DETERMINANTS OF MORTALITY IN CHILDREN YOUNGER THAN FIVE YEARS ADMITTED WITH SEVERE ACUTE MALNUTRITION TO THREE HOSPITALS IN VHEMBE DISTRICT, LIMPOPO.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MSc in Child Health (Community Paediatrics)

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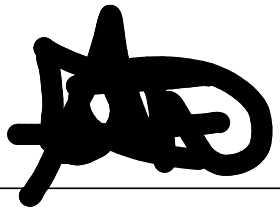
Johannesburg, 2023

DECLARATION

I, Dakalo Fakudze declare that this research report is my own, unaided work. It is being submitted for the degree of MSc in Child Health (Community Paediatrics) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____ (Signature of candidate)

22 June 2023 in Johannesburg

DEDICATION

To my dear husband Dr Sandile Vusumuzi Fakudze for his support and love from conception of the study to the end. He has been a pillar of strength and encouragement in completing the course.

To the head of the paediatric clinical unit at Tshilidzini Regional Hospital, Dr Ntodeni Thelma Ravuluvulu, who encouraged me to enrol for and complete this course and afforded me time to attend set course modules and the research paper.

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PUBLICATIONS

This research report has not been published in any journal and is being presented in the submissible format.

I intend to submit the report to PLoS ONE for publication. The submissible paper has been written to meet their submission criteria (presented in Appendix D).

Table of Contents

COVER PAGE

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TITLE PAGE

Long title

Socio-demographic, clinical and laboratory factors contributing to mortality in severely malnourished children younger than 5 years admitted to three hospitals in Vhembe district, Limpopo, South Africa.

Short title

Determinants of mortality in children under five years admitted with severe acute malnutrition

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ABSTRACT

Background

In 2014, one-third of child deaths occurring in South African hospitals were attributed to severe acute malnutrition. This study sought to determine demographic, family, socio-economic, clinical, and case-management factors contributing to mortality in severely malnourished children younger than 5 years admitted to three hospitals in Vhembe district, Limpopo, South Africa.

Methods

A retrospective record review of children aged 6 to 59 months admitted with severe acute malnutrition over 30 months was conducted. Bivariable and multivariable regression analyses of determinants of mortality were undertaken.

Results

Two hundred and forty-five children with severe acute malnutrition were identified. Their median (interquartile [IQR]) age was 14 (10, 18) months. The overall mortality was 26.9% (66/245). Determinants of mortality, based on the multivariable analysis, included diarrhoea on presentation (odds ratio [OR]=3.34, 95% CI 1.38, 8.10); anaemia (OR=3.30, 95% CI 1.28, 8.50]); a raised CRP (OR=9.29, 95% CI 2.81, 30.76]); and hyponatraemia (OR=6.64, 95% CI 2.70, 16.31). HIV status and a diagnosis of shock were not significant determinants of mortality.

Conclusion

Severe acute malnutrition mortality was high, particularly for a high middle-income country setting. Factors that may be amenable to intervention include better management of the presenting illness, particularly diarrhoea, a focus on electrolyte imbalance correction, and treatment of anaemia.

INTRODUCTION

Childhood undernutrition is recognised by the World Health Organization (WHO) as a major health problem globally,[1] contributing to almost half of all mortality in children under the age of 5 years.[2,3] Annually, severe acute malnutrition (SAM) affects about 13 million children younger than 5 years in sub-Saharan Africa of whom an estimated one million die.[4]

Substantial differences in SAM mortality rates observed globally may be related to the severity of illness and anthropometric compromise at presentation, comorbid conditions such as human immunodeficiency virus (HIV) infection, delayed referral and presentation, substandard case management, in addition to underlying socio-demographic and health system factors.[5–8]

The South African Child Problem Identification Programme (Child PIP) identified that one-third of hospital child deaths were attributable to SAM in 2014.[9] By 2019, 24% of deaths were attributable to SAM.[9,10] In 2015-16, the South African national SAM case fatality rate was 8.9%; some 1 380 deaths among the 15 537 SAM hospital admissions.[11] By 2018-19, this had reduced to 7.1%; 806 deaths among 11 280 SAM admissions.[12] Limpopo Province has traditionally had a higher SAM case fatality rate than the national average (for example, 11.6% vs 8.9% in 2016), with Vhembe, a predominantly rural district in the same province, having an even higher case fatality rate (13.0% in 2016). [11] This rate is similar to those described in many less-resourced settings such as in Ethiopia, Uganda and Malawi.[7,13–15]

Although studies on contributors to SAM mortality in hospital have been carried out in various African settings,[13,16–19] few emanate from South Africa,[20] a relatively better resourced high middle-income country. Establishing determinants of mortality among severely malnourished children is essential to improve survival and the quality of care offered.[21] This study sought to identify demographic, family, socio-economic, clinical, and case-management factors

contributing to mortality in severely malnourished children, aged six months to five years, admitted to three hospitals in Vhembe district, Limpopo, South Africa.

METHODS

Study setting

The study was conducted in Vhembe district, one of five districts in Limpopo Province, South Africa. The district is predominantly rural with approximately 774 villages and covers 21 407 km^2. It is the northernmost district of the country and shares borders with Zimbabwe and Botswana. Children under-5 years constitute 13% of the district population.

The three hospitals purposively chosen for this study were Tshilidzini, Donald Fraser and Malamulele hospitals. Tshilidzini is the regional hospital and receives referrals from six district hospitals, including Donald Fraser and Malamulele. Donald Fraser had a higher number of beds compared to other district hospitals and Malamulele had a high case-load of SAM. Hospitalised children received standard in-patient treatment according to the South African SAM guideline,[22] which is based on WHO recommendations.[1] The district has four paediatricians located at the regional hospital each of whom undertake a once-weekly outreach visit to each of the associated district hospitals. No formal training on SAM treatment guidelines was offered, but individual cases were selected for consultant opinion by resident medical officers.

Study design and population

This was a retrospective, descriptive study, with analytic components, reviewing patient hospital records. The study enrolled all children aged 6 months to 5 years admitted for SAM from 1 January 2016 to 30 June 2018 (30 months). Severe acute malnutrition was defined by the presence of a weight for height/length z-score less than -3, or a mid-upper arm circumference less than 11.5 cm, or bilateral pedal oedema.[1]

Inclusion and exclusion criteria

Any child aged 6 months to 5 years meeting the definition of SAM was included in the study. Children with long-term health conditions such as cerebral palsy, trisomy 21, or congenital diseases were excluded. Children younger than six months were also excluded because of the difficulty in reliably diagnosing SAM in this age group.[3,23,24]

Data collection

Data was collected using a structured, pre-coded data collection tool developed following a literature review and considering WHO and South African SAM treatment guidelines.[1,22] The questionnaire was pre-tested on pre-study-period hospital records. To avoid missing eligible participants, a list of children admitted with diagnostic terms such as malnutrition, failure to thrive, kwashiorkor, protein energy malnutrition, marasmus and severe acute malnutrition was compiled using admission and discharge registers. Hospital records of these children were obtained and screened, and eligibility assessed. Across the hospitals, record retrieval was compromised by staff shortages at the file registry. At the regional hospital, students assisted in retrieving records. The poor filing system also contributed to challenges in retrieving files. There was no way of establishing if the available files differed from those not retrieved. Variables of interest extracted included demographic characteristics, family details, triage and clinical presentation, ward case management, laboratory markers, comorbid conditions, and child outcome status.

Data collection procedure

The principal investigator retrieved anthropometric data from patient records and manually plotted these on the WHO 2006 growth charts.[3] Patients who met the study criteria were then included in the study. Subsequently, the anthropometric data were also entered into WHO anthropometric data software,[25] and those with implausible values were excluded. Measurements were usually done by enrolled nurses and repeated by the dietician in the wards.

Electronic weighing scales were used for weight determinations and a tape measure to obtain lengths and heights.

Data was sourced from various documents. Sociodemographic data, HIV status, TB screening and nutritional data were extracted from the nursing structured admission forms. Charts containing vital signs, feeding and treatment information were thoroughly examined. Clinical and therapeutic responses and actions were categorised as appropriate, partial (if not completely followed), or poor (if not completed) based on the investigator's opinion. Records with doctors' orders but with no accompanying charts were categorised as 'unable to assess'. The principal investigator (DF), a doctor with experience in paediatrics and SAM treatment guidelines, assessed appropriateness of hospital care based on WHO and national guidelines.[1,22] Dietary history, assessments and feeds prescriptions were collected from the hospital dieticians' notes. Doctors' clinical notes in both the admission area and wards were assessed. Laboratory results were obtained from patients' files or electronically from the National Health Laboratory Services (NHLS) website.

Participant data from the Child Healthcare Problem Identification Program (Child PIP), a national mortality auditing tool,[26,27] and Vhembe district clinical case reporting forms were reviewed to determine modifiable factors that contributed to mortality. The Child PIP process identifies missed opportunities and any substandard care, the context of each death and improvement plans at different levels where the child received care extending from the home, clinic or outpatient department, in transit, on admission and in emergency areas, up to the ward.[26,27] Once enrolled, participants remained in the study even if their records were incomplete or if they were discharged prematurely.

Sample size

A study sample size of 300 children was anticipated, which was sufficient to identify a doubling in any mortality risk factor, with a power of 80% and an alpha (p-value) of 0.05, assuming an

11.6% mortality. Fewer children were identified than anticipated but with a much higher mortality rate allowing for a 1.6-fold higher difference in any mortality risk factor to be identified as significant.

