. Bong C-N, Yu JK-L, Chiang H-C, Huang W-L, Hsieh T-C, Schouten EJ, et al. Risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi. AIDS. 2007;21(13):1805-10.
114. Walker AS, Prendergast AJ, Mugyenyi P, Munderi P, Hakim J, Kekitiinwa A, et al. Mortality in the Year Following Antiretroviral Therapy Initiation in HIV-Infected Adults and Children in Uganda and Zimbabwe. Clinical Infectous Disease. 2012;55.
115. Collins J, Diala U, Adah A, Lar A, Envuladu E A, Adedeji I, et al. Survival and nutritional status of children with severe acute malnutrition, six months post-discharge from outpatient treatment in Jigawa state, Nigeria. Plos One. 2018.
116. O'Sullivan NP, Lilijveld N, Rutishanser-Perera A, Kerac M, P. J. Follow-up between 6 and 24 months after discharge from treatment for severe acute malnutrition in children aged 6-59 months: A systematic review. PloS One. 2018;13(8).
117. Wiens MO, Pawluk S, Kissoon N, Kumbakumba E, Ansermino JM, Singer J, et al. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. Plos One. 2013;8(6).
118. Moïsi JC, Gatakaa H, Berkley JA, Maitland K, Mturi N, Newton CR, et al. Excess child mortality after discharge from hospital in Kilifi,

Kenya: a retrospective cohort analysis. Bull World Health Organ 2011;89:725-32A.
119. Veirum J E, Sodeman M, Biai S, Hedegard K, Aaby P. Increased mortality in the year following discharge from a paediatric ward in Bissau, Guinea-Bissau. Acta Paediatrica. 2007;96:1832-8.
120. Roy S, Chowdhury A, Rahaman M. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. British Medical Journal. 1983;287(6399):1097-9.
121. Chisti M J, Graham S M, Duke T, Ahmed T, Faruque ASG, Ashraf H, et al. Post-Discharge Mortality in Children with Severe Malnutrition and Pneumonia in Bangladesh. Plos One. 2014;9(9).

122. Khanum S, Ashworth A, Huttly S R A. Growth, morbidity, and mortality of children in Dhaka after treatment for severe malnutrition: a prospective study. American Journal of Clinical Nutrition. 1998;67:940-5.
123. Aprameya H, Kamath S, Kini P, Baliga B, Shenoy U, Jain A, et al. Socioepidemiological determinants of severe acute malnutrition and effectiveness of nutritional rehabilitation center in its management. International Journal of Health & Allied Sciences. 2015;4(3):148-53.
124. Chisti M J, Graham S M, Duke T, Ahmed T, Syed A, Golam FaruqueG, et al. Post-Discharge Mortality in Children with SevereMalnutrition and Pneumonia in Bangladesh. Plos One. 2014;9(9).
125. Kerac M, Bunn J, George Chagaluka G, Bahwere P, Tomkins A, Collins S, et al. Follow-Up of Post-Discharge Growth and Mortality after Treatment for Severe Acute Malnutrition (FuSAM Study): A Prospective Cohort Study. Plos One. 2014;9(6).
126. Kerac M, Bunn J, George Chagaluka G, Bahwere P, Tomkins A, Collins S, et al. Follow-Up of Post-Discharge Growth and Mortality after

Treatment for Severe Acute Malnutrition (FuSAM Study):

A Prospective Cohort Study. Plos One. 2014;9(6).
127. Chhibber A V, Hill P C, Jafali J, Jasseh M, Hossain M I, Ndiaye M, et al. Child Mortality after Discharge from a Health Facility following Suspected Pneumonia, Meningitis or Septicaemia in Rural Gambia: A Cohort Study. Plos One. 2015;10(9).
128. Ngari MM, Mwalekwa L, Timbwa M, Hamid F, Ali R, Iversen PO, et al. Changes in susceptibility to life-threatening infections after treatment for complicated severe malnutrition in Kenya. American Journal of Clinical Nutrition. 2018;107:626-34.
129. Ashraf H, Alam NH, Chisti M J, Mahmud SR, Hossain M, Ahmed T, et al. A Follow-up Experience of 6 months after Treatment of Children with Severe Acute Malnutrition in Dhaka, Bangladesh. Journal of Tropical Pediatrics. 2012;58(4):253-7.
130. Girma T, James PT, Abdissa A, Luo H, Getu Y, Fantaye Y, et al. Nutrition status and morbidity of Ethiopian children after recovery from severe acute malnutrition: Prospective matched cohort study. PloS One. 2022;17(3).
131. Lenters LM, Wazny K, Webb P, Ahmed T, Bhutta ZA. Treatment of severe and moderate acute malnutrition in low- and middle-income settings: a systematic review, meta-analysis and Delphi

process. BMC Public Health. 2013;13 (Supp 3):S23.
132. Stobaugh H, Mayberry A, McGrath M, Bahwere P, Zagre NM, Manary MJ, et al. Relapse after severe acute malnutrition: A systematic literature review and secondary data analysis. Maternal and Child Nutrition. 2018:e12702.
133. Burza S, Mahajan R, Marino E, T S, Shandilya C, Tabrez M, et al. Seasonal effect and long-term nutritional status following exit from a Community-Based Management of Severe Acute Malnutrition program in Bihar, India. European Journal of Clinical Nutrition. 2016;70:437–44.
134. Berkley JA, Ngari M, Johnstone T, Mwalekwa L, Timbwa M, Hamid F, et al. Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial. Lancet Global Health. 2016;4(7):e464 - e73.
135. Gonzales GB, Ngari MM, Njunge JM, Thitiri J, Mwalekwa L, Mturi N, et al. Phenotype is sustained during hospital readmissions following treatment for complicated severe malnutrition among Kenyan children: A retrospective cohort study. Maternal and Child Nutrition. 2019.
136. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, MA. A, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature. 2014;510(7505):417-21.
137. Murphy A, White M, Davies P. Body composition of children with cancer. The American journal of clinical nutrition. 2010;92(1): 55–60. .
138. Thibault R, Pichard C. The Evaluation of Body Composition: A Useful Tool for Clinical Practice. Annals of Nutrition and Metabolism. 2012;60:6-16.
139. Bellizzi V, Scalfi L, Terracciano V, De Nicola L, Minutolo R, Marra M, et al. Early Changes in Bioelectrical Estimates of Body Composition in Chronic Kidney Disease. Journal of the American Society of Nephrology. 2006;17(5):1481-7.

140. Eke CB, Chukwu BF, Ikefuna AN, Ezenwosu OU, Emodi IJ. Bioelectric Impedance Analysis of Body Composition of Children and Adolescents with Sickle Cell Anemia in Enugu, Nigeria. Pediatric Hematology and Oncology. 2015;32(4):258-68.
141. Marcelli D, Usvyat LA, Kotanko P, Bayh I, Canaud B, Etter M, et al. Body Composition and Survival in Dialysis Patients: Results from an International Cohort Study. Clinical Journal of the American Society of Nephrology. 2015;10(7):1192-200.
142. Pirlich M, Schütz T, Norman K, Gastell S, Lübke HJ, Bischoff SC, et al. The German hospital malnutrition study. Clinical Nutrition. 2006;25(4):563-72.
143. Wolfe RR. The underappreciated role of muscle in health and disease. American Journal of Clinical Nutrition. 2006;84:475-82.
144. Lara-Pompa N, Hill S, Williams J, Macdonald S, Fawbert K, Valente J, et al. Use of standardized body composition measurements and malnutrition screening tools to detect malnutrition risk and predict clinical outcomes in children with chronic conditions. The American journal of clinical nutrition. 2020;112(6):1456-67.
145. Wells JCK. Body composition of children with moderate and severe undernutrition and after treatment: a narrative review BMC Medicine. 2019;17(215).
146. Kangas ST, Kaestel P, Salpéteur C, Nikièma V, Talley L, Briend A, et al. Body composition during outpatient treatment of severe acute malnutrition: Results from a randomised trial testing different doses of ready-to-use therapeutic foods. Clinical Nutrition. 2020;39(11):3426-33.
147. Girma T, Kaestel P, Mølgaard C, Michaelsen K F, Friis H, Wells J C K. Utility of bio-electrical impedance vector analysis for monitoring treatment of severe acute malnutrition in children. Clinical Nutrition. 2021;40(2):624-31.
148. Lelijveld M, Seal A, Wells J C, Kirkby J, Opondo C, Chimwezi E, et al. Chronic disease outcomes after severe acute malnutrition in

Malawian children (ChroSAM): a cohort study. Lancet Global Health. 2016;4:e654-62.
149. Kasonka L, Munthali G, Rehman AM, Chisenga M, Wells S, Wells J, et al. Anthropometry, body composition and chronic disease risk factors among Zambian school-aged children who experienced severe malnutrition in early childhood

. British Journal of Nutrition 2021;128(3):453-60.
150. Bahwere P, Balaluka B, Wells JC, Mbiribindi CN, Sadler K, Akomo P, et al. Cereals and pulse-based ready-to-use therapeutic food as an alternative to the standard milk- and peanut paste–based formulation for treating severe acute malnutrition: a noninferiority, individually randomized controlled efficacy clinical trial. The American journal of clinical nutrition. 2016;103(4):1145-61.
151. Chloe Angood, Tanya Khara, Carmel Dolan, James A. Berkley, WaSt Technical Interest Group. Research Priorities on the Relationship between Wasting and Stunting. Plos One. 2016;11(5).
152. Wells J, Devakumar D, Manandhar D, Saville N, Chaube S, Costello A, et al. Associations of stunting at 2 years with body composition and blood pressure at 8 years of age: longitudinal cohort analysis from lowland Nepal. European Journal of Clinical Nutrition. 2019;73(2):302-10.
153. Skau J, Grenov B, Chamnan C, Chea M, Wieringa F, Dijkhuizen M, et al. Stunting, wasting and breastfeeding as correlates of body composition in Cambodian children at 6 and 15 months of age. British Journal of Nutrition. 2019;121(6):688-98.
154. Sinha RK, Kumar P, Daniel A, Shah H, Sriswan R, Kokane A, et al. Association between anthropometric criteria and body composition among children aged 6-59 months with severe acute malnutrition: a cross-sectional assessment from India. BMC Nutrition

. 2022;8(1).
155. Bwakura-Dangarembizi M, Amadi B, Bourke C D, Robertson R C, Mwapenya B, Chandwe K, et al. Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. BMJ open. 2019;9(1):e023077-e.
156. Zambia Central Statistical Office (CSO), Zambia Ministry of Health, International. aI. Zambia Demographic and Health Survey 2013-14. Maryland, USA; 2014.
157. Zimbabwe National Statistics Agency, ICF International. Zimbabwe Demographic and Health Survey 2015: Final Report. Rockville, Maryland, USA; 2016.
158. Lohman T, Roche A, Martorell R. Anthropometric Standardization Reference Manual: Human Kinetics Books; 1991.

159. Chinkhumba J, Tomkins A, Banda C, Mkangama C, Fergusson P. The impact of HIV on mortality during in-patient rehabilitation of severely malnourished children in Malawi. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008;102(7):639-44.
160. Chisti M J, Graham S M, Duke T, Ahmed T, Syed A, Golam FaruqueG, et al. Post-Discharge Mortality in Children with Severe Malnutrition and Pneumonia in Bangladesh. Plos One. 2014;9(9).
161. Rytter MJH, Kolte L, Briend A, Friis H, B. CV. The Immune System in Children with Malnutrition—A Systematic Review. Plos One. 2014;9(8).
162. UNICEF. The State of the World's Children. UNICEF, New York; 1998.
163. Thurstans S, Kerac M, Maleta K, Banda T, A. N. HIV prevalence in severely malnourished children admitted to nutrition rehabilitation units in Malawi: geographical & seasonal variations a cross-sectional study. BMC Pediatr. 2008;8(22).
164. Blaise Savadogo LG, Donnen P, Kouéta F, Kafando E, Hennart P, Dramaix M. Impact of HIV/AIDS on mortality and nutritional recovery among hospitalized severely malnourished children before starting antiretroviral treatment. Open Journal of Pediatrics. 2013;3:340-5.
165. World Health Organisation. Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, Recomendations for a public health approach. Geneva, Switzerland; 2013.
166. Bwakura-Dangarembizi M, Amadi B, Bourke CD, Robertson RC, Mwapenya B, Chandwe K, et al. Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. . BMJ Open. 2019;9.
167. Fergusson P, Chinkhumba J, Grijalva-Eternod C, Banda T, Mkangama C, Tomkins A. Nutritional recovery in HIV-infected and HIV uninfected children with severe acute malnutrition. Archives of Diseases in Children. 2009;94:512-6.
168. Jesson J, Leroy V. Challenges of malnutrition care among HIV-infected children onantiretroviral treatment in Africa. Médecine et maladies infectieuses. 2015;45:149-56.
169. Katona P, Katona-Apte J. The Interaction between Nutrition and Infection. Clinical Practice. 2008;46:1582-8.
170. Rogerson SR, Gladstone M, Callaghan M, Erhart L, Rogerson SJ, Borgstein E, et al. HIV infection among paediatric in-patients in Blantyre, Malawi. Trans R Soc Trop Med Hyg

. 2004;98(9):544-52.
171. Nosek CA, Buck WC, Caviness AC, Foust A, Nyondo Y, Bottomani M, et al. Hospital admissions from a pediatric HIV care and treatment program in Malawi. BMC Pediatrics. 2016;16(22).
172. Sutcliffe CG, van Dijk JH, Munsanje B, Hamangaba F, Siniwymaanzi P TP, WJ. M. Risk Factors for Pre-Treatment Mortality among HIVInfected Children in Rural Zambia: A Cohort Study. PLoS ONE. 2011;6(12).
173. Njunge JM, Gwela A, Kibinge NK, Ngari M, Nyamako L, Nyatichi E, et al. Biomarkers of post-discharge mortality among children with complicated severe acute malnutrition. Scientific Reports. 2019;9(5981).
174. Wiens MO, Kumbakumba E, Larson CP, Ansermino JM, Singer J, Kissoon N, et al. Postdischarge mortality in children with acute infectious diseases: derivation of postdischarge mortality prediction models

. BMJ Open. 2015;5(11):e009449. .
175. Thurstans S, Kerac M, Maleta K, Banda T, Nesbitt A. HIV prevalence in severely malnourished children admitted to nutrition rehabilitation units in Malawi: geographical & seasonal variations a cross-sectional study. BMC Pediatrics. 2008;8(22).
176. Prazuck T, Tall F, Nacro B, Rochereau A, Traore A, Sanou T, et al. HIV infection and severe malnutrition: a clinical and epidemiological study in Burkina Faso. AIDS. 1993;7(1):103-8.
177. Asafo-Agyei SB, Antwi S, Nguah SB. HIV infection in severely malnourished children in Kumasi, Ghana: a cross-sectional prospective study. BMC Pediatrics. 2013;13(181).
178. Mgone CS, Mhalu FS, Shao JF, Britton S, Sandström A, Bredberg-Råden U, et al. Prevalence of HIV-1 infection and symptomatology of AIDS in severely malnourished children in Dar Es Salaam, Tanzania. 1991;4(9):910-3.

179. Waterlow JC. Protein-Energy Malnutrition. United Kingdom: Smith-Gordon 2006.
180. Phiri KS, Calis JCJ, Faragher B, Nkhoma E, Ng'oma K, Mangochi B, et al. Long Term Outcome of Severe Anaemia in Malawian Children. Plos One. 2008;3(8).
181. Lackritz EM, Campbell CC, Ruebush TK, Hightower AW, Wakube W, Were JBO, et al. Effect of blood transfusion on survival among children in a Kenyan hospital. The Lancet 1992;340:524-8.
182. Rytter MJH, Kolte L, Briend A, Friis H, Christensen VB. The Immune System in Children with Malnutrition—A Systematic Review. Plos One. 2014;9(8).
183. World Bank, World Health Organisation, Fund. UCs. Levels and trends in child malnutrition: UNICEF/WHO/World Bank Group Joint Child Malnutrition Estimates, Key findings of the 2018 edition. 2018.
184. Bwakura-Dangarembizi M, Dumbura C, Amadi B, Ngosa D, Majo F D, Nathoo K J, et al. Risk factors for postdischarge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia. The American journal of clinical nutrition. 2021;113(3):665-74.
185. Mulenga V, Ford D, Walker AS, Mwenya D, Mwansa J, Sinyinza F, et al. Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. AIDS. 2007;21:77-84.
186. Chintu C, G J Bhat, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet. 2004;364:1865-71.
187. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. . Geneva 1968. Contract No.: PMID: 4976616.
188. Kau AL, Ahern PP, Griffin NW, Goodman AL, JI. G. Human nutrition, the gut microbiome and the immune system. Nature. 2011;474(7351):327-36.
189. Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, Maleta KM, et al. Antibiotics as part of the management of severe acute malnutrition. New England Journal of Medicine. 2013;368(5):425-35.
190. Somassè YE, Dramaix M, Bahwere P, P. D. Relapses from acute malnutrition and related factors in a community-based management programme in Burkina Faso. . Matern Child Nutr 2016;12(4):908-17.
191. James PK, Sadler K, Wondafrash M, Argaw A, Luo H, Geleta B, et al. Children with Moderate Acute Malnutrition with No Access to Supplementary Feeding Programmes Experience High Rates of Deterioration and No Improvement: Results from a Prospective Cohort Study in Rural Ethiopia. Plos One. 2016.
192. Chang CY, Trehan I, Wang R J, Thakwalakwa C, Maleta K, Deitchler M, et al. Children Successfully Treated for Moderate Acute Malnutrition Remain at Risk for Malnutrition and Death in the Subsequent Year after Recovery. Journal of Nutrition. 2013;143:215-20.
193. Isanaka S, Hitchings MDT, Berthé F, Briend A, Grais RF. Linear growth faltering and the role of weight attainment: Prospective analysis of young children recovering from severe wasting in Niger. Maternal and Child Nutrition. 2019;15(4).
194. Bell KL, Samson-Fang L. Nutritional management of children with cerebral palsy. European Journal of Clinical Nutrition. 2013;67:S13-S6.
195. Muller MJ, Bosy-Westphal A, Later W, Haas V, Heller M. Functional body composition: insights into the regulation of energy metabolism and some clinical applications. European Journal of Clinical Nutrition. 2009;63:1045-56.
196. Wells J C. Measuring body composition. Archives of Diseases in Childhood. 2006;91(7):612-7.
197. Wells JCK, Fewtrell MS. Is body composition inportant for paediatricians? Archives of Diseases in Childhood. 2008;93:168-72.
198. Bwakura-Dangarembizi M, Dumbura C, Amadi B, Chasekwa B, Ngosa D, Majo FD, et al. Recovery of children following hospitalisation for complicated severe acute malnutrition. Maternal & child nutrition. 2022;18(2):e13302.
199. Briend A, Garenne M, Maire B, Fontaine O, Dieng K. Nutritional Status, age and survival: The muscle mass hypothesis. European Journal of Clinical Nutrition. 1989;43(10):715-26.
200. Howard J, Lord G, Matarese G, Vendetti S, Ghatei M, Ritter M, et al. Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. The Journal of clinical investigation. 1999;104(8):1051-9.

201. Sánchez-Margalet V, Martín-Romero C, Santos-Alvarez J, Goberna R, Najib S, Gonzalez-Yanes C. Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. Clin Exp Immunol. 2003;133(1):11-9.
202. Lelijveld N, Musyoki E, Adongo SW, Mayberry A, Wells JC, Opondo C, et al. Relapse and post-discharge body composition of children treated for acute malnutrition using a simplified, combined protocol: A nested cohort from the ComPAS RCT. . Plos One. 2021;16(2).
203. Grinspoon S, Mulligan K, Department of Health, Human Services Working Group on the Prevention Treatment of Wasting Weight Loss. Weight Loss and Wasting in Patients Infected with Human Immunodeficiency Virus. Clinical Infectious Diseases. 2003;36(Supplement_2):S69-S78.
204. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and Ageing. 2010;39(4):412-23.
205. Chen L-K, Woo J, Assantachai P, Auyeung T-W, Chou M-Y, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. Journal of the American Medical Directors Association. 2020;21(3):300-7.e2.
206. Ooi Poh Hwa, Thompson-Hodgetts Sandra, Pritchard-Wiart Lesley, Gilmour Susan M, R. MD. Pediatric Sarcopenia: A Paradigm in the Overall Definition of Malnutrition in Children? Journal of Parenteral and Enteral Nutrition. 2020;44(3):407-18.
207. Dedhia PH, White Y, Dillman JR, Adler J, Jarboe MD, Teitelbaum DH, et al. Reduced paraspinous muscle area is associated with post-colectomy complications in children with ulcerative colitis. Journal of Pediatric Surgery. 2017;53(3):477-82.
208. Hume-Nixon M, Kuper H. The association between malnutrition and childhood disability in low- and middle- income countries: systematic review and meta-analysis of observational studies. Tropical Medicine & International Health. 2018;23(11):1158-75.
209. Olusanya BO, Gladstone M, Wright SM, Hadders-Algra M, Boo NY, Nair MKC, et al. Cerebral palsy and developmental intellectual disability in children younger than 5 years: Findings from the GBD-WHO Rehabilitation Database 2019. Frontiers in Public Health. 2022.

8. APPENDICES

Appendix A: HREC Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Mutsawashe Bwakura-Dangarembizi et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180113

NAME: (Principal Investigator)	Dr Mutsawashe Bwakura-Dangarembizi et al
DEPARTMENT:	Paediatrics Harare Children's Hospital, Parirenyatwa Group of Hospitals Harare, Zimbabwe University Teaching Hospital, Lusaka, Zambia
PROJECT TITLE:	Long-term outcomes of Children (0-59 months) following Inpatient Management of Severe Acute Malnutrition
DATE CONSIDERED:	26/01/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A.J. Prendergast
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/06/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: MRCZ Approval

Telephone: 791792/791193
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

APPROVAL

REF: MRCZ/A/2044

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2016 -06- 01
APPROVED
P.O. BOX CY 573 CAUSEWAY, HARARE

2 June, 2016

Dr A Prendegast
Zvitambo
Institute for Maternal and Child Health Research
16 Lauchlan Avenue
Meyrick Parck
Harare

RE:-Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM)

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review:-

- HOPE-SAM Protocol version 1.2 dated 26 January, 2016
- HOPE-SAM Research Summary dated 2 February, 2016
- HOPE-SAM Form_1_Caregiver Sensitization Sheet v1.0 dated 16 November, 2015.**English/Shona**
- HOPE-SAM Form_2_Observational Cohort Informed Consent Form v1.3 dated 11 March, 2016.**English/Shona**
- HOPE-SAM Form_3_Study Checklist v1.1 dated 26 January, 2016.**English**
- HOPE-SAM Form_4_Acute Admission Form v1.1 dated 26 January, 2016.**English**
- HOPE-SAM Form_5_Baseline Form v1.1 dated 26 January, 2016.**English**
- HOPE-SAM Form_6_ Long Term Specimen Storage and Future Use Consent form v1.2 dated 11 March, 2016.**English/Shona**
- HOPE-SAM Form_7_Daily Follow-up Form v1.1 dated 29 January, 2016.**English**
- HOPE-SAM Form_8_Discharge Form v1.0 dated 29 January, 2016.**English**
- HOPE-SAM Form_9_Locator Information v1.0 dated 26 January 2016. **English**
- HOPE-SAM Form_10_Morbidity Diary v1.0 dated 29 January 2016. **English**
- HOPE-SAM Form_11_Clinical Follow-up Form v1.0 dated 29 January, 2016. **English**
- HOPE-SAM Form_12_Nurse Follow-up Form v1.0 dated 29 January, 2016. **English**
- HOPE-SAM Form_13_Death form v1.0 dated 29 January, 2016.**English**
- HOPE-SAM Form_14_Enteropathy Sub-study Case Consent Form v1.3 dated 11 March, 2016 **English/Shona**
- HOPE-SAM Form_15_ Enteropathy Sub-study Control Consent Form v1.3 dated 11 March, 2016.**English/Shona**
- HOPE-SAM Form_16_Control Data Collection Form v1.0 dated 29 January, 2016.**English**
- HOPE-SAM Form_17_Exit Form v1.0 dated 29 January, 2016.**English**
- HOPE_SAM Form_18_Event Form v1.0 29 January, 2016.**English**

- **APPROVAL NUMBER : MRCZ/A/2044**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING : Full Board**
- **EFFECTIVE APPROVAL DATE : 01 June, 2016**
- **EXPIRATION DATE : 31 May, 2017**

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Appendix C: UNZABREC Approval

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
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Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

Assurance No. FWA00000338
IRB00001131 of IORG0000774

17th June, 2016.

Your Ref: 010-02-16.

Dr. Beatrice Amadi,
TROPGAN,
University of Zambia,
School of Medicine,
Department of Medicine,
P.O Box 50398,
Lusaka.

Dear Dr. Amadi,

RE: **RESUBMITTED RESEARCH PROPOSAL: "HOPE-SAM: HEALTH OUTCOMES, PATHOGENESIS AND EPIDEMIOLOGY OF SEVERE ACUTE MALNUTRITION" (REF. NO. 010-02-16)**

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 15th June, 2016. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,

Dr. S.H Nzala
VICE-CHAIRPERSON

Date of approval: 17th June, 2016. **Date of expiry:** 16th June, 2017.

Appendix D: Parental information and consent document

INFORMED CONSENT FORM
FOR CAREGIVER CONSENT

Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM)

OBSERVATIONAL COHORT STUDY

Principal Investigator: Dr Andrew J Prendergast
Co-Investigator(s): Dr Mutsa Bwakura-Dangarembizi, Prof Kusum J Nathoo
Phone number(s) 04-306028 or 04-306056 or 0772 601 735

What you should know about this research study:

- You are being asked to join a research study.
- We give you this consent form so that you may read about the purpose, risks, and benefits of this research study
- We cannot promise that this research will benefit your child directly. The main goal of research studies is to gain knowledge that may help future patients.
- It is voluntary. You can choose not to take part, or agree for your child to take part now and change your mind later.
- Whatever you decide, it will not affect your child's regular care.
- Please review this consent form carefully. Ask any questions before you make a decision.

Purpose of the study
HOPE-SAM is a research project that is recruiting children with severe acute malnutrition (SAM) in Zimbabwe and Zambia. SAM is a serious form of malnutrition that often requires children to be admitted to hospital to get better. Some children with SAM also have HIV infection. We know that children who have HIV infection as well as SAM tend to be sicker and take longer to recover, but we do not fully understand why this is.

The purpose of HOPE-SAM is to find out more about how well children recover from SAM in hospital, and how healthy they remain once they have been discharged home. Your child has been invited to join HOPE-SAM because he/she has been admitted to hospital with severe acute malnutrition.

The study is being done by doctors and researchers from the University of Zimbabwe and the Zvitambo Institute for Maternal and Child Health Research in Harare, in partnership with Queen Mary, University of London, UK.

What does my child have to do in the study?
If you agree to join this study, your child will be seen by the study team each day while he/she is in hospital and then 5 times after discharge from hospital (after 2 weeks, then after 4, 12, 24 and 48 weeks). Each time we see your child, we will ask you some questions and examine him/her, and on certain visits we will collect a blood sample from your child or do some other tests.

First visit in hospital
We will first ask you some questions about your child, yourself and your family. If you feel uncomfortable answering any of these questions, you do not have to answer them. The questions will include:

- Your child's medical history, including details about his/her health and what symptoms, medications, and illnesses your child has had in the past.
- What you are feeding your child
- Whether anyone in your family earns money and what possessions you have at home.

A doctor from the HOPE-SAM study will examine your child, including measuring his/her length, weight, leg length, mid upper arm measurement, head measurement, and vital signs (temperature, heart rate and breathing rate), listening to his/her chest and feeling his/her tummy. We will record the results of vital signs from your child's hospital charts, and the results of blood tests that the ward doctors have done so far. We may carry out some extra monitoring on your child, such as measuring his/her heart rate using some wires attached to the chest. We will measure your child's body composition using a machine called a bioimpedance analyzer. This machine passes a tiny electric current through the body, which cannot be felt. It gives us information about how much muscle, fat and water are in your child's body.

We will collect a small blood sample from your child (5.4ml, which is about one teaspoon). Wherever possible, we will make sure this extra blood is collected at the same time as any routine blood tests being done by your child's doctors. We will use the extra blood to measure his/her blood count (to check for anaemia) and to test for HIV if this has not yet been done during this admission. Because HIV can affect the way your child responds to nutritional treatment, it is important that we know his/her HIV status for this research study. Knowing your child's HIV status means we can start antiretroviral treatment if needed.

If your child has HIV infection, we will measure his/her CD4 count, to see how strong the immune system is, and the amount of virus in his/her blood (viral load). We will give you the results of these tests. We will also use your child's blood sample to measure the protein level in his/her blood and to measure the way his/her body is responding to infections.

This visit will take about one and half hours (1 ½ hours) to complete.

Each day in hospital
Every day during this hospital admission, a doctor from the HOPE-SAM study will examine your child, including measuring his/her weight, mid upper arm measurement and vital signs (temperature, heart rate and breathing rate), listening to his/her chest and feeling his/her tummy. We will also record the results of vital signs from your child's hospital charts, and the results of blood tests that the ward doctors have done so far.

At the time of discharge from hospital
Once your child is ready to be discharged, we will record details about how well he/she has responded to treatment. We will measure your child's length, weight, leg length, mid upper arm measurement, mid-thigh measurement and head measurement again. We will measure the thickness of your child's skin using some calipers, and measure your child's body composition again, to understand how well your child has recovered from SAM.

We will also ask you some questions about how you plan to care for your child at home. We will give you a diary and some stickers to take home and ask you to record any episodes of illness your child has each day (diarrhea, blood in the stools, cough, fast breathing, hot body, poor feeding and lethargy). We will show you how to fill in the diary and will answer any questions you may have. We will phone you or send you an SMS reminder each week to fill in the illness diary.

After discharge from hospital
We will ask you to bring your child to a special study follow-up clinic so that we can see how healthy he/she is and look for any signs of malnutrition returning. We would like to see your child 5 times over the next year (after 2 weeks, then after 4, 12, 24 and 48 weeks). We will remind you by phone about each appointment and we will provide you with transport money for you and your child to attend. At each visit, we will ask you about your child's health, what food she/he is eating and any illnesses s/he may have had after discharge from hospital. We will review the illness diary and give you a new diary and stickers to continue recording any illnesses your child has. We will also ask you to bring your child's hand-held medical records to review any clinic attendances or admissions to hospital.

At each visit we will examine your child to look for any signs of illness, and measure his/her length, weight, leg length, mid upper arm measurement, mid-thigh measurement and head measurement. We will repeat the skin thickness and body composition tests that were done before your child left hospital. All these assessments will help us to understand how well your child is recovering from malnutrition. If your child shows signs of malnutrition, we will provide nutritional supplements if needed free of charge, or refer your child to hospital. If your child has any acute illnesses that can be treated in the clinic, we will provide the appropriate treatment free of charge, or else refer your child to hospital.

At three visits (12, 24 and 48 weeks after discharge from hospital), we will take another blood sample from your child (5.4ml, which is about one teaspoon) to measure his/her blood count (to check for anaemia). If your child has HIV infection, we will also measure his/her CD4 count, to see how strong the immune system is, and the amount of virus in his/her blood (viral load). We will give you the results of these tests. We will also use your child's blood sample to measure the protein level in his/her blood and to measure the way his/her body is responding to infections.

Each visit will take about one and half hours (1½ hours) to complete.

In the event that you fail to come for your scheduled visit, the study team will contact you by phone and/or conduct a home visit.

If your child gets readmitted to this hospital with SAM at any time during the follow-up period, we would like to collect the same information and specimens as during his/her initial admission, to understand how quickly he/she recovers next time from SAM.

How many children will take part in this study?
We plan to recruit all children who are admitted with SAM over a two-year period at three different hospitals (Parirenyatwa Hospital and Harare Children's Hospital in Zimbabwe, and University Teaching Hospital in Lusaka, Zambia), which is estimated to be up to 800 children in total.

How long will my child be in the study?
Your child will be followed up in the study for 1 year.

What are the risks of the study?
When we collect the blood sample from your child, it will sting momentarily, but we can use a local anaesthetic cream to numb the skin if you wish. Your child may cry for a short time after taking the blood sample but this will not last long. Sometimes people get a small amount of bleeding or bruising where the blood sample was taken, but it will only last a few days and is usually not painful. Very rarely, some people may feel dizzy or faint when they have a blood test, or get a minor infection of the skin at the site where the blood was taken. Measuring your child's skin thickness and body composition will not hurt, although children sometimes cry when they are held for these measurements.

Are there any benefits to taking part in this study?
The main goal of research studies is to gain knowledge that may help future patients. We therefore do not promise that your child will receive any direct benefits from this study. Your child will receive the standard treatment while s/he is in hospital. However, your child will also be examined every day by a study doctor, and will be seen after discharge in the study clinic by a doctor and nurse, where we will regularly weigh your child, screen him/her for malnutrition and treat any acute illnesses your child has free of charge, or refer him/her for treatment.

What are the costs to me?
There is no cost to you for the study visits, examinations or blood tests. You will be reimbursed for transport and time spent in the study clinic whenever you attend at USD5 per visit.

We hope this study will benefit future children with SAM, by understanding better how children respond to malnutrition treatment in hospital and how they recover long-term. We will hold a caregivers' meeting to inform you of the findings of this study and to give you an opportunity visit the research laboratory to understand how we use your child's biological specimens.

Confidentiality
Information about you and your child will be kept confidential and will not be made available to anyone who is not connected with the HOPE-SAM study. Your names will never be used for study information or stored blood samples; these will be identified only by a study number. There will be one list which links this study number to your child's name, and this list will be safely kept private in a locked cabinet. Any publication of this study will not use your child's name or identify your child personally.

Under some circumstances, the Medical Research Council of Zimbabwe (MRCZ), Research Council of Zimbabwe (RCZ) or the study Sponsor (Queen Mary, University of London) may need to review patient records to ensure that the study is being carried out correctly.

Biological specimens and data
The specimens and data collected from you and your child during this study are important to science. These specimens and data have been gifted to the study. You will not receive any financial benefit from any product or idea created by the investigators using the data or materials collected from you or your child. Dr Prendergast will be responsible for any specimens or data collected from your child and you may contact him on +263-(0)4-306028 or +263-(0)4-306056 if you have any questions regarding the samples and data you provide.

What other choices do I have for my child besides this study?

Participation in this study is voluntary. You may choose not to have your child participate in this study. Your choice will not affect the treatment your child will get or your relationship with staff at any of the hospitals or clinics where you receive your usual care. If you decide to allow your child to participate, you are free to withdraw your consent and discontinue participation at any time without penalty. You can refuse for your child to participate in any part of the study, including collection of biological samples at any time. If you have any questions we will be happy to answer them now or at any point during the study. Also, you can ask the researchers in charge of the study, listed below, if you do not understand anything about the study now, or after it has started.

What happens if my child is harmed in this study?
We do not anticipate any harm as a result of your child's participation in this study. In the event of any direct injury or harm resulting from your child's participation in this study, arrangements have been made for compensation.

Sharing of new findings
We will share any new information that we learn from this study with you and other caregivers by holding a meeting at the end of the study, which you will be invited to join.

What do I do if I have questions or problems?
For questions about this study, contact one of the investigators, Dr Prendergast (04-306028/306056) or Dr Bwakura-Dangarembizi (0772 601 735).

For questions about your child's rights as a research subject, contact:

Medical Research Council of Zimbabwe
Cnr Mazowe /Josiah Tongogara Avenue
Harare
04 791792/791193
Mobile 0772 433 166

Authorization
You are making a decision about whether or not to allow your child to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to allow your child to participate.

What your signature means
I, the person signing below, have been told about the purposes, procedures and possible risks and benefits of this study. I agree to my child having specimens collected as explained in this consent form and agree to my child being tested for HIV. I have signed a copy of this consent form. I have been given the chance to ask questions before I sign. I have been told that I can ask other questions at any time. I freely choose and agree for my child to be in this study. I am free to stop my child being in the study at any time. If I want my child to stop being in the study, I will not have to explain why. If I stop my child being in the study, I know I can still get all the medical care and assistance available to me at hospitals and clinics. I will tell the research staff immediately about any problems my child is having during the study.

<u>Shipment of the samples to a laboratory outside of Zimbabwe</u>
Some of the tests we plan to do on your child's samples as part of the current study, or future approved studies, require us to ship them to a laboratory outside Zimbabwe for tests. Only enough of the sample needed to complete the tests required will be shipped. Once those tests have been done and that study has ended, any samples left over in that laboratory will be destroyed or returned to Zimbabwe to go back into long-term storage.

I allow my baby's samples to be shipped to external laboratories for testing.

Yes _____ No _____ Date _____

_____
Child's name (please print)

_____ _____

Name of Caregiver (please print) Date

Relationship of Caregiver to the child

Signature of Caregiver or legally authorized representative Time

Signature of Witness (if caregiver unable to read or write)
Must be different to the person obtaining consent

Name of Research Staff obtaining consent Date

Signature of Research Staff obtaining consent

Signed copies of this consent form must be 1) retained on file by the Principal Investigator; 2) given to the caregiver and 3) placed in the subject's research record.

NOT VALID WITHOUT MRCZ STAMP OF APPROVAL

Appendix E: Baseline form

Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM)
Acute Admission Form

SECTION 1: ADMISSION DETAILS

No.	Question	Response	Codes and notation
4-1.1	Participant ID (PID)	|__|__|__|__|__|	
4-1.2	Sex	|__|__|	01 = Male 02 = Female
4-1.3	Date of birth	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy
4-1.4	Age	|__|__|	Completed months
4-1.5	Date of initial assessment in hospital	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy
4-1.6	Time of initial assessment in hospital	|__|__|:|__|__|	00:00 – 23:59
4-1.7	Are you the main person who cares for the child each day?	|__|__|	00 = No → **RESCHEDULE INTERVIEW** 01 = Yes
4-1.8	What is your relationship to the child?	|__|__|	01=Mother → **SKIP TO SECTION 2** 02=Father 03=Sister 04=Brother 05=Grandmother 06=Grandfather 06=Aunt 07=Uncle 08=Family Friend 77=Other
4-1.9	Where is the mother?	|__|__|	01 = Mother died 02 = Mother away 03 = Mother's whereabouts unknown

PID |__|__|__|__|__| Date of form |__|__|/|__|__|__|/|__|__|__|__| Start time |__|__|:|__|__| Staff initials _____

SECTION 2: CURRENT HISTORY

4-2.1	How long has your child been unwell with this current illness?	|__|__| amount of time |__|__| unit of time	**Unit of time:** 01=Hours 02=Days 03=Weeks 04=Months 05=Years 88=Don't know 99/99=NA
4-2.2	Who did you seek help from prior to hospitalization? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = Did not seek help 01=Village Health Worker 02=Relative Or Community Leader Not Trained In Health 03=Traditional Healer 04=Faith Healer / church 05=Clinic 06=Hospital 07=Private Doctor 08=Pharmacy 09=Friend 77=Other, Please Specify 88 = Don't know
4-2.3	Has the child already been admitted to hospital during this current episode of illness?	|__|__|	00 = No 01 = Yes 88 = Don't know

No.	Question **I want you to think now about whether your child has any of the following problems in the past day or in the past 2 weeks.**	Response A	Response B
4-2.4	Fever/hot body?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.5	Cold hands and feet?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.6	Night sweats?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.7	Cough?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes

PID |__|__|__|__|__| Date of form |__|__|/|__|__|__|/|__|__|__|__| Start time |__|__|:|__|__| Staff initials _____

		88 = Don't know	88 = Don't know
4-2.8	Fast or difficult breathing?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.9	Diarrhoea? (3 or more loose or watery stools in 24 hours)	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.10	If yes, how many days of diarrhoea has your child had in a row?	|__|__| **Help mother to estimate number of consecutive days of diarrhoea** **Try to discriminate between acute diarrhoea and persistent diarrhoea (>14 days)** **Code 99 if NA**	
4-2.11	How long ago did this diarrhoea problem first begin?	|__|__| amount of time |__|__| unit of time	**Unit of time:** 01=Hours 02=Days 03=Weeks 04=Months 05=Years 88 = Don't know 99/99=NA

4-2.12	Blood in the stools?	Does your child have this now? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.13	Vomiting?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.14	Poor or reduced appetite?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.15	Weight loss (or poor weight gain)?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.16	Swelling of any part of their body?	Has your child had this in the past day? |__|__|	Has your child had this in the past 2 weeks? |__|__|

PID |__|__|__|__|__| Date of form |__|__|/|__|__|__|/|__|__|__|__| Start time |__|__|:|__|__| Staff initials _____

		00 = No 01 = Yes 88 = Don't know	00 = No 01 = Yes 88 = Don't know
4-2.17	Convulsions / fits?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.18	Drowsy or difficult to wake?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.19	Has your child experienced any other symptoms during this illness?	|__|__|	00=No → **SKIP TO SECTION 3** 01=Yes → **CONTINUE** 88=Don't Know → **SKIP TO SECTION 3**
4-2.20	Problem: |_____|	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
4-2.21	Problem: |_____|	Has your child had this in the past day? |__|__|	Has your child had this in the past 2 weeks? |__|__|

		00 = No 01 = Yes 88 = Don't know 99 = NA	00 = No 01 = Yes 88 = Don't know 99 = NA
4-2.22	Problem: |_____|	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know 99 = NA	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know 99 = NA

SECTION 3: DRUG HISTORY

No.	Question	Response	Codes and notation
4-3.1	Has your child taken any medications or nutritional supplements in the past two weeks?	|__|__|	00=No >> **SKIP TO SECTION 4** 01=Yes 88=Don't Know >> **SKIP TO SECTION 4**
4-3.2	Has he/she taken any antibiotics in the past 2 weeks?	|__|__|	00 = No → **SKIP TO 4-3.4** 01 = Yes 88 = Don't know → **SKIP TO 4-3.4**
4-3.3	Which antibiotics? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Amoxicillin 02 = Ampicillin 03 = Azithromycin 04 = Benzylpenicillin 05 = Cefotaxime 06 = Ceftriaxone 07 = Chloramphenicol 08 = Ciprofloxacin 09 = Clarithromycin 10 = Clindamycin 11 = Co-amoxiclav 12 = Cotrimoxazole 13 = Erythromycin 14 = Flucloxacillin / cloxacillin 15 = Gentamicin 16 = Imipenem 17 = Meropenem 18 = Metronidazole

			19 = Nalidixic acid 20 = Nitrofurantoin 21 = Vancomycin 22 = Unknown injection 23 = Unknown oral antibiotic 77 = Other (specify) 88 = Don't Know / not recorded
4-3.4	Has he/she taken any TB medications in the past 2 weeks?	|__|__|	00 = No → **SKIP TO 4-3.6** 01 = Yes 88 = Don't know → **SKIP TO 4-3.6**
4-3.5	Which drugs? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Rifampicin 02 = Isoniazid 03 = Ethambutol 04 = Pyrazinamide 05 = Streptomycin 06 = Drug-resistant TB regimen 77 = Other (specify) 88 = Don't Know
4-3.6	Has he/she taken any antiretroviral (anti-HIV) medicines in the past 2 weeks?	|__|__|	00 = No → **SKIP TO 4-3.8** 01 = Yes 88 = Don't know → **SKIP TO 4-3.8**
4-3.7	Which drugs? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Zidovudine (AZT or ZDV) 02 = Lamivudine (3TC) 03 = Emtricitabine (FTC) 04 = Abacavir (ABC) 05 = Stavudine (d4T) 06 = Tenofovir (TDF) 07 = Nevirapine (NVP) 08 = Efavirenz (EFV)

			09 = Lopinavir/ritonavir (Kaletra/Alluvia) 10 = Atazanavir (ATZ) 11 = Ritonavir (RTV) 77 = Other (specify) 88 = Don't Know
4-3.8	Has he/she taken any nutritional supplements in the past 2 weeks?	|__|__|	00 = No → **SKIP TO 4-3.10** 01 = Yes 88 = Don't know → **SKIP TO 4-3.10**
4-3.9	What type? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01=Plumpynut / RUTF 02=Food Supplements 03=CSB (corn soya blend) / HEPS 04=Mahewu/Supershake/other drink 05=Milk powder 77=Other, Specify 88=Don't Know
4-3.10	Has he/she taken any other medication in the past 2 weeks?	|__|__|	00 = No → **SKIP TO SECTION 4** 01 = Yes 88 = Don't know → **SKIP TO SECTION 4**
4-3.11	Which drugs? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Paracetamol 02 = Ibuprofen / other NSAID 03 = Zinc 04 = Vitamin A 05 = Multivitamins 06 = Pyridoxine 07 = Albendazole/mebendazole 08 = Praziquantel 09 = Antifungal 10 = Herbal medicine 11 = Antimalarial 12 = Ranitidine 13 = Omeprazole/lansoprazole (PPI)

			14 = Prednisolone/other steroid 15 = Antihistamine 16 = Anticonvulsant 17 = Diuretics 18 = ACE inhibitor 19 = Potassium chloride 20 = Iron 21 = Folate 22 = Potassium permanganate 23 = Zinc oxide 77 = Other (state) 88 = Don't know

SECTION 4: BIRTH AND PAST MEDICAL HISTORY

Please ask the caregiver for the child's handheld records or birth record if available

4-4.1	What sort of delivery did this child have?	|__|__| Other:_____	01=Normal Vaginal Delivery 02=Instrumental Delivery (forceps/ventouse) 03=Planned Caesarean section 04=Emergency Caesarean section 77=Other (specify) 88=Don't know
4-4.2	Was this child born premature (early)?	|__|__|	00 = No 01 = Yes 88 = Don't know
4-4.3	What was the weight of this child at birth? **Try to find details in child health records**	|__|.|__|__|	Weight in kg 8.88=Unknown / not recorded
4-4.4	What was the length of this child at birth? **Try to find details in child health records**	|__|__|.|__|	Length in centimetres 88.8 = Unknown / not recorded
4-4.5	Has your child had any of these medical conditions now or in the past? **READ THE LIST TO THE MOTHER AND CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| Other:_____	00 = None 01 = Cerebral palsy 02 = Hydrocephalus 03 = Other disability (specify) 04 = Congenital cardiac disease 05 = Tuberculosis 06 = Cleft palate 07 = Tracheo-oeseophageal fistula 08 = Previous abdominal surgery 09 = Malignancy 10 = Other (specify)

SECTION 5: FEEDING AND NUTRITION HISTORY

4-5.1	Is this child currently being breastfed?	|__|__|	00=No 01=Yes → **SKIP TO SECTION 4.5.4**
4-5.2	How old was the child when he/she stopped breastfeeding?	|__|__|	Age in months 88 = Don't know
4-5.3	Why did you stop breastfeeding? **PROBE FOR ALL ANSWERS THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Mother ill/weak 02 = Baby ill/weak 03 = Nipple/breast problem 04 = Insufficient milk 05 = Mother working 06 = Baby refused 07 = Baby began biting 08 = Weaning age/age of stop 09 = Became pregnant 10 = Husband disapproved 11 = Other family member disapproved 12 = Concerned about infecting child with HIV 13= Baby living elsewhere 14=Mother died 77 = Other (specify) 88 = Don't know 99=N/A
4-5.4	Is this child currently receiving solid foods?	|__|__|	00=No → **SKIP TO SECTION 4-5.6** 01=Yes
4-5.5	At what age did he/she first have solid foods?	|__|__|	Age in months 88 = Don't know

PID |__|__|__|__|__| Date of form |__|__|/|__|__|__|/|__|__|__|__| Start time |__|__|:|__|__| Staff initials _____

4-5.6	Has this child ever been admitted to hospital and received therapeutic milk (e.g. F75) before this episode?	|__|__|	00=No → **SKIP TO SECTION 4-5.8** 01=Yes 88=Don't Know → **SKIP TO SECTION 4-5.8**
4-5.7	How many times has your child been admitted to hospital and received therapeutic milk (not including this episode) **Probe for best estimate**	|__|__|	Number of times 88=Don't know
4-5.8	Has this child ever been treated for malnutrition in the community?	|__|__|	00=No → **SKIP TO SECTION 4-5.10** 01=Yes 88=Don't Know → **SKIP TO SECTION 4-5.10**
4-5.9	How many episodes of malnutrition have been treated in the community (not including this episode)? **Probe for best estimate**	|__|__|	Number of times 88=Don't know
4-5.10	Has your child ever had persistent diarrhoea (loose stools for at least 14 days in a row)?	|__|__|	00 = No 01 = Yes 88 = Don't know

SECTION 6: HIV HISTORY

4-6.1	What was your last HIV test result?	|__|__|	00=Negative 01=Positive → **SKIP TO SECTION 4-6.3** 88=Don't know 99=Never tested / not mother → **SKIP TO 4-6.6**
4-6.2	When was that test? **Probe for good estimates**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy → **SKIP TO 4-6.6** (Code 88/888/8888 if not able to estimate)
4-6.3	Was the mother HIV positive during pregnancy, delivery or breastfeeding of this child? **Probe for good estimates if mother not sure**	|__|__|	00 = No 01 = Yes 88 = Don't know
4-6.4	Is the mother currently taking ARV's?	|__|__|	00 = No → **SKIP TO 4-6.6** 01 = Yes 88 = Don't know → **SKIP TO 4-6.6**
4-6.5	When were these ARVs started?	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy (Code 88/888/8888 if not able to estimate)
4-6.6	What is the HIV status of the child?	|__|__|	00 = HIV-negative → **SKIP TO SECTION 7** 01 = HIV-positive 02 = HIV-exposed → **SKIP TO SECTION 7** 88 = Don't know → **SKIP TO SECTION 7**

4-6.7	Was the child diagnosed with HIV prior to this hospital admission?	|__|__|	00 = No 01 = Yes 88 = Don't know
4-6.8	Is the child currently taking cotrimoxazole?	|__|__|	00 = No 01 = Yes 88 = Don't know
4-6.9	Is the child currently taking ARV's?	|__|__|	00 = No → **SKIP TO SECTION 7** 01 = Yes 88 = Don't know → **SKIP TO SECTION 7**
4-6.10	When were these ARV's started? **PROBE FOR GOOD ESTIMATES IF NOT SURE**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy (Code 88/888/8888 if not able to estimate)
4-6.11	Which drugs is the child taking? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Zidovudine (AZT or ZDV) 02 = Lamivudine (3TC) 03 = Emtricitabine (FTC) 04 = Abacavir (ABC) 05 = Stavudine (d4T) 06 = Tenofovir (TDF) 07 = Nevirapine (NVP) 08 = Efavirenz (EFV) 09 = Lopinavir/ritonavir (Kaletra/Alluvia) 10 = Atazanavir (ATZ) 11 = Ritonavir (RTV) 77 = Other (specify) 88 = Don't Know

SECTION 7: ANTHROPOMETRY

No	Question	Response	Codes and notation
4-7.1	Weight	|__|__|.|__|__| |__|__|.|__|__| |__|__|.|__|__|	Kilograms
4-7.2	Length	|__|__|__|.|__| |__|__|__|.|__| |__|__|__|.|__|	Centimetres
4-7.3	MUAC	|__|__|__| |__|__|__| |__|__|__|	mm
4-7.4	Head circumference	|__|__|.|__| |__|__|.|__| |__|__|.|__|	Centimetres
4-7.5	Oedema	|__|__|	00=None (-) 01=Mild, feet only (+) 02=Moderate, legs/arms (++) 03=Severe, including face (+++)
4-7.6	Was an adequate body composition assessment undertaken?	|__|__|	00 = No → **END FORM** 01 = Yes
4-7.7	Bodystat 1500MDD test number (first reading)	|__|__|__|	
4-7.8	Wellness index	|__|.|__|__|__|	Z50/Z5
4-7.9	Z5 (Impedance at 5kHz)	|__|__|__|	Ohms
4-7.10	Z50 (Impedance at 50kHz)	|__|__|__|	Ohms
4-7.11	R50 (Resistance at 50kHz)	|__|__|__|	Ohms
4-7.12	Xc50 (Reactance at 50kHz)	|__|__|	Ohms
4-7.13	PA50 (Phase angle at 50kHz)	|__|__|.|__|	Degrees

PID |__|__|__|__|__| Date of form |__|__|/|__|__|__|/|__|__|__|__| Start time |__|__|:|__|__| Staff initials _____

4-7.14	Bodystat 1500MDD test number (second reading)	|__|__|__|	
4-7.15	Wellness index	|__|.|__|__|__|	Z50/Z5
4-7.16	Z5 (Impedance at 5kHz)	|__|__|__|	Ohms
4-7.17	Z50 (Impedance at 50kHz)	|__|__|__|	Ohms
4-7.18	R50 (Resistance at 50kHz)	|__|__|__|	Ohms
4-7.19	Xc50 (Reactance at 50kHz)	|__|__|	Ohms
4-7.20	PA50 (Phase angle at 50kHz)	|__|__|.|__|	Degrees

Appendix F: Discharge form

Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM)
Discharge Form

SECTION 1: IDENTIFICATION

No.	Question	Response	Codes and notation
8-1.1	Participant ID (PID)	|__|__|__|__|__|	
8-1.2	Date of discharge	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy
8-1.3	Is the child being discharged against medical advice?	|__|__|	00=No 01=Yes 88=Don't know
8-1.4	Are you the main person who cares for the child each day?	|__|__|	00=No 01=Yes 88=Don't know
8-1.5	What is your relationship to the child?	|__|__|	01=Mother 02=Father 03=Sister 04=Brother 05=Grandmother 06=Grandfather 06=Aunt 07=Uncle 08=Family Friend 77=Other
8-1.6	Where is the child being discharged to?	|__|__| Other: _____	01 = Usual home 02 = Temporary home (rural) 03 = Temporary home (urban) 04 = Transfer to another hospital 05 = Children's Home 06 = Other (state) 88 = Don't know

SECTION 2: DISCHARGE ANTHROPOMETRY

No	Question	Response	Codes and notation
8-2.1	Weight at discharge	|__|__|.|__|__| |__|__|.|__|__| |__|__|.|__|__|	Kilograms
8-2.2	Length at discharge	|__|__|__|.|__| |__|__|__|.|__| |__|__|__|.|__|	Centimetres
8-2.3	MUAC at discharge	|__|__|__| |__|__|__| |__|__|__|	mm
8-2.4	Head circumference at discharge	|__|__|.|__| |__|__|.|__| |__|__|.|__|	Centimetres
8-2.5	Oedema at discharge	|__|__|	00=None (-) 01=Mild, feet only (+) 02=Moderate, legs/arms (++) 03=Severe, including face (+++)
8-2.6	Mid-thigh circumference at discharge	|__|__|.|__| |__|__|.|__| |__|__|.|__|	Centimetres Code 88.8 if not done
8-2.7	Leg length at discharge	|__|__|.|__| |__|__|.|__| |__|__|.|__|	Centimetres Code 88.8 if not done
8-2.8	Triceps skinfold thickness	|__|__|__| |__|__|__| |__|__|__|	mm Code 888 if not done
8-2.9	Subscapular skinfold thickness	|__|__|__| |__|__|__| |__|__|__|	mm Code 888 if not done

8-2.10	Supra-iliac skinfold thickness	|__|__|__| |__|__|__| |__|__|__|	mm Code 888 if not done
8-2.11	Was an adequate body composition assessment undertaken?	|__|__|	00 = No → **SKIP TO SECTION 3** 01 = Yes
8-2.12	Bodystat 1500MDD test number (first reading)	|__|__|__|	
8-2.13	Wellness index	|__|.|__|__|__|	Z50/Z5
8-2.14	Z5 (Impedance at 5kHz)	|__|__|__|	Ohms
8-2.15	Z50 (Impedance at 50kHz)	|__|__|__|	Ohms
8-2.16	R50 (Resistance at 50kHz)	|__|__|__|	Ohms
8-2.17	Xc50 (Reactance at 50kHz)	|__|__|	Ohms
8-2.18	PA50 (Phase angle at 50kHz)	|__|__|.|__|	Degrees
8-2.19	Bodystat 1500MDD test number (second reading)	|__|__|__|	
8-2.20	Wellness index	|__|.|__|__|__|	Z50/Z5
8-2.21	Z5 (Impedance at 5kHz)	|__|__|__|	Ohms
8-2.22	Z50 (Impedance at 50kHz)	|__|__|__|	Ohms
8-2.23	R50 (Resistance at 50kHz)	|__|__|__|	Ohms
8-2.24	Xc50 (Reactance at 50kHz)	|__|__|	Ohms
8-2.25	PA50 (Phase angle at 50kHz)	|__|__|.|__|	Degrees

SECTION 3: DISCHARGE MEDICATION

No.	Question	Response	Codes and notation
8-3.1	What antibiotics has the child been discharged with? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Amoxicillin 02 = Ampicillin 03 = Azithromycin 04 = Benzylpenicillin 05 = Cefotaxime 06 = Ceftriaxone 07 = Chloramphenicol 08 = Ciprofloxacin 09 = Clarithromycin 10 = Clindamycin 11 = Co-amoxiclav 12 = Cotrimoxazole 13 = Erythromycin 14 = Flucloxacillin / cloxacillin 15 = Gentamicin 16 = Imipenem 17 = Meropenem 18 = Metronidazole 19 = Nalidixic acid 20 = Nitrofurantoin 21 = Vancomycin 22 = Unknown injection 23 = Unknown oral antibiotic 77 = Other (specify) 88 = Don't Know / not recorded
8-3.2	What TB medicines has the child been discharged with? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Rifampicin 02 = Isoniazid 03 = Ethambutol 04 = Pyrazinamide 05 = Streptomycin

Appendix G: Doctor Follow up form

SECTION 1 – VITAL STATUS AND PROGRESS		
11-1.1	Follow up visit	☐ Week 2 ☐ Week 4 ☐ Week 12 ☐ Week 24 ☐ Week 48
11-1.2	Vital status	☐ Alive ☐ Died → **ALSO COMPLETE HOPE-SAM_Form_13_Death Form**
11-1.3	General clinical progress since last seen	☐ Stable ☐ Improving ☐ Deteriorating

SECTION 2 – CURRENT PROBLEM LIST

1. Dehydration |__|__|	2. Shock |__|__|	3. Hypothermia |__|__|	4. Fever |__|__|	5. Poor appetite |__|__|	6. Hypoglycaemia |__|__|
7. Eye signs |__|__|	8. Heart failure |__|__|	9. Oedema |__|__|	10. Acute diarrhoea |__|__|	11. Persistent diarrhoea |__|__|	12. Vomiting |__|__|
13. Respiratory distress |__|__|	14. Cough |__|__|	15. Sepsis |__|__|	16. Meningitis |__|__|	17. Measles in past 3mo |__|__|	18. Malaria |__|__|
19. Ear discharge |__|__|	20. HIV infected |__|__|	21. HIV exposed |__|__|	22. TB (inc suspected) |__|__|	23. Dermatosis |__|__|	24. Skin infection |__|__|
25. Oral thrush |__|__|	26. Cannula site infection |__|__|	27. UTI |__|__|	28. Abnormal electrolytes |__|__|	29. Cerebral palsy |__|__|	30. Seizures |__|__|
31. Other:	32. Other:	33. Other:	34. Other:	35. Other:	36. Other:

SECTION 3 – EXAMINATION (UNDERTAKEN AT TIME OF FORM COMPLETION) 00 = NO 01 = YES 88 = DON'T KNOW

1. Observations	A. Weight |__|__|.|__|__| kg	B. Respiratory rate |__|__|__| /min	C. Heart rate |__|__|__| /min	D. Temperature |__|__|.|__| °C	
2. General	A. Well |__|__|	B. Ill-looking |__|__|	C. Apathetic |__|__|	D. Irritable |__|__|	E. Lethargic |__|__|
	F. Some pallor |__|__|	G. Severe pallor |__|__|	H. Generalized LN |__|__|	I. Oral thrush |__|__|	J. Vitamin A eye signs |__|__|
	K. Dehydration |__|__|	L. Perineal damage |__|__|	M. Hair changes |__|__|	N. Oedema + |__|__|	O. Oedema ++ |__|__|
	P. Oedema +++ |__|__|	Q. Dermatosis + |__|__|	R. Dermatosis ++ |__|__|	S. Dermatosis +++ |__|__|	T. Other:
3. Adjuncts/support	A. Oxygen |__|__|	B. IV fluids |__|__|	C. Nasogastric tube |__|__|	D. Urinary catheter |__|__|	E. Other:
4. Cardiovascular	A. Normal heart sounds |__|__|	B. Murmur |__|__|	C. Gallop rhythm |__|__|	D. Distended jugular veins |__|__|	E. Cold hands/feet |__|__|
	F. Rapid/weak pulse |__|__|	G. Capillary refill |__| secs	H. Other:	I. Other:	J. Other:
5. Respiratory	A. Respiratory distress |__|__|	B. Wheeze |__|__|	C. Crepitations |__|__|	D. Bronchial breathing |__|__|	E. Central cyanosis |__|__|
6. Gastroenterology	A. Abdomen distended |__|__|	B. Absent bowel sounds |__|__|	C. Hepatomegaly |__|__|	D. Splenomegaly |__|__|	E. Jaundice |__|__|
7. Neurology and other:	A. Alert |__|__|	B. Responsive to voice |__|__|	C. Responsive to pain |__|__|	D. Unresponsive |__|__|	E. Neck stiffness |__|__|
	F. Bulging fontanelle |__|__|	G. Other:	H. Other:	I. Other:	J. Other:

PID \|__\|__\|__\|__\|__\| Date of form \|__\|__\|/\|__\|__\|__\|/\|__\|__\|__\|__\| Time started \|__\|__\|:\|__\|__\| Staff initials _____ 1

SECTION 4 – MORBIDITY RECALL

No.	Question	Response	Codes and notation
11-4.1	Has the child been admitted to hospital for at least one night since the last visit?	|__|__|	00 = No → **SKIP TO 11-4.14** 01 = Yes 88 = Don't know → **SKIP TO 11-4.14**
11-4.2	Date of admission 1 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known
11-4.3	Duration of admission 1	|__|__|	Days 88 = Don't know
11-4.4	Reason for admission 1 **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know

11-4.5	Date of admission 2 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known Code 99/999/9999 if NA
11-4.6	Duration of admission 2	|__|__|	Days 88 = Don't know 99 = NA
11-4.7	Reason for admission 2	|__|__| |__|__| |__|__| |__|__| Other: _____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.8	Date of admission 3 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known Code 99/999/9999 if NA
11-4.9	Duration of admission 3	|__|__|	Days

			88 = Don't know
11-4.10	Reason for admission 3	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.11	Date of admission 4 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known Code 99/999/9999 if NA
11-4.12	Duration of admission 4	|__|__|	Days 88 = Don't know
11-4.13	Reason for admission 4	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea

			07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.14	Has the child been taken to clinic/outpatients since the last visit (for non routine reasons)?	|__|__|	00 = No → **SKIP TO 11-4.23** 01 = Yes 88 = Don't know → **SKIP TO 11-4.23**
11-4.15	Date of clinic visit 1 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy
11-4.16	Reason for visit 1 **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache

			15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.17	Date of clinic visit 2 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known Code 99/999/9999 if NA
11-4.18	Reason for visit 2 **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.19	Date of clinic visit 3	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy

	Help caregiver to get best estimate		Code 88/888/8888 if not known Code 99/999/9999 if NA
11-4.20	Reason for visit 3 **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.21	Date of clinic visit 4 **Help caregiver to get best estimate**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known Code 99/999/9999 if NA
11-4.22	Reason for visit 4 **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea

			08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria 22 = Other (specify) 88 = Don't know
11-4.23	Has the child had a relapse of severe acute malnutrition (whether or not hospitalised)?	|__|__|	00 = No 01 = Yes 88 = Don't know
11-4.24	What is the child's HIV status?	|__|__|	00 = HIV-negative → **SKIP TO 11-4.31** 01 = HIV-positive 02 = HIV-exposed → **SKIP TO 11-4.27** 88 = Don't know → **SKIP TO 11-4.31**
11-4.25	Which WHO stage 3 illnesses has the child had since the last visit? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__|	00 = None 01 = Unexplained moderate malnutrition 02 = Unexplained persistent diarrhoea 03 = Unexplained persistent fever >1mo 04 = Persistent oral candidiasis 05 = Oral hairy leukoplakia 06 = Lymph node TB 07 = Pulmonary TB 08 = Severe recurrent bacterial pneumonia 09 = Acute necrotizing gingivitis or periodontitis 10 = Unexplained anaemia, neutropenia or thrombocytopenia 11 = Symptomatic LIP 12 = Chronic HIV lung disease, inc bronchiectasis

			88 = Not known
11-4.26	Which WHO stage 4 illnesses has the child had since the last visit? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__|	00 = None 01 = Unexplained severe wasting 02 = PCP pneumonia 03 = Recurrent severe bacterial infections 04 = Chronic herpes simplex 05 = Oesophageal candidiasis 06 = Extra-pulmonary TB 07 = Kaposi sarcoma 08 = CMV infection 09 = CNS toxoplasmosis 10 = HIV encephalopathy 11 = Cryptococcal disease 12 = Disseminated NTM infection 13 = PML 14 = Chronic cryptosporidiosis with diarrhoea 15 = Chronic isosporiasis 16 = Disseminated endemic mycosis 17 = Non-Hodgkin lymphoma 18 = HIV-associated Nephropathy or cardiomyopathy 88 = Not known
11-4.27	Is the child taking cotrimoxazole?	|__|__|	00 = No 01 = Yes 88 = Don't know
11-4.28	Is the child taking ART?	|__|__|	00 = No → **SKIP TO 11-4.31** 01 = Yes 88 = Don't know → **SKIP TO 11-4.31** 99 = NA → **SKIP TO 11-4.31**
11-4.29	When was ART started? **Check handheld notebook or provide best estimate if not known**	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy Code 88/888/8888 if not known
11-4.30	Which antiretroviral drugs is the child taking?	|__|__| |__|__| |__|__|	00 = None 01 = Zidovudine (AZT) 02 = Lamivudine (3TC)

	CODE ALL THAT APPLY	|__|__| Other:_____	03 = Emtricitabine (FTC) 04 = Abacavir (ABC) 05 = Stavudine (d4T) 06 = Tenofovir (TDF) 07 = Nevirapine (NVP) 08 = Efavirenz (EFV) 09 = Lopinavir/ritonavir (Kaletra or Alluvia) 10 = Atazanavir (ATZ) 11 = Ritonavir (RTV) 77 = Other 88 = Don't Know
11-4.31	Is the child on TB treatment?	|__|__|	00 = No → **SKIP TO 11-4.33** 01 = Yes 88 = Don't know → **SKIP TO 11-4.33**
11-4.32	Which TB drugs is the child taking?	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Rifampicin 02 = Isoniazid 03 = Ethambutol 04 = Pyrazinamide 05 = Streptomycin 06 = Drug-resistant TB regimen 77 = Other (specify) 88 = Don't Know
11-4.33	What antibiotics has the child received in the previous 2 weeks? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Amoxicillin 02 = Ampicillin 03 = Azithromycin 04 = Benzylpenicillin 05 = Cefotaxime 06 = Ceftriaxone 07 = Chloramphenicol 08 = Ciprofloxacin 09 = Clarithromycin 10 = Clindamycin 11 = Co-amoxiclav 12 = Cotrimoxazole 13 = Erythromycin

			14 = Flucloxacillin / cloxacillin 15 = Gentamicin 16 = Imipenem 17 = Meropenem 18 = Metronidazole 19 = Nalidixic acid 20 = Nitrofurantoin 21 = Vancomycin 22 = Unknown injection 23 = Unknown oral antibiotic 77 = Other (specify) 88 = Don't Know / not recorded
11-4.34	What other drugs has the child received in the previous 2 weeks? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Paracetamol 02 = Ibuprofen / other NSAID 03 = Zinc 04 = Vitamin A 05 = Multivitamins 06 = Pyridoxine 07 = Albendazole/mebendazole 08 = Praziquantel 09 = Antifungal 10 = Herbal medicine 11 = Antimalarial 12 = Ranitidine 13 = Omeprazole/lansoprazole (PPI) 14 = Prednisolone/other steroid 15 = Antihistamine 16 = Anticonvulsant 17 = Diuretics 18 = ACE inhibitor 19 = Potassium chloride 20 = Iron 21 = Folate 22 = Potassium permanganate 23 = Zinc oxide 77=Other (specify) 88=Don't know

SECTION 5 – SYMPTOM CHECK

No.	Question **I want you to think now about whether your child has any of the following problems in the past day or in the past 2 weeks.**	Response A	Response B
11-5.1	Fever/hot body?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.2	Cold hands and feet?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.3	Night sweats?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.4	Cough?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know

11-5.5	Fast or difficult breathing?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.6	Diarrhoea? (3 or more loose or watery stools in 24 hours)	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.7	If yes, how many days of diarrhoea has your child had in a row?	|__|__| **Help mother to estimate number of consecutive days of diarrhoea** **Try to discriminate between acute diarrhoea and persistent diarrhoea (>14 days)** **Code 99 if NA**	
11-5.8	How long ago did this diarrhoea problem first begin?	|__|__| amount of time |__|__| unit of time	**Unit of time:** 01=Hours 02=Days 03=Weeks 04=Months 05=Years 88 = Don't know 99/99=NA
11-5.9	Blood in the stools?	Does your child have this now? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know

11-5.10	Vomiting?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.11	Poor or reduced appetite?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.12	Weight loss (or poor weight gain)?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.13	Swelling of any part of their body?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.14	Convulsions / fits?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know

11-5.15	Drowsy or difficult to wake?	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.16	Has your child experienced any other symptoms during this illness?	|__|__|	00=No → **SKIP TO SECTION 6** 01=Yes 88=Don't Know → **SKIP TO SECTION 6**
11-5.17	Problem: |_____|	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know
11-5.18	Problem: |_____|	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know 99 = NA	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know 99 = NA
11-5.19	Problem: |_____|	Has your child had this in the past day? |__|__| 00 = No 01 = Yes 88 = Don't know 99 = NA	Has your child had this in the past 2 weeks? |__|__| 00 = No 01 = Yes 88 = Don't know 99 = NA

SECTION 6 – OTHER INFORMATION

No.	Question	Response
11-6.1	Record any other significant events since the child was last seen (e.g. death of caregiver, relocation or other social upheaval)	

SECTION 7: NEW DIAGNOSES AND MANAGEMENT

No.	Question	Response	Codes and notation
11-7.1	Does the child have moderate acute malnutrition currently? (MUAC <125mm, WHZ <-2)	|__|__|	00 = No 01 = Yes 88 = Don't know / unable to assess
11-7.2	Does the child have severe acute malnutrition currently? (MUAC <115mm, WHZ <-3, bilateral oedema)	|__|__|	00 = No → **SKIP TO 11-7.4** 01 = Yes 88 = Don't know / unable to assess → **SKIP TO 11-7.4**
11-7.3	Does the child have uncomplicated or complicated SAM?	|__|__|	01 = Uncomplicated 02 = Complicated 88 = Don't know / unable to assess
11-7.4	Does the child have any acute illness currently?	|__|__|	00 = No → **SKIP TO 11-7.6** 01 = Yes 88 = Don't know / unable to assess
11-7.5	Diagnosis	|__|__| |__|__| |__|__| Other:_____	01 = Respiratory tract infection / cough / difficult breathing 02 = Meningitis 03 = Sepsis 04 = UTI 05 = Fever, no cause found 06 = Acute diarrhoea 07 = Persistent diarrhoea 08 = Malnutrition / weight loss 09 = Difficulty feeding 10 = Vomiting 11 = Rash 12 = Anaemia 13 = Abdominal pain 14 = Headache 15 = Jaundice 16 = Sore mouth / ulcers / thrush 17 = Ear infection / discharge 18 = Surgical cause / foreign body / trauma 19 = Viral illness / upper respiratory tract infection / flu 20 = TB 21 = Malaria

			22 = Other (specify) 88 = Don't know
11-7.6	Were any antibiotics prescribed at this visit?	|__|__|	00 = No → **SKIP TO 11-7.7** 01 = Yes
11-7.7	Which antibiotics	|__|__| |__|__| |__|__| Other:_____	00 = None 01 = Amoxicillin 02 = Ampicillin 03 = Azithromycin 04 = Benzylpenicillin 05 = Cefotaxime 06 = Ceftriaxone 07 = Chloramphenicol 08 = Ciprofloxacin 09 = Clarithromycin 10 = Clindamycin 11 = Co-amoxiclav 12 = Cotrimoxazole 13 = Erythromycin 14 = Flucloxacillin / cloxacillin 15 = Gentamicin 16 = Imipenem 17 = Meropenem 18 = Metronidazole 19 = Nalidixic acid 20 = Nitrofurantoin 21 = Vancomycin 22 = Unknown injection 23 = Unknown oral antibiotic 77 = Other (specify) 88 = Don't Know / not recorded
11-7.8	Was any TB medicine prescribed at this visit?	|__|__|	00 = No → **SKIP TO 11-7.10** 01 = Yes
11-7.9	Which TB medicines?	|__|__| |__|__| |__|__| |__|__|	00 = None 01 = Rifampicin 02 = Isoniazid 03 = Ethambutol

		Other:_____	04 = Pyrazinamide 05 = Streptomycin 06 = Drug-resistant TB regimen 77 = Other (specify) 88 = Don't Know
11-7.10	Were any antiretroviral medicines prescribed at this visit?	|__|__|	00 = No → **SKIP TO 11-7.12** 01 = Yes
11-7.11	Which antiretrovirals? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Zidovudine (AZT) 02 = Lamivudine (3TC) 03 = Emtricitabine (FTC) 04 = Abacavir (ABC) 05 = Stavudine (d4T) 06 = Tenofovir (TDF) 07 = Nevirapine (NVP) 08 = Efavirenz (EFV) 09 = Lopinavir/ritonavir (Kaletra or Alluvia) 10 = Atazanavir (ATZ) 11 = Ritonavir (RTV) 77 = Other 88 = Don't Know
11-7.12	Were any other medicines prescribed at this visit?	|__|__|	00 = No → **SKIP TO 11-7.14** 01 = Yes
11-7.13	Which medicines? **CODE ALL THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	00 = None 01 = Paracetamol 02 = Ibuprofen / other NSAID 03 = Zinc 04 = Vitamin A 05 = Multivitamins 06 = Pyridoxine 07 = Albendazole/mebendazole 08 = Praziquantel 09 = Antifungal 10 = Herbal medicine 11 = Antimalarial 12 = Ranitidine

			13 = Omeprazole/lansoprazole (PPI) 14 = Prednisolone/other steroid 15 = Antihistamine 16 = Anticonvulsant 17 = Diuretics 18 = ACE inhibitor 19 = Potassium chloride 20 = Iron 21 = Folate 22 = Potassium permanganate 23 = Zinc oxide 77=Other (specify)
11-7.14	Were any nutritional supplements prescribed at this visit?	|__|__|	00 = No → **SKIP TO 11-7.17** 01 = Yes
11-7.15	Which supplements?	|__|__| Other:_____	01 = Plumpy'nut / RUTF 02 = High energy protein supplement (HEPS) 03 = Corn-soya blend 04 = Food supplements 05 = Other (specify) 88 = Don't know
11-7.16	How many days' supply were provided?	|__|__|	Number of days
11-7.17	Outcome	|__|__|	01 = Discharged home 02 = Referred to hospital

Appendix H: Nurse Follow up form

12.3-21	Any chicken, duck, or other birds (e.g. guinea foul)?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-22	Oil, fats (e.g. lard), or butter added to food or used for cooking?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-23	Any sugary foods such as pastries, cakes, chocolates, sweets or candies, sugary drinks such as fizzy drinks?	|__|__|	00=No 01=Yes 88 = Don't know

SECTION 3: FEEDING AND NUTRITION HISTORY

12-3.1	Is this child currently being breastfed?	|__|__|	00=No 01=Yes → **SKIP TO SECTION 12-3.4** 88 = Don't know → **SKIP TO SECTION 12-3.4**
12-3.2	How old was the child when he/she stopped breastfeeding?	|__|__|	Age in months 88 = Don't know
12-3.3	Why did you stop breastfeeding? **PROBE FOR ALL ANSWERS THAT APPLY**	|__|__| |__|__| |__|__| |__|__| Other:_____	01 = Mother ill/weak 02 = Baby ill/weak 03 = Nipple/breast problem 04 = Insufficient milk 05 = Mother working 06 = Baby refused 07 = Baby began biting 08 = Weaning age/age of stop 09 = Became pregnant 10 = Husband disapproved 11 = Other family member disapproved 12 = Concerned about infecting child with HIV 13= Baby living elsewhere 14=Mother died 77 = Other (specify) 88 = Don't know 99=N/A
12-3.4	Is this child currently receiving solid foods?	|__|__|	00=No 01=Yes 88 = Don't know
12-3.5	Has the child received any nutritional supplements since the last visit?	|__|__|	00=No → **SKIP TO SECTION 4**

			01=Yes 88 = Don't know → **SKIP TO SECTION 4**
12-3.6	What type? **CODE ALL THAT APPLY**	|__|__| |__|__| Other:_____	01 = Plumpy'nut / RUTF 02 = High energy protein supplement (HEPS) 03 = Corn-soya blend 04 = Food supplements 05 = Other (specify) 88 = Don't know
12-3.7	On how many days since the last visit did the child receive nutritional supplements? **CHECK IN HANDHELD NOTEBOOK OR HELP THE CAREGIVER TO ESTIMATE**	|__|__|	Number of days Code 88 if not known
12-3.8	Is the child still taking nutritional supplements now?	|__|__|	00=No 01=Yes 88 = Don't know
Have you or anyone else given your child any of the following foods between sunrise yesterday and sunrise today (i.e. the past 24 hours):			
12.3-9	Commercially produced infant formula?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-10	Dairy products e.g. yoghurt or milk other than breast milk, such as tinned, powdered, or fresh animal milk?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-11	Grains, roots and tubers, e.g .maize, potatoes, cassava?	|__|__|	00=No 01=Yes 88 = Don't know

12.3-12	Any sadza/nshima, bread, rice, noodles, or foods made from grains?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-13	Vitamin A rich fruits and vegetables e.g. mangoes, pawpaws, carrots or any vegetables that are yellow or orange inside such as pumpkin, carrots, squash, yams or sweet potatoes?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-14	Any dark-green leafy vegetables such as spinach or rape?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-15	Any other fruits?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-16	Any other vegetables?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-17	Any food made from cowpeas, beans, other peas, lentils, peanut butter or other food from nuts?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-18	Eggs?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-19	Fresh or dried fish (excluding small, dried fish such as kapenta/matemba)?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-20	Any beef, pork, lamb, goat, rabbit, game meat or any liver, kidney, heart, or other organ meats?	|__|__|	00=No 01=Yes 88 = Don't know

12.3-21	Any chicken, duck, or other birds (e.g. guinea foul)?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-22	Oil, fats (e.g. lard), or butter added to food or used for cooking?	|__|__|	00=No 01=Yes 88 = Don't know
12.3-23	Any sugary foods such as pastries, cakes, chocolates, sweets or candies, sugary drinks such as fizzy drinks?	|__|__|	00=No 01=Yes 88 = Don't know

SECTION 4: FOLLOW-UP INVESTIGATIONS

No.	Question	Response	Codes and notation
12-4.1	Has the child had blood samples collected? **Complete specimen transmittal form**	|__|__|	00 = No → **SKIP TO 12-4.4** 01 = Yes
12-4.2	Were any of the following clinical tests requested today? **CODE ALL THAT APPLY** **COMPLETE A CLINIC RESULTS FORM**	|__|__| |__|__| |__|__| |__|__| |__|__|	00 = None 01 = HIV DNA PCR 02 = HIV serology 03 = CD4 count 04 = Viral load 05 = Full blood count
12-4.3	Child HIV status **REQUEST HIV TEST IF STATUS UNKNOWN**	|__|__|	00 = HIV negative → **SKIP TO 12-4.11** 01 = HIV positive 02 = HIV-exposed → **SKIP TO 12-4.11** 03 = Unknown → **SKIP TO 12-4.11**
12-4.4	Has the child had a recent CD4 count? **CHECK HANDHELD NOTES**	|__|__|	00 = No → **SKIP TO 12-4.8** 01 = Yes 88 = Don't know / no result → **SKIP TO 12-4.8**
12-4.5	Date of CD4 count	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy
12-4.6	Absolute CD4 count	|__|__|__|__|	cells/uL
12-4.7	CD4 percentage	|__|__|.|__|	Percentage Code 99.9 if not done
12-4.8	Has the child had a recent viral load? **CHECK HANDHELD NOTES**	|__|__|	00 = No → **SKIP TO 12-4.11** 01 = Yes 88 = Don't know / not recorded → **SKIP TO 12-4.11**

12-4.9	Date of viral load	|__|__|/|__|__|__|/|__|__|__|__|	dd/mmm/yyyy
12-4.10	Viral load result	|__|__|__|__|__|__|__|	Copies/mL
12-4.11	Is the child in the enteropathy substudy?	|__|__|	00 = No → **SKIP TO SECTION 5** 01 = Yes
12-4.12	Has the child had a stool sample collected? **Complete specimen transmittal form**	|__|__|	00 = No 01 = Yes 99 = NA (not due this visit)
12-4.13	Has the child had a lactulose mannitol test done? **Complete LM test proforma**	|__|__|	00 = No 01 = Yes 99 = NA (not due this visit)

SECTION 5: FOLLOW-UP CHECKLIST

No.	Question	Response	Codes and notation
12-5.1	Has the old morbidity diary been reviewed and collected?	|__|__|	00 = No 01 = Yes
12-5.2	Have new morbidity diary and stickers been given?	|__|__|	00 = No 01 = Yes
12-5.3	Has a stool collection pack been given?	|__|__|	00 = No 01 = Yes 99 = NA (not needed next visit)
12-5.4	Has locator information (Form 9) been reviewed and updated?	|__|__|	00 = No 01 = Yes
12-5.5	Next visit type	☐ Week 2 ☐ Week 4 ☐ Week 12 ☐ Week 24 ☐ Week 48	
12-5.6	Date of next follow-up visit	|__|__|/|__|__|__|/|__|__|__|__|	DD/MMM/YYYY

Appendix I: Morbidity diary

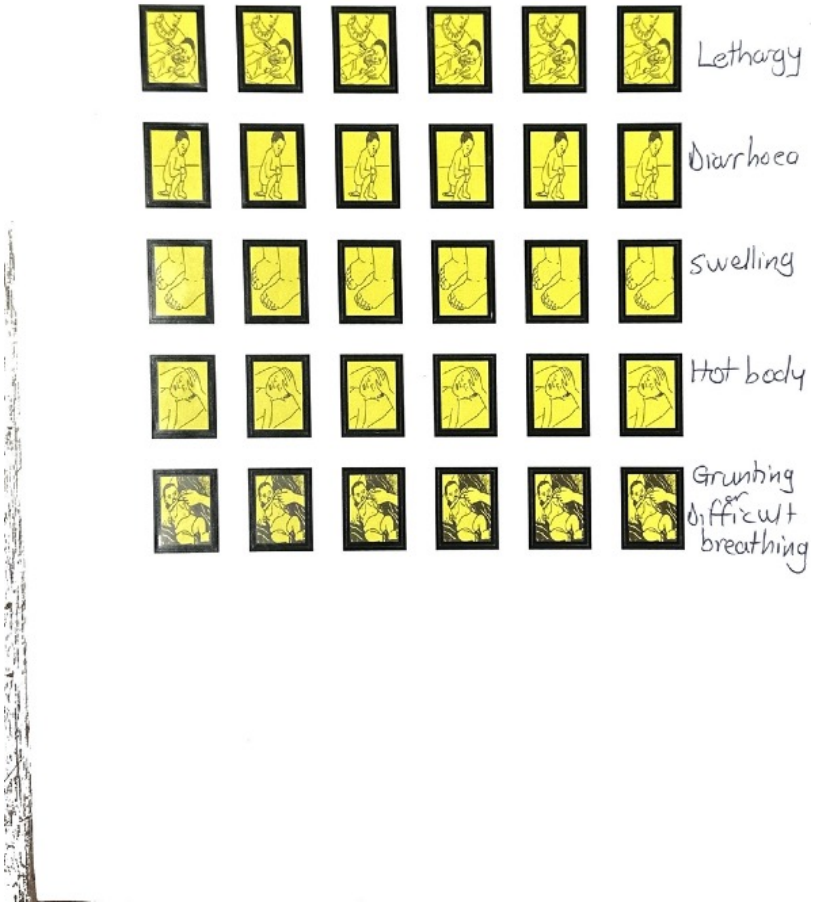
HOPE-SAM Form_10_Morbidity Diary, version 1.1, 7th May 2016

PID |__|__|__|__|__|__| **MONTH**……**YEAR**……

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
DATE	DATE	DATE	DATE	DATE	DATE	DATE
DATE	DATE	DATE	DATE	DATE	DATE	DATE
DATE	DATE	DATE	DATE	DATE	DATE	DATE
DATE	DATE	DATE	DATE	DATE	DATE	DATE
DATE	DATE	DATE	DATE	DATE	DATE	DATE

Date issued |__|__|/|__|__|__|/|__|__|__|__| Date collected |__|__|/|__|__|__|/|__|__|__|__| Date data entered |__|__|/|__|__|__|/|__|__|__|__|
Initials_____ Initials_____ Initials_____

Appendix J: Morbidity diary stickers



Appendix K: Co-authors Declaration

Declaration: Student's contribution to articles and agreement of co-authors

I, Mutsawashe Bwakura-Dangarembizi, student number 1636628 declare that the Thesis is my own work and that I contributed adequately towards research findings published in the articles stated below which are included in my Thesis.

Signature of Student: Date: 25 March 2023

Name of Primary Supervisor: Professor Andrew J. Prendergast

Signature of Primary Supervisor: Date: 25 March 2023

Agreement by co-authors

By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for her degree purposes.

Article 1

Risk factors for post discharge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia, The American Journal of Clinical Nutrition 2021;113 (3): 665–674

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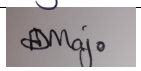
3rd author	B. Amadi		25/03/2023
4th author	D. Ngosa		25/03/2023
5th author	F. D. Majo		25/03/2023
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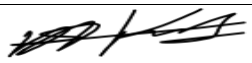
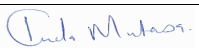
7th author	S Mwakamui		25/03/2023
8th author	K. Mutasa		25/03/2023
9th author	B. Chasekwa		25/03/2023
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12th author	A. J. Prendergast		25/03/2023

Comments by primary supervisor_____

Article 2

Recovery of children following hospitalisation for complicated severe acute malnutrition.

Matern Child Nutr. 2021 Dec 22:e13302. doi: 10.1111/mcn.13302.

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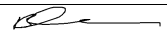
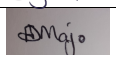
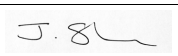
3rd author	B. Amadi		25/03/2023
4th author	B. Chasekwa		25/03/2023
5th author	D. Ngosa		25/03/2023
6th author	F. D. Majo		25/03/2023
7th author	J. P. Sturgeon		25/03/2023
8th author	K. Chandwe		25/03/2023
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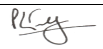
15th author	P. Kelly		25/03/2023
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Comments by primary supervisor:

_____

_____

Article 3

Fat and lean mass predict time to hospital readmission or mortality in children treated for complicated severe acute malnutrition in Zimbabwe and Zambia. *The British journal of nutrition*, 1–10. Advance online publication. https://doi.org/10.1017/S0007114522004056

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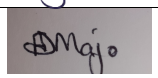
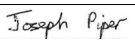
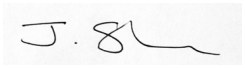
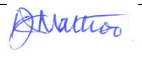
4th author	F. D. Majo		25/03/2023
5th author	J. D. Piper		25/03/2023
6th author	J. P. Sturgeon		25/03/2023
7th author	K. J. Nathoo		25/03/2023
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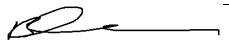
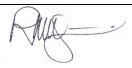
9th author	S. A. Norris		25/03/2023
10th author	C.D. Bourke		25/03/2023
11th author	B. Chasekwa		25/03/2023
12th author	R. Ntozini		25/03/2023

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Appendix L: Article 1 – Chapter 3

Original Research Communications

Risk factors for postdischarge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia

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ABSTRACT

Background: Children discharged from hospital following management of complicated severe acute malnutrition (SAM) have a high risk of mortality, especially HIV-positive children. Few studies have examined mortality in the antiretroviral therapy (ART) era.

Objectives: Our objectives were to ascertain 52-wk mortality in children discharged from hospital for management of complicated SAM, and to identify independent predictors of mortality.

Methods: A prospective cohort study was conducted in children enrolled from 3 hospitals in Zambia and Zimbabwe between July 2016 and March 2018. The primary outcome was mortality at 52 wk. Univariable and multivariable Cox regression models were used to identify independent risk factors for death, and to investigate whether HIV modifies these associations.

Results: Of 745 children, median age at enrolment was 17.4 mo (IQR: 12.8, 22.1 mo), 21.7% were HIV-positive, and 64.4% had edema. Seventy children (9.4%; 95% CI: 7.4, 11.7%) died and 26 exited during hospitalization; 649 were followed postdischarge. At discharge, 43.9% had ongoing SAM and only 50.8% of HIV-positive children were receiving ART. Vital status was ascertained for 604 (93.1%), of whom 55 (9.1%; 95% CI: 6.9, 11.7%) died at median 16.6 wk (IQR: 9.4, 21.9 wk). Overall, 20.0% (95% CI: 13.5, 27.9%) and 5.6% (95% CI: 3.8, 7.9%) of HIV-positive and HIV-negative children, respectively, died [adjusted hazard ratio (aHR): 3.83; 95% CI: 2.15, 6.82]. Additional independent risk factors for mortality were ongoing SAM (aHR: 2.28; 95% CI: 1.22, 4.25), cerebral palsy (aHR: 5.60; 95% CI: 2.72, 11.50) and nonedematous SAM (aHR: 2.23; 95% CI: 1.24, 4.01), with no evidence of interaction with HIV status.

Conclusions: HIV-positive children have an almost 4-fold higher mortality than HIV-negative children in the year following hospitalization for complicated SAM. A better understanding of causes of death, an improved continuum of care for HIV and SAM, and targeted interventions to improve convalescence are needed. *Am J Clin Nutr* 2021;00:1–10.

Keywords: mortality, postdischarge, severe acute malnutrition, HIV, ART, Africa

Introduction

Malnutrition underlies almost 50% of deaths in children aged <5 y (1). Severe acute malnutrition (SAM) is characterized by muscle wasting with or without edema and is classified into complicated and uncomplicated forms to guide clinical management. Children with a preserved appetite who are clinically well have uncomplicated SAM and are managed in the community. Those with poor appetite, severe edema, medical complications, or ≥1 integrated management of childhood illness danger signs (inability to drink, vomiting everything, convulsions, lethargic, or unconscious) have complicated SAM and are hospitalized (2). Despite standardized treatment guidelines (3), in-hospital mortality of children with complicated SAM in sub-Saharan Africa remains at 10–40% (4–6).

Children are discharged from hospital after resolution of complications and return of appetite to continue community-based nutritional rehabilitation. Emerging data suggest that there

Members of the HOPE-SAM study team are listed in the Acknowledgments section.

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Supplemental Tables 1–3 and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Data described in the manuscript, code book, and analytic code will be made available upon request.