Statistical analysis

Data were entered into Microsoft Excel 2016 (Microsoft, Seattle, USA) and then exported to IBM Statistical Package for Social Science (SPSS) statistics version 27.0 (SPSS Inc, Chicago, USA) for further cleaning and analysis. World Health Organization Anthro software v3.2.2 (WHO, Geneva, Switzerland) was used to convert anthropometric measurements to weight-for-height/length z-scores.[25]

Factors potentially contributing to death were grouped in broader categories such as socio-demographic, clinical and laboratory. To compare differences in characteristics between children who died and those who survived, chi-square tests were used to assess differences in proportions for categorical variables. If continuous variables were non-parametric, a Mann-Whitney rank-sum test was used.

We used binary logistic regression to identify the factors that influenced mortality rates in children with severe acute malnutrition. Variables that had a p-value of ≤ 0.15 in the initial bivariable analysis were included into the multivariable logistic regression model, where the entry and removal probabilities were set at 0.05 and 0.15 respectively. Variables of clinical importance, such as age and sex, although not meeting the cut–off value for multivariable analysis were also included into the model. A stepwise logistic regression analysis for variables with a p-value of less than 0.05 was then conducted to arrive at the final model for determining mortality determinants.

Independent variables with more than 20% missing data at bivariable analysis were excluded during multivariable data analysis. Variables that were missing in patients' records were treated as missing during the data analysis. The adjusted odds ratio and corresponding 95% confidence

intervals (95% CI), and p-values are reported, with a p-value of less than 0.05 considered statistically significant.

Ethical clearance was obtained from the Committee for Research in Human Subjects at the University of the Witwatersrand, Johannesburg (clearance number M181051). Permission was also granted by the Limpopo provincial health department research committee, Vhembe district health authority and the individual hospitals involved in the study.

RESULTS

Some 734 children with possible SAM (as previously defined) were admitted to the three hospitals from January 2016 to June 2018. Only 401 hospital records (55%) were found. Of these, 245 participants (61%) met the study definition of SAM and were enrolled. Exclusions related to not meeting SAM or study age criteria or having long-term health conditions defined as ineligible (figure 1). Most participants (109 [44.5%]) were admitted to Tshilidzini Regional Hospital, 88 (35.9%) to Malamulele Hospital and 48 (19.6%) to Donald Fraser Hospital.

Final outcome

One hundred and seventy children with SAM (69.4%) were discharged alive, 66 children (26.9%) died, seven children (2.9%) were transferred to higher levels of care, and the caregivers of two children (0.8%) discharged themselves prematurely from hospital care (figure 1).

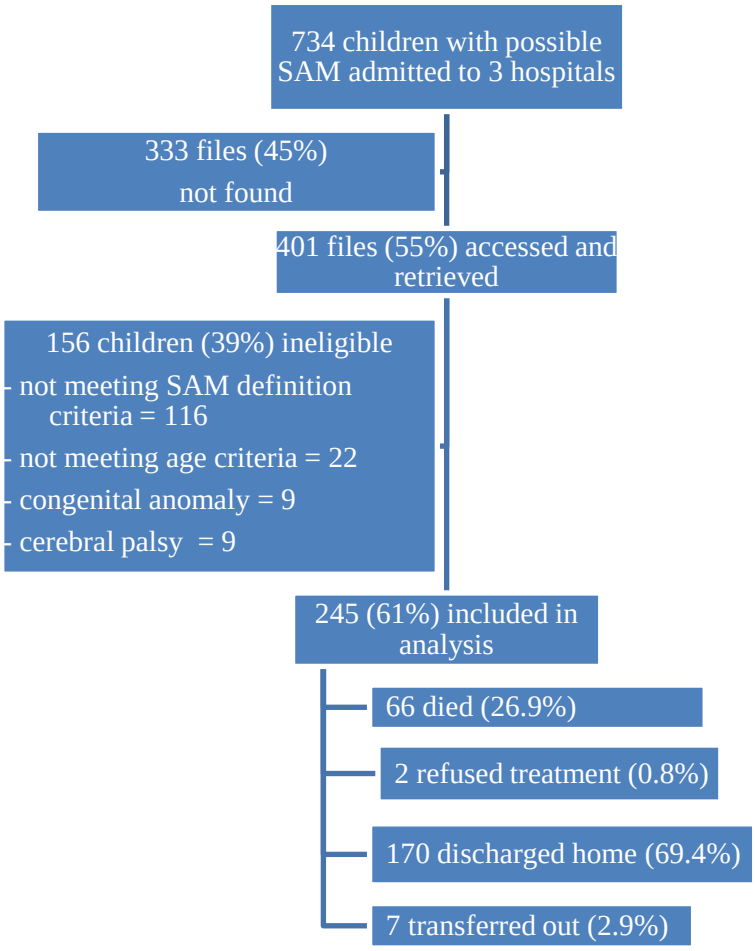

Figure 1. Flow diagram of children admitted with possible malnutrition at three hospitals in Vhembe district

Mortality

Sixty-six of the 245 participants died; a 26.9% mortality rate. Malamulele Hospital had a higher death rate (30/88 [34%]) compared to Tshilidzini Hospital (25/109 [22.9%]) and Donald Fraser Hospital (11/48 [22.9%]), who had identical rates. The median (interquartile range [IQR]) time to death was 100.5 (33, 240) hours, with 14 deaths (21.2%) occurring within 24 hours of admission. Nineteen deaths (28.8%) occurred within 48 hours with almost two-thirds (63.6%) occurring within the first week of admission.

Causes of death

The leading immediate causes of death included diarrhoea (17 [25.8%]), pneumonia (14 [21.2%]), sepsis (6 [9.1%]), acute kidney injury (5 [7.6%]) and hypoglycaemia (4 [6.1%])

(figure 2). Over one-half of children had complications documented on the day of death, mainly shock (22 [61.1%]); primarily related to hypovolaemia (13 [36.1%]), sepsis (6 [16.7%]), and hypoglycaemia (11 [30.6%]).

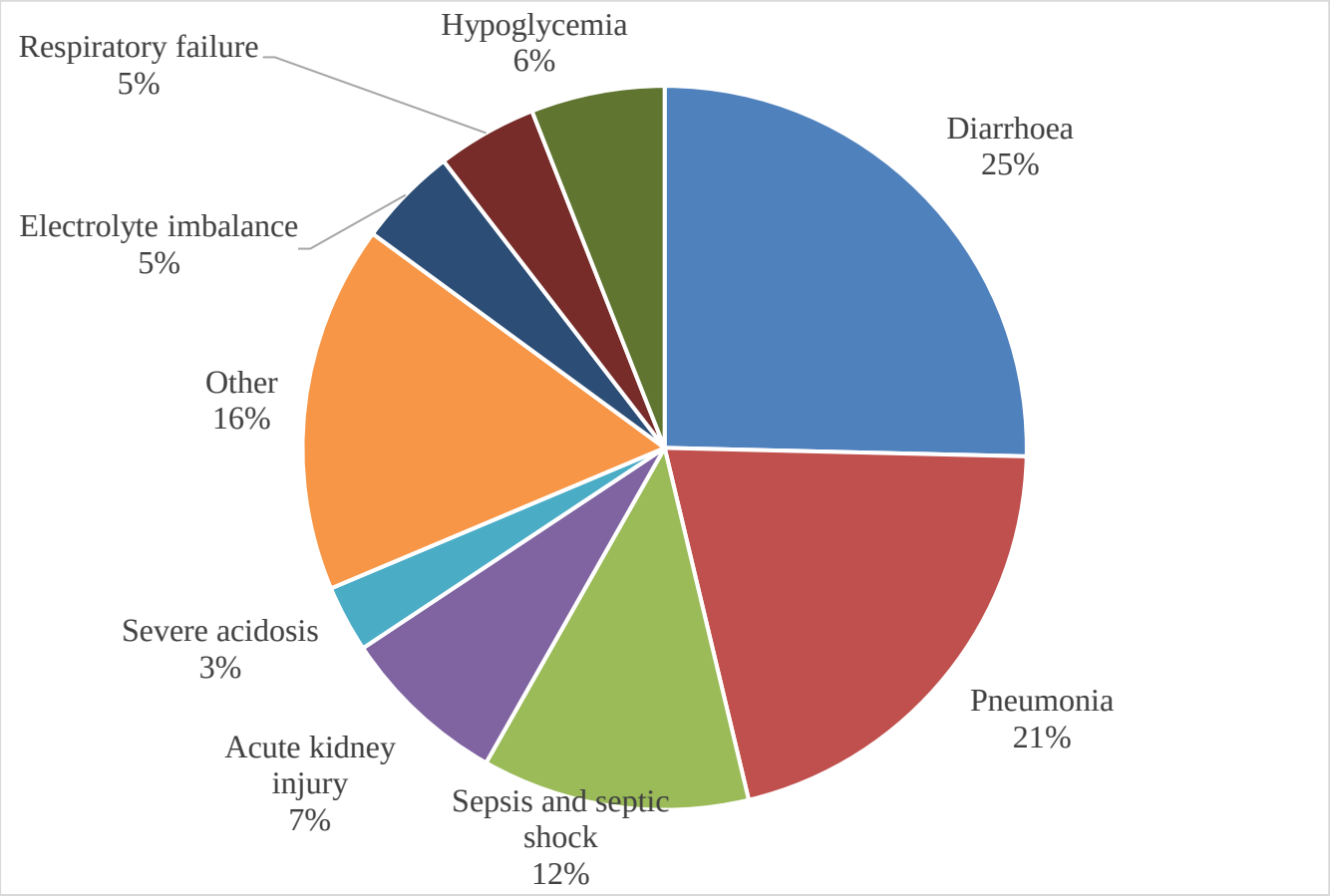

Figure 2. Immediate causes of death for children with severe acute malnutrition (n=66)

Sociodemographic and baseline characteristics

More male children were admitted (144 [58.8%]) and died (41/66 [62%]). The median (IQR) age of the children was 14 (10, 18) months. Over half the children were aged between 13 and 24 months (136 [55.5%]). There was no difference in the median age of children who died and survived.