Abbreviations used: aHR, adjusted hazard ratio; ART, antiretroviral therapy; HOPE-SAM, Health Outcomes, Pathogenesis, and Epidemiology of Severe Acute Malnutrition; MUAC, midupper arm circumference; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; TB, tuberculosis; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

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is high ongoing mortality risk following hospital discharge (7) and discharge from treatment programs (4). A recent systematic review reported mortality rates between 0.6% and 10.4%, 6–24 mo after discharge from community-based therapeutic feeding centers following nutritional rehabilitation for uncomplicated SAM (8). Some of these studies had high loss to follow-up, implying that actual mortality could be greater (9, 10). It is likely that children hospitalized for complicated SAM have poorer outcomes than those with uncomplicated SAM, but there were too few studies to differentiate mortality risk in these groups.

The ongoing risk of postdischarge mortality in children recovering from complicated SAM is likely due to incomplete nutritional and immune recovery, leading to an elevated risk of death from infections (11–13). In addition, children frequently return to a home environment characterized by poverty, poor water and sanitation, and inadequate health services, which are all recognized underlying determinants of child undernutrition (14). Another major factor underlying mortality in sub-Saharan Africa is concurrent HIV infection (15, 16). HIV has changed the epidemiology, clinical presentation, and pathophysiology of SAM (5), resulting in a 3-fold higher risk of death compared with HIV-negative children prior to the availability of antiretroviral therapy (ART) (5, 17, 18). It remains unclear whether this risk has changed since the introduction of 2013 WHO recommendations to treat all HIV-positive children regardless of clinical or immunological disease stage (19).

There is therefore an urgent need to ascertain risk factors for mortality after discharge from hospital with a view to providing additional support to those at highest risk and improving long-term outcomes. This study reports 1-y postdischarge mortality in children with complicated SAM and determines the risk factors for mortality. Our hypothesis was that children with HIV and SAM have higher mortality than children with SAM alone, despite availability of ART, and that biological and social risk factors predict postdischarge mortality.

Methods

Study design

Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM) was an observational cohort study in children hospitalized for complicated SAM at 3 urban tertiary referral hospitals in Zambia (University Teaching Hospital) and Zimbabwe (Harare Central and Parirenyatwa hospitals), between July 2016 and March 2019. These hospitals serve a catchment population of urban, periurban, and rural districts. The study design has previously been reported in detail (20). The main study outcomes were mortality, morbidity, and growth over 1 y of follow-up. The protocol, standard operating procedures, and case report forms are available at https://osf.io/29uaw/.

Study population

Caregivers were given information about the study, and children were enrolled as soon as possible after hospitalization. Eligible children were aged <60 mo and hospitalized with complicated SAM, which was defined as weight-for-height *z*-score (WHZ) <−3, midupper arm circumference (MUAC) <115 mm, or the presence of bilateral edema in children aged >6 mo; and WHZ <−3 or nutritional edema in those aged <6 mo, based on WHO criteria (2). Children who had malignancy, died prior to study enrolment, or whose caregiver was not willing to learn the child's HIV status were ineligible. Study participants hospitalized more than once during the study period were only enrolled during their first admission. The primary outcome was 1-y postdischarge mortality following the index hospitalization.

Study procedures and follow-up

Baseline clinical, demographic, household, and caregiver data were collected using a standardized case report form. Hospitals implemented country guidelines for provider-initiated counseling and testing for HIV for the caregiver and child; where HIV status was not confirmed in hospital, testing was undertaken by the study. HIV status for mothers and for children aged >18 mo was determined using a rapid antibody test algorithm, and for children <18 mo using HIV DNA PCR. Children were managed by the ward clinical teams and reviewed daily by a study physician during hospitalization to record data on clinical management and progress. Inpatient management of SAM and HIV, and discharge criteria following nutritional rehabilitation, followed WHO-adapted country guidelines (2, 21). Anthropometry was undertaken at baseline, discharge, and follow-up visits. Weight in infants was recorded to the nearest 10 g using an electronic scale (Seca 384) and in older children to the nearest 100 g using an electronic mother-baby scale (Seca 874); both scales were calibrated weekly. MUAC was measured using WHO/UNICEF color-coded tapes to the nearest 1 mm. Length (<2 y or those unable to stand) or height were measured using a UNICEF measuring board.

Children received ready-to-use therapeutic food (RUTF) after discharge in local clinics or hospital outpatient departments, according to country-specific guidelines on management of SAM. Hospital follow-up was conducted in dedicated study clinics at 2, 4, 12, 24, and 48 wk postdischarge, with window periods created around each visit to maximize follow-up. The original window period for the endline visit (44–52 wk) was subsequently extended to 72 wk to maximize follow-up. Mortality analysis was conducted through 52 wk postdischarge. Data were collected at each visit from caregiver interview and review of hand-held medical records where available. Illnesses identified at follow-up visits were managed by study doctors, with referral to hospital if needed. Follow-up phone calls were made to reschedule missed appointments, and home visits were undertaken for chronic defaulters where possible. Vital status was ascertained by telephone calls for those who had defaulted follow-up. All data were captured on paper case report forms and double-entered onto a custom-developed online database, with resolution of queries by study nurses and physicians.

Sample size

The observational cohort aimed to enrol ≤800 children with complicated SAM. We estimated that a mortality of 15% and overall loss to follow-up of 15% would provide 560 evaluable children at 1 y, of whom 224 would have HIV-SAM based on an estimated prevalence of 40% in hospitalized children (17). This would provide >80% power at 5% significance to detect absolute

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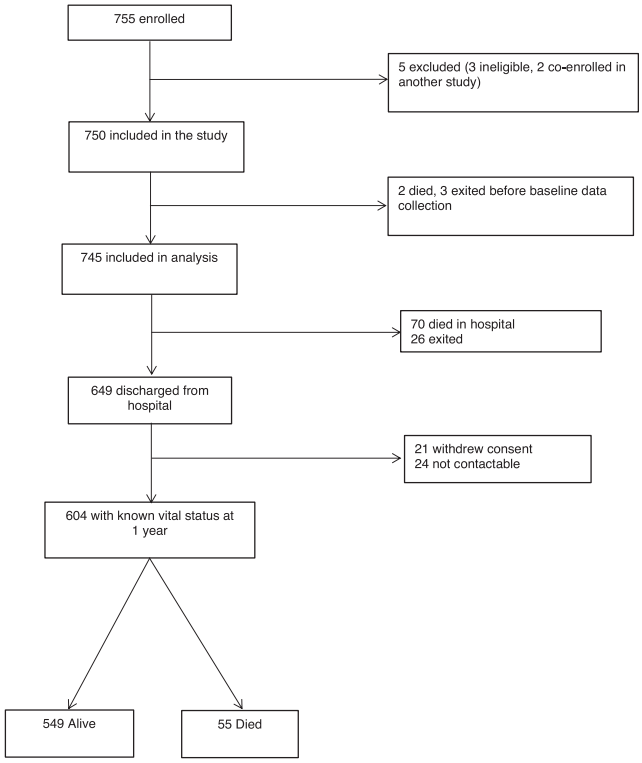

FIGURE 1 HOPE-SAM (Health Outcomes, Pathogenesis, and Epidemiology of Severe Acute Malnutrition) study flow.

differences of 17% in binary outcomes between HIV-positive and HIV-negative children with SAM, and of 0.33 SDs in continuous outcomes.

Statistical methods

A prespecified analysis plan is available at https://osf.io/29uaw/. Baseline variables were compared between HIV-positive and HIV-negative groups using χ^2 or Fisher exact tests for categorical variables and *t* tests for continuous variables. Anthropometric *z*-scores were calculated using 2006 WHO growth standards. Univariable and multivariable Cox regression models were used to explore associations between exposure variables and postdischarge mortality. The time at risk was calculated from hospital discharge to 52 wk, or the date last seen, reported alive, or the date of death. Selection of exposure variables was based on biological plausibility and the existing literature (20). All models included (regardless of statistical significance) the following a priori variables: age, sex, country, edema at admission, SAM at discharge, and HIV status. SAM at discharge was used as a composite variable because WHZ and MUAC showed collinearity (**Supplemental Figure 1**). Backwards elimination with exit P value = 0.1 was undertaken for other risk factors, to produce a final "main effects" model. All available data were included, and no variable was missing for >2.5% of the participants. We investigated and accounted for nonlinearity of effects of continuous predictors using multivariable fractional polynomials. We investigated interactions between each included risk factor and HIV status to ascertain whether HIV modifies the association between risk factors and mortality. Analyses were conducted using Stata version 14.0 (StataCorp).

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Ethical considerations

Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee, and the Medical Research Council of Zimbabwe. The ethics committee of Queen Mary University of London provided an advisory review. Primary caregivers gave written informed consent for each participant.

Results

Study enrolment

Seven hundred and fifty-five children hospitalized with SAM were enrolled between July 13, 2016 and March 31, 2018. Five children were subsequently excluded from analysis. Among the 750 eligible children, 2 died and 3 withdrew consent prior to baseline data collection (**Figure 1**). Of the 745 children included in the analyses, 37.3%, 32.3%, and 30.3% were from Harare Central Hospital, University Teaching Hospital, and Parirenyatwa Hospital, respectively.

Baseline characteristics

Table 1 shows the baseline characteristics of children with SAM, of whom one-fifth were HIV-positive. Of the HIV-negative children, 16.6% were HIV-exposed but uninfected. Just over half of children were male; median age was 17.4 mo (IQR: 12.8, 22.1 mo), with 2.7% aged <6 mo. Almost two-thirds of children had edematous malnutrition. Compared with HIV-negative children, HIV-positive children were significantly older, more wasted, more underweight, more stunted, and less likely to have edema (Table 1). A small proportion of children had chronic underlying conditions. Significantly more HIV-positive compared with HIV-negative children were taking tuberculosis (TB) medication at admission, and just over 40% of HIV-positive children were receiving ART.

Baseline caregiver and household characteristics are shown in **Supplemental Table 1**. Most children were cared for by their biological mothers. There was no difference in caregiver age by HIV status. Caregivers of HIV-positive compared with HIV-negative children were less likely to be married and had fewer years of formal education. Households of HIV-positive compared with HIV-negative children were more likely to be periurban, with poorer sanitation facilities. There were no other significant differences between groups.

Discharge characteristics

The median duration of hospitalization was 6 d (IQR: 2, 11 d). Seventy (9.4%; 95% CI: 7.4, 11.7%) children died in hospital, leading to an incident death rate of 5.4 (95% CI: 4.2, 6.8) per 100 child-weeks. Twenty-six children (3.4%) exited during hospitalization, meaning 649 children were followed up postdischarge (Figure 1). At discharge, anthropometry had improved compared with values at hospital admission for WHZ, weight-for-age *z*-score (WAZ), and MUAC; almost half of children had ongoing SAM at the time of discharge, as defined by WHO criteria (Table 1). There was a 4-fold increase in the number of children discharged on TB treatment compared with admission. Only half (50.8%) of the HIV-positive children were discharged on ART; another 48 (36.9%) started ART postdischarge, and 16 (12.3%) never started ART during follow-up.

Postdischarge mortality

Of the 649 children discharged from hospital, vital status was ascertained for 93.1% at 1 y (Figure 1). Baseline characteristics of children with and without available vital status were similar (**Supplemental Table 2**). The median follow-up time was 48.4 wk (IQR: 39.9, 50.9 wk). Of the 55 children known to have died, 32 (58.2%; 95% CI: 44.1, 71.3%) died in the community and 23 (41.8%; 95% CI: 28.7, 55.9%) during a subsequent hospital readmission. The median time to death was 16.6 wk (IQR: 9.4, 21.9) but there was evidence of high ongoing mortality risk throughout follow-up (**Figure 2**). The incident death rate decreased from 0.4 (95% CI: 0.2, 1.0) per 100 child-weeks during weeks 0–2 postdischarge, to 0.15 (95% CI: 0.1, 0.2) per 100 child-weeks during weeks 24–48 postdischarge.

Risk factors for mortality

Baseline characteristics of children who were alive at the end of follow-up and those who died are shown in **Supplemental Table 3**. Children who died were more wasted (mean WHZ = −3.4 compared with −2.1, $P < 0.001$; mean MUAC = 110 mm compared with 124 mm, $P < 0.001$), underweight (mean WAZ = −4.7 compared with −3.2, $P < 0.001$), and stunted [mean height-for-age *z*-score (HAZ) = −3.7 compared with −3.0, $P = 0.002$], and had been hospitalized longer than those who survived [median 16 d (IQR: 8, 21 d) compared with 12 d (IQR: 7, 14 d), $P = 0.002$]. In the final multivariable model, 4 factors were significant independent predictors of death: HIV, nonedematous malnutrition, SAM at discharge, and cerebral palsy (**Table 2**). HIV-positive compared with HIV-negative children had almost 4-fold higher mortality, with 20.0% (95% CI: 13.5, 27.9%) of HIV-positive children dying compared with 5.6% (95% CI: 3.8, 7.9%) of HIV-negative children [adjusted hazard ratio (aHR): 3.83; 95% CI: 2.15, 6.82] (**Figure 3**A). In HIV-positive children, mortality was not significantly different according to ART status at the time of discharge (HR: 1.09; 95% CI: 0.49, 2.45) (**Supplemental Figure 2**). Children with nonedematous compared with edematous SAM at admission to hospital had twice the mortality risk over the first year postdischarge (aHR: 2.23; 95% CI: 1.24, 4.01) (Figure 3B). Compared with children who did not still have SAM at the time of discharge, those with SAM had >2-fold higher postdischarge mortality (aHR: 2.28; 95% CI: 1.22, 4.25) (Figure 3C). Children with cerebral palsy had an almost 6-fold higher mortality than children without cerebral palsy (aHR: 5.60; 95% CI: 2.72, 11.50) (Figure 3D). Sex, age, duration of hospitalization, or primary caregiver and household characteristics were not associated with postdischarge mortality. There was no evidence of interaction between HIV status and SAM at discharge ($P = 0.33$), cerebral palsy ($P = 0.22$), or edema ($P = 0.19$) in the analyses of postdischarge mortality.

Discussion

Children hospitalized for complicated SAM have high inpatient mortality, but few studies have reported the ongoing

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TABLE 1 Characteristics of children at hospitalization and discharge[1]

	Admission				Discharge			
	All $n = 745$	HIV-positive $n = 162$	HIV-negative $n = 583$	P value[2]	All $n = 649$	HIV-positive $n = 130$	HIV-negative $n = 519$	P value[2]
Male	390/745 (52.4%)	82/162 (50.6%)	308/583 (52.8%)	0.62	344/649 (53.0%)	66/130 (50.8%)	278/519 (53.6%)	0.57
Median age, mo (IQR)	17.4 (12.8, 22.1)	19.3 (13.6, 24.1)	17.1 (12.7, 21.5)	0.002	18.2 (13.6, 22.6)	19.4 (14.3, 24.5)	17.3 (13.2, 21.9)	<0.001
1–5 mo	20/745 (2.7%)	4/162 (2.5%)	16/583 (2.7%)	0.07	17/649 (2.6%)	3/130 (2.3%)	14/519 (2.7%)	0.008
6–11 mo	131/745 (17.6%)	27/162 (16.7%)	104/583 (17.8%)		89/649 (13.7%)	13/130 (10.0%)	76/519 (14.6%)	
12–23 mo	458/745 (61.5%)	90/162 (55.6%)	368/583 (63.2%)		412/649 (63.5%)	74/130 (56.9%)	338/519 (65.2%)	
24–59 mo	136/745 (18.3%)	41/162 (25.3%)	95/583 (16.3%)		131/649 (20.2%)	40/130 (30.8%)	91/519 (17.5%)	
Type of SAM at hospitalization								
Edematous	480/745 (64.4%)	86/162 (53.1%)	394/583 (67.6%)	0.001	53/649 (8.2%)	8/130 (6.2%)	45/519 (8.6%)	0.35
Nonedematous	265/745 (35.6%)	76/162 (46.9%)	189/583 (32.4%)		596/649 (91.8%)	122/130 (93.8%)	474/519 (91.4%)	
Nutritional status at discharge								
SAM	N/A	N/A	N/A	N/A	285/649 (43.9%)	72/130 (55.4%)	213/519 (41.1%)	0.003
No SAM	N/A	N/A	N/A		364/649 (56.1%)	58/130 (44.6%)	306/519 (59.0%)	
Anthropometry								
WHZ, mean ± SD	−2.9 ± 1.8	−3.6 ± 1.8	−2.7 ± 1.8	<0.001	−2.2 ± 1.5	−2.4 ± 1.4	−2.1 ± 1.5	0.05
WAZ, mean ± SD	−3.8 ± 1.8	−4.4 ± 1.5	−3.6 ± 1.8	<0.001	−3.3 ± 1.6	−3.7 ± 1.2	−3.2 ± 1.7	0.002
HAZ, mean ± SD	−3.0 ± 1.6	−3.3 ± 1.3	−2.9 ± 1.6	0.005	−3.1 ± 1.5	−3.5 ± 1.2	−3.0 ± 1.6	0.003
MUAC, mm; mean ± SD	118 ± 17	110 ± 15	120 ± 17	<0.001	123 ± 16	117 ± 14	124 ± 16	<0.001
Chronic underlying conditions								
Cerebral palsy	32/745 (4.3%)	1/162 (0.6%)	31/583 (5.3%)	0.009	30/649 (4.6%)	1/130 (0.8%)	29/519 (5.6%)	0.02
Hydrocephalus	5/745 (0.7%)	0/162 (0.0%)	5/583 (0.9%)	0.24	3/649 (0.5%)	0/130 (0.0%)	3/519 (0.6%)	0.39
Congenital heart disease	14/745 (1.8%)	1/162 (0.6%)	13/583 (2.2%)	0.18	14/649 (2.1%)	1/130 (0.8%)	13/519 (2.5%)	0.22
Cleft palate	4/745 (0.5%)	0/162 (0.0%)	4/583 (0.7%)	0.29	3/649 (0.5%)	0/130 (0.0%)	3/519 (0.6%)	0.39
Medications								
TB medication	24/745 (3.2%)	13/162 (8.0%)	11/583 (1.9%)	<0.001	88/649 (13.6%)	40/130 (30.7%)	48/519 (9.2%)	<0.001
ART medication	N/A	66/162 (40.7%)	N/A	N/A	N/A	66/130 (50.8%)	N/A	N/A
Hemoglobin g/dL; median (IQR)[3]	N/A	N/A	N/A	N/A	9.3 (8.2, 10.3)	8.8 (7.7, 9.6)	9.4 (8.3, 10.4)	<0.001
Anemia[4]								
None (≥11 g/dL)	N/A	N/A	N/A	N/A	97/621 (15.6%)	13/123 (10.5%)	84/498 (16.9%)	0.02
Mild (10–10.9 g/dL)	N/A	N/A	N/A	N/A	102/621 (16.4%)	12/123 (9.8%)	90/498 (18.1%)	
Moderate (7–9.9 g/dL)	N/A	N/A	N/A	N/A	368/621 (59.3%)	84/123 (68.3%)	284/498 (57.0%)	
Severe (<7 g/dL)	N/A	N/A	N/A	N/A	54/621 (8.7%)	14/123 (11.4%)	40/498 (8.0%)	

[1] Data are *n*/total (column %) unless otherwise stated. ART, antiretroviral therapy; HAZ, height-for-age *z*-score; MUAC, midupper arm circumference; N/A: not applicable, SAM, severe acute malnutrition; TB: tuberculosis; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

[2] P value comparing HIV-positive and HIV-negative groups.

[3] Hemoglobin was measured at discharge; if no discharge hemoglobin measurement was available, the value closest to discharge was used.

[4] Anemia was defined according to WHO guidelines (2011).

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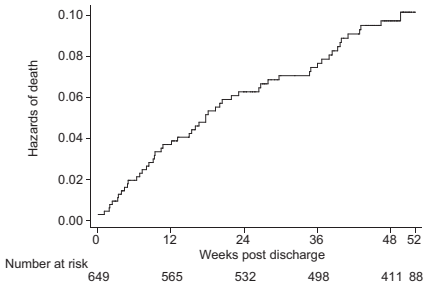

FIGURE 2 Hazard of death in children discharged after management of complicated severe acute malnutrition. Six hundred and forty-nine children were discharged from hospital, and 448 children attended their endline visit. The target date was 48 wk postdischarge, with an allowable visit window of 44–52 wk, which was subsequently extended to 72 wk to maximize follow-up. For those who did not attend their study visit, a phone call was made during the visit window to ascertain vital status from the primary caregiver. Children were censored as alive at their last contact. If they were seen after 52 wk ($n = 88$; 13.6%), they were censored for analysis at 52 wk. No child died after 52 wk. Twenty-four (3.7%) children were not contactable and were censored when last seen.

risk of death after hospital discharge. In this longitudinal study from a high HIV prevalence setting, we show that almost 1 in 10 children died in the year following discharge. Mortality was particularly high in HIV-positive children, who had an almost 4-fold higher risk of death than HIV-negative children, regardless of ART initiation. Although the incident death rate fell over time following discharge from hospital, the cumulative mortality was almost 10%, which was similar to inpatient mortality during the index admission. We identified 3 additional independent predictors of mortality: ongoing SAM at the time of discharge, nonedematous malnutrition, and underlying cerebral palsy. The high mortality shown here highlights the long period of vulnerability in children treated for SAM in hospital, particularly in those with HIV infection. Collectively, our data highlight the urgent need for additional interventions during convalescence to improve long-term outcomes of children with complicated SAM.

We specifically set out to stratify postdischarge mortality by HIV status, because studies conducted in the pre-ART era, or when ART initiation was guided by the degree of immunosuppression, reported higher mortality in HIV-positive compared with HIV-negative children with SAM (4, 22, 23). Our findings confirm that postdischarge mortality remains almost 4-fold higher in HIV-positive children, despite guidelines recommending ART when a diagnosis of HIV is made. Malnutrition and HIV interact in a vicious cycle driven by shared biological, immunological, and socioeconomic factors (24, 25). Malnutrition remains one of the commonest presentations of pediatric HIV infection (15, 26–28), with wasting being a risk factor for mortality even after initiation of ART (29). Chronic inflammation, particularly in children with concurrent HIV and SAM, likely contributes to wasting and has been associated with mortality and hospitalization (29, 30). HIV-positive children have greater nutritional needs than HIV-negative children. WHO recommends that calories should be increased by 10% for an asymptomatic HIV-positive child, by 20–30% with chronic illness, and by 50–100% with severe malnutrition, until weight is recovered (31). There are currently no guidelines regarding adjustment to therapeutic feeds for HIV-positive children to accommodate additional energy requirements, and this was not practiced in our study hospitals. There is uncertainty regarding the optimal timing of ART initiation in children with complicated SAM. Clinicians are often concerned about starting ART in sick children due to potential toxicity, immune reconstitution inflammatory syndrome, and poor adherence; however, early ART initiation is safe and feasible (32), and WHO recommends starting ART as soon as possible after stabilization (2). Despite these recommendations, it is striking that only half of HIV-positive children were on treatment at the time of discharge; in those not on ART, one-quarter never started during the subsequent year of follow-up. Mortality did not differ significantly between children who had started or not started ART at discharge. We therefore cannot determine whether inpatient ART initiation would have reduced mortality in this high-risk group, but clearly unnecessary delays arise from onward referral to HIV clinics for ART initiation. Maintaining a continuum of care from hospital discharge into a community-based model offering integrated HIV and nutrition care could improve the outcome of children with these highly interdependent conditions.

Mortality was >2-fold higher in children with SAM at the time of hospital discharge, compared with those who no longer met WHO criteria for SAM. Although most children had lost their edema at the time of discharge, 43.9% had SAM at discharge. Current WHO discharge recommendations from inpatient care are based on resolution of medical and metabolic complications with a view to continuing nutritional rehabilitation as outpatients (2). Data from this cohort confirm the ongoing mortality risk associated with incomplete nutritional recovery. Current treatment protocols do not address underlying causes of malnutrition such as household food insecurity, caregiver wellbeing, and suboptimal home environments. We found no associations between death and caregiver or household characteristics in this cohort, but this could reflect the limited range of variables we evaluated. Factors such as maternal mental health, caregiving capabilities, and access to healthcare were not evaluated. Nearly 60% of deaths in HOPE-SAM occurred in the community, similar to a Ugandan study of postdischarge mortality in children with acute infections (33). This could reflect the impoverished home environment and poor access to functional health systems. Several prior studies have reported that the highest risk of mortality occurs in the first 3 mo postdischarge (4, 34, 35). By contrast, our study showed that the risk of death remained consistent throughout the first year postdischarge. This suggests that if our follow-up period had been >1 y, mortality could have been higher, suggesting a much more protracted window of vulnerability than is generally recognized.

Consistent with several other studies (36, 16, 37–39), HIV-positive compared with HIV-negative children were less likely to have edematous SAM, suggesting that a degree of immune competence is required to generate edema. Nutritional edema is an acute condition, and children with moderate underlying deficits in weight and height but relatively well-preserved body fat appear to respond well to treatment in the absence

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TABLE 2 Univariable and multivariable analyses of factors associated with postdischarge mortality[1]

	Survived $n = 594$	Died $n = 55$	Unadjusted HR[2] (95% CI)	Adjusted HR[3] (95% CI)	P value[4]
Child characteristics					
Country					
Zimbabwe	420 (91.1%)	41 (8.9%)	Reference		
Zambia	174 (92.6%)	14 (7.4%)	0.94 (0.51, 1.72)	0.72 (0.39, 1.35)	0.31
Sex					
Female	275 (90.2%)	30 (9.8%)	Reference		
Male	319 (92.8%)	25 (7.2%)	1.37 (0.81, 2.33)	1.15 (0.67, 1.97)	0.62
Median age at discharge, mo (IQR)	18.4 (13.6, 22.7)	17.0 (10.1, 22.0)	0.97 (0.94, 1.01)	0.98 (0.94, 1.01)	0.17
HIV status					
HIV-negative	490 (94.4%)	29 (5.6%)	Reference		
HIV-positive	104 (80.0%)	26 (20.0%)	3.69 (2.17, 6.26)	3.83 (2.15, 6.82)	<0.001
Type of SAM at hospitalization					
Edematous	402 (95.3%)	20 (4.7%)	Reference		
Nonedematous	192 (84.6%)	35 (15.4%)	3.45 (1.99, 5.97)	2.23 (1.24, 4.01)	0.007
Nutritional status at discharge					
No SAM	349 (95.9%)	15 (4.1%)	Reference		
SAM	245 (85.9%)	40 (14.1%)	3.69 (2.04, 6.68)	2.28 (1.22, 4.25)	0.010
Chronic underlying conditions[5]					
No cerebral palsy	574/619 (92.7%)	45/619 (7.3%)	Reference		
Cerebral palsy[6]	20/30 (66.7%)	10/30 (33.3%)	5.12 (2.58, 10.16)	5.60 (2.72, 11.50)	<0.001

[1]Data are *n*/total (row %) unless otherwise stated. HAZ, height-for-age *z*-score; mfp, multiple fractional polynomial; MUAC, midupper arm circumference; SAM, severe acute malnutrition; TB, tuberculosis; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

[2]Unadjusted HRs were estimated using Cox regression analysis.

[3]Adjusted HRs were derived from a multivariable fractional polynomial model that contained all other variables in the table.

[4]*P* value from mfp Cox regression model.

[5]Children who had heart disease and cleft palate excluded due to small numbers.

[6]One child had both cerebral palsy and hydrocephalus.

The following variables were offered up to the backward stepwise regression model: site, country, residence, anemia, hemoglobin, sex, age at discharge, HIV status, WHZ at discharge, HAZ at discharge, WAZ at discharge, mean MUAC at discharge, edema at admission, edema at discharge, SAM at discharge, TB at discharge, cerebral palsy, duration of illness, duration of hospitalization, discharge against medical advice, primary caregiver, maternal age, maternal education, caregiver marital status, caregiver employment, water source, type of toilet, electricity, cooking location. The following variables were retained ($P < 0.1$) by the backward stepwise regression procedure: site, country, residence, age at discharge, edema at admission, HAZ at discharge, WAZ at discharge, hemoglobin, HIV status, cerebral palsy, primary caregiver, caregiver marital status, caregiver employment, cooking facilities. These variables were all offered to the final mfp model, except HAZ and WAZ at discharge, which were collinear with SAM at discharge. The table shows the variables that were either retained by the final mfp model at $P < 0.05$, or were forced into the model as a priori variables (age, sex, country, edema at admission, SAM at discharge, and HIV status).

of complications (40). Wasting, by contrast, is a more long-term process, and children without edema in our cohort had lower anthropometric *z*-scores. The underlying tissue loss and metabolic dysregulation could require a longer period of recovery, leading to an extended window of vulnerability. Cerebral palsy affected a minority of children but was associated with an almost 6-fold higher mortality; one-third of children with cerebral palsy died after discharge from hospital. Many children with cerebral palsy have inherent feeding difficulties and could require more targeted support following hospital discharge.

This is one of the largest longitudinal studies of children hospitalized for complicated SAM to date. We achieved a high ascertainment of vital status 1 y after discharge through cellphone contact and home visits in an extremely mobile population. We prespecified that we would stratify outcomes by HIV status, whereas many studies have not specifically ascertained HIV status in children with SAM (4, 35). Our study has limitations: in particular, we did not have data on several potential risk factors for mortality, including birth weight, gestational age, health-seeking behavior, adherence to RUTF, and coinfections. Where hemoglobin was not measured at the time of discharge, we used values measured closer to the time of admission. Severe anemia during hospitalization has been identified as a risk factor for postdischarge mortality in sub-Saharan Africa regardless of underlying malnutrition (41, 42); whereas most children in this cohort were anemic, <10% had severe anemia, which could have influenced our results. Lastly, our hospital study did not collect data on community-based nutritional rehabilitation postdischarge, which could have influenced mortality.