Three-quarters of children (182 [74.3%]) had their mother as the primary caregiver while about a fifth (46 [18.8%]) were cared for by their grandmother. Most mothers (177 [72.2%]) were

unemployed. The median (IQR) age of mothers was 26 (21, 32) years. Details of mothers' level of education as well as details relating to fathers and siblings were not consistently available.

The majority of admissions (205 [83.7%]) were first-time SAM admissions. More children (138 [56%]) had the clinical syndrome of oedematous SAM ('kwashiorkor') compared to non-oedematous SAM ('marasmus').

Most children were breastfed (219 [89%]) at some time. Information on how many children were still breastfeeding at the time of admission was not well documented. The mean length of breastfeeding was 9 months. Only about one-half of children (134 [54.7%]) had their immunisations up to date, a fifth (45 [18.4%)]) were partially immunised while one-quarter (66 [26.9%]) had no immunisation details recorded. A recent history of consultation with a traditional healer prior to hospitalisation was elicited for 108 children (44%). Eight children (4%) had a history of a tuberculosis contact in the previous 12 months.

On bivariable analysis, factors found to be statistically significant determinants of mortality were a positive TB contact in the last 12 months (62.5% vs. 32.5%, OR=6.71, 95%CI 1.54, 29.33], $p<0.001$), a recent history of traditional healer consult (54.9% vs. 40.6%, OR=7.02, 95% CI 2.87, 17.23, $p< 0.001$) and the child being HIV positive (60.6% vs. 39.4%, OR=2.29, 95% CI 1.04, 5.08, $p=0.04$) (table 1). However, there were missing data for each of these variables in a sizeable proportion of participants. There was a trend towards children who had a previous hospitalisation for SAM and those on HIV antiretroviral therapy having a higher odds of dying, but this was not statistically significant.

Table 1. Sociodemographic and admission characteristics of children with SAM stratified by survival status (n=245)

Characteristic	All children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
Sex					
Male	144	41 (28.5)	103 (71.5)	1.21 (0.68 - 2.16)	0.52
Female	101	25 (24.8)	76 (75.2)	Reference	
Age (months)					
13-59	147	43 (29.3)	104 (70.7)	1.30 (0.73 – 2.34)	0.37
6 -12	98	23 (23.5)	75 (76.5)	Reference	
Admission type (SAM)					
Readmission	40	14 (35.0)	26 (65.0)	1.58 (0.77 - 3.26)	0.21
New admission	205	52 (25.4)	153 (74.6)	Reference	
Attending day care centre					
Yes	8	2 (25.0)	6 (75.0)	1.24 (6.34 - 0.80)	0.8
No	212	45 (21.2)	167 (78.8)	Reference	
Unknown	25	19 (76.0)	6 (24.0)		
Feeding practices					
Breastfed					
Yes	219	57 (26.0)	162 (74.0)	0.88 (0.27 - 2.92)	0.83
No	14	4 (28.6)	10 (71.4)	Reference	
Unknown	12	5 (41.7)	7 (58.3)		
Immunisation					
Missed immunization	66	18 (27.3)	48 (72.7)	1.56 (0.78 - 3.11)	0.21
Up to date	134	26 (19.4)	108 (80.6)	Reference	
Unknown	45	22 (48.9)	23 (51.1)		
HIV status of the child					
HIV positive					
Yes	33	13 (39.4)	20 (60.6)	2.29 (1.04 - 5.08)	0.04
No	154	34 (22.1)	120 (77.9)	Reference	
Unknown	58	19 (32.8)	39 (67.2)		
On ART					
Yes	12	4 (33.3)	8 (66.7)	4.40 (0.90 - 21.78)	0.06
No	16	5 (31.3)	11 (68.8)	Reference	
Unknown	5	2 (40.0)	3 (60.0)		
HIV exposed					
Yes	86	28 (32.6)	58 (67.4)	1.68 (0.93 - 3.05)	0.09
No	148	33 (22.3)	115 (77.7)	Reference	
Unknown	11	5 (45.5)	6 (54.5)		
Received PMTCT					
Yes	65	20 (30.8)	45 (69.2)	0.59 (0.12 - 2.90)	0.52
No	7	3 (42.9)	4 (57.1)	Reference	
Unknown	14	6 (42.9)	8 (57.1)		
TB Contact last 12 months					
Yes	8	5 (62.5)	3 (37.5)	6.71 (1.54 - 29.33)	0.004
No	191	38 (19.9)	153 (80.1)	Reference	
Unknown	46	23 (50.0)	23 (50.0)		
TB treatment current					

Yes	7	3 (42.9)	4 (57.1)	2.75 (0.59 - 12.74)	0.18
No	210	45 (21.4)	165 (78.6)	Reference	
Unknown	28	18 (64.3)	10 (35.7)		
Was child ever admitted to hospital before?					
Yes	71	20 (28.2)	51 (71.8)	1.91 (0.97 - 3.77)	0.06
No	141	24 (17.0)	117 (83.0)	Reference	
Unknown	33	22 (66.7)	11 (33.3)		
Consulted traditional healer					
Yes	32	19 (54.9)	13 (40.6)	7.02 (2.87 - 17.23)	<0.001
No	87	15 (17.2)	72 (82.8)	Reference	
Unknown	126	32 (25.4)	94 (74.6)		

Abbreviations: ART=antiretroviral therapy, CHC = community health centre, GP = general practitioner, OR=odds ratio, PMTCT= prevention of mother to child transmission, SAM = severe acute malnutrition, TB = tuberculosis

Table 2. Maternal and sociodemographic characteristics of children with SAM stratified by survival status (n=245)

Characteristic	All Children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
Mother					
Alive	239	63 (26.4)	176 (73.6)	0.36 (0.07 - 1.82)	0.20
Unknown	6	3 (50.0%)	3 (50.0%)	Reference	
Died	0				
Mother's marital status					
Single	61	9 (14.8%)	52 (85.2)	0.50 (0.21 - 1.22)	0.12
Married	70	18 (25.7)	52 (74.3)	Reference	
Unknown	114	39 (34.2)	75 (65.8)		
Mother's occupation					
Unemployed	177	42 (23.7)	135 (76.3)	1.87 (0.61 - 5.69)	0.27
Employed	28	4 (14.3)	24 (85.7)	Reference	
Unknown	40	20 (50)	20 (50)		
Caregiver					
Other (Grandmother, Father, Aunt, other relatives)	63	15 (23.8)	48 (76.2	0.80 (0.41 -1.56)	0.52
Mother	182	51(28.0)	131(72.0)	Reference	

Case definition and anthropometry

At admission, 96 children (39.2%) had nutritional oedema as the only admission criteria, 86 (35.1%) had a weight-for-height or -length z–score of <-3 and 63 (25.7%) had a MUAC <11.5 cm (table 3). Seventy-one children (29.0%) had a combination of case definition criteria, with the most common combination being a low WLZ and a low MUAC (11.0%). Seven children

(2.9%) met all three case definition criteria. None of the anthropometric indicators were predictors of mortality by themselves or in combination (table 4).

Table 3. Case definition of children with SAM stratified by survival status (n=245)

Characteristic	All children	Died No. (%)	Survived No. (%)	p-value
Case definition				
Nutritional oedema	96	30 (31.3)	66 (68.8)	0.47
Weight-for-length/height z-score < -3	86	21 (24.4)	65 (75.6)	
MUAC < 11.5 cm	63	15 (23.8)	48 (76.2)	
Case definition combinations				
Weight/length z-score < -3 and MUAC < 11.5 cm	29	5 (17.2)	24 (82.8)	0.23
Weight/length z-score < -3 and nutritional oedema	20	6 (30.0)	14 (70.0)	
MUAC < 11.5 cm and nutritional oedema	15	7 (46.7)	8 (53.3)	
Weight/length z-score < -3, MUAC < 11.5 cm and nutritional oedema	7	2 (28.6)	5 (71.4)	

Abbreviations: MUAC=mid upper arm circumference

Table 4. Anthropometric data of children with SAM stratified by survival status (n=245)

Characteristic	All children	Died No. (%)	Survived No. (%)	OR (95%CI)	p-value
Weight- for – length/height z-score					
< -3 z-score	92	21 (22.8)	71 (77.2)	1.6 (0.80 - 3.2)	0.19
≥ -3 z-score	121	19 (15.7)	102 (84.3)	Reference	
Unknown	32	26 (81.3)	6 (18.8)		
Mid upper arm circumference					
< 11.5 cm	97	24 (24.7)	73 (75.3)	1.5 (0.76 - 2.8)	0.25
≥ 11.5 cm	125	23 (18.4)	102 (81.2)	Reference	
Unknown	23	19 (82.6)	4 (17.4)		
Oedema					
Yes	138	42 (30.4)	96 (69.6)	1.7 (0.89 - 3.2)	0.11
No	80	17 (21.3)	63 (78.8)	Reference	
Unknown	27	7 (25.9)	20 (74.1)		

Referral and triage

Almost three-quarter of children (192 [73.4%]) were referred from a health facility or by a health practitioner - either a clinic, community health centre (CHC) or a general practitioner (table 5). Although the majority (206 [84.1%]) had a SAM diagnosis made prior to hospital ward admission, 35 children (14.3%) had the SAM diagnosis made only once in the ward.