In summary, postdischarge mortality over 1 y following management of complicated SAM remains unacceptably high, and is similar to inpatient mortality. Overall, 1 in 5 children managed for complicated SAM died either in hospital or in the community. Mortality was almost 4-fold higher in HIV-positive compared with HIV-negative children. Thus, efforts to eliminate mother-to-child HIV transmission and identify HIV-positive infants early are critical to improving health outcomes. Furthermore, ART-naïve children with HIV and complicated SAM should start ART during hospitalization to avoid missing a window of opportunity, and be discharged to

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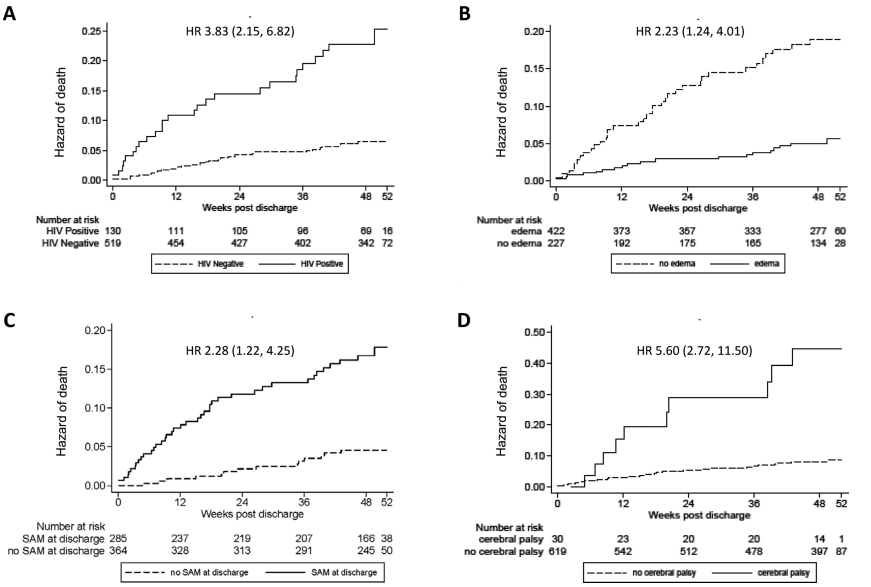

FIGURE 3 Risk factors for postdischarge mortality. Kaplan–Meier plots showing the hazard of postdischarge death associated with (A) HIV status, (B) edema at hospitalization, (C) ongoing severe acute malnutrition (SAM) at discharge, and (D) cerebral palsy. Adjusted HRs were derived from a multivariable Cox regression model.

a clearly defined and functional continuum of integrated care. ART alone appears insufficient to reduce the excess postdischarge mortality in HIV-positive children with SAM, and additional intervention strategies should be evaluated. Almost half the children in this study were discharged from hospital with ongoing SAM, and had twice the mortality risk compared with children who no longer met the criteria for SAM following inpatient nutritional rehabilitation. Ensuring that the necessary resources and services for outpatient care are available and accessible is important to bridge this period of vulnerability. We found that children in our setting with nonedematous SAM and with underlying cerebral palsy are particularly vulnerable and require more intensive follow-up. Further study into the causes of postdischarge death, and the caregiver and home environment, would inform a more comprehensive package of care to reduce the unacceptably high burden of postdischarge mortality in children with complicated SAM.

We thank all the caregivers and children who participated in the HOPE-SAM study.

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The authors' responsibilities were as follows—MB-D, BA, DN, FDM: recruited participants and collected data; MB-D, CD, BC, RN: analyzed data; SM, KM: conducted laboratory analyses; MB-D, CD, BA, KJN, BC, RN, PK, AJP: interpreted data; MB-D, AJP: wrote the first draft of the manuscript; MB-D, BA, KJN, PK, AJP: obtained funding; MB-D, BA, FDM, KJN, PK, AJP: performed study oversight; MB-D, BC, RN, AJP: had primary responsibility for final content; and all authors: revised the manuscript for intellectual content and read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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References

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–51.
2. World Health Organization. Guideline updates on the management of severe acute malnutrition in infants and children. Geneva: WHO; 2013.
3. Ashworth A, Khanum S, Jackson A, Schofield C. Guidelines for the treatment of severely malnourished children. Geneva, Switzerland: WHO; 2003.
4. Kerac M, Bunn J, George Chagaluka G, Bahwere P, Tomkins A, Collins S, Seal A. Follow-up of post-discharge growth and mortality after treatment for severe acute malnutrition (FuSAM study): a prospective cohort study. PLoS One 2014;9(6):e96030.
5. Heikens GT, Bunn J, Amadi A, Manary M, Chhagan M, Berkley JA, Rollins N, Kelly P, Maitland K, Tomkins A. Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence. Lancet 2008;371:1305–7.
6. Chinkhumba J, Tomkins A, Banda C, Mkangama C, Fergusson P. The impact of HIV on mortality during in-patient rehabilitation of severely malnourished children in Malawi. Trans R Soc Trop Med Hyg 2008;102(7):639–44.
7. Chisti MJ, Graham SM, Duke T, Ahmed T, Faruque ASG, Ashraf H, Kumar Bardhan PK, Shahid A, Shahunja KM, et al. Post-discharge mortality in children with severe malnutrition and pneumonia in Bangladesh. PLoS One 2014;9(9):e107663.
8. O'Sullivan NP, Lilijveld N, Rutishanser-Perera A, Kerac M, James P. Follow-up between 6 and 24 months after discharge from treatment for severe acute malnutrition in children aged 6–59 months: a systematic review. PLoS One 2018;13(8):e0202053.
9. Aprameya H, Kamath S, Kini P, Baliga B, Shenoy U, Jain A, Rao B. Socioepidemiological determinants of severe acute malnutrition and effectiveness of nutritional rehabilitation center in its management. Int J Health Allied Sci 2015;4(3):148–53.
10. Khanum S, Ashworth A, Huttly SR. Growth, morbidity, and mortality of children in Dhaka after treatment for severe malnutrition: a prospective study. Am J Clin Nutr 1998;67:940–5.
11. Bourke CD, Berkley JA, Prendergast AJ. Immune dysfunction as a cause and consequence of malnutrition. Trends Immunol 2016;37(6):386–9.
12. Jones KD, Thitiri J, Ngari M, Berkley JA. Childhood malnutrition: toward an understanding of infections, inflammation, and antimicrobials. Food Nutr Bull 2014;35(2Suppl):S64–70.
13. Rytter MJH, Kolte L, Briend A, Friis H, Christensen VB. The immune system in children with malnutrition—a systematic review. PLoS One 2014;9(8):e105017.
14. UNICEF. The state of the world's children. New York: UNICEF; 1998.
15. Chimhuya S, Kambarami RA, Mujuru H. The levels of malnutrition and risk factors for mortality at Harare Central Hospital-Zimbabwe: an observational study. Cent Afr J Med 2007;53:30–4.
16. Thurstans S, Kerac M, Maleta K, Banda T, Nesbitt A. HIV prevalence in severely malnourished children admitted to nutrition rehabilitation units in Malawi: geographical & seasonal variations a cross-sectional study. BMC Pediatr 2008;8:22.
17. Fergusson P, Tomkins A. HIV prevalence and mortality among children undergoing treatment for severe acute malnutrition in sub-Saharan Africa: a systematic review and meta-analysis. Trans R Soc Trop Med Hyg 2009;103(6):541–8.
18. Blaise Savadogo LG, Donnen P, Kouéta F, Kafando E, Hennart P, Dramaix M. Impact of HIV/AIDS on mortality and nutritional recovery among hospitalized severely malnourished children before starting antiretroviral treatment. Open J Pediatr 2013;3:340–5.
19. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, recommendations for a public health approach. Geneva, Switzerland: WHO; 2013.
20. Bwakura-Dangarembizi M, Amadi B, Bourke CD, Robertson RC, Mwapenya B, Chandwe K, Kapoma C, Chifunda K, Majo F, Ngosa D, et al. Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. BMJ Open 2019;9.
21. World Health Organization. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: WHO; 1999.
22. Fergusson P, Chinkhumba J, Grijalva-Eternod C, Banda T, Mkangama C, Tomkins A. Nutritional recovery in HIV-infected and HIV-uninfected children with severe acute malnutrition. Arch Dis Child 2009;94:512–6.
23. Moïsi JC, Gatakaa H, Berkley JA, Maitland K, Mturi N, Newton CR, Njuguna P, Nokes J, Ojal J, Bauni E, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. Bull World Health Org 2011;89:725–32A.
24. Jesson J, Leroy V. Challenges of malnutrition care among HIV-infected children on antiretroviral treatment in Africa. Med Mal Infect 2015;45:149–56.
25. Katona P, Katona-Apte J. The interaction between nutrition and infection. Clin Infect Dis 2008;46:1582–8.
26. Rogerson SR, Gladstone M, Callaghan M, Erhart L, Rogerson SJ, Borgstein E, Broadhead RL. HIV infection among paediatric in-patients in Blantyre, Malawi. Trans R Soc Trop Med Hyg 2004;98(9):544–52.
27. Nosek CA, Buck WC, Caviness AC, Foust A, Nyondo Y, Bottomani M, Kazembe PN. Hospital admissions from a pediatric HIV care and treatment program in Malawi. BMC Pediatrics 2016;16:22.
28. Sutcliffe CG, van Dijk JH, Munsanje B, Hamangaba F, Siniwymaanzi PTP, Moss WJ. Risk Factors for pre-treatment mortality among HIV-infected children in rural Zambia: a cohort study. PLoS One 2011;6(12):e29294.
29. Prendergast A, Bwakura-Dangarembizi MF, Cook AD, Bakeera-Kitaka S, Natukunda E, Nahirya Ntegee P, Nathoo KJ, Karungi C, Lutaakome J, Kekitiinwa A, et al. Hospitalization for severe malnutrition among HIV-infected children starting antiretroviral therapy. AIDS 2011;25:951–6.
30. Njunge JM, Gwela A, Kibinge NK, Ngari M, Nyamako L, Nyatichi E, Thitiri J, Gonzales GB, Bandsma RHJ, Walson JL, et al. Biomarkers of post-discharge mortality among children with complicated severe acute malnutrition. Sci Rep 2019;9:5981.
31. World Health Organization. Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 month-14 years) [Internet]. WHO; 2009. Available from: https://www.who.int/nutrition/publications/hivaids/9789241597524/en/.
32. Njuguna IN, Cranmer LM, Otieno VO, Mugo C, Okinyi HM, Benki-Nugent S, Richardson B, Stern J, Maleche-Obimbo E, Wamalwa DC, et al. Urgent versus post-stabilisation antiretroviral treatment in hospitalised HIV-infected children in Kenya (PUSH): a randomised controlled trial. Lancet HIV 2018;5:e12–22.
33. Wiens MO, Kumbakumba E, Larson CP, Ansermino JM, Singer J, Kissoon N, Wong H, Ndamira A, Kabakyenga J, Kiwanuka, et al. Postdischarge mortality in children with acute infectious diseases: derivation of postdischarge mortality prediction models. BMJ Open 2015;5(11):e009449.
34. Veirum JE, Sodeman M, Biai S, Hedegard K, Aaby P. Increased mortality in the year following discharge from a paediatric ward in Bissau, Guinea-Bissau. Acta Paediatr 2007;96:1832–8.
35. Chhibber AV, Hill PC, Jafali J, Jasseh M, Hossain MI, Ndiaye M, Pathirana JC, Greenwood B, Mackenzie GA. Child mortality after discharge from a health facility following suspected pneumonia, meningitis or septicaemia in rural Gambia: a cohort study. PLoS One 2015;10(9):e0137095.
36. Kessler L, Daley H, Malenga G, Graham S. The impact of HIV infection on the clinical presentation of severe malnutrition in children at QECH. Malawi Med J 2001;13(3):30–3.
37. Prazuck T, Tall F, Nacro B, Rochereau A, Traore A, Sanou T, Malkin JE, Apaire-Marchais V, Masson D, Dublanchet A, et al. HIV infection and severe malnutrition: a clinical and epidemiological study in Burkina Faso. AIDS 1993;7(1):103–8.
38. Asafo-Agyei SB, Antwi S, Nguah SB. HIV infection in severely malnourished children in Kumasi, Ghana: a cross-sectional prospective study. BMC Pediatr 2013;13:181.

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39. Mgone CS, Mhalu FS, Shao JF, Britton S, Sandström A, Bredberg-Råden U, Biberfeld G. Prevalence of HIV-1 infection and symptomatology of AIDS in severely malnourished children in Dar es Salaam, Tanzania. J Acquir Immune Defic Syndr 1991;4(9):910–3.
40. Waterlow JC. Protein-energy malnutrition. Smith-Gordon; 2006.
41. Phiri KS, Calis JCJ, Faragher B, Nkhoma E, Ng'oma K, Mangochi B, Molyneux ME, van Hensbroek MB. Long term outcome of severe anaemia in Malawian children. PLoS One 2008;3(8):e2903.
42. Lackritz EM, Campbell CC, Ruebush TK, Hightower AW, Wakube W, Were JBO. Effect of blood transfusion on survival among children in a Kenyan hospital. Lancet 1992;340:524–8.

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Appendix M: Article 2 – Chapter 4

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ORIGINAL ARTICLE

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Recovery of children following hospitalisation for complicated severe acute malnutrition

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Abstract

Nutritional recovery and hospital readmission following inpatient management of complicated severe acute malnutrition (SAM) are poorly characterised. We aimed to ascertain patterns and factors associated with hospital readmission, nutritional recovery and morbidity, in children discharged from hospital following management of complicated SAM in Zambia and Zimbabwe over 52-weeks posthospitalization. Multivariable Fine-Gray subdistribution hazard models, with death and loss to follow-up as competing risks, were used to identify factors associated with hospital readmission; negative binomial regression to assess time to hospitalisation and ordinal logistic regression to model factors associated with nutritional recovery. A total of 649 children (53% male, median age 18.2 months) were discharged to continue community nutritional rehabilitation. All-cause hospital readmission was 15.4% (95% CI 12.7, 18.6) over 52 weeks. Independent risk factors for time to readmission were cerebral palsy (adjusted subhazard ratio (aSHR): 2.96, 95% CI 1.56, 5.61) and nonoedematous SAM (aSHR: 1.64, 95%CI 1.03, 2.64). Unit increases in height-for-age Z-score (HAZ) (aSHR: 0.82, 95% CI 0.71, 0.95) and enrolment in Zambia (aSHR: 0.52, 95% CI 0.28, 0.97) were associated with reduced subhazard of time to readmission. Young age, SAM at discharge, nonoedematous SAM and cerebral palsy were associated with poor nutritional recovery throughout follow-up. Collectively, nonoedematous SAM, ongoing SAM at discharge, cerebral palsy and low HAZ are independent risk factors for readmission and poor nutritional recovery following complicated SAM. Children with these high-risk features should be prioritised for additional convalescent care to improve long-term outcomes.

KEYWORDS

HIV, morbidity, nutritional recovery, readmission, severe acute malnutrition

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1 | INTRODUCTION

Severe acute malnutrition (SAM) is defined by the presence of bilateral nutritional oedema, severe wasting (weight for height Z-score (WHZ) <−3), and/or mid-upper arm circumference (MUAC) <115 mm, and is associated with a high risk of death, mainly from infections (Rytter et al., 2014). An estimated 16.4 million children below 5 years of age were affected by SAM globally in 2017 (World Bank, World Health Organisation & United Nations Children's Fund, 2018). The vicious cycle of malnutrition and infection is well recognised, and often leads to clinical complications (Katona & Katona-Apte, 2008; Rytter et al., 2014). Complicated SAM, which is characterised by clinical instability and lack of appetite, is managed in inpatient facilities where medical complications and acute infections are treated (World Health Organisation, 2013). The goals of managing SAM are to prevent short-term morbidity and mortality, achieve sustained nutritional recovery, and support long-term neurocognitive development (Bhutta et al., 2017). Discharge from hospital to continue outpatient therapeutic feeding is based on return of appetite and resolution of medical complications rather than improvements in anthropometry. Subsequent discharge from outpatient treatment programmes occurs when there is adequate nutritional recovery (defined as WHZ > −2, or MUAC > 125 mm and/or resolution of oedema for 2 weeks) (World Health Organisation, 2013).

Following discharge from in-patient treatment for complicated SAM, children have persistent vulnerabilities, leading to an ongoing high mortality risk (Lenters et al., 2013). Contributing factors include immune impairment, chronic infections such as tuberculosis (TB) and HIV, and a return to the same poor social environment (Ngari et al., 2018). Data from the Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM) cohort in Zimbabwe and Zambia showed that 43.9% of children had ongoing SAM (by WHO criteria) at the time of discharge from hospital and these children had more than twofold increased risk of dying in the first year postdischarge, compared to children who had anthropometric recovery at discharge. Children with HIV infection had threefold higher mortality than children with SAM alone, and this mortality risk persisted despite antiretroviral therapy (ART). Nonoedematous SAM and cerebral palsy were additional risk factors for postdischarge mortality in this cohort (Bwakura-Dangarembizi et al., 2021).

Achieving good short-term and long-term health outcomes after treatment of SAM is challenging, especially in poorly resourced settings with fragile health systems (Khanum et al., 1998; Stobaugh, Rogers, et al., 2018; Wiens et al., 2013). Few studies have systematically mapped patterns of nutritional recovery and morbidity after discharge from hospital following management of complicated SAM. Understanding the factors associated with nutritional recovery and hospital readmission would help identify the most vulnerable children at the time of discharge and may inform additional interventions to improve outcomes. Here, we present further data from the HOPE-SAM cohort, in which children were followed for 1 year after hospital discharge following management of complicated SAM. Our hypotheses were, first, that HIV-positive compared to HIV-negative children with SAM have earlier and more frequent hospital readmissions, more illness episodes and poorer nutritional recovery, despite the availability of ART and, second, that a combination of biological and social risk factors predict readmission and nutritional recovery.

Key messages

- One-in-six children managed for SAM were readmitted into hospital over the first year after discharge and one-in-eight remained undernourished by 52 weeks of follow-up.
- Nonoedematous SAM, ongoing SAM at the time of discharge and underlying cerebral palsy were independent risk factors for hospital readmission and poor nutritional recovery.
- Low HAZ was a risk factor for hospital readmission and poor nutritional recovery.
- Postdischarge care should focus on children with disability, nonoedematous SAM at initial hospitalisation and have ongoing SAM at the time of discharge.
- Stunting should be considered in the management of children with SAM.

2 | METHODS

2.1 | Study design

HOPE-SAM was an observational cohort study that enroled children under 5 years of age hospitalised for complicated SAM at three tertiary referral hospitals in Lusaka, Zambia and Harare, Zimbabwe between August 2016 and March 2018 (Bwakura-Dangarembizi et al., 2019). The protocol, standard operating procedures and case report forms (CRFs) are available at https://osf.io/29uaw/. Here, we report readmissions, morbidity and nutritional recovery over the first-year postdischarge and factors associated with these outcomes.

2.2 | Study population

Eligible children were aged below 60 months, admitted at three tertiary hospitals in the two countries with SAM, defined as WHZ <−3, MUAC < 115 mm and/or the presence of nutritional oedema in children above 6 months of age (and WHZ <−3 or nutritional oedema in those below 6 months) (World Health Organisation, 2013). Primary caregivers gave written informed consent for their children to participate in the study.

2.3 | Study procedures and follow-up

Study procedures have been previously described (Bwakura-Dangarembizi et al., 2019). We used standardised CRFs to collect

baseline clinical, demographic, household and caregiver data. Child HIV status was determined using rapid antibody or DNA polymerase chain reaction (PCR) testing according to age. Inpatient care was provided by the ward clinical teams according to WHO-adapted country-specific guidelines for the management of complicated SAM. A study physician reviewed participants daily during hospitalisation to document progress. Discharge was based on clinical recovery (World Health Organisation, 1999, 2013).

Postdischarge care was provided outside of the study and followed WHO-adapted country-specific guidelines. Caregivers were given a supply of ready-to-use therapeutic food (RUTF) (usually 2 weeks, depending on availability) and counselled on how to feed the child. RUTF was dispensed until children achieved moderate acute malnutrition (MAM) status on anthropometry; however, in Zimbabwe, there were frequent stock-outs of RUTF in the urban and peri-urban areas. In Zimbabwe, once children attained MAM status, RUTF was stopped and no supplementary food was available; caregivers were counselled on using locally available food. In Zambia, children with MAM received High Energy Protein Supplement (HEPS) or Corn Soya Blend and the caregiver was counselled on how to prepare HEPS porridge and the appropriate frequency of feeds, in addition to nutritional counselling on 'what to give, how much and how often' according to the Supplementary Feeding Programme for moderately malnourished children.

Children were seen in a dedicated study clinic at 2, 4, 12, 24 and 48 weeks postdischarge, with window periods around each timepoint. Endline visits, therefore, occurred at a median of 49.3 (48.1, 51.4) weeks postdischarge, with 21.3% of attending children seen by 48 weeks and 84.2% of children seen by 52 weeks. Endline visits for all analyses were censored at 52 weeks.

Anthropometric measurements were undertaken using standardised methods at study enrolment, hospital discharge and at each of five scheduled follow-up visits. Nutritional status was classified as adequately nourished (WHZ ≥ −2 and/or MUAC ≥ 125 mm), MAM (WHZ between -2 and −3 and/or MUAC of 115–124 mm) and SAM (WHZ <−3 or MUAC < 115 mm, or bilateral nutritional oedema) (World Health Organisation, G. 2013). If WHZ score and MUAC classified children differently, the lower nutritional category was used. Morbidity was assessed by all-cause readmission into hospital and caregiver-reported symptoms in the previous 2 weeks at each study visit. Details of the clinic and hospital visits were verified during study visits from caregivers' hand-held child health cards. RUTF and ART were provided from government clinics and admitting hospitals. Referrals were made from the study clinic for hospital readmission when indicated. When a child failed to attend the study clinic for their scheduled visit, phone calls were made to reschedule the visit; children missing multiple study visits were visited at home where possible.

2.4 | Sample size

We aimed to enrol a minimum of 600 and a maximum of 800 children with complicated SAM. We estimated that mortality of 15% and overall loss to follow-up of 15% would provide 560 evaluable children at 1 year, of whom 224 would have HIV-SAM based on an estimated prevalence of 40% in hospitalised children. This would provide >80% power to detect absolute differences of 17% in binary outcomes between HIV-positive children and HIV-negative children with SAM, and of 0.33 standard deviations in continuous outcomes.

2.5 | Statistical methods

A pre-specified analysis plan is available at https://osf.io/29uaw/. Data collected onto paper CRFs were double-entered onto the study database. Anthropometric Z-scores were calculated using 2006 WHO growth standards. Baseline variables were compared between HIV-positive and HIV-negative children using χ^2 or Fisher's exact tests for categorical variables, and *t* tests or Mann–Whitney tests for continuous variables, depending on distributions. Morbidity, readmission and nutritional recovery analyses were conducted 52 weeks postdischarge. Analyses were conducted using STATA version 14.0 (StataCorp.).

2.5.1 | Time to first hospital readmission

Fine-Gray subdistribution hazard models were used to estimate the hazard ratios for hospital readmission, with death and loss to follow-up as competing risks. We also ran a Cox proportional hazards model, assuming no competing risks, as a sensitivity analysis. Cumulative incidence curves were used to describe the time to first hospital readmission. The selection of exposure variables was based on biological plausibility. The full list of variables is provided in Supporting Informations. Strength of association with time to first hospital readmission was initially assessed using univariable analyses. Variables significant at $p < 0.25$ were included in a multivariable competing risks regression model together with a set of pre-specified variables that were forced to remain in the model: age, sex, country, oedema on admission, SAM at discharge, cerebral palsy and HIV status. Variables with $p < 0.05$ in the final model were deemed associated factors.

2.5.2 | The incident rate of hospital readmissions

Negative binomial regression models which account for overdispersion were used to estimate the incidence rate of readmissions. Risk factors for readmission were identified using the same approach as for the time to first hospital readmission.

2.5.3 | Morbidity analysis

The following morbidity outcomes were assessed at each study visit by caregiver recall: fever, diarrhoea, respiratory symptoms (defined as

cough or difficult breathing), poor appetite and weight loss. The period prevalence of illness episodes was estimated as the proportion of children with any caregiver-reported symptom in the 2 weeks preceding each visit, stratified by HIV status.

2.5.4 | Nutritional recovery

Nutritional status was assessed at five-time points postdischarge using regression models with WHZ and MUAC as outcomes. Ordinal logistic regression was also used to identify factors associated with nutritional recovery, defined as moving from a lower to a higher nutritional category (i.e., from SAM to either MAM or adequately nourished and from MAM to adequately nourished). Exposure variables were chosen in the same way as those for hospitalisation.

2.6 | Ethical considerations

Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee, and the Medical Research Council of Zimbabwe. The ethics committee of the Queen Mary University of London provided an advisory review.

3 | RESULTS

3.1 | Study enrolment

A total of 755 children with SAM were enroled between 13 July 2016 and 31 March 2018; Figure S1 summarises their enrolment and follow-up. Five children were excluded due to co-enrolment in other studies or ineligibility. Among 750 eligible children, two died and three withdrew consent before baseline data collection, leaving 745 children in the study. Seventy children died during their initial hospitalisation and 26 exited the study before discharge, leaving 649 children who were discharged from the hospital and included in these analyses. Fifty-five children died and 21 withdrew consent during postdischarge follow-up. Postdischarge follow-up at each scheduled study visit ranged between 72.8% and 78.2% (Figure S1).

3.2 | Discharge characteristics

Child, caregiver and household characteristics are shown in Table 1. The median age of children at discharge from the hospital was 18.2 months (IQR: 13.6, 22.6), with 53% males; 20% of children were HIV-positive. Sixty-five percent of children had oedematous malnutrition on admission to hospital and 78% were stunted (HAZ <−2). HIV-positive compared to HIV-negative children were significantly older, more wasted, underweight and stunted and more likely to have had previous SAM or persistent diarrhoea; they were also hospitalised for longer, were more anaemic and were more likely to be discharged on TB medication (Table 1). Only 25% of the cohort were breastfeeding at the time of hospital discharge; 31.4% had stopped before 12 months of age (at median 8 months; IQR: 6, 9). Nearly all (93.2%) children were cared for by their biological mother, who had median of 11 years of education (IQR: 10, 11). Seventy-one (10.9%) children discharged from hospital never attended a subsequent follow-up visit; these children had significantly younger mothers than those attending at least one follow-up visit (median 23 vs. 27 years, $p < 0.001$) and were less likely to be on TB medication (5.6% vs. 14.5%, $p = 0.04$) but were otherwise similar to the follow-up cohort (Table S1).

3.3 | Rates of hospital readmission

Table S2 shows the unadjusted and adjusted incident rate ratios for hospital readmission for each explanatory variable. Among the 89 children who were readmitted to the hospital, 25 (28.1%) were admitted more than once and 13/89 (14.6%) died. We found two factors to be independently associated with readmission incidence: nonoedematous SAM and HAZ. Children with nonoedematous SAM had a 65% increased readmission rate compared to those with oedematous SAM (aIRR: 1.65, 95% CI: 1.05, 2.61). Better linear growth was associated with a lower rate of readmission: for every unit increase in HAZ there was a 19% lower rate of hospital readmission (aIRR: 0.81, 95% CI: 0.71, 0.94). There was some evidence of lower readmission rate for children in Zambia versus Zimbabwe (aIRR: 0.62, 95% CI: 0.37, 1.05) and higher readmission rate among children with cerebral palsy (aIRR: 2.02, 95% CI: 0.89, 4.59). No other factors predicted hospital readmission rate.

3.4 | Time to first hospitalisation

Of the 649 children discharged from the hospital, data on readmission were available for 578 (89%). Of these, 89 (15.4%; 95% CI: 12.7, 18.6) were readmitted through Week 52, with 52.8% of admissions occurring in the first 12 weeks after discharge (Figure 1a). Time to readmission did not differ significantly between HIV-positive and HIV-negative children (Figure 1b). We found four factors that were independently associated with time to first hospital readmission, using both the Fine-Gray hazard model which accounted for death and loss to follow up as competing risks and the Cox proportional hazards model (Table 2). Nonoedematous compared to oedematous SAM was associated with a 64% increased subhazard of readmission (aSHR: 1.64, 95% CI: 1.03, 2.64; Figure 1c). Unit increases in HAZ were associated with an 18% lower subhazard of readmission (aSHR: 0.82, 95% CI: 0.71, 0.95); this association remained even after adjusting for WHZ (data not shown). Children with cerebral palsy were three times more likely to be readmitted (aSHR: 2.96, 95% CI: 1.56, 5.61; Figure 1d). Finally, there was evidence that children enroled in Zambia had a longer time period to hospital readmission compared to those enroled in Zimbabwe (aSHR: 0.52, 95% CI: 0.28, 0.97).

TABLE 1 Child, caregiver and household characteristics at hospital discharge

	All (*N* = 649)	HIV-positive (*N* = 130)	HIV-negative (*N* = 519)	*p* value[a]
Country				
• Zambia	188/649 (29.0%)	56/130 (43.1%)	132/519 (25.4%)	<0.001
◻ Zimbabwe	461/649 (71.0%)	74/130 (56.9%)	387/519 (74.6%)	
Age, months; median (IQR)	18.2 (13.6, 22.6)	20.0. (14.5, 24.9)	17.5 (13.4, 22.1)	<0.001
Male	344/649 (53.0%)	66/130 (50.8%)	278/519 (53.6%)	0.57
Oedematous SAM at hospitalisation	422/649 (65.0%)	67/130 (51.5%)	355/519 (68.4%)	<0.001
Stunted (HAZ <−2)	504/649 (77.7%)	117/130 (90.0%)	387/519 (74.6%)	<0.001
Anthropometry				
◻ WHZ, mean (SD)	−2.2 (1.5)	−2.4 (1.4)	−2.1 (1.5)	0.05
◻ WAZ, mean (SD)	−3.3 (1.6)	−3.7 (1.2)	−3.2 (1.7)	0.002
◻ HAZ, mean (SD)	−3.1 (1.5)	−3.5 (1.2)	−3.0 (1.6)	0.003
◻ MUAC, cm; mean (SD)	12.3 (1.6)	11.7 (1.4)	12.4 (1.6)	<0.001
Past history				
• Complicated SAM	92/638 (14.4%)	30/129 (23.3%)	62/509 (12.2%)	0.001
◻ Uncomplicated SAM	124/622 (19.9%)	40/124 (32.3%)	84/498 (16.9%)	<0.001
◻ Persistent diarrhoea (past 14 days)	352/649 (54.2%)	84/130 (64.6%)	268/519 (51.6%)	0.008
Breastfeeding				
◻ Currently breastfeeding	165/649 (25.4%)	30/130 (23.1%)	135/519 (26.0%)	0.49
◻ Premature breastfeeding cessation (<12months of age)	162/516 (31.4%)	29/105 (27.6%)	133/411 (32.4%)	0.35
◻ Duration of breastfeeding, months; median (IQR)	8 (6, 9)	8 (6, 9)	8 (6, 9)	0.90
Duration of hospitalisation, days; median (IQR)	7 (4, 12)	10 (6, 17)	7 (4, 11)	<0.001
Haemoglobin, g/dl; median (IQR)[b]	9.3 (8.2, 10.3)	8.8 (7.7, 9.6)	9.4 (8.3, 10.4)	<0.001
Chronic underlying conditions				
◻ Cerebral palsy	30/649 (4.6%)	1/130 (0.8%)	29/519 (5.6%)	0.02
◻ Hydrocephalus	3/649 (0.5%)	0/130 (0%)	3/519 (0.6%)	0.39
◻ Congenital heart disease	14/649 (2.2%)	1/130 (0.8%)	13/519 (2.5%)	0.22
Medications at discharge				
◻ TB medication	88/649 (13.6%)	40/130 (30.8%)	48/519 (9.2%)	<0.001
◻ ART medication	N/A	66/130 (50.8%)	N/A	N/A
Primary caregiver characteristics				
Relationship to the child				
◻ Mother	590/633 (93.2%)	116/125 (92.8%)	474/508 (93.3%)	0.84
◻ Mother's age, years; median (IQR)	26 (22, 30)	28 (23, 32)	26 (22, 31)	0.19
Caregiver marital status				
◻ Married/stable union	471/633 (74.4%)	88/125 (70.4%)	383/508 (75.4%)	0.25
Caregiver education, years; median (IQR) caregiver employment				
◻ None	373/630 (59.2%)	67/125 (53.6%)	306/505 (60.6%)	0.07
◻ Skilled	46/630 (7.3%)	6/125 (4.8%)	40/505 (7.9%)	
◻ Unskilled	211/630 (33.5%)	52/125 (41.6%)	159/505 (31.5%)	

(Continues)

TABLE 1 (Continued)

	All (*N* = 649)	HIV-positive (*N* = 130)	HIV-negative (*N* = 519)	*p* value[a]
Household characteristics				
Place of residence				
□ Rural	99/645 (15.3%)	20/130 (15.4%)	79/515 (15.3%)	0.02
□ Urban	404/645 (62.6%)	70/130 (53.8%)	102/515 (19.8%)	
□ Peri-urban	142/645 (22.0%)	40/130 (30.7%)	334/515 (64.9%)	
Household drinking water source				
□ Improved	599/641 (93.4%)	123/130 (94.6%)	476/511 (93.2%)	0.54
Household toilet facilities				
□ Improved	568/643 (88.3%)	105/129 (81.4%)	463/514 (90.1%)	0.01
□ Unimproved	51/643 (7.9%)	18/129 (14.0%)	33/514 (6.4%)	
□ None	24/643 (3.7%)	6/129 (4.7%)	18/514 (3.5%)	
Household electricity				
Yes	295/634 (46.5%)	55/126 (43.7%)	240/508 (47.2%)	0.47

Note: Data are n/N (column %) unless otherwise stated.