For four children (1.6%) the diagnosis of SAM was first considered post-mortem during the death audit.

Self-referral (OR = 2.26, 95% CI 1.01, 5.09, p=0.04) was associated with higher mortality (table 5). Only one-quarter of the children (60 [25%]) were triaged using either the Emergency Triage Assessment and Treatment (ETAT) or South African Triage Scale (SATS) tools. Triage was mostly conducted at Donald Fraser Hospital (46 [76,7%]). However, use of a triage tool did not significantly influence mortality.

Table 5. Referral and site of diagnosis of children with SAM stratified by survival status (n=245)

Characteristic	All children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
Referral from:					
Self-referral	28	12 (42.9)	16 (57.1)	2.26 (1.01 - 5.09)	0.04
Health facility (clinic, CHC, district hospital. general practitioner)	192	42 (21.9)	150 (78.1)	Reference	
Unknown	9	4 (44.4)	5 (55.6)		
SAM diagnosis made at:					
Hospital	117	37 (31.4)	80 (68.6)	1.73 (0.96 – 3.09)	0.07
Clinic and CHC	123	26 (21.1)	97 (78.9)	Reference	
Unknown	5	3 (75.0)	2 (25.0)		
Triaged					
No	158	31 (19.6)	127 (80.4)	0.88 (0.43 – 1.83)	0.74
Yes	60	13 (21.7)	47 (78.3)	Reference	
Unknown	27	22 (81.5)	5 (18.5)		

Abbreviations: CHC=community health centre

Duration of illness and time to death

The mean (standard deviation [SD]) duration of the presenting complaint was 7 (6) days for children who died and 6 (7) days for survivors. The median (IQR) duration of prior ill-health was not statistically different for children who died compared to survivors (30 (14, 90) vs. 21 (7, 40) days, p=0.12). The median (IQR) length of hospital stay was shorter for children who died compared to survivors (5 (2, 10) vs. 11 (8, 18) days, p <0.001).

Presenting complaints

Diarrhoea was the most common presenting complaint, occurring in 41% of children (table 6). Vomiting and a poor appetite were two other commonly recorded symptoms, occurring in more than a quarter of children. Diarrhoea (OR=3.0, 95% CI 1.61, 5.5, p<0.001) and difficulty breathing (OR=4.7, 95% CI 2.01, 11.2, p<0.001) at presentation were statistically significant risk factors for death (table 6). Children described by caregiver's as having poor weight gain (OR=0.35, 95% CI 0.15, 0.81, p=0.01) were less likely to die (table 6). Poor appetite was not a determinant of mortality (OR=0.51, 95% CI 0.25, 1.03, p=0.06).

Initial assessment of critical signs

The presence of hypothermia, hypoglycaemia and dehydration was assessed by the doctor in only 144 (65.8%), 68 (31.6%) and 113 (52.3%) of children, respectively. Although measurements and dehydration assessment were done for more children by the nurses as depicted in table 7 below. When sought, the sign was identified in 7 (5%), 14 (20.6%) and 105 (92.5%) children, respectively. When identified, it was poorly managed in 4 (57.1%), 7 (50.0%) and 65 (61.9%) of instances, respectively.

The presence of an abnormal neurological status at admission increased the odds of dying by almost seven times (OR=6.9, 95% CI 3.1, 15.7, p<0.001). Shocked children with severe acute malnutrition had six-fold greater odds of dying (OR=6.4, 95% CI 1.9, 22.3, p=0.002), while those with severe respiratory distress were almost 20 times more likely to die (OR=19.9, 95% CI 7.2, 55.1, p<0.001). Children dehydrated on admission were about six times more likely to die compared to those without dehydration (OR=6.75, 95% CI 1.52, 29.98, p=0.01). Hypothermia increased death probability by five-fold (OR=4.94, 95% CI 1.07, 22.89, p=0.002). Hypoglycaemia at admission was not a statistically significant determinant of death (but was frequently not assessed).

Table 6. Presenting symptoms in children with SAM stratified by survival status (n=245)

Characteristic	All Children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
Diarrhoea					
Yes	101	37 (36.6)	64 (63.4)	2.97 (1.61 - 5.47)	<0.001
No	135	22 (16.3)	113 (83.7)	Reference	
Unknown	9	7 (77.8)	2 (22.2)		
Cough					
Yes	98	31 (31.6)	67 (68.4)	1.80 (0.99 - 3.27)	0.05
No	137	28 (2.04)	109 (79.6)	Reference	
Unknown	10	7 (70.0)	3 (30.0)		
Poor weight gain					
Yes	57	7 (12.3)	50 (87.7)	0.35 (0.15 - 0.81)	0.01
No	177	51 (28.8)	126 (71.2)	Reference	
Unknown	11	8 (72.7)	3 (27.3)		
Fever					
Yes	57	13 (22.8)	44 (77.2)	0.87 (0.43 - 1.75)	0.69
No	177	45 (25.4)	132 (74.6)	Reference	
Unknown	11	8 (72.7)	3 (27.3)		
Difficulty breathing					
Yes	25	14 (56.0)	11 (44.0)	4.74 (2.01 - 11.18)	<0.001
No	208	44 (21.2)	164 (78.8)	Reference	
Unknown	12	8 (66.7)	4 (33.3)		
Vomiting					
Yes	66	18 (27.3)	48 (72.7)	1.11 (0.58 - 2.10)	0.75
No	174	44 (25.3)	130 (74.7)	Reference	
Unknown	5	4 (80.0)	1 (20.0)		
Generalised body swelling					
Yes	29	9 (31.0)	20 (69.0)	1.34 (0.58 - 3.13)	0.50
No	211	53 (25.1)	158 (74.9)	Reference	
Unknown	5	4 (80.0)	1 (20.0)		
Poor appetite					
Yes	69	12 (17.4)	57 (82.6)	0.51 (0.25 - 1.03)	0.06
No	171	50 (29.2)	121 (70.1)	Reference	
Unknown	5	4 (80.0)	1 (20.0)		
Swelling of limbs					
Yes	40	12 (30.0)	28 (70.0)	1.34 (0.63 - 2.84)	0.44
No	198	48 (24.2)	150 (75.8)	Reference	
Unknown	7	6 (85.7)	1 (14.3)		
Oral sores					
Yes	27	10 (37.0)	17 (63.0)	1.81 (0.78 - 4.20)	0.16
No	212	52 (24.5)	160 (75.5)	Reference	
Unknown	6	4 (66.7)	2 (33.3)		

Table 7. Signs at time of presentation in children with SAM, stratified by survival status (n=245)

Characteristic	All Children	Died	Survived	OR (95% CI)	p-value
		No. (%)	No. (%)		
Neurological status					
Abnormal (lethargic, decreased consciousness)	51	21 (41.2)	30 (58.8)	6.94 (3.07 - 15.67)	<0.001
Normal	131	12 (9.2)	119 (90.8)	Reference	
Unknown	63	33 (53.2)	30 (47.6)		
Airway & breathing					
Severe respiratory distress	28	17 (60.7)	11 (39.3)	19.92 (7.20 - 55.10)	<0.001
Normal	125	9 (7.2)	116 (92.8)	Reference	
Unknown	92	40 (43.5)	52 (56.5)		
Shock (Circulation)					
Yes	16	9 (56.3)	7 (43.8)	6.43 (1.85 - 22.34)	0.002
No	48	8 (16.7)	40 (83.3)	Reference	
Unknown	181	49 (27.1)	132 (72.9)		
Dehydration					
Severe and some dehydration	108	36 (33.3)	72 (66.7)	6.75 (1.52 - 29.98)	0.01
No dehydration (Absent)	29	2 (6.9)	27 (93.1)	Reference	
Unknown	108	28 (25.9)	80 (74.1)		
Hypothermia					
Yes	7	4 (57.1)	3 (42.9)	4.94 (1.07 - 22.89)	0.03
No	207	44 (21.3)	163 (78.7)	Reference	
Unknown	31	18 (58.1)	13 (41.9)		
Hypoglycaemia					
Yes	14	6 (42.9)	8 (57.1)	1.90 (0.61 - 5.94)	0.26
No	106	30 (28.3)	76 (71.7)	Reference	
Unknown	125	30 (24.0)	95 (76.0)		
Pallor					
Yes	2	1 (50.0)	1 (50.0)	3.11 (0.19 - 50.49)	0.4
No	230	56 (24.3)	174 (75.7)	Reference	
Unknown	13	9 (69.2)	4 (30.8)		

Initial management

Antibiotics were prescribed in most children with SAM (196 (86.3%)). Almost two-thirds had intravenous fluids (139 (63.5%)) initiated on admission (table 8). Administration of intravenous fluids was associated with 3-fold increased odds of death (OR=3.39, 95% CI 1.49, 7.69, p=0.002).

Table 8. Initial management strategies in children with SAM stratified by survival (n=245)

Characteristic	All Children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
Hypoglycaemia management					
Poor	7	1 (14.3)	6 (85.7)	0.08 (0.01 - 1.26)	0.05
Appropriate	6	4 (66.7)	2 (33.3)	Reference	
Unknown	1				
Hypothermia management					
Poor	4	3 (75.0)	1 (25.0)	6.00 (0.22 - 162.53)	0.27
Appropriate	3	1 (33.3)	2 (66.7)	Reference	
Dehydration management					
Poor	65	23 (35.4)	42 (64.6)	1.70 (0.69 - 4.22)	0.25
Appropriate	37	9 (24.3)	28 (75.7)	Reference	
Unknown	6				
Antibiotics prescription					
Poor	112	18 (16.1)	94 (83.9)	0.46 (0.24 - 0.87)	0.02
Appropriate	115	34 (29.6)	81 (70.4)	Reference	
Unknown	18	14 (77.8)	4 (22.2)		
Supplement prescription					
Poor	99	24 (24.2)	75 (75.8)	1.52 (0.79 - 2.94)	0.21
Appropriate	121	21 (17.4)	100 (82.6)	Reference	
Unknown	25	21 (84.0)	4 (16.0)		
Intravenous fluids prescription					
Poor	109	32 (29.4)	77 (70.6)	2.12 (0.98 - 4.55)	0.05
Appropriate	67	11 (16.4)	56 (83.6)	Reference	
Unknown	69	23 (33.3)	46 (66.7)		

Compliance with WHO 10 steps of SAM management in the ward

a) **Monitoring**

Glucose and dehydration monitoring

Glucose and hydration monitoring was generally inadequately performed (supplementary table 1). Poor monitoring of hydration status increased the risk of dying in the first 24 hours

(OR=2.21, 95% CI 1.00, 4.90, p=0.05), with this becoming statistically significant at 25 to 48 hours after admission (OR=4.86, 95% CI 2.09, 11.31, p<0.001).

Feeds

Most children (82%) were fed in the first 24 hours; 81% of feeds were appropriate. Children who received F-75 feeds, compared to those who had standard formula or normal full ward diet had a reduced risk of death (OR=0.09, 95% CI 0.03, 0.27, p<0.001) at 0–24 hours.

Catchup growth

Severely malnourished children who had their growth monitored in the ward were less likely to die (OR=0.13, 95% CI 0.03, 0.65, p=0.004)**.**

Temperature

All three facilities satisfactorily prevented and treated hypothermia (Supplementary table 1).

b) Management

Dehydration management

Children who received poor rehydration management in the first 48 hours were significantly more likely to die (supplementary table 2); (OR=4.91, 95% CI 2.11, 11.38, p<0.001) at 24 hours and at 25 to 48 hours (OR=7.81, 95% CI 3.33, 18.35, p<0.001).

Feeds

Children who failed to receive three-hourly feeding in the first 24 hrs of admission were six-fold more likely to die (OR=6.51, 95% CI 2.26, 18.70, p<0.001).

Supplements

Supplements consisted of zinc and multivitamins. The odds of death was not statistically significant for children offered supplements (OR=0.35, 95% CI 0.12, 1.03, p=0.05) at 0–24 hrs.

Laboratory investigations

The most frequent investigations undertaken were a full blood count, urea and electrolytes, and a C-reactive protein (CRP). Abnormalities associated with mortality on bivariable analysis included an elevated CRP (>12) (OR=7.54, 95% CI 2.93, 21.06, p<0.001), hyponatraemia (< 130 mmol/L) (OR=4.65, 95% CI 2.36, 9.16, p<0.001), hypokalaemia (< 3.5 mmol/L) (OR=2.88, 95% CI 1.50, 5.51, p=0.001) and hypoalbuminaemia (< 30 mmol/L) (OR=2.77, 95% CI 0.98, 7.82, p=0.048) (supplementary table 2). Absence of mycobacterium tuberculosis on sputum Gene-Xpert (OR=0.18, 95% CI 0.04, 0.98, p=0.03) was associated with better survival. A high white cell count or raised serum transaminases did not change mortality risk.

Determinants of mortality (multivariable analysis)

Table 9 presents the results of the multivariable analysis. The odds of dying were almost three times higher for children who presented with diarrhoea (OR=3.34, 95% CI 1.38, 8.10, p=0.008). Additionally, children with SAM who had anaemia (Hb < 10 g/dl) were thrice more likely to die (OR=3.30, 95% CI 1.28, 8.50, p=0.014). Children with a raised CRP (> 12) (OR=9.29, 95% CI 2.81, 30.76, p<0.001) and hyponatraemia (OR=6.64, 95% CI 2.70, 16.31, p<0.001) within the first 48 hours of admission had an increased likelihood of mortality.

Table 9. Multivariable analysis of determinants of mortality for categorical variables

Variable				
Characteristic	**Crude OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Sex				
Male	1.21 (0.68 - 2.16)	0.52	1.17 (0.64 - 2.13)	0.61
Female	Reference		Reference	
Age (months)				
13 – 59	1.30 (0.73 - 2.34)	0.37	1.17 (0.64 - 2.15)	0.61
6 -12 months	Reference		Reference	
HIV positive				
Yes	2.29 (1.04 - 5.08)	0.04	1.36 (0.53 - 3.49)	0.52
No	Reference		Reference	
HIV exposed				
Yes	1.68 (0.93 - 3.05)	0.09	1.77 (0.97 - 3.23)	0.06
No	Reference		Reference	
TB contact last 12 months				
Yes	6.71 (1.54 - 29.33)	0.004	4.03 (0.62 - 26.31)	0.146
No	Reference		Reference	
Ever admitted to hospital previously				
Yes	1.91 (0.97 - 3.77)	0.06	2.12 (0.99 - 4.53)	0.05
No	Reference			
Oedema				
Yes	1.7 (0.89 - 3.2)	0.11	1.67 (0.87 - 3.19)	0.12
No	Reference		Reference	
Diarrhoea				
Yes	2.97 (1.61 - 5.47)	<0.001	3.34 (1.38 - 8.10)	0.008
No	Reference		Reference	
Cough				
Yes	1.80 (0.99 - 3.27)	0.05	1.47 (0.77 - 2.83)	0.25
No	Reference		Reference	
Poor weight gain				
Yes	0.35 (0.15 - 0.81)	0.01	0.53 (0.22 - 1.30)	0.17
No	Reference		Reference	
Difficulty breathing				
Yes	4.74 (2.01 - 11.18)	<0.001	3.41 (0.90 - 13.01)	0.072
No	Reference		Reference	
Poor appetite				
Yes	0.51 (0.25 - 1.03)	0.06	0.65 (0.31 -1.37)	0.25
No	Reference		Reference	
Referral from:				

Self-referral	2.26 (1.01 - 5.09)	0.04	2.22 (0.74 - 6.62)	0.154
Health facility (clinic, CHC, District hospital. General practitioner)	Reference		Reference	
SAM diagnosis made at:				
Hospital	0.64 (0.36 -1.13)	0.12	0.81 (0.33 - 1.97)	0.64
Clinic, General practitioner and Community health centre	Reference		Reference	
Haemoglobin (Hb) (g/dL)				
Anaemia (Hb <10)	1.90 (0.99 -3.63)	0.05	3.30 (1.28 - 8.50)	0.014
Normal ≥10	Reference		Reference	
C-reactive protein (CRP) (mg/dL)				
≥12	7.54 (2.93 - 21.06)	<0.001	9.29 (2.81 - 30.76)	<0.001
<12	Reference		Reference	
Sodium (Na+) (mmol/L)				
Hyponatraemia (<130)	4.65 (2.36 - 9.16)	<0.001	6.64 (2.70 - 16.31)	<0.001
Normal (≥130)	Reference		Reference	
Potassium (K) (mmol/L)				
Hypokalaemia (<3.5)	2.88 (1.50 - 5.51)	0.001	1.91 (0.79 - 4.60)	0.15
Normal (≥ 3.5)	Reference			

Child Problem Identification Programme

Modifiable factors that were identified by clinicians during the Child Health Identification Programme mortality audit were mostly clinical personnel related factors, (supplementary table 3). Home level factors that contributed to mortality were inadequate quality of food (50 [78%]), caregiver delay in seeking medical care (40 [61%]), caregiver not recognising danger signs or severity of illness (40 [61%]) and giving traditional remedies with negative outcome to the child (20 [30%]). Minimal contributory factors were identified at clinic and referral facility level. The admission area and ward had several contributory factors identified, mostly related to clinicians' practices such as inadequate history taking (22 [33%]) and physical examination

(12 [18%]), inadequate assessment of shock (15 [23%]) and HIV and TB, inadequate monitoring of blood glucose, no handover of critically ill children by the admitting doctor to the ward doctor (12 [18%]) and inadequate review of children with severe dehydration (17 [26%]), amongst others.

DISCUSSION

The study identified diarrhoea, anaemia, a raised CRP, and hyponatraemia as significant factors contributing to mortality among children younger than five years admitted with severe acute malnutrition to three hospitals in Vhembe district, Limpopo Province.

Mortality rate

The overall case-fatality rate was 26.9% which is much higher than the international and national standards for children with SAM.[1,11,28,29] The WHO has suggested that a 5% SAM mortality is reasonable.[1,] The high mortality rate found is consistent with that found in a previous study conducted in another district in the same province published in 2020 which reported a 25.9% mortality rate, and in a 2017 Ugandan study.[20,30] However, the mortality rate differs starkly from recent SAM mortality rates reported in other sub-Saharan African settings of 8-17%,[13,17–19] and the South African national data for the period corresponding to the study period of 7.1% to 8.9%, as captured by routine health information data systems.[11,12] The mortality rate also differs from the Vhembe district's reported SAM mortality rate of 7.4% and 7.2% for the study period.[29,31]

It is likely that the study mortality rate is a better reflection of the true mortality rate in the district compared to other estimates, since the study tried to identify all children who had SAM (including those who may have been misclassified and missed) and used stringent SAM classification criteria. Few SAM deaths are likely to have occurred in non-hospital settings and

care at the three selected hospitals is unlikely to differ markedly from that in other hospitals in the district.