Abbreviations: ART, antiretroviral therapy; HAZ, height-for-age Z-score; IQR, Interquartile range; MUAC, mid-upper arm circumference; N/A, not applicable; SAM, severe acute malnutrition; SD, standard deviation; TB, tuberculosis; WAZ, weight-for-age Z score; WHZ, weight-for-height Z score.

[a]*p* value comparing HIV-positive and HIV-negative groups at discharge.

[b]Haemoglobin was measured at discharge; if no discharge haemoglobin measurement was available, the value measured at the time point closest to discharge was used.

3.5 | Morbidity

Nearly half (48.8%) of children had at least one caregiver-reported symptom of ill-health within 4 weeks of discharge, with a gradual decline at later follow-up visits. Fever and respiratory illnesses were the most commonly reported symptoms overall; both declined markedly between 24 and 52 weeks. There were more caregiver-reported symptoms in HIV-positive versus HIV-negative children [63.9% [(95% CI: 53.7%, 73.0%) vs. 44.7% (39.6%, 49.9%); $p = 0.001$] at Week 4, driven particularly by differences in weight loss and appetite, but groups were otherwise similar during follow-up. There was a significant interaction between HIV status and reported weight loss [OR: 0.71 (0.57,0.90) $p = 0.004$] as well as diarrhoea [OR: 0.83 (0.70, 0.99) $p = 0.036$] over time.

3.6 | Nutritional recovery

We next looked at the nutritional status over the follow-up period (Figure 2). At the time of hospital discharge, 43.9% (95% CI: 40.1, 47.8) of children had SAM, 27.6% (24.3, 31.2) had MAM and 28.5% (25.2, 32.1) were well-nourished. The proportion of children with SAM declined to 22.4% (95% CI: 18.9, 26.4) by Week 4, 12.4% (9.6, 15.8) by Week 12, 11.9% (9.2, 15.2) by Week 24, and 4.5% (2.9, 6.8) by Week 52 Overall, 28.8% (95% CI: 24.8, 33.2) and 12.1% (9.4, 15.5) of children were still undernourished (i.e., WHZ <−2; i.e., SAM or MAM) 24 and 52 weeks after discharge from hospital, respectively. While the proportion with nutritional recovery at 52 weeks was similar between HIV-positive and HIV-negative children (88.6% vs. 87.8%, respectively), HIV-positive children generally had a slower recovery rate following hospital discharge (Figure S2). There was a significant difference in the proportion of children classified as SAM, MAM and adequately nourished between HIV-positive and HIV-negative children at Week 2 ($p = 0.003$) and Week 4 ($p = 0.02$), but no significant difference between groups from Week 12 onwards.

Table S3 shows the regression model of nutritional recovery using WHZ and MUAC as outcome factors and Figure 3 shows the trend in mean WHZ and MUAC over the period of follow-up. Females compared to males had a better recovery by WHZ, while males had a better recovery when MUAC was used. Young age at discharge (<12 months) was associated with poor recovery throughout the period of follow-up compared to older children. HIV-positive compared to HIV-negative children had a faster recovery in WHZ compared to MUAC. Children who had non-oedematous SAM at hospitalisation recovered at a slower rate than those who had oedema; similarly, children with ongoing SAM at discharge recovered more slowly than those who did not have SAM at discharge. Recovery of children with cerebral palsy remained poor through the period of follow-up.

We identified six independent factors associated with moving from a lower to a higher nutritional status in the multivariable ordinal logistic regression model (Table S4). Two factors (age at discharge and HIV) were associated with early recovery (at Weeks 2 and 4 only), while four factors (nonoedematous SAM at hospitalisation,

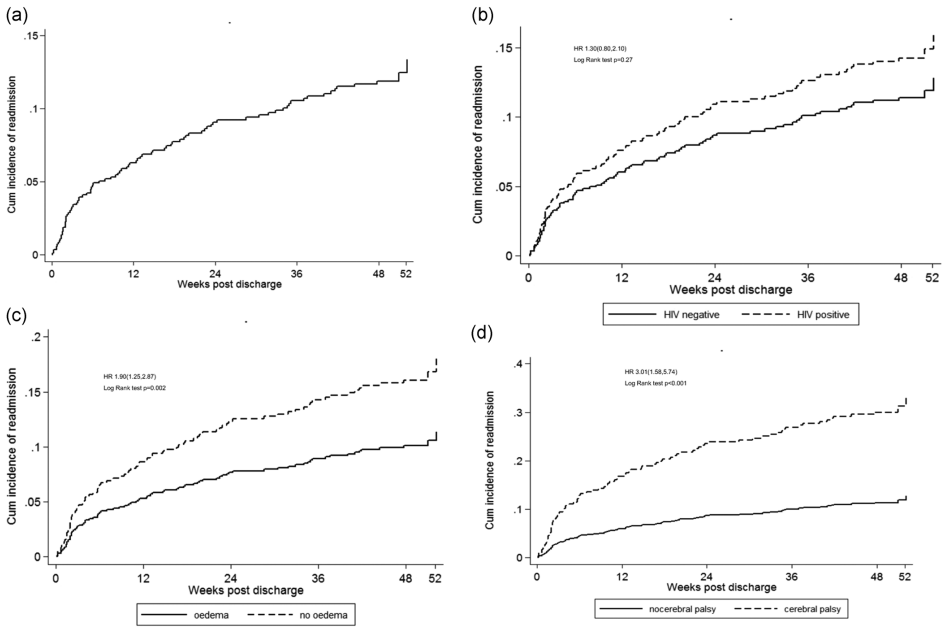

FIGURE 1 Cumulative incidence readmission among children discharged from hospital after treatment for complicated SAM. Curves showing cumulative incidence of readmission (death and loss to follow up as competing risks) postdischarge and log rank test *p* value. (a) overall cumulative incidence of readmission; (b) cumulative incidence of readmission by child HIV status; (c) cumulative incidence of readmission among children with oedematous versus nonoedematous SAM at the time of initial hospitalisation; (d) cumulative incidence of readmission in children with cerebral palsy versus those without cerebral palsy. Univariable subhazard ratios and log rank test *p* values were used to compare the differences in time to readmission between groups. Adjusted subhazard ratios are shown in Table 2

ongoing SAM at discharge, cerebral palsy and HAZ) were consistently associated with recovery throughout the follow-up period. Every 1-month increase in age was associated with a 4% higher odds (aOR: 1.04, 95% CI: 1.01, 1.06) of moving from a lower to a higher nutritional status at 4 weeks, while HIV was associated with a 41% lower odds (aOR: 0.59, 95% CI: 0.36, 0.97) of moving to a higher nutritional status. Children with nonoedematous compared to oedematous SAM had 71% lower odds (aOR: 0.29, 95% CI: 0.19, 0.44) of moving from a lower to a higher nutritional status at Week 4. Children with ongoing SAM at hospital discharge had 86% lower odds (aOR: 0.14, 95% CI: 0.09, 0.21) and children with cerebral palsy had an 84% lower odds (aOR: 0.16, 95% CI: 0.06, 0.40) of moving to a higher nutritional status by Week 4. Finally, in this cohort where 78% of the children were stunted, every unit increase in HAZ was associated with a 40% increased odds of moving from a lower to a higher nutritional status (aOR: 1.40, 95% CI: 1.20, 1.61) by Week 4. Effect size estimates for the four consistent risk factors remained similar throughout follow-up, except for the association between SAM at discharge and nutritional recovery, which attenuated over time (Table S4). Sex, being on TB medication, premature cessation of breastfeeding, and household toilet type were not significantly associated with nutritional recovery at any time point.

4 | DISCUSSION

Children discharged from the hospital after the management of complicated SAM continue to be at high risk of illness, hospital readmission and poor nutritional recovery. In this longitudinal study of children followed up after hospital discharge for SAM at three sites in southern Africa, one-in-six were readmitted into hospital over the first year postdischarge. Children had frequent illness episodes, and one-in-eight children remained undernourished by 52 weeks postdischarge. We identified four consistent risk factors for hospital readmission and nutritional recovery over 1 year of follow up: nonoedematous SAM at hospitalisation, ongoing SAM at discharge, discharge HAZ and underlying cerebral palsy. Contrary to our initial hypothesis, and despite our previous finding that it is a predictor of

TABLE 2 Factors associated with time to readmission

	Never hospitalised (*N* = 560 (%))	Hospitalised (*N* = 89(%))	Cox proportional hazards model for time to readmission	*p* value	Competing risk regression model time to readmissionaSHR (95% CI)	*p* value
Country						
□ Zimbabwe	392/461 (85.0%)	69/461 (15.0%)	Reference	0.06	Reference	0.04
□ Zambia	168/188 (89.4%)	20/188 (10.6%)	0.60 (0.35, 1.01)		0.52 (0.28,0.97)	
Sex						
□ Male	289/344 (84.0%)	55/344 (16.0%)	Reference	0.20	Reference	0.13
□ Female	271/305 (88.9%)	34/305 (11.1%)	0.75 (0.48, 1.17)		0.70 (0.45,1.11)	
Age at discharge (months), median (IQR)	18.4 (13.8, 22.5)	17.2 (11.8, 23.4)	0.98 (0.96, 1.01)	0.23	0.99 (0.95,1.02)	0.36
HIV status						
□ Negative	452/519 (87.1%)	67/519 (12.9%)	Reference	0.24	Reference	0.41
□ Positive	108/130 (83.1%)	22/130 (16.9%)	1.37 (0.81, 2.32)		1.27 (0.72,2.25)	
Type of SAM at hospitalisation						
□ Oedematous	377/422 (89.3%)	45/422 (10.7%)	Reference	0.03	Reference	0.04
□ Nonoedematous	183/227 (80.6%)	44/227 (19.4%)	1.63 (1.04, 2.55)		1.64 (1.03,2.64)	
Nutritional status at discharge						
□ No SAM	325/364 (89.3%)	39/364 (10.7%)	Reference	0.41	Reference	0.58
□ SAM	235/285 (82.5%)	50/285 (17.5%)	1.21 (0.77, 1.90)		1.14 (0.72,1.81)	
Discharge HAZ, mean (SD)	−3.0 (1.5)	−3.7 (1.7)	0.81 (0.70, 0.93)	0.002	0.82 (0.71,0.95)	0.007
Chronic underlying conditions						
□ No cerebral palsy	540/619 (87.2%)	79/619 (12.8%)	Reference	0.001	Reference	0.001
□ Cerebral palsy	20/30 (66.7%)	10/30 (33.3%)	3.06 (1.54, 6.08)		2.96 (1.56,5.61)	

Note: Data are *n* (row %) unless stated. Univariable analysis was carried out to determine the strength of association of each of the 17 variables; country, residence, sex, age, oedema at hospitalisation, HIV status, duration of hospitalisation, stunting, HAZ, cerebral palsy, haemoglobin, premature cessation of breastfeeding, SAM at discharge, tuberculosis at discharge, caregiver education, caregiver marital status and toilet type with incidence of readmission using a cut-off of $p < 0.25$. The five variables that were significant at $p < 0.25$ (duration of hospitalisation, HAZ, premature cessation of breastfeeding, toilet type and TB at discharge) and the seven a priori variables (country, sex, age at discharge, HIV status, baseline oedema, SAM at discharge and cerebral palsy) were offered up to the multivariable model. The table shows the adjusted hazards (cox regression model) and adjusted subhazard ratios obtained from the final model where death and loss to follow up were treated as competing risks. Duration of hospitalisation, premature cessation of breastfeeding, TB at discharge and toilet type were not retained in the final model.

Abbreviations: aSHR, adjusted subhazard ratio from competing risks model (treating death and loss to follow up before readmission as competing risks); HAZ, height-for-age Z-score; IQR, Interquartile range; SAM: severe acute malnutrition; SD, standard deviation; TB, tuberculosis.

postdischarge mortality (Bwakura-Dangarembizi et al., 2021), HIV was not associated with time to hospital readmission. However, HIV infection and young age at discharge were associated with poor nutritional recovery assessed using WHZ or MUAC. Overall, our data define clear vulnerable population groups among children recovering from complicated SAM and identify risk factors that are congruent with our previous analyses of postdischarge mortality risk in the same cohort (Bwakura-Dangarembizi et al., 2021). Children with non-oedematous SAM, stunting and disability in particular need to be considered for targeted convalescent care after discharge from hospital following complicated SAM. Infants below 12 months of age should be particularly prioritised for care during the period of post-discharge convalescence, given their slower recovery compared to older children.

WHO guidelines recommend that complicated SAM should be managed in hospital, followed by referral to a community-based nutritional rehabilitation facility (World Health Organisation, 1999, 2013). Adherence to this model of care depends on functional health systems and access to resources. The period from hospital discharge to nutritional recovery is fraught with vulnerabilities from

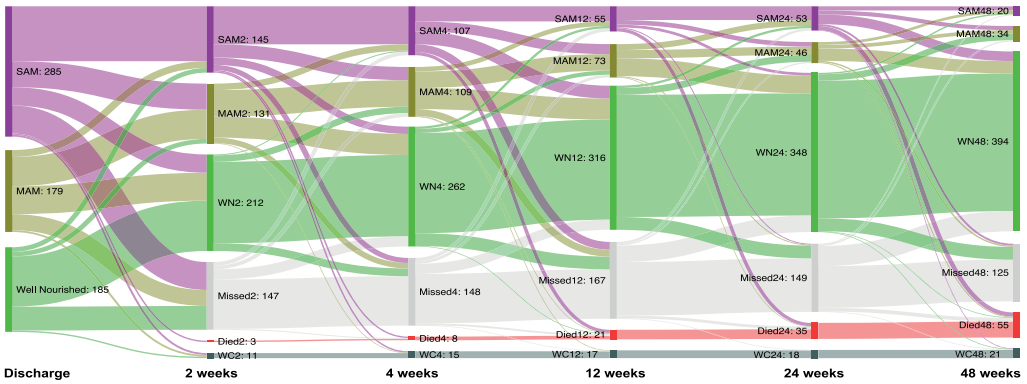

FIGURE 2 Patterns of nutritional recovery among children discharged from hospital after treatment for complicated severe acute malnutrition (SAM). Sankey diagram showing the pattern of nutritional recovery between hospital discharge and 52 weeks postdischarge. Nutritional status was assessed at every study visit and classified as SAM, moderate acute malnutrition (MAM) or adequately nourished (AN). The purple colour represents SAM, yellow MAM, and green AN. Children who withdrew consent were classified as (WC) and those who missed visits but turned up later were classified as missed

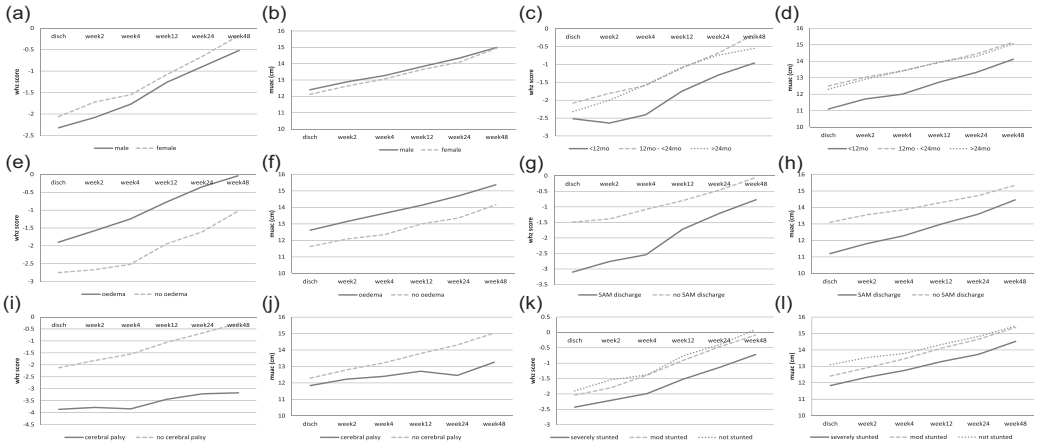

FIGURE 3 Mean weight for height Z-score (WHZ) and mid-upper arm circumference (MUAC) trend over the follow-up time. Graphs showing mean change in WHZ and MUAC over the period of follow up for the following variables; sex, age, baseline oedema, severe acute malnutrition at discharge, cerebral palsy and stunting

ongoing undernutrition, unresolved infections, hospital-acquired infections, perturbed physiological pathways and ongoing immune impairment (Ngari et al., 2018). Children discharged from hospitals in sub-Saharan Africa following SAM have a particularly high risk of mortality and hospital readmission (Gonzales et al., 2019), with several comorbidities (including HIV) being recognised risk factors in previous studies (Wiens et al., 2013, 2015). Interestingly, HIV infection was not a risk factor for readmission in this cohort, though it was

one of the major risk factors we previously identified for post-discharge mortality (Bwakura-Dangarembizi et al., 2021). It is possible that the higher death rate among children with HIV, almost half of which occurred in the community, proportionately reduced the number of readmissions in this group. Alternatively, HIV-positive children may be protected from readmission (but not mortality) by cotrimoxazole prophylaxis, since hospitalisation in children with malnutrition is usually triggered by infections (Chintu et al., 2004; Mulenga et al., 2007). By contrast, cotrimoxazole prophylaxis did not reduce mortality or hospital readmissions in HIV-negative children discharged from hospital following complicated SAM in Kenya (Berkley et al., 2016). Low HAZ is an indicator of poor linear growth and was an independent risk factor for hospital readmission. Diagnosis of SAM does not take into account stunting (HAZ <−2), which reflects chronic malnutrition associated with multiple causes such as poverty, food insecurity, repeated infections and intrauterine growth restriction (Stobaugh, Rogers, et al., 2018). There is increasing evidence that children with concurrent wasting and stunting are at greater risk for both mortality and morbidity (McDonald et al., 2013; Stobaugh, Rogers, et al., 2018; Wells et al., 2019). This increased risk is hypothesised to be mediated through decreased muscle mass and fat mass (seen in both wasting and stunting) resulting in low levels of the hormone leptin, which has a key role in both innate and adaptive immunity (Briend et al., 2015). Our observation that HAZ is associated with hospital readmission supports the need to better understand the pathophysiology of stunting in children with SAM. The observation that children enroled in Zambia had a longer time to first hospital readmission compared to children enroled in Zimbabwe, may be a result of continued nutritional support once children were categorised with MAM, which was not the practice in Zimbabwe.

This study reports the pattern of illness during follow-up after complicated SAM. Consistent with other studies, fever, respiratory illness and diarrhoea were the most commonly reported symptoms postdischarge (Ashraf et al., 2012; Khanum et al., 1998). The pattern of morbidity in children treated for SAM, therefore, reflects the typical infectious disease burden seen in LMICs. Our cohort showed a sharp decline in reported symptoms after 24 weeks of follow-up, suggesting that the first 6 months following discharge is a critical time for comorbidities. The high prevalence of illness during these first few months highlights the need for continued surveillance and interventions to prevent and treat infections after discharge. It has long been proposed that a cycle exists whereby malnutrition impairs immunity, thereby increasing host susceptibility to infection, which in turn intensifies the severity of malnutrition (Katona & Katona-Apte, 2008; Kau et al., 2011; Scrimshaw et al., 1968; Walson & A, 2018). This is a hypothesis that is being explored using biological specimens collected from HOPE-SAM participants (Bwakura-Dangarembizi et al., 2019). The effect of antimicrobials in children recovering from complicated SAM requires further study, especially since they may have additional benefits for weight gain and nutritional recovery (Trehan et al., 2013). For example, an ongoing study among children with uncomplicated SAM in Burkina Faso is providing azithromycin as an adjunct to standard outpatient treatment (ClinicalTrials. gov Identifier: NCT03568643).

At the time of hospital discharge, 44% of children had ongoing SAM. Most studies on nutritional recovery evaluate children after discharge from community-based therapeutic feeding centres, thus missing the immediate postdischarge period (Khanum et al., 1998; Somassè et al., 2016). Even then, there is no standard definition of relapse following treatment of SAM from existing studies due to different follow-up periods, treatment protocols and inconsistent reporting of point prevalence, cumulative prevalence and incidence rates (Stobaugh, Mayberry, et al., 2018). Our study showed that 6 months after discharge from hospital, 22% of children had not achieved nutritional recovery (here defined as improvement in anthropometry from SAM to either MAM or adequately-nourished, or from MAM to adequately-nourished). One-year after discharge, 12% of children still had MAM or SAM. Consistent with our observation that ongoing SAM at discharge was a predictor of poor nutritional recovery, a study of Ethiopian children with MAM who did not receive supplementary feeds, showed that the most wasted children at baseline had the lowest chance of recovering after 28 weeks of follow-up (James et al., 2016). Previous studies have found a strong association between poor linear growth and nutritional recovery in children with MAM and SAM (Chang et al., 2013; Stobaugh, Rogers, et al., 2018). Management of SAM is the same regardless of whether or not children are stunted. However, children who have both SAM and stunting may need additional interventions as the overlapping effects of stunting and wasting compound the risk of poor outcomes (Isanaka et al., 2019; McDonald et al., 2013; Stobaugh, Rogers, et al., 2018).

Our study showed that HIV infection slowed nutritional recovery in the early weeks following hospital discharge; at Weeks 2 and 4 postdischarge children with HIV had a lower odds of nutritional recovery, but this effect was not seen from Week 12 onwards. Overall our findings are similar to a study by Fergusson et al. (2009) from Malawi, where nutritional recovery of HIV-positive and HIV-negative children was similar at 4 months after discharge from hospital. Unlike the children in our cohort (in whom 28.5% had a WHZ > −2 at discharge), children in the Malawi cohort were discharged after attaining a WHZ of 85% (equivalent to WHZ ≥ −1). The odds of nutritional recovery were extremely poor in children with cerebral palsy. Children with disabilities are at risk for poor nutritional status, especially if they have a severe gross motor impairment and oropharyngeal dysfunction, leading to reduced food intake, increased nutrient loss, additional nutrient requirements and significantly increased energy expenditure (Bell & Samson-Fang, 2013). In the analysis models where MUAC and WHZ were used as continuous variables, young age at discharge, nonoedematous SAM at the time of initial hospitalisation, SAM at discharge and cerebral palsy were associated with poor nutritional recovery throughout the period of follow-up. This indicates that the public health approach which uses cut-offs for nutritional status may miss children who have poor nutritional recovery.

HIV-positive children had slower recovery than HIV-negative children up to 4 weeks postdischarge. Taken together, our study provides clear evidence that a proportion of children do not achieve nutritional recovery 1 year after discharge from hospital, with severe wasting, disability and stunting as key risk factors. Our findings support what Stobaugh described as 'different trajectories of recovery', suggesting that uniform outpatient management for all children recovering from SAM may not ensure sustainable recovery (Stobaugh, Mayberry, et al., 2018). Here we demonstrate that existing nutritional rehabilitation is insufficient to promote full and lasting recovery in all children. Future studies need to evaluate whether enhanced convalescent care and/or adjunctive therapies improve outcomes for the children most vulnerable to relapse and readmission.

Our study has strengths and limitations. We achieved relatively high rates of follow-up among this highly mobile and vulnerable population compared to other studies, through phone calls, text messages, free study clinics and home visits. However, we were not able to collect anthropometry and morbidity data on 15.8% of the study population at 52 weeks, which could have biased our findings. Where there were missing risk factors for analysis, imputation led to no major changes in the inferences obtained. We relied on caregiver-reported data for children who were hospitalised at nonstudy sites, which may have underestimated the proportion of children readmitted. A major limitation was that we did not systematically record nutritional rehabilitation provided in the community. We collected data on the home environment but we may not have captured key factors associated with clinical outcomes such as feeding practices, household food security and caregiver health-seeking behaviours. An in-depth social science study of the same population is underway to address this issue. Relapse of malnutrition may have been underestimated as we were only able to capture events at the time of the study visits. For example, it is well known that nutritional oedema can be transient and mild cases could have resolved between study visits (Alvarez et al., 2016).

Few longitudinal studies have defined morbidity and nutritional recovery of children discharged from hospital for complicated SAM. Here, we found high rates of hospital readmission and caregiver-reported illness in the first 6 months after discharge, and failure to achieve nutritional recovery by 1-year postdischarge in 12% of the cohort. The current study, together with our previous findings on mortality in the same cohort, identify a small number of consistent risk factors for adverse outcomes following discharge from hospital: HIV, nonoedematous SAM, cerebral palsy and ongoing SAM at the time of discharge (Bwakura-Dangarembizi et al., 2021). The current classification of malnutrition into acute and chronic and subsequent approaches to management ignores the contribution of poor linear growth to the poor outcomes in children who are both wasted and stunted namely relapse of malnutrition and associated morbidity (Stobaugh, Rogers, et al., 2018). HAZ should be considered in identifying severely malnourished children who are at risk for poorer outcomes. Prioritising these high-risk groups for more intensive follow-up may be beneficial. Providing additional and holistic convalescent care for all children discharged from hospitals following SAM may contribute to improving long-term outcomes for this vulnerable population.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Mutsa Bwakura-Dangarembizi, Beatrice Amadi, Kusum J. Nathoo, Shane A. Norris, Paul Kelly and Andrew J. Prendergast designed and oversaw the research study. Mutsa Bwakura-Dangarembizi, Beatrice Amadi, Claire D. Bourke, Ruairi C. Robertson, Kusum J. Nathoo, Paul Kelly and Andrew J. Prendergast secured funding for the study. Mutsa Bwakura-Dangarembizi, Kanta Chandwe, Chanda Kapoma, Beatrice Amadi, Deophine Ngosa and Florence D. Majo collected the data. Mutsa Bwakura-Dangarembizi, Andrew J. Prendergast, Cherlynn Dumbura, Bernard Chasekwa, Jonathan P. Sturgeon, Claire D. Bourke, Ruairi C. Robertson and Robert Ntozini cleaned, analysed and interpreted the data. Mutsa Bwakura-Dangarembizi and Andrew J. Prendergast wrote the first draft of the paper. All authors critically revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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REFERENCES

Alvarez, J. L., Dent, N., Browne, L., Myatt, M. & Briend, A. (2016). Putting child kwashiorkor on the map. https://www.ennonline.net/childkwashiorkor

Ashraf, H., Alam, N. H., Chisti, M. J., Mahmud, S. R., Hossain, M., Ahmed, T., & Nur, H. A. (2012). A follow-up experience of 6 months after treatment of children with severe acute malnutrition in Dhaka, Bangladesh. *Journal of Tropical Pediatrics*, *58*(4), 253–257.

Bell, K. L., & Samson-Fang, L. (2013). Nutritional management of children with cerebral palsy. *European Journal of Clinical Nutrition*, *67*, S13–S16.

Berkley, J. A., Ngari, M., Johnstone, T., Mwalekwa, L., Timbwa, M., Hamid, F., & Fegan, G. (2016). Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: A multicentre, double-blind, randomised placebo-controlled trial. *Lancet Global Health*, *4*(7), e464–e473.

Bhutta, Z. A., Berkley, J. A., Bandsma, R. H. J., Kerac, M., Trehan, I., & A., B. (2017). Severe childhood malnutrition. *Nature Reviews Disease Primers*, *3*, 17067. https://doi.org/10.1038/nrdp.2017.67

Briend, A., Khara, T., & Dolan, C. (2015). Wasting and stunting—similarities and differences: Policy and programmatic implications. *Food and Nutrition Bulletin*, *36*(1), S15–S23.

Bwakura-Dangarembizi, M., Amadi, B., Bourke, C. D., Robertson, R. C., Mwapenya, B., & Chandwe, K., Hope-SAM study team. (2019). Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): Rationale and methods of a longitudinal observational study. *BMJ Open*, *9*(1), e023077. https://doi.org/10.1136/bmjopen-2018-023077

Bwakura-Dangarembizi, M., Dumbura, C., Amadi, B., Ngosa, D., Majo, F. D., Nathoo, K. J., Mutasa, K., Chasekwa, B., Ntozini, R., Kelly, P., Prendergast, A. J., & the HOPE-SAM, study team (2021). Risk factors for postdischarge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia. *American Journal of Clinical Nutrition*, *113*(3), 665–674.

Chang, C. Y., Trehan, I., Wang, R. J., Thakwalakwa, C., Maleta, K., Deitchler, M., & J, M. M. (2013). Children successfully treated for moderate acute malnutrition remain at risk for malnutrition and death in the subsequent year after recovery. *Journal of Nutrition*, *143*, 215–220.