Some of the difference compared to other studies could be due to differences in study design,[14,32] exclusion of critically ill children with SAM in those studies,[33] and the type of hospital in which those studies were conducted. Tertiary and regional facilities having the availability of a paediatrician, unlike the two district hospitals in our study where services are provided by community service doctors and medical officers, could be expected to have different mortality rates. [34]

The high mortality in our study is postulated to relate to children's condition on arrival, practitioner expertise, patient-nurse ratios and poor case management and inadequate adherence to SAM treatment guidelines (as explained later), but none of these hypotheses can be adequately defended based on the study findings alone. The difference in SAM case fatality rates between the two district hospitals (Malamulele Hospital (34%) and Donald Fraser Hospital (22.9%)) supports this view. The high (22.9%) case fatality at the regional hospital, Tshilidzini, is disturbing, considering that it had paediatricians conducting daily rounds on-site. Subtle differences, such as Donald Fraser Hospital triaging children during admission, with the triage tool incorporated into their nursing admission tool, were noted during the study but were not subjected to analysis, since examining differences in hospital practices was not a study objective.

Causes of death

Diarrhoea was the most common cause of death within the first 24 hours of admission and the prevalent complication that accompanied these deaths was hypovolaemic shock. Many studies show that diarrhoea is a risk factor for death among malnourished children, but most studies do not indicate timing of death in those with diarrhoea.[14,35–37] Poor fluid management and monitoring contribute towards malnourished children with diarrhoea dying early. Children who

died after 24 hours had their immediate cause of death often related to infection (pneumonia, sepsis, septic shock) or the consequences of fluid and electrolyte or organ dysfunction (e.g., hypovolaemic shock, hypoglycaemia, acute kidney injury).

Mortality timing

Almost two-thirds of deaths occurred within the first week of admission. Similar finds were reported in Ghana and Uganda.[18,30,32] The first twenty-four-hour mortality of 21% in our study is lower than that reported by Kenyan and Zambian studies which reported a mortality of 40% and 29% respectively.[4,38] Their higher 24-hour mortality could be due to them being tertiary hospitals admitting children who were more severely ill and who had multiple co-morbid conditions.

In contrast, another study conducted in the same province as ours reported a much lower 24 hour mortality of 14.1%.[20] This difference could be related to the child's condition at time of presentation (since late presentation to the hospital is not infrequent in our setting because of caregivers' first point of care-seeking being the traditional healer or a faith healer), lower clinician skills in case management and poorer adherence to protocols. The median time to death was 101 hours (4 days), not much different from an Ethiopian study which reported three days as the time to death.[39]

Determinants of mortality

Children with SAM who presented with diarrhoea had a three-fold higher likelihood of death. Diarrhoea is a major cause of mortality in children aged under five years and it is amongst the most common co-morbid condition with negative outcomes for children with severe acute malnutrition.[14,35–37,40] Children with SAM often have gut barrier dysfunction and bacterial overgrowth which makes them prone to diarrhoea.[41]

Children with anaemia were also thrice more likely to die. This finding concurs with previous studies.[20,42,43] Two Indonesian studies found that children with SAM and anaemia were almost

nine-fold and four-times more likely to die, respectively.[44,45] The poor dietary diversity in children with severe acute malnutrition and infections contribute to development of anaemia, as does blood loss from worm infestation, for example.

Children with raised C-reactive protein (CRP) were nine times more likely to die. Raised CRP reflects inflammation and infection, which are known comorbid conditions associated with severe acute malnutrition and recognised to increase mortality in children with SAM.[33,46] Electrolyte imbalance is common in children with SAM and can be compounded by the comorbid diarrhoea.

Our study identified hyponatraemia within the first 72 hours of admission to be associated with poor outcomes. This finding is similar to a study in India, where children with SAM having hyponatraemia were found to be seven times more likely to die.[47]

Unlike other studies, our study did not identify factors such as age, sex, breastfeeding practice, poor appetite, poor weight gain, anthropometric measurements (mid upper arm circumference, weight for height), shock, and HIV to be contributors to mortality.[6,20,48–51] Our study design – a retrospective record review – could explain our failure to identify these additional associations since poor history-taking or limited recording of findings (such as poor appetite and poor weight gain at presentation,), inadequate investigation (e.g., almost a quarter of children's HIV status was not recorded and poor documentation of clinical findings and management (e.g. shock in the admission area and ward, poor hydration reviews and management) might have resulted in the contribution of these determinants being under-recognised. The finding of poor reported weight gain as protective of mortality during bivariable analysis was unexpected and paradoxical. It may relate to mother's who identified poor growth in their child being more alert and responsive to their child's needs, although the child still ended up being malnourished, but of lesser severity.

Clinical malnutrition syndromes

More children in our study (56%) had oedematous rather than non-oedematous SAM. This finding in unusual in South African settings. Two recently published South African studies reported non-oedematous SAM to be more prevalent at 65% and 61%, respectively.[20,49] A Zambian study and a Ugandan study, nevertheless, described 62% and 66% of SAM children having kwashiorkor (oedematous SAM) respectively.[4,14] The clinical syndrome type is recognised to influence outcome with oedematous SAM having a poorer initial outcome, including death, but with better long-term outcomes.[52,53]

HIV and TB

HIV and TB are known to cause severe wasting and have been reported to be associated with negative outcomes in children with severe acute malnutrition in the South African setting and in other countries.[49,54–58] Although there was a statistically significant association of TB contact and HIV positive status with death on bivariable analysis in the current study, this association became insignificant during multivariate analysis. The failure to find an association could be a result of a poor work-up for possible TB and low number of HIV-infected children in the study.

Care and management

The health professionals responsible for caring for children did not always adhere to the national standard treatment guidelines or the WHO 10 steps of SAM management, with poor management of hypoglycaemia, dehydration, and electrolyte imbalance, in particular. Multiple earlier studies have alluded to poor adherence to WHO severe acute malnutrition guidelines as a contributor to mortality.[18,38] The retrospective nature of this study did not allow for interrogation of the underlying cause for deficiencies. Neither did it allow for any conclusions about whether factors such as health care workers skills and experience, and high staff turnover might be contributing to poor adherence to guideline

Modifiable factors

The modifiable factors that contributed to death were examined at three levels; namely home, at the time of admission and in the ward.[26] At home level, the three factors that emerged that required attention were recognising danger signs, getting caregivers to seek medical care earlier, and highlighting the dangers of using herbal medicine. Admission level modifiable factors identified included no handover of critically ill patients by the admitting doctor to the ward doctor or, inadequate history taking and shock assessment for early deaths, while for late deaths inadequate physical examination on admission and failure to institute a rehydration plan contributed to death. Specific deficiencies identified included insufficient charting of clinical care, unsatisfactory continuous monitoring of hydration status in children with severe dehydration, infrequent blood glucose monitoring, and incomplete HIV and TB assessments.

Preventive and promotive measures

A potentially addressable cause of SAM deaths is infection prevention through immunisation. Only one-half of children had their immunisations up to date. A multicentre study revealed that children with SAM who are partially or not vaccinated are 1.9 and 1.6 times more likely to die, respectively, compared to those fully vaccinated.[59]

Study strengths

The main strength of this study is that it comprehensively examined the full set of possible determinants of mortality extending from sociodemographic factors to referral and triage, presenting symptoms and signs, management through the entire stay (including investigations, laboratory findings and therapeutic choices). Further it specifically reviewed modifiable factors at the home, referral, and hospital level. Extensive screening of possible eligible cases and stringent application of qualifying anthropometric criteria is another strength. Finally,

subjecting the extensive dataset to a multivariable analysis assisted in identifying a subset of priority factors requiring attention.

Study limitations

The limitation of the study mainly relates to the study design and its reliance on patient records. A sizeable proportion of hospital records could not be retrieved because of a dysfunctional record filing system and missing records. A poor level of recording of pertinent patient detail, such as dietary history, anthropometric measurements, clinical information, and management was anticipated and materialised. This was partially compensated for by, for instance, re-calculating all anthropometric z-scores and extracting data from all available patient management data sources. A large amount of missing data for several variables hindered adequate multivariable analysis.

Recommendations

A sizeable set of recommendations have emerged to respond to the study findings. Three priority recommendations to reduce the high SAM mortality in the study setting are highlighted below. First, a system of red flagging children with SAM with identified risk factors for special attention and care from the time of arrival at the hospital is warranted. Secondly, induction programmes for interns and community service doctors (who mostly manage these children) need to specifically include training on SAM management guidelines and childhood diarrhoeal disease management, with a focus on the deficiencies identified in our study. A specific focus on SAM treatment guidelines during consultant outreach visits and quarterly monitoring of adherence to management guidelines is warranted. Finally, the conduct and outcomes of monthly and quarterly mortality and morbidity meetings involving individual hospitals and the wider health service need to be modified to specifically address modifiable factors and recurring practice deficiencies rather than merely reporting and acknowledging these.

CONCLUSION

This SAM mortality rate at the study hospitals was much higher than that recommended by national and international standards. Diarrhoea, anaemia, a raised CRP and hyponatraemia at presentation were identified as key determinants of mortality in children with severe acute malnutrition. Although these risk factors have been identified in previous studies, recognition of their particular importance in the study setting may assist in galvanising efforts to prioritise addressing these, while acknowledging the need to also attend to the multiple other risk factors identified.

Author contributions

DF, TM and HS conceived and designed the study

DF collected, analysed the data and wrote first draft. All authors edited the manuscript and approved the final version.

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Competing interest

The authors declare that they have no competing interest

Availability of data and materials

Data is available from the corresponding author upon reasonable request

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SUPPLEMENTARY TABLES

Supplementary Table 1. Compliance with WHO 10 steps of SAM management stratified by survival status (n=245)

Characteristic	All Children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
Blood sugar monitoring (0 - 24 hrs)					
Appropriate	19	8 (42.1)	11 (57.9)	Reference	
Poor	198	37 (18.7)	161 (81.3)	0.32 (0.12 - 0.84)	0.02
Unable to assess	28	21 (75.0)	7 (25.0)		
Blood sugar management (0 - 24 hrs)					
Appropriate	41	9 (22.0)	32 (78.0)	Reference	
Poor	37	6 (16.2)	31 (83.3)	0.69 (0.22 - 2.16)	0.52
Unable to assess	167	51 (30.5)	116 (69.5)		
Blood sugar monitoring (25 - 48 hrs)					
Appropriate	29	9 (31.0)	20 (69.0)	Reference	
Poor	175	27 (15.4)	148 (84.6)	0.41 (0.17 - 0.98)	0.04
Unable to assess	41	30 (73.2)	11 (26.8)		
Blood sugar management (25 - 48 hrs)					
Appropriate	57	11 (19.3)	46 (80.7)	Reference	
Poor	33	7 (21.2)	26 (78.8)	1.13 (0.39 - 3.26)	0.83
Unable to assess	155	48 (33.1)	107 (73.8)		
Temperature monitoring (0 - 24 hrs)					
Appropriate	216	45 (20.8)	171 (79.2)	Reference	
Poor	5	0 (0.0)	5 (100.0)	1.26 (1.18 - 1.35)	0.25
Unable to assess	24	21 (87.5)	3 (12.5)		
Temperature management (0 - 24 hrs)					
Appropriate	218	44 (20.2)	174 (79.8)	Reference	
Poor	1	1 (100.0)	0 (0.0)	4.96 (3.81 - 6.45)	0.05
Unable to assess	26	21 (80.7)	5 (19.2)		
Temperature monitoring (25 - 48 hrs)					
Appropriate	207	35 (16.9)	172 (83.1)	Reference	
Poor	2	0 (0.0)	2 (100.0)	1.20 (1.13 - 1.28)	0.52
Unable to assess	36	31 (86.1)	5 (13.8)		
Temperature management (25 - 48 hrs)					
Appropriate	207	36 (17.4)	171 (82.6)	Reference	
Poor	4	0 (0.0)	4 (100.0)	1.21 (1.14 - 1.29)	0.36
Unable to assess	34	30 (88.2)	4 (10.8)		
Hydration status monitoring (0 - 24 hrs)					
Appropriate	96	14 (14.6)	82 (85.4)	Reference	
Poor	62	17 (27.4)	45 (72.6)	2.21 (1.00 - 4.90)	0.05
Unable to assess	87	35 (40.2)	52 (59.8)		

Rehydration management (0 - 24 hrs)					
Appropriate	92	9 (9.8)	83 (90.2)	Reference	
Poor	72	25 (34.7)	47 (65.3)	4.91 (2.11 -11.38)	<0.001
Unable to assess	81	32 (39.5)	55 (63.2)		
Hydration status monitoring (25 - 48 hrs)					
Appropriate	112	11 (9.8)	101 (90.2)	Reference	
Poor	52	18 (34.6)	34 (65.4)	4.86 (2.09 -11.31)	<0.001
Unable to assess	17	37 (45.7)	44 (54.3)		
Rehydration management (25 - 48 hrs)					
Appropriate	113	10 (8.8)	103 (91.2)	Reference	
Poor	51	22 (43.1)	29 (56.9)	7.81 (3.33 -18.35)	<0.001
Unable to assess	81	34 (42.0)	47 (58.0)		
Feeds (F75) (0 - 24 hrs)					
Not given	16	11 (68.8)	5 (31.3)	Reference	
Given	201	33 (16.4)	168 (83.6)	0.09 (0.03 - 0.27)	<0.001
Unknown	28	22 (78.6)	6 (21.4)		
Feeds (F75) management (0 - 24 hrs)					
Appropriate	200	33 (16.5)	167 (83.5)	Reference	
Poor	16	9 (56.3)	7 (43.8)	6.51 (2.26 -18.70)	<0.001
Unable to assess	29	24 (82.7)	5 (17.2)		
Feeds(F75) (25 - 48 hrs)					
Not given	3	1 (33.3)	2 (66.7)	Reference	
Given	204	34 (16.7)	170 (83.3)	0.40 (0.04 - 4.54)	0.45
Unable to assess	38	31 (81.8)	7 (18.4)		
Feeds (F75) management (25 - 28 hrs)					
Appropriate	199	33 (16.6)	166 (83.4)	Reference	
Poor	7	1 (14.3)	6 (85.7)	0.84 (0.10 - 7.20)	0.87
Unable to assess	39	32 (82.1)	7 (17.9)		
Antibiotics (Ampicillin & Gentamicin) (0 - 24 hrs)					
Not given	20	3 (15.0)	17 (85.0)	Reference	
Given	198	44 (22.2)	154 (77.8)	1.62 (0.45 - 5.78)	0.45
Unable to assess	27	19 (70.4)	8 (29.6)		
Antibiotics management (0 - 24 hrs)					
Appropriate	130	33 (25.4)	97 (74.6)	Reference	
Poor	89	14 (15.7)	75 (84.3)	0.55 (0.27 - 1.10)	0.09
Unable to assess	26	19 (73.1)	7 (26.9)		
Antibiotics (Ampicillin & Gentamicin) (25 - 48 hrs)					
Not given	11	1 (9.1)	10 (90.1)	Reference	
Given	197	36 (18.3)	161 (81.7)	2.24 (0.28 -18.03)	0.44
Unable to assess	37	29 (78.4)	8(21.6)		
Antibiotics management (25 - 48 hrs)					
Appropriate	145	33 (22.8)	112 (77.2)	Reference	
Poor	64	4 (6.2)	60 (93.8)	0.23 (0.08 - 0.67)	0.004
Unable to assess	36	29 (80.6)	7 (19.4)		
Potassium (0 - 24 hrs)					

Not given	169	25 (14.8)	144 (85.2)	Reference	
Given	43	19 (44.2)	24 (55.8)	4.56 (2.18 - 9.53)	<0.001
Unable to assess	33	22 (66.7)	11 (33.3)		
Potassium management (0 - 24 hrs)					
Appropriate	158	30 (19.0)	128 (81.0)	Reference	
Poor	43	14 (32.6)	29 (67.4)	2.06 (0.97 - 4.37)	0.06
Unable to assess	44	22 (50.0)	22 (50.0)		
Potassium (25 - 48 hrs)					
Not given	142	17 (12.0)	125 (88.0)	Reference	
Given	60	19 (31.7)	41 (68.3)	3.41 (1.62 - 7.17)	0.001
Unable to assess	43	20 (46.5)	23 (53.5)		
Potassium management (25 - 48 hrs)					
Appropriate	173	29 (16.8)	144 (83.2)	Reference	
Poor	20	7 (35.0)	13 (65.0)	2.67 (0.98 - 7.28)	0.05
Unable to assess	52	30 (57.7)	22 (42.3)		
Supplements (0 - 24 hrs)					
Not given	15	6 (40.0)	9 (60.0)	Reference	
Given	203	38 (18.7)	165 (81.3)	0.35 (0.12 - 1.03)	0.05
Unable to assess	27	22 (81.5)	5 (18.5)		
Supplements management (0 - 24 hrs)					
Appropriate	166	30 (18.1)	136 (81.9)	Reference	
Poor	52	14 (26.9)	38 (73.1)	1.67 (0.81 - 3.46)	0.17
Unable to assess	27	22 (81.5)	5 (18.5)		
Supplements (25 - 48 hrs)					
Not given	9	3 (33.3)	6 (66.7)	Reference	
Given	197	31 (15.7)	166 (84.3)	0.37 (0.09 - 1.57)	0.16
Unable to assess	39	32 (82.1)	7 (17.9)		
Supplements management (25 - 48 hrs)					
Appropriate	178	28 (15.7)	150 (83.4)	Reference	
Poor	29	7 (24.1)	22 (75.9)	1.71 (0.67 - 4.37)	0.26
Unable to assess	38	35 (92.1)	3 (7.9)		
Catch-up growth					
Not done	7	3 (42.9)	4 (57.1)	Reference	
Done	187	17 (9.1)	170 (90.9)	0.13 (0.03 - 0.65)	0.004
Unable to assess	51	46 (90.2)	5 (9.8)		
Catch-up growth appropriately carried out					
Appropriate	177	15 (8.5)	162 (91.5)	Reference	
Poor	16	5 (31.3)	11 (68.8)	4.91 (1.51 - 16.01)	0.004
Unable to assess	52	46 (88.5)	6 (11.5)		
Stimulation					
Not done	112	12 (10.7)	100 (89.3)	Reference	
Done	78	7 (9.0)	71 (91.0)	0.82 (0.31 - 2.19)	0.69
Unable to assess	55	47 (85.5)	8 (14.5)		
Stimulation appropriately carried out					
Appropriate	50	3 (6.0)	47 (94.0)	Reference	

Poor	138	15 (10.9)	123 (89.1)	1.91 (0.53 - 6.90)	0.32
Unable to assess	57	48 (84.2)	9 (15.8)		

Unable to assess= there's doctor order but no accompanying management chart or allied health notes. Not done= no doctor's order, no allied health notes and no management chart.