Chintu, C., Bhat, G. J., Walker, A. S., Mulenga, V., Sinyinza, F., Lishimpi, K., Farrelly, L., Kaganson, N., Zumla, A., Gillespie, S. H., Nunn, A. J., Gibb, D. M., & CHAP trial, t (2004). Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): A double-blind randomised placebo-controlled trial. *Lancet*, *364*, 1865–1871.

Fergusson, P., Chinkhumba, J., Grijalva-Eternod, C., Banda, T., Mkangama, C., & Tomkins, A. (2009). Nutritional recovery in HIV-infected and HIVuninfected children with severe acute malnutrition. *Archives of Diseases in Children*, *94*, 512–516.

Gonzales, G. B., Ngari, M. M., Njunge, J. M., Thitiri, J., Mwalekwa, L., Mturi, N., & JA., B. (2019). Phenotype is sustained during hospital readmissions following treatment for complicated severe malnutrition among Kenyan children: A retrospective cohort study. *Maternal & child nutrition*. https://doi.org/10.1111/mcn.12913

Isanaka, S., Hitchings, M. D. T., Berthé, F., Briend, A., & Grais, R. F. (2019). Linear growth faltering and the role of weight attainment: Prospective analysis of young children recovering from severe wasting in Niger. *Maternal & child nutrition*, *15*(4), 12817. https://doi.org/10.1111/mcn.12817

James, P. K., Sadler, K., Wondafrash, M., Argaw, A., Luo, H., Geleta, B., & P, B. (2016). Children with moderate acute malnutrition with no access to supplementary feeding programmes experience high rates of deterioration and no improvement: Results from a prospective cohort study in rural ethiopia. *PLoS One*, *11*:e0153530. https://doi.org/10.1371/journal.pone.0153530

Katona, P., & Katona-Apte, J. (2008). The interaction between nutrition and infection. *Clinical Practice*, *46*, 1582–1588.

Kau, A. L., Ahern, P. P., Griffin, N. W., Goodman, A. L., & Jl., G. (2011). Human nutrition, the gut microbiome and the immune system. *Nature*, *474*(7351), 327–336.

Khanum, S., Ashworth, A., & Huttly, S. R. A. (1998). Growth, morbidity, and mortality of children in Dhaka after treatment for severe malnutrition: A prospective study. *American Journal of Clinical Nutrition*, *67*, 940–945.

Lenters, L. M., Wazny, K., Webb, P., Ahmed, T., & Bhutta, Z. A. (2013). Treatment of severe and moderate acute malnutrition in low- and middle-income settings: A systematic review, meta-analysis and Delphi process. *BMC Public Health*, *13*(Supp 3), S23.

McDonald, C. M., Olofin, I., Flaxman, S., Fawzi, W. W., Spiegelman, D., Caufield, L. E., & Black, R. E. (2013). The effect of multiple anthropometric deficits on child mortality: Meta-analysis of individual data in 10 prospective studies from developing countries. *American Journal of Clinical Nutrition*, *97*(4), 896–901. https://doi.org/10.3945/ajcn.112.047639

Mulenga, V., Ford, D., Walker, A. S., Mwenya, D., Mwansa, J., Sinyinza, F., Lishimpi, K., Nunn, A., Gillespie, S., Zumla, A., Chintu, C., Gibb, D. M., & CHAP Trial, T. (2007). Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. *AIDS*, *21*, 77–84.

Ngari, M. M., Mwalekwa, L., Timbwa, M., Hamid, F., Ali, R., Iversen, P. O., Fegan, G. W., & Berkley, J. A. (2018). Changes in susceptibility to life-threatening infections after treatment for complicated severe malnutrition in Kenya. *American Journal of Clinical Nutrition*, *107*, 626–634.

Rytter, M. J. H., Kolte, L., Briend, A., Friis, H., & Christensen, V. B. (2014). The immune system in children with malnutrition—A systematic review. *PLoS One*, *9*(8), 105017.

Scrimshaw, N. S., Taylor, C. E., & Gordon, J. E. (1968). Interactions of nutrition and infection. *Monograph Series. World Health Organization*, *57*, 3–329.

Somassè, Y. E., Dramaix, M., Bahwere, P., & P., D. (2016). Relapses from acute malnutrition and related factors in a community-based management programme in Burkina Faso. *Maternal & child nutrition*, *12*(4), 908–917.

Stobaugh, H. C., Rogers, B. L., Rosenberg, I. H., Webb, P., Maleta, K. M., Manary, M. J., & Trehan, I. (2018). Children with poor linear growth are at risk for repeated relapse to wasting after recovery from moderate acute malnutrition. *The Journal of Nutrition*, *148*(6), 974–979.

Stobaugh, H. C., Mayberry, A., McGrath, M., Bahwere, P., Zagre, N. M., Manary, M. J., Black, R., & Lelijveld, N. (2018). Relapse after severe acute malnutrition: A systematic literature review and secondary data analysis. *Maternal & Child Nutrition*, *15*, e12702. https://doi.org/10.1111/mcn.12702

Trehan, I., Goldbach, H. S., LaGrone, L. N., Meuli, G. J., Wang, R. J., Maleta, K. M., & Manary, M. J. (2013). Antibiotics as part of the management of severe acute malnutrition. *New England Journal of Medicine*, *368*(5), 425–435.

Walson, J. L., & Berkley, J. A. (2018). The impact of malnutrition on childhood infections. *Current Opinion in Infectious Diseases*, *31*, 231–236.

Wells, J. C. K., Briend, A., Boyd, E. M., Berkely, J. A., Hall, A., Isanaka, S., & Dolan, C. (2019). Beyond wasted and stunted—a major shift to fight child undernutrition. *The Lancet Child & Adolescent Health*, *3*, 831–834.

Wiens, M. O., Kumbakumba, E., Larson, C. P., Ansermino, J. M., Singer, J., Kissoon, N., & G., Z. (2015). Postdischarge mortality in children with acute infectious diseases: Derivation of postdischarge mortality prediction models. *BMJ Open*, *5*(11), e009449. https://doi.org/10.1136/bmjopen-2015-009449

Wiens, M. O., Pawluk, S., Kissoon, N., Kumbakumba, E., Ansermino, J. M., Singer, J., & C., L. (2013). Pediatric post-discharge mortality in resource poor countries: A systematic review. *PLoS One*, *8*(6), 66698.

World Bank, World Health Organisation, & United Nations Children's Fund. (2018). Levels and trends in child malnutrition: UNICEF/WHO/World Bank Group Joint Child Malnutrition Estimates, Key findings of the 2018 edition. https://www.who.int/nutrition/publications/jointchildmalnutrition_2018_estimates/en/

World Health Organisation. (1999). Management of severe malnutrition: A manual for physicians and other senior health workers.

World Health Organisation. (2013). *Guideline: Updates on the management of severe acute malnutrition in infants and children*. https://www.who.int/publications/i/item/9789241506328

SUPPORTING INFORMATION

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Appendix N: Article 3 – Chapter 5

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Accepted manuscript

Fat and lean mass predict time to hospital readmission or mortality in children treated for complicated severe acute malnutrition in Zimbabwe and Zambia

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Data described in the manuscript, code book, and analytic code will be made available upon request

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ABSTRACT

HIV and severe wasting are associated with post-discharge mortality and hospital readmission among children with complicated severe acute malnutrition (SAM); however, the reasons remain unclear. We assessed body composition at hospital discharge, stratified by HIV and oedema status, in a cohort of children with complicated SAM in three hospitals in Zambia and Zimbabwe. We measured skinfold thicknesses and bioelectrical impedance analysis (BIA) to investigate whether fat and lean mass were independent predictors of time to death or readmission. Cox proportional hazards models were used to estimate the association between death/readmission and discharge body composition. Mixed effects models were fitted to compare longitudinal changes in body composition over one year. At discharge, 284 and 546 children had complete BIA and skinfold measurements, respectively. Low discharge lean and peripheral fat mass were independently associated with death/hospital readmission. Each unit z-score increase in impedance index and triceps skinfolds was associated with 48% (aHR 0.52, 95%CI 0.30,0.90) and 17% (aHR 0.83, 95%CI 0.71, 0.96) lower hazard of death/readmission respectively. HIV-positive versus HIV-negative children had lower gains in sum of skinfolds (mean difference -1.49, 95%CI -2.01, -0.97) and impedance index z-scores (-0.13 , 95%CI -0.24, -0.01) over 52 weeks. Children with non-oedematous versus oedematous SAM had lower mean changes in sum of skinfolds (-1.47, 95%CI -1.97, -0.97) and impedance index z-scores (-0.23, 95%CI -0.36, -0.09). Risk stratification to identify children at risk for mortality or readmission, and interventions to increase lean and peripheral fat mass, should be considered in the post-discharge care of these children.

Key words: Lean mass, fat mass, mortality, hospitalization, severe acute malnutrition, HIV

Abbreviations

aHR	adjusted Hazard ratio
BIA	Bio-electrical impedance analysis
CRF	Case Report Forms
DAG	Directed Acyclic Graph
HAZ	Height-for-age z-score
HIV	Human Immunodeficiency Virus
Ht	Height
HR	Hazard ratio
LMI	Lean Mass Index
MUAC	Mid-upper arm circumference
OR	Odds ratio
PA	Phase angle

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R	Resistance
R/H	Height-adjusted resistance
SAM	Severe acute malnutrition
WAZ	Weight-for-age z-score
WHO	World Health Organization
WHZ	Weight-for-height z-score
X_c	Reactance

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INTRODUCTION

Malnutrition remains a global health challenge contributing to nearly 50% of all deaths in children below the age of 5 years[1]. Severe acute malnutrition (SAM), defined as a weight-for-height Z-score (WHZ) <-3, mid-upper arm circumference (MUAC) <115mm, and/or bilateral nutritional oedema, has particularly high mortality when associated with clinical complications requiring hospitalisation. SAM is classified into oedematous and non-oedematous forms and treatment success is defined by a target WHZ, MUAC or resolution of oedema, depending on the criteria initially used for classification[2; 3]. Children hospitalized for complicated SAM remain at high risk for mortality in the year following hospital discharge. In a cohort of children in southern Africa, we recently showed that non-oedematous SAM, ongoing SAM at the time of discharge, cerebral palsy and HIV infection were independent predictors of mortality[4].

None of the anthropometric measures used to define SAM estimate the restoration of associated physiological and functional deficits [5; 6]. Body composition, measured as fat mass (FM) and lean mass (LM), has been shown to predict clinical outcomes in conditions such as cancer[7; 8], chronic kidney disease[9] and sickle cell disease in children and adolescents[10]. Lean mass comprises skeletal muscle, the skeleton, soft lean tissues and vital organs, while fat mass is distributed into central and peripheral fat stores[11; 12]. Loss of lean mass has been associated with decreased survival, worse clinical outcomes, increased rate of infections, complications, duration of hospitalisation and prolonged recovery in adults with chronic diseases[13; 14; 15] and similar data are emerging for children[16].

Interest in measuring body composition in undernourished children and exploring the long-term consequences for the development of non-communicable diseases has increased over the past few decades as mortality from SAM falls and children survive into adulthood[17]. Wasting is associated with deficits in both lean and fat mass [18] and body composition can be used to evaluate physiological recovery following SAM[3; 19]. However, there are few published data on the relationship between body composition and mortality, readmission and growth recovery in children managed for SAM. Assessing body composition may improve our understanding of underlying mechanistic pathways, recovery of physiological function and how to optimise clinical outcomes[6].

We measured body composition in a longitudinal cohort of children followed for 52 weeks after discharge from hospital in Zambia and Zimbabwe following management of complicated SAM. We hypothesized that low lean and fat mass would identify children most at risk of death or hospital readmission following hospital discharge for complicated SAM, and that body composition differences by HIV and oedema status may partly explain the differential long-term outcomes between children [4; 20].

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METHODS

Study design

This cohort was enrolled in the Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM) study, which has been described in detail elsewhere[21]. In brief, HOPE-SAM was a longitudinal observational cohort of children under 5 years of age hospitalised for complicated SAM at three tertiary referral hospitals in Zambia and Zimbabwe between August 2016 and March 2018 [22]. The unit at the University Teaching Hospital in Lusaka Zambia had a dedicated standalone facility that provided care for children hospitalised with complicated SAM and in Zimbabwe children received care in the general paediatric wards under different medical teams. Parents of children hospitalised for complicated SAM were sensitized about the study within 24 hour of admission and enrolled upon consenting. Body composition and anthropometric measurements were done on admission during hospitalisation, upon discharge and during the post-discharge period. Follow-up care in both countries was provided by the HOPE SAM study teams. The protocol, standard operating procedures and pre-specified analysis plan for this manuscript are available at https://osf.io/29uaw/. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the University of Zambia Biomedical Research Ethics Committee (010-02-16), and the Medical Research Council of Zimbabwe (MRCZ/A/2044). The ethics committee of Queen Mary University of London provided an advisory review. Written informed consent was obtained from the participants' parents/caregivers.

The main objectives of the current analysis were to (1) to determine the relationship between body composition and time to death or first hospital readmission over 52 weeks of follow-up; (2) compare body composition at discharge and over 52 weeks of follow-up between children with and without HIV infection, and between children with non-oedematous versus oedematous SAM; and (3) identify groups of children who share common body composition characteristics to determine whether the highest-risk children can be identified at the time of hospital discharge.

Study population

The HOPE-SAM study enrolled children admitted below 60 months of age into medical wards with complicated SAM, defined as WHZ <-3 and/or MUAC <115mm and/or the presence of nutritional oedema (in children above 6 months of age), and WHZ <-3 or nutritional oedema in those below 6 months, based on WHO criteria[2]. Children who had malignancy, who died prior to study enrolment, or whose caregiver was not willing to learn the child's HIV status were not included in the study.

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Study procedures and follow-up

The study procedures have been described previously [22]. Baseline demographics, clinical, household and caregiver data were collected on paper case report forms (CRFs) and double data-entered into a study database. Inpatient care was provided by ward staff separate from the research team, using WHO country-adapted guidelines for management of complicated SAM[2; 23]; however, progress during hospitalisation was documented daily by a study physician, with advice provided to the clinical teams on management. Children were seen in a dedicated study clinic at 2, 4, 12, 24 and 48 weeks after discharge. Details of hospital readmission and time to readmission were verified during study visits from children's hand-held cards. Mortality was determined through telephone calls and home visits for those who defaulted follow-up. Each study visit had a window period around the target date. The 48-week visit window was deliberately wide (up to 72 weeks) to minimise loss to follow-up at the end of the study; since 86.4% of data were collected by 52 weeks post-discharge, all analyses were censored at 52 weeks.

Anthropometry measures

The following measurements were done on hospital admission, discharge and at 2, 4-, 12-, 24- and 48-weeks post discharge: weight, height and MUAC using standardised methods[4]; body composition measured by bio-electrical impedance analysis (BIA); and triceps, subscapular and supra-iliac skinfold thickness.

Bioelectrical impedance analysis measurements

Body composition was measured by whole-body (wrist-ankle) BIA using a BodyStat 1500MD machine (BodyStat Ltd., Douglas, Isle of Man). BIA is a non-invasive method used to estimate body composition parameters. The technique involves placing two electrodes each on different parts of the body (e.g. the hand and feet) and passing a painless alternating electrical current through the body which measures the opposition or impedance (Z) to current flow in Ohms through various tissues at 5kHz (Z5) and 50 kHz (Z50)[24]. Impedance comprises resistance (R) which is opposition of tissue to the flow of current and reactance (X_c) which reflects the capacitative losses caused by cell membranes. Tissues containing large amounts of fluid and electrolytes have high conductivity and therefore low impedance, while fat and bone have low conductivity and high impedance[24]. Phase angle (PA) is a marker of the quality and quantity of soft tissue mass[25]; a smaller PA suggests cell death, reduced cell integrity and breakdown in cell membrane permeability[26]. BIA measurements were repeated until two impedance measurements taken at 50kHz were within 5 Ohms. Additional readings were taken if the impedance measurements had a difference of more than 5 Ohms. If it was not possible to obtain two acceptable readings after five tests, the procedure was abandoned. Outlying values (defined as R >1600 Ω, R <300 Ω, X_c >500 Ω, or PA >8°) were discarded as implausible. If any one of the readings for resistance, reactance, phase angle or

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impedance was missing or excluded at a particular time-point, all the other readings for that time-point were excluded.

From the raw data of R, Z50 and Xc, we obtained proxies for lean mass and lean mass index (lean mass/height^2).The impedance index (Ht^2/Z) is strongly associated with lean mass in any population and in epidemiological analyses behaves almost identically to lean mass when calibration equations are not available[27], though oedema reduces the strength of this association[28] .To correct for body size, lean mass is often adjusted for the square of height (Ht^2) to give lean mass index (LMI). This means that the reciprocal of impedance expressed as 1/Z in units of 1/ohms again behaves almost identically to lean mass index in epidemiological analyses [27] Both of these proxies were used in the current analyses. PA was also analysed as an independent composite marker of lean mass quality and quantity[25].

Skinfold thickness measurements

Skinfold thickness measurements are a simple and inexpensive method of estimating the size of the subcutaneous fat depot, which in turn correlates strongly with total body fat [29; 30]. Subscapular, triceps and suprailiac skinfolds were taken on the left side of the body to the nearest 0.2mm using calipers (Holtain Ltd., Crymych, UK). Triceps skinfolds provided a measure of peripheral fat, while subscapular and suprailiac skinfolds provided a measure of central fat. Total skinfold thickness was taken as the sum of subscapular, triceps and suprailiac skinfolds. Skinfold readings were measured in triplicate and medians, means and standard deviations of the values generated. Skinfold measurements were converted to Z-scores using 2006 WHO standards; we created our own internal Z-scores for suprailiac skinfolds for which there are no WHO standards. Longitudinal values of skinfolds were assessed for plausibility over the follow-up period; measures that were out of range based on WHO standards were verified on source documents and excluded as implausible.

Statistical methods

Survival Analysis

The primary outcome for this analysis was a composite of mortality or time to first hospital readmission. Children were censored at the last known alive date or at week 52 after discharge. Cox proportional hazards models were used to estimate hazard ratios of death or hospital readmission with body composition variables as exposures, after adjusting for the following minimum set of covariates obtained from a Directed Acyclic Graph (DAG): age at discharge, sex, HAZ and WHZ at discharge, HIV status, oedema at hospitalisation, and maternal employment (Supplementary Methods).

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Longitudinal changes in body composition

Data were first checked for consistency and completeness. All available data from participant discharge to study discontinuation were summarised. Non-overlapping visit windows were used and the measurement closest to the study visit week was used for analyses. Mixed effects models were used to compare longitudinal skinfolds z-scores and BIA data converted to internal z-scores between children with and without HIV infection and between children with and without oedema at initial hospitalisation, using HIV or oedema as fixed effects and participant identifier as the random effect. DAGs constructed using DAGitty version 3.0 were used to select the minimum set of covariates for adjustment (Supplementary Methods). The minimum covariate set for HIV status as an exposure were birthweight, sex, age at discharge, oedema at initial hospitalisation, HAZ and WHZ at discharge, hospital readmission, toilet type and maternal employment. The minimum covariate set for oedema as an exposure were birthweight, HIV status, age at discharge, hospital readmission, maternal employment and toilet type. Coefficients and confidence intervals obtained from the univariable and multivariable mixed effects models were interpreted. Margins plots were used to show the change in body composition by HIV status and baseline oedema status over 52 weeks of follow-up.

Clustering analysis

We conducted hierarchical clustering to identify groups of children sharing common characteristics based on discharge body composition measurements and anthropometric factors previously associated with mortality in the same cohort (oedema status at initial hospitalisation, HAZ and WHZ at discharge) [(4)]. The number of clusters was identified using the Calinski-Harabasz stopping rule. Comparison of characteristics and outcomes of children across groups was made using logistic regression for categorical variables and linear regression for continuous variables. All analyses were conducted using STATA version 14.0 (StataCorp. College Station, USA).

RESULTS

Study enrolment

Of 750 children enrolled from July 2016 to March 2018, 5 were excluded and 745 were followed in hospital; 649 were discharged to continue nutritional rehabilitation in the community. Forty-five children left hospital before any measurements were done, leaving 604 children with discharge measurements (Supplementary Figure 1). Complete BIA and skinfolds data were collected in 334 and 563 children, respectively. Following data cleaning and removal of implausible values, 284 (47%) children contributed complete BIA data and 546 (90.4%) skinfolds measurements at hospital discharge. Baseline characteristics of the children with and without discharge BIA measurements were broadly similar, except for small differences in country, caregiver employment, and

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anthropometry: children with missing data had a marginally lower WHZ, but higher HAZ than those with available BIA data, and no differences in WAZ or MUAC (Supplementary Table 1).

Discharge Characteristics

We have previously shown that post-discharge mortality is higher in children living with HIV compared to those without HIV and in children with non-oedematous compared to oedematous SAM[4]. We therefore stratified discharge characteristics by HIV and oedema status. At discharge, HIV-positive compared to HIV-negative children were significantly older, and were more likely to have non-oedematous SAM at admission and ongoing SAM at discharge. Anthropometry (WAZ, HAZ and MUAC), sum of skinfolds, impedance and lean mass indices were significantly lower in HIV-positive compared to HIV-negative children at the time of hospital discharge. Children with oedematous SAM were significantly older, less likely to be HIV-positive, and less likely to have ongoing SAM at the time of hospital discharge compared to those with non-oedematous SAM. Children with non-oedematous SAM were more stunted and had significantly less fat and lean mass than children with oedematous SAM (Table 1).

Associations between discharge body composition and time to death or hospital readmission

In the adjusted Cox regression model (Table 2), both lean and peripheral fat mass were independently associated with mortality or readmission into hospital. Each z-score increase in lean mass index and impedance index, was associated with a 33% (aHR 0.67, 95%CI 0.47, 0.98) and 48% (aHR 0.52, 95%CI 0.30, 0.90) reduction in hazard of death or hospital readmission. Each z-score increase in triceps skinfold was associated with a 17% (aHR 0.83, 95%CI 0.71, 0.96) reduction in death or readmission. By contrast, subscapular and suprailiac skinfolds, and phase angle were not associated with death or time to readmission. We tested for interaction of each body composition variable by HIV and oedema status and found evidence of interaction between LMI and oedema status only. Stratified analysis showed that among children with oedema, each unit increase in LMI was associated with a 61% (aHR 0.39, 95%CI 0.20, 0.75) reduction in the hazards of death or readmission; by contrast, there was no association between LMI and death/readmission in children without oedema. In summary, lean mass and peripheral fat mass were independently associated with hospital readmission.

We further analysed the components of the composite variable separately and found that readmission and not death was significantly associated with low lean mass and peripheral fat mass (Supplementary tables 2a and 2b).

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Body composition over 52 weeks of follow-up

Figure 1 shows the change in skinfolds (representing fat mass) and impedance index (representing lean mass) over time stratified by HIV status and oedema status. Individual trajectories are shown as spaghetti plots in Supplementary Figure 2. Over the 52 weeks of follow-up, all children showed a general increase in fat and lean mass. Triceps skinfolds (a measure of peripheral fat) increased throughout the period of follow-up; subscapular skinfolds (a measure of central fat) increased up to 24 weeks followed by a decline; and sum of skinfolds (a marker of total fat) increased up to 24 weeks, then plateaued.

Association between anthropometry and body composition with baseline oedema and HIV status

Table 3 shows the univariable and multivariable mixed effects analysis of the association between HIV and baseline oedema status, with anthropometry and body composition during follow-up. HIV-positive compared to HIV-negative children had lower gains in anthropometry, fat mass and lean mass over 52 weeks. Mean changes in MUAC (-0.44cm, (95% CI -0.62, -0.25)) and HAZ (-0.32 z-score (95% CI -0.60,-0.04)) were lower in HIV-positive compared to HIV-negative children. Fat mass gains were lower in HIV-positive compared to HIV-negative children: -1.49 z-scores (95%CI 2.01, -0.97) for total fat mass, -0.66 z-scores (95%CI -0.91, -0.41) for central fat mass, and -0.60 z-scores (95% CI -083, -0.37) for peripheral fat mass. Change in lean mass measured by impedance index was also lower in HIV-positive compared to HIV-negative children (-0.13 (95%CI -0.24, -0.01) over 52 weeks.

Compared to children with oedema at the time of initial hospitalisation, mean changes in MUAC, WHZ and WAZ were significantly lower in children with non-oedematous SAM, while HAZ was not different between groups. Both fat and lean mass were significantly lower in children without oedema: -1.47 z-score (95% CI -1.97, -0.97) for total fat mass and -0.23 z-scores (95%CI -0.36, -0.09) for impedance index z-score.

Taken together, whilst children showed overall gains in lean and fat mass and anthropometry during 52 weeks of follow-up, changes were significantly lower for HIV-positive children and for those with non-oedematous malnutrition.

Clustering analysis

Hierarchical clustering based on body composition and anthropometry identified three groups of children at the time of hospital discharge, group 1 (n=110, 40.7%), group 2 (n=24, 8.9%) and group 3 (n=136, 50.4%), whose characteristics were strongly associated with time to readmission or death (Figure 2; Supplementary Table 3, Supplementary Figure 3). Group 1 children had the highest proportion of oedema at hospitalisation (85.5%), the highest fat mass and the lowest HIV infection rates. Group 2 had the highest lean mass compared to the other groups. Group 3 had the lowest fat

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and lean mass, WHZ and HAZ, the highest proportion of HIV-positive children (32.4%) and ongoing SAM at the time of hospital discharge (66.2%) compared to group 2 and 3.

While group 1 had the highest fat mass and group 2 had the highest lean mass, the two groups had similar weight-for-height Z-score, height-for-age Z-score, rates of HIV positivity and SAM at discharge. Interestingly the odds of death or death or readmission were similar between groups 1 and 2, suggesting that there may be different pathways to survival involving the preservation of fat and lean mass, respectively. Overall, compared to group 1, children in group 3 had a 2.7-fold increased odds of death or readmission to hospital (aOR 2.7 (95%CI 1.3, 5.4) after adjusting for age (Supplementary Table 3) .

DISCUSSION

In this cohort of children treated for complicated SAM and discharged from three hospitals in southern Africa, we show that body composition, in addition to anthropometry, is an important determinant of mortality or hospital readmission in the year following hospital discharge. Specifically, low lean and peripheral fat mass (using BIA and skinfold measurements) were independently associated with the composite outcome of death or readmission. Furthermore, a distinct phenotypic group of children at the highest risk for mortality and hospital readmission were characterised by particularly low WHZ, HAZ, lean and fat mass, high prevalence of HIV infection and ongoing SAM at the time of discharge. Collectively, these findings highlight the importance of considering body composition in the assessment of nutritional recovery and risk stratification of children with SAM in order to optimise post-discharge outcomes.

The most important clinical outcomes in the year post-discharge from hospital are readmission or death. In this study, we showed that greater peripheral fat and lean mass were associated with reduced risk of readmission or death. Clinical studies in adults have shown that higher muscle mass is a major determinant of survival independent of body mass index [(31)]. Children have a lower muscle mass in relation to body weight compared to adults, and those with complicated SAM stand to suffer more from the acute muscle wasting resulting from food insufficiency, infection and inflammation. Early studies on nutritional status and muscle mass showed that muscle mass was an important determinant of survival[(32)], but few studies have evaluated lean mass in children with SAM. Here, we confirm that greater lean mass at discharge from hospital is associated with reduced mortality or hospital readmission, regardless of HIV status, although the relationship between lean mass and clinical outcomes appeared to be confined to children with oedema. Only higher triceps skinfold was associated with mortality or readmission , suggesting that the pattern of fat loss or preservation is important [(18)]. Fat is used as a metabolic fuel during periods of food deprivation and this is reflected in peripheral fat loss. During complicated SAM, which is characterised by infection and inflammation, leptin from central fat stores plays a role in stimulating the immune system

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through lymphopoiesis[33], and upregulation of the innate and adaptive immune response[34]. Advances in the measurement of fat and lean mass in malnourished children is set to provide more insight into monitoring growth and development, disease progression and response to treatment[10]. We have previously shown that oedematous SAM accounted for nearly two-thirds of children hospitalised for complicated SAM in this cohort, and that those with no oedema had twice the mortality risk one year post-discharge[4]. Children with non-oedematous SAM had slower anthropometric recovery and gained less fat and lean mass over the year following hospital discharge. Children hospitalised with oedema tend to recover anthropometric parameters faster than wasted children whose condition is more likely to have been longstanding. Non-oedematous SAM is characterised by loss of subcutaneous fat and muscle wasting which takes a longer time to recover, in contrast to oedematous SAM in which subcutaneous fat and muscle mass is better preserved. Change in lean mass was significantly lower in children with non-oedematous SAM suggesting that they take longer to recover from the insult of infection, inflammation and food deprivation. Results for phase angle were null, indicating that it is the gross amount of lean tissue, rather than more subtle markers of membrane quality, that is important for survival.

There are sparse data[18; 35] on body composition in children recovering from complicated severe acute malnutrition. In this longitudinal study of under-five children in Zambia and Zimbabwe, we showed that both fat and lean mass were significantly lower in HIV-positive compared to HIV-negative children at the time of hospital discharge. Weight loss in HIV infected persons affects both lean and fat tissue and remains a significant problem even in the era of combination antiretroviral therapy [36]. While there was a general increase in fat over one year of follow-up, the mean changes in regional and total fat were significantly lower in HIV-positive compared to HIV-negative children. These findings differ from a study on nutritional recovery among HIV-positive and HIV-negative children with SAM from Malawi which showed similar improvements in triceps (peripheral fat) and subscapular (central fat) skinfolds over four months of follow-up [37]. The difference between studies may be because the Malawi study enrolled children with uncomplicated SAM, whereas we enrolled children discharged from hospital after management of complicated SAM. The additional burden of infection, inflammation and metabolic derangements in children with complicated SAM are likely to exert additional nutrient demands during the recovery period, and may fundamentally alter body composition parameters. Studies have shown that the additional metabolic demands for amino acids to support the generation of acute phase proteins and an adaptive immune response exerts a catabolic effect, particularly on skeletal muscle [31; 38], resulting in loss of lean mass.

We were able to define three phenotypic groups based on anthropometry and body composition, with differences in mortality or readmission one year after discharge from hospital. The group with

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the worst anthropometry, body composition markers, ongoing SAM and highest HIV infection rates had the highest odds of death or readmission compared to the other two groups. The similar odds of death or readmission among groups 1 and 2 whose main difference was fat mass and lean mass suggest that for a similar weight-for-height and height-for-age, the amount of lean or fat mass are associated with survival. The current classification of malnutrition that is based on body size may not have any link with the physiological changes that contribute to the poor outcomes in these children. Children with complicated SAM have disrupted metabolic, organ and immunological function, and consideration should be given to using more physiological measures for risk stratification and development of interventions that restore healthy function.

The main strength of this study is that we had a large cohort that was followed longitudinally from hospital discharge to 52 weeks, in a setting of high HIV prevalence, and used rarely-deployed techniques to measure body composition at the time of discharge. Our high outcome ascertainment for death and readmission due to close follow-up of this cohort strengthens our inferences regarding body composition and clinical outcomes. Limitations of this study include the inability to obtain bioelectrical impedance data on more than half of participants. While BIA is a non-invasive and technically straightforward assessment of body composition, it requires cooperation from the child who must be relaxed and still; this was not always easy, particularly at the time of discharge from hospital. Nevertheless, the sample of children with BIA measurements had similar discharge characteristics to those without measurements, and their rates of mortality and readmission were similar. We were not able to determine the exact fat mass and fat-free mass which requires isotope calibration against a reference standard; however, our proxy markers of impedance index and lean mass index provided robust relative measures of lean mass that behave similarly to calibrated values in epidemiological analyses. Another potential limitation is survivor bias, where the sickest children (including those who were living with HIV) died early and had less opportunity to be readmitted into hospital.

CONCLUSION

In summary, we show that body composition (in particular lean mass and peripheral fat) at the time of hospital discharge are important determinants of mortality and hospital readmission in children managed for complicated SAM. Complicated SAM is characterised by multiple deranged metabolic, immune and hormonal pathways. There is therefore need for interventions that address the inflammatory state that characterises complicated SAM during the convalescent period using therapeutic foods that reduce metabolic stress, modulate inflammation and increase nutrient bioavailability, to improve fat and lean mass recovery, particularly in the highest risk children with non-oedematous SAM and HIV infection. In this cohort, anthropometry and body composition identified specific groups of children with poor outcomes over the year following discharge from

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hospital. Body composition measurements reflect the physiological changes accompanying response to treatment and recovery. Screening children prior to discharge using BIA and triceps skinfold measurement may be additional tools to identify those at risk for poor outcomes and would need more targeted interventions to improve their outcomes.

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References

1. Black R E, Victora C G, Walker S P *et al.* (2013) Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* **382**, 427–451.

2. World Health Organisation (2013) *Guideline Updates on the management of severe acute malnutrition in infants and children*. Geneva: World Health Organisation.

3. Kangas ST, Kaestel P, Salpéteur C *et al.* (2020) Body composition during outpatient treatment of severe acute malnutrition: Results from a randomised trial testing different doses of ready-to-use therapeutic foods. *Clinical Nutrition* **39**, 3426-3433.

4. Bwakura-Dangarembizi M, Dumbura C, Amadi B *et al.* (2021) Risk factors for postdischarge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia. *The American journal of clinical nutrition* **113**, 665-674.

5. Wells JCK, Briend A, Boyd EM *et al.* (2019) Beyond wasted and stunted—a major shift to fight child undernutrition. *The Lancet Child & Adolescent Health,* **3**, 831-834.

6. Renault S, Kangas S, Dailey-Chwalibóg T *et al.* (2018) *" Moving beyond anthropometry : Conducting BIA to measure body composition of acutely malnourished children : lessons from operational research ".* . Action Against Hunger

7. Murphy AJ, White M, Davies PS (2010) Body composition of children with cancer. . *The American journal of clinical nutrition* **92**, 55–60. .

8. Thibault R, Pichard C (2012) The Evaluation of Body Composition: A Useful Tool for Clinical Practice. *Annals of Nutrition and Metabolism* **60**, 6-16.

9. Bellizzi V, Scalfi L, Terracciano V *et al.* (2006) Early Changes in Bioelectrical Estimates of Body Composition in Chronic Kidney Disease. *Journal of the American Society of Nephrology* **17**, 1481-1487.

10. Eke CB, Chukwu BF, Ikefuna AN *et al.* (2015) Bioelectric Impedance Analysis of Body Composition of Children and Adolescents with Sickle Cell Anemia in Enugu, Nigeria. *Pediatric Hematology and Oncology* **32**, 258-268.

11. Muller MJ, Bosy-Westphal A, Later W *et al.* (2009) Functional body composition: insights into the regulation of energy metabolism and some clinical applications. *European Journal of Clinical Nutrition* **63**, 1045-1056.

12. Wells J C (2006) Measuring body composition. *Archives of Diseases in Childhood* **91**, 612-617.

13. Marcelli D, Usvyat LA, Kotanko P *et al.* (2015) Body Composition and Survival in Dialysis Patients: Results from an International Cohort Study. *Clinical Journal of the American Society of Nephrology* **10**, 1192-1200.

14. Pirlich M, Schütz T, Norman K *et al.* (2006) The German hospital malnutrition study. *Clinical Nutrition* **25**, 563-572.

https://doi.org/10.1017/S0007114522004056 Published online by Cambridge University Press

15. Wolfe RR (2006) The underappreciated role of muscle in health and disease. *American Journal of Clinical Nutrition* **84**, 475-482.

16. Lara-Pompa NE, Hill S, Williams J *et al.* (2020) Use of standardized body composition measurements and malnutrition screening tools to detect malnutrition risk and predict clinical outcomes in children with chronic conditions. . *The American journal of clinical nutrition* **112**, 1456-1467.

17. Wells JCK, Fewtrell MS (2008) Is body composition inportant for paediatricians? *Archives of Diseases in Childhood* **93**, 168-172.

18. Wells JCK (2019) Body composition of children with moderate and severe undernutrition and after treatment: a narrative review. . *BMC Med* **17**.

19. Girma T, Kaestel P, Mølgaard C *et al.* (2021) Utility of bio-electrical impedance vector analysis for monitoring treatment of severe acute malnutrition in children. *Clinical Nutrition* **40**, 624-631.

20. Bwakura-Dangarembizi M, Dumbura C, Amadi B *et al.* (2022) Recovery of children following hospitalisation for complicated severe acute malnutrition. *Maternal & child nutrition* **18**, e13302.

21. Bwakura-Dangarembizi M, Amadi B, Bourke CD *et al.* (2019) Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. . *BMJ Open* **9**.

22. Bwakura-Dangarembizi M, Amadi B, Bourke C D *et al.* (2019) Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. *BMJ open* **9**, e023077-e023077.

23. World Health Organisation G (1999) Management of severe malnutrition : a manual for physicians and other senior health workers.

24. Brantlov S, Jødal L, Lange A *et al.* (2017) Standardisation of bioelectrical impedance analysis for the estimation of body composition in healthy paediatric populations: a systematic review. . *Journal of Medical Engineering & Technology*

25. Norman K, Stobäus N, Pirlich M *et al.* (2012) Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters
. *Clinical Nutrition* **31**, 854-861.

26. Barrea L, Muscogiuri G, Pugliese G *et al.* (2021) Phase Angle as an Easy Diagnostic Tool of Meta-Inflammation for the Nutritionist. *Nutrients* **13**, 1446.

27. Wells JCK, Williams JE, Fewtrell M *et al.* (2007) A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. *International Journal of Obesity* **31**, 507-514.

28. Girma T, Kæstel P, Workeneh N *et al.* (2015) Bioimpedance index for measurement of total body water in severely malnourished children: Assessing the effect of nutritional oedema. *Clinical Nutrition* **35**, 713-717.

https://doi.org/10.1017/S0007114522004056 Published online by Cambridge University Press

29. Wendel D, Weber D, Leonard MB *et al.* (2017) Body composition estimation using skinfolds in children with and without health conditions affecting growth and body composition. *Annals of human biology,* **44**, 108-120.

30. Westsrate JA, P. D (1989) Body compostion in children: proposal for a method for calculating body fat percentage from total body density or skinfold-thickness measurements. *Am J Clin Nutr* **50**, 1104-1115.

31. Briend A, Khara T, Dolan C (2015) Wasting and stunting—similarities and differences: Policy and programmatic implications. *Food and Nutrition Bulletin* **36**, S15-23.

32. Briend A, Garenne M, Maire B *et al.* (1989) Nutritional Status, age and survival: The muscle mass hypothesis. *European Journal of Clinical Nutrition* **43**, 715-726.

33. Howard JK, Lord GM, Matarese G *et al.* (1099) Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. *The Journal of clinical investigation* **104**, 1051-1059.

34. Sánchez-Margalet V, Martín-Romero C, Santos-Alvarez J *et al.* (2003) Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. *Clin Exp Immunol* **133**, 11-19.

35. Lelijveld N, Musyoki E, Adongo SW *et al.* (2021) Relapse and post-discharge body composition of children treated for acute malnutrition using a simplified, combined protocol: A nested cohort from the ComPAS RCT. PloS one, 16(2), . *Plos One* **16**.

36. Grinspoon S, Mulligan K, Health Do *et al.* (2003) Weight Loss and Wasting in Patients Infected with Human Immunodeficiency Virus. *Clinical Infectious Diseases* **36**, S69-S78.

37. Fergusson P, Chinkhumba J, Grijalva-Eternod C *et al.* (2009) Nutritional recovery in HIV-infected and HIV uninfected children with severe acute malnutrition. *Archives of Diseases in Children* **94**, 512-516.

38. Bhutta ZA, Berkley J A, Bandsma RHJ *et al.* (2017) Severe childhood malnutrition. *Nature Reviews Disease Primers* **3**.

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Table 1 Discharge anthropometry and body composition

	All N= 604	**HIV-positive N=121**	**HIV-negative N=483**	**P-value [a]**	**Oedema at Baseline N=391**	**No oedema at baseline N=213**	**P value[b]**
Male	322/604 (53.3%)	60/121 (49.6%)	262/483 (54.2%)	0.36	208/391 (53.2%)	114/213 (53.5%)	0.94
Age, months; median (IQR)	18.0 (13.6, 22.8)	20.2 (15.4, 26.0)	17.5 (13.4, 22.1)	<0.001	19.3 (14.8, 23.3)	15.7 (11.2, 21.2)	<0.001
Oedema at hospitalisation	391/604 (64.7%)	63/121 (52.1%)	328/483 (67.9%)	0.001	n/a	n/a	n/a
HIV-positive	n/a	n/a	n/a		63/391 (16.1%)	58/213 (27.2%)	0.001
SAM at discharge	264/604 (43.7%)	66/121 (54.6%)	198/483 (41.0%)	0.007	146/391 (37.3%)	118/213 (55.4%)	<0.001

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Anthropometry at discharge							
WHZ, mean (SD)	-2.2 (1.5)	-2.4 (1.4)	-2.1 (1.5)	0.09	-1.9 (1.4)	-2.7 (1.4)	<0.001
WAZ, mean (SD)	-3.3 (1.6)	-3.7 (1.2)	-3.2 (1.7)	0.006	-3.0 (1.5)	-4.0 (1.5)	<0.001
HAZ, mean (SD)	-3.1 (1.5)	-3.4 (1.2)	-3.0 (1.6)	0.007	-2.9 (1.5)	-3.4 (1.6)	<0.001
MUAC, mm; mean (SD)	123.0 (15.7)	116.9 (13.5)	124.6 (15.9)	<0.00	126.5 (15.6)	116.5 (13.8)	<0.001
MUAC z-score (SD)	-2.4 (1.61)	-3.16 (1.40)	-2.23 (1.61)	1	-2.10 (1.61)	-3.00 (1.45)	<0.001
				<0.00			
				1			
Body composition at discharge							
Triceps skinfolds, mm, mean (SD)	6.65 (2.35)	5.54 (1.59)	6.94 (2.43)	<0.00	6.98 (2.54)	6.01 (1.78)	<0.001
Triceps skinfolds z-score, mean	-1.19 (1.69)	-2.02 (1.45)	-0.97 (1.68)	1	-0.93 (1.71)	-1.69 (1.52)	<0.001
(SD)	5.21 (1.97)	4.46 (1.70)	5.35 (2.00)	<0.00	5.36 (2.18)	4.92 (1.43)	0.01
Subscapular skinfolds, mm, mean	-1.49 (2.02)	-2.10 (2.02)	-1.34 (1.99)	1	-1.34 (2.13)	-1.79 (1.76)	0.01
(SD)	4.48 (2.00)	3.63 (1.70)	4.70 (2.02)	<0.00	4.65 (2.07)	4.16 (1.82)	0.006
Subscapular skinfolds z-score,	0.002 (1.00)	0.11 (1.01)	-0.42 (0.85)	1	0.08 (1.03)	-0.16 (0.92)	0.007
mean (SD)	16.39 (5.07)	14.10 (4.29)	17.02 (5.07)	<0.00	17.04 (5.35)	15.10 (4.18)	<0.001
Suprailiac skinfolds, mm, mean	0.008 (1.00)	-0.47 (0.84)	0.13 (1.00)	1	0.14 (1.05)	-0.24 (0.82)	<0.001
(SD)	0.63 (0.19)	0.59 (0.17)	0.64 (0.20)	<0.00	0.67 (0.18)	0.56 (0.19)	<0.001
Suprailiac skinfolds z-score, mean	0.01 (1.00)	-0.20 (0.90)	0.06 (1.02)	1	0.22 (0.95)	-0.37 (0.98)	<0.001
(SD)	11.73 (2.43)	10.97 (2.12)	11.92 (2.47)	<0.00	11.96 (2.32)	11.30 (2.56)	0.03
Sum of skinfolds, mm, mean (SD)	0.009 (-0.11)	-0.30 (0.88)	0.09 (1.02)	1	0.10 (0.96)	-0.17 (1.06)	0.03
Sum of skinfolds z-score, mean	3.26 (1.27)	3.31 (1.34)	3.25 (1.26)	<0.00	3.23 (1.26)	3.33 (1.30)	0.54

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(SD)	0.001 (-0.11)	0.04 (1.05)	-0.01 (1.00)	1	-0.03 (1.00)	0.05 (1.02)	0.54
Impedance index, cm^2/Ω; mean				<0.00			
(SD)				1			
Impedance index z-score, mean				0.07			
(SD)				0.07			
Lean mass index, 1/ Ω; mean				0.008			
(SD)				0.008			
Lean mass index z -score, mean				0.77			
(SD				0.77			
Phase angle							
Phase angle z-score							

Data are n/total (column %) unless otherwise stated. 1/ Z (Ω) was used as a proxy for lean mass index. HAZ, height-for-age z-score; IQR, interquartile range; MUAC, mid-upper-arm circumference; SAM, severe acute malnutrition; SD, standard deviation; WAZ, weight-for-age z-score, [a]P value comparing HIV-positive and HIV-negative groups, [b]P value comparing children with and without oedema at initial hospitalisation

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Table 2 Cox regression model of discharge body composition factors associated with time to death or readmission

	N	Unadjusted HR(95%CI)	P-value	Adjusted HR* (95%CI)	P-value
Bioimpedance analysis					
• Lean mass index Z-score, • Impedance index Z-score • Phase angle Z-score	N=284 N=286 N=296	0.53 (0.37, 0.75) 0.48 (0.33, 0.71) 1.0 3(0.79,1.36)	0.002 <0.001 0.84	0.62 (0.41, 0.94) 0.48 (0.24, 0.83) 1.07 (0.81,1.43)	0.02 0.01 0.63
Skin folds					
• Triceps skinfold Z-score • Subscapular skinfold Z-score • Suprailiac skinfold Z-score • Sum of skinfolds Z-score	N= 557 N= 550 N= 563 N= 551	0.72 (0.63,0.83) 0.86 (0.76, 0.97) 0.75 (0.58, 0.97) 0.63 (0.47, 0.83)	<0.001 0.01 0.03 0.001	0.77 (0.64, 0.91) 0.89 (0.79, 1.02) 0.90 (0.68, 1.19) 0.69 (0.49, 0.98)	0.002 0.09 0.46 0.04

*Multivariable models included a minimum adjustment set identified from a directed acyclic graph: age at discharge, sex, baseline oedema, WHZ , HAZ, HIV status, and maternal employment

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Table 3 Univariable and multivariable mixed effects analysis of body composition, and anthropometry over 52 weeks of follow-up

Variable	HIV-positive versus HIV-negative		Non-oedematous versus oedematous	
	Unadjusted Coefficient (95% CI) P value	**Adjusted Coefficient (95% CI) P value**	**Unadjusted Coefficient (95% CI) P value**	**Adjusted Coefficient (95% CI) P value**
Mid-upper arm circumference, cm	-0.81 (-1.07, -0.54) <0.001	-0.44 (-0.62, -0.25) <0.001	-1.09 (-1.30, -0.88) <0.001	-0.76 (-0.98, -0.54) <0001
MUAC Z-score	-0.79 (-1.05,-0.53) <0.001	-0.44 (-0.62,-0.25) <0.001	-1.02 (-1.23, -0.81) <0.001	-0.70 (-0.92,-0.48) <0.001
Weight-for-height Z-score	-0.25 (-0.51, 0.01) 0.06	-0.11 (-0.05, 0.27) 0.18	-1.07 (-1.27, -0.87) <0.001	-0.89 (-1.10, -0.67) <0.001
Height-for-age Z-score	-0.39 (-0.67, -0.12) 0.005	-0.32 (-0.60, -0.04) 0.03	-0.51 (-0.74, -0.28) <0.001	-0.19 (-0.44, 0.05) 0.12
Weight-for-age Z-score	-0.45 (-0.78, -0.15 0.004	-0.04 (-0.11, -0.18) 0.63	-1.14 (-1.38, -0.90) <0.001	-0.77 (-1.01, -0.52) <0.001
Triceps skinfold Z-score	-0.86 (-1.11,-0.62) <0.001	-0.60 (-0.83, -0.37) <0.001	-0.85 (-1.07, -0.64) <0.001	-0.63 (-0.85, -0.41) <0.001
Subscapular skinfold Z-score	-0.93 (-1.19, -0.67) <0.001	-0.66 (-0.91, -0.41) <0.001	-0.91 (-1.13, -0.69) <0.001	-0.73 (-1.00, -0.45) <0.001

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Suprailiac skinfold Z-score	-0.34 (-0.48, -0.20) <0.001	-0.30 (-0.45, -0.15) <0.001	-0.22 (-0.34, -0.11) <0.001	-0.11 (-0.24, 0.02) 0.09
Total skinfolds Z-score	-2.08 (-2.64, -1.52) <0.001	-1.49 (-2.01, -0.97) <0.001	-1.95 (-2.42, -1.48) <0.001	-1.47 (-1.97, -0.97) <0.001
Lean mass index Z-score	-0.21(-0.37, -0.06) 0.007	-0.11 (-0.27, 0.04) 0.16	-0.27 (-0.40, -0.14) <0.001	-0.23 (-0.37, -0.08) 0.002
Impedance index Z-score,	-0.31 (-0.46, -0.16) <0.001	-0.13 (-0.24, -0.01) 0.04	-0.37 (-0.50, -0.24) <0.001	-0.23 (-0.36, -0.09) 0.002
Phase angle Z-score	0.01 (-0.15,0.13) 0.90	-0.001 (-0.15,0.15) 1.0	-0.08 (-0.04,0.20) 0.21	0.08 (-0.06,0.21) 0.25

All values are mean differences (95% CI) from a multivariable mixed effects model, with HIV or oedema as fixed effects and participant identifier as the random effect. Adjustment set for HIV status: sex, birthweight, age at discharge, oedema at hospitalisation, HAZ, WHZ, maternal employment, toilet type and hospital readmission. Adjustment set for oedema status: birthweight, age at discharge, HIV status, hospital readmission, toilet type and maternal employment status

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Figure Legends

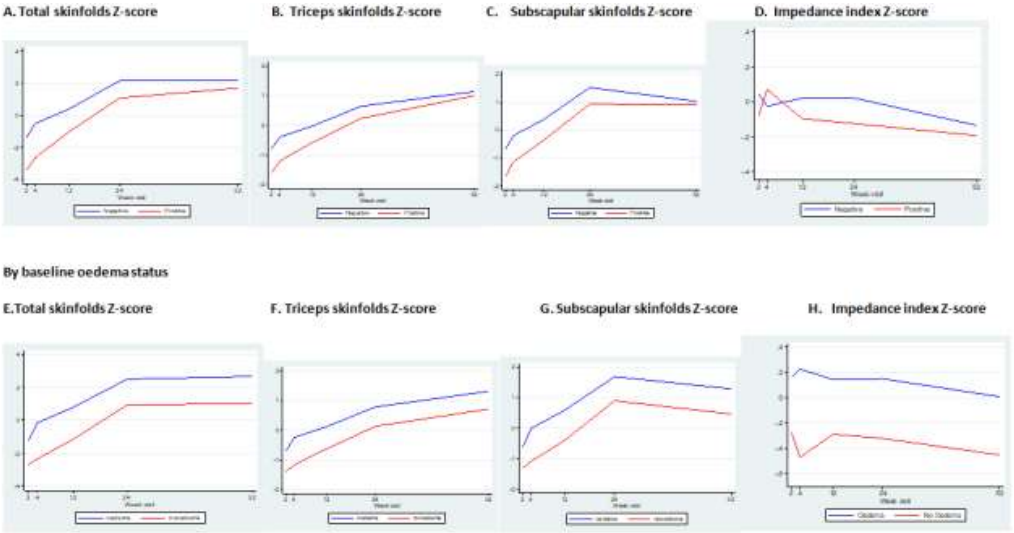

Figure 1

Margins plots of change in body composition over 52 weeks of follow-up stratified by HIV status and oedema status at initial hospitalisation.

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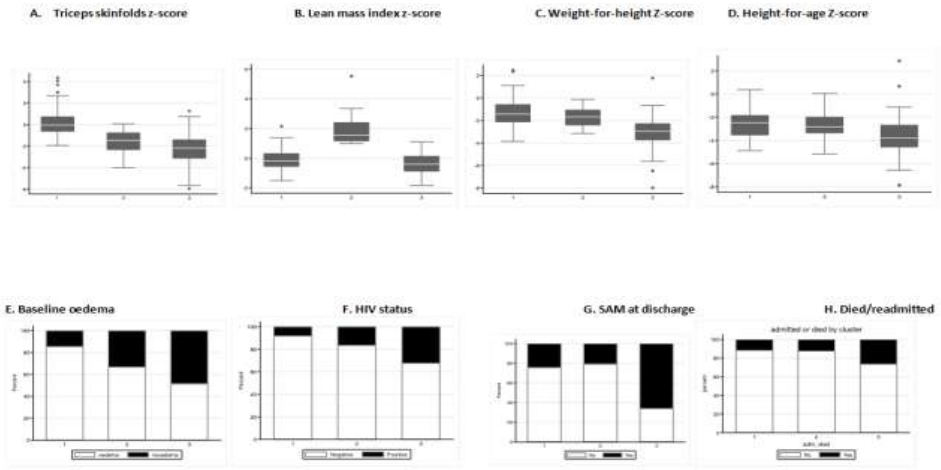

Figure 2: Characteristics of subgroups of children at discharge

Three groups were identified by hierarchical clustering; (Group 1 n=110, Group 2 n=24 and Group 3 n=136). The group characteristics are shown as proportions for each variable associated with poor outcomes (A. Triceps skinfolds z-score, B. Lean mass index z-score, C. WHZ, D. HAZ, E. baseline oedema, F. HIV status, G. SAM at discharge and H. composite outcome of died/readmitted).

https://doi.org/10.1017/S0007114522004056 Published online by Cambridge University Press

Accepted manuscript

References

1. Black R E, Victora C G, Walker S P *et al.* (2013) Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* **382**, 427–451.

2. World Health Organisation (2013) *Guideline Updates on the management of severe acute malnutrition in infants and children*. Geneva: World Health Organisation.

3. Kangas ST, Kaestel P, Salpéteur C *et al.* (2020) Body composition during outpatient treatment of severe acute malnutrition: Results from a randomised trial testing different doses of ready-to-use therapeutic foods. *Clinical Nutrition* **39**, 3426-3433.

4. Bwakura-Dangarembizi M, Dumbura C, Amadi B *et al.* (2021) Risk factors for postdischarge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia. *The American journal of clinical nutrition* **113**, 665-674.

5. Wells JCK, Briend A, Boyd EM *et al.* (2019) Beyond wasted and stunted—a major shift to fight child undernutrition. *The Lancet Child & Adolescent Health,* **3**, 831-834.

6. Renault S, Kangas S, Dailey-Chwalibóg T *et al.* (2018) *" Moving beyond anthropometry : Conducting BIA to measure body composition of acutely malnourished children : lessons from operational research ".* . Action Against Hunger

7. Murphy AJ, White M, Davies PS (2010) Body composition of children with cancer. . *The American journal of clinical nutrition* **92**, 55–60. .

8. Thibault R, Pichard C (2012) The Evaluation of Body Composition: A Useful Tool for Clinical Practice. *Annals of Nutrition and Metabolism* **60**, 6-16.

9. Bellizzi V, Scalfi L, Terracciano V *et al.* (2006) Early Changes in Bioelectrical Estimates of Body Composition in Chronic Kidney Disease. *Journal of the American Society of Nephrology* **17**, 1481-1487.

10. Eke CB, Chukwu BF, Ikefuna AN *et al.* (2015) Bioelectric Impedance Analysis of Body Composition of Children and Adolescents with Sickle Cell Anemia in Enugu, Nigeria. *Pediatric Hematology and Oncology* **32**, 258-268.

11. Muller MJ, Bosy-Westphal A, Later W *et al.* (2009) Functional body composition: insights into the regulation of energy metabolism and some clinical applications. *European Journal of Clinical Nutrition* **63**, 1045-1056.

12. Wells J C (2006) Measuring body composition. *Archives of Diseases in Childhood* **91**, 612-617.

13. Marcelli D, Usvyat LA, Kotanko P *et al.* (2015) Body Composition and Survival in Dialysis Patients: Results from an International Cohort Study. *Clinical Journal of the American Society of Nephrology* **10**, 1192-1200.

14. Pirlich M, Schütz T, Norman K *et al.* (2006) The German hospital malnutrition study. *Clinical Nutrition* **25**, 563-572.

https://doi.org/10.1017/S0007114522004056 Published online by Cambridge University Press

15. Wolfe RR (2006) The underappreciated role of muscle in health and disease. *American Journal of Clinical Nutrition* **84**, 475-482.

16. Lara-Pompa NE, Hill S, Williams J *et al.* (2020) Use of standardized body composition measurements and malnutrition screening tools to detect malnutrition risk and predict clinical outcomes in children with chronic conditions. . *The American journal of clinical nutrition* **112**, 1456-1467.

17. Wells JCK, Fewtrell MS (2008) Is body composition inportant for paediatricians? *Archives of Diseases in Childhood* **93**, 168-172.

18. Wells JCK (2019) Body composition of children with moderate and severe undernutrition and after treatment: a narrative review. . *BMC Med* **17**.

19. Girma T, Kaestel P, Mølgaard C *et al.* (2021) Utility of bio-electrical impedance vector analysis for monitoring treatment of severe acute malnutrition in children. *Clinical Nutrition* **40**, 624-631.

20. Bwakura-Dangarembizi M, Dumbura C, Amadi B *et al.* (2022) Recovery of children following hospitalisation for complicated severe acute malnutrition. *Maternal & child nutrition* **18**, e13302.

21. Bwakura-Dangarembizi M, Amadi B, Bourke CD *et al.* (2019) Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. . *BMJ Open* **9**.

22. Bwakura-Dangarembizi M, Amadi B, Bourke C D *et al.* (2019) Health Outcomes, Pathogenesis and Epidemiology of Severe Acute Malnutrition (HOPE-SAM): rationale and methods of a longitudinal observational study. *BMJ open* **9**, e023077-e023077.

23. World Health Organisation G (1999) Management of severe malnutrition : a manual for physicians and other senior health workers.

24. Brantlov S, Jødal L, Lange A *et al.* (2017) Standardisation of bioelectrical impedance analysis for the estimation of body composition in healthy paediatric populations: a systematic review. . *Journal of Medical Engineering & Technology*

25. Norman K, Stobäus N, Pirlich M *et al.* (2012) Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters
. *Clinical Nutrition* **31**, 854-861.

26. Barrea L, Muscogiuri G, Pugliese G *et al.* (2021) Phase Angle as an Easy Diagnostic Tool of Meta-Inflammation for the Nutritionist. *Nutrients* **13**, 1446.

27. Wells JCK, Williams JE, Fewtrell M *et al.* (2007) A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. *International Journal of Obesity* **31**, 507-514.

28. Girma T, Kæstel P, Workeneh N *et al.* (2015) Bioimpedance index for measurement of total body water in severely malnourished children: Assessing the effect of nutritional oedema. *Clinical Nutrition* **35**, 713-717.

https://doi.org/10.1017/S0007114522004056 Published online by Cambridge University Press

29. Wendel D, Weber D, Leonard MB *et al.* (2017) Body composition estimation using skinfolds in children with and without health conditions affecting growth and body composition. *Annals of human biology,* **44**, 108-120.

30. Westsrate JA, P. D (1989) Body compostion in children: proposal for a method for calculating body fat percentage from total body density or skinfold-thickness measurements. *Am J Clin Nutr* **50**, 1104-1115.

31. Briend A, Khara T, Dolan C (2015) Wasting and stunting—similarities and differences: Policy and programmatic implications. *Food and Nutrition Bulletin* **36**, S15-23.

32. Briend A, Garenne M, Maire B *et al.* (1989) Nutritional Status, age and survival: The muscle mass hypothesis. *European Journal of Clinical Nutrition* **43**, 715-726.

33. Howard JK, Lord GM, Matarese G *et al.* (1099) Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. *The Journal of clinical investigation* **104**, 1051-1059.

34. Sánchez-Margalet V, Martín-Romero C, Santos-Alvarez J *et al.* (2003) Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. *Clin Exp Immunol* **133**, 11-19.

35. Lelijveld N, Musyoki E, Adongo SW *et al.* (2021) Relapse and post-discharge body composition of children treated for acute malnutrition using a simplified, combined protocol: A nested cohort from the ComPAS RCT. PloS one, 16(2), . *Plos One* **16**.

36. Grinspoon S, Mulligan K, Health Do *et al.* (2003) Weight Loss and Wasting in Patients Infected with Human Immunodeficiency Virus. *Clinical Infectious Diseases* **36**, S69-S78.

37. Fergusson P, Chinkhumba J, Grijalva-Eternod C *et al.* (2009) Nutritional recovery in HIV-infected and HIV uninfected children with severe acute malnutrition. *Archives of Diseases in Children* **94**, 512-516.

38. Bhutta ZA, Berkley J A, Bandsma RHJ *et al.* (2017) Severe childhood malnutrition. *Nature Reviews Disease Primers* **3**.