Supplementary Table 2. Laboratory results in the first 72 hours in children with SAM stratified by survival status (n=245)

Characteristic	All Children	Died No. (%)	Survived No. (%)	OR (95% CI)	p-value
White cell count(wcc) (x109/L)					
≥12	141	37 (26.2)	104 (73.8)	1.63 (0.82 - 3.24)	0.16
<12	78	14 (17.9)	64 (82.1)	Reference	
Unknown	26	15 (57.7)	11 (42.3)		
Haemoglobin (Hb) (g/dL)					
Anaemia (Hb <10)	116	33 (28.4)	83 (75.6)	1.90 (0.99 -3.63)	0.05
Normal	104	18 (17.3)	86 (82.7)	Reference	
Unknown	25	15 (60.0)	10 (40.0)		
C-Reactive Protein (CRP) (mg/dL)					
≥12	112	41 (36.6)	71 (63.4)	7.54 (2.93 - 21.06)	<0.001
<12	73	5 (6.8)	68 (93.2)	Reference	
Unknown	60	20 (33.3)	40 (66.7)		
Sodium (Na^+) (mmol/L)					
Hyponatraemia <130	57	26 (45.6)	31 (54.4)	4.65 (2.36 - 9.16)	<0.001
Normal ≥130	157	24 (15.3)	133 (84.7)	Reference	
Unknown	31	16 (51.6)	15(48.4)		
Potassium(K) (mmol/L)					
Hypokalaemia (k^+ <3.5)	78	28 (35.9)	50 (64.1)	2.88 (1.50 - 5.51)	0.001
Normal ≥ 3.5	135	22 (18.5)	113 (83.7)	Reference	
Unknown	32	16 (50.0)	16 (50.0)		
Albumin (g/L)					
Hypolbuminaemia <30	96	29 (30.2)	67 (69.8)	2.77 (0.98 -7.82)	0.048
Normal albumin >30	37	5 (13.5)	32 (86.5)	Reference	
Unknown	112				
Alanine transaminase (ALT) (U/L)					
Raised ALT (> 40)	44	13 (29.5)	31 (70.5)	1.36 (0.58 - 3.16)	0.48
Normal ≤ 40	72	17 (23.6)	55 (76.4)	Reference	
Unknown	129	36 (27.9)	93 (72.1)		
Aspartate transaminase (AST) (U/L)					
Raise AST (>35)	96	24 (25.0)	72 (75.0)	0.67 (0.24 - 1.85)	0.43
Normal ≤35	21	7 (33.1)	14 (66.7)	Reference	
Unknown	128	35 (27.3)	93 (72.7)		
TB workup					
MTB not detected	66	8 (12.1)	58 (87.9)	0.18 (0.04 - 0.98)	0.03
Patient already on treatment	7	3 (42.9)	4 (57.1)	Reference	
Unknown	172	55 (32.0)	117 (68.0)		
Urine dipsticks					

Leukocytes present	3	1 (33.3)	2 (66.7)	2.02 (0.18 - 23.33)	0.57
Normal	111	22 (19.8)	89 (80.2)	Reference	
Unknown	131	43 (32.8)	88 (67.2)		
Urine MCS					
Positive	11	2 (18.2)	9 (81.8)	0.22 (0.02 - 2.04)	0.17
Negative	6	3 (50.0)	3 (50.0)	Reference	
Unknown	228	61 (26.8)	167 (73.2)		
Blood culture					
Positive	23	8 (34.8)	15 (65.2)	0.33 (0.08 - 1.36)	0.12
Negative	13	8 (61.5)	5 (38.5)	Reference	
Unknown	209	50 (24.1)	159 (76.1)		

Supplementary Table 3. Child PIP data on modifiable factors of death of children with SAM (n=66)

Where	Whom					
	Caregiver		**Clinical personnel**		**Administrator**	
	Description	**No. (%)**	**Description**	**No. (%)**	**Description**	**No. (%)**
Home						
	Child not provided with adequate food	50 (75.8)				
	Caregiver did not recognize danger signs/ severity of illness	40 (60.1)				
	Traditional remedy given from traditional healer with negative effect on child	20 (30.3)				
Clinic/ Outpatient						
			IMCI not used	6 (9.1)	No plan for transporting child to receiving facility	3 (4.5)
			Missed SAM classification	3 (4.5)		
Referring facility						
			Delayed referral to higher level of care	3 (4.5)	Lack of high care in own facility	1 (1.5)
Admission area & Emergency unit						
			Inadequate history	22 (33.3)		
			Inadequate assessment of shock	15 (22.7)		
			Child not triaged	13 (19.7)		
			Inadequate physical examination	12 (18.2)		
			No handover of critically ill children from admitting doctor to ward doctor	12 (18.2)		

			Inadequate rehydration plan 7/66	7 (10.6)		
			Shock not monitored while awaiting ward admission	3 (4.5)		
Ward						
			Inadequate monitoring of blood glucose	21 (31.8)	Lack of high care in own facility	1 (1.5)
			Inadequate review of child with severe dehydration	17 (25.8)		
			Inadequate TB assessment	12 (18.2)		
			Insufficient notes on clinical care	11 (16.7)		
			Inadequate history taking	10 (15.2)		
			Inadequate HIV review in ward	6 (9.1)		
			Inadequate monitoring of shocked SAM child	6 (9.1)		
			WHO 10 steps not followed	4 (6.1)		
			Inadequate septic workup	4 (6.1)		

APPENDICES

Appendix A Data collection tool

Data collection sheet (Determinants of mortality in children admitted with SAM)

Study reference details

Child demographic details

1.	**Study No**					
2.	**Hospital name**	1=Tshilidzini	2= Malamulele	3=Donald Fraser		
3.	**DOA**	/ /201_				
4.	**Admission type**	1= New	2= Readmission			
5.	**DOD**	/ /201__				
6.	**Status**	1=Discharge	2=Death	3=Transfer	4= RHT	9=Other
7.	**Length of hospital stay**	_____ days				
8.	**Case definition**	1=Wt/length (ht)	2=MUAC	3=nutritional oedema		

9.	**Age**	_____ months	**10.**	Residential area_____						**11.**	Nearest clinic_____
12.	**Caregiver**	1=mother	2=father	3=granny	4= aunt	5=uncle	6=older sibling	7=other relatives	9=other	**13.**	**Attending day care Centre** 1=Yes 2=No

Anthropometry

14.	**Wt**	kg	**15.**	**Height**	cm	**16.**	**MUAC**	Cm
17.	**Wt/age z-score**		**18.**	**Ht/age z-score**		**19.**	**Wt/Ht z-score**	
20.	**Oedema on admission**	1=Yes 2=No 3=unknown						

Family details

21.	**Mother**	1=Alive			2=Dead		
	(a)Age	_____Years					
	(b) Marital status	1=Single	2=Married	3=Separated	4=Unknown	9=Other _____	
	(c) Occupation	1=Employed	2=Unemployed	3=Farmer	4=Salesman	9=Other _____	
	(d) Highest level achieved	1=None	2= Grade_____	3= Tertiary education	4= unknown	9=Other _____	
22.	**Father**	1=Alive	2=Dead	3=Unknown			
	(a) Age	_____Years					
	(b) Marital status	1=Single	2=Married	3=Separated	4=Unknown	9=Other	
	(c) Occupation	1=Employed	2=Unemployed	3=Farmer	4=Salesman	9=Other	
	(d) Highest level achieved	1=None	2= Grade_____	3= Tertiary education	4= unknown	9=Other	
23.	**Primary caregiver (if not mother)**						
	(a)Relationship with child	1= Grandmother	2= Grandfather	3= Aunt	4= Uncle	5= Older sibling	6= cousin	7= other relatives	9=other
	(b)Age	_____Years					
	(c)Sex	1= Female	2= Male				
	(d)Marital status	1=Single	2=Married	3=Separated	4=Unknown	9=Other	
	(e)Occupation	1=Employed	2=Unemployed	3=Farmer	4=Salesman	9=Other	
	(f)Highest level achieved	1=None	2= Grade_____	3= Tertiary education	4= unknown	9=Other	
24.	**Siblings**	Total no.	How many dead				
	Ages	**1_____months**	**2**_____	**3**	**4**_____	**5**_____	
		6_____ **7**_____					

Feeding practices

		Given	Standard met			
53.	**Antibiotics**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND
54.	**Supplements**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND
55.	**Fluids**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND

25.	**Was the child ever breastfed/still breastfeeding?**	1=Yes	2=No	3= Never	**26.**	**Total duration of Breastfeeding** _____months		
27.	**How long was child Exclusively Breastfed**	_____months	**28.**	**Complimentary feeds initiated at** _____months				
29.	**Current diet**	1=Vegetables	2=Green leaves	3=Fruits	4=Red meat	5=chicken	6=liver	7=egg
		8=fish	9=other	10=maas	11=Tea	12=bread		13=Pap
		14=Cow's milk	15=soft porridge					

Past medical history

30.	**HIV**	(a)Positive 1=Yes 2=No	(b)If positive, on HAART? 1=Yes 2=No 3=defaulted	(c) HIV exposed 1=Yes 2=No	(d)Received PMTCT 1=Yes 2=No 781=ND
31.	**TB**	(a)=is there TB contact in the last 12 months? 1= Yes 2=No (b)= is the child currently on TB Rx? 1=Yes 2=No			
32.	**Was the child ever admitted to hospital before?**	1=Yes 2= No If yes, how many times? __			
33.	**Immunization**	1=Up to date	2=Missed immunization	3=Not immunized	781=ND
34.	**Underlying condition**	1= Cerebral palsy	2=Congenital abnormality	3=Chronic disease(s) (state: a=HIV b=Chronic lung disease c=malignancy)	9=other

Current hospitalization

35.	**Referral from**	1=clinic	2=CHC	3=district hospital	4=self-referral	9=other	
36.	**Brought by**	1=mother	2=father	3=granny	4=aunt	5=uncle	6=older sibling	7=other relative	9=other
37.	**Consulted traditional healer**	1=Yes ☐ 2=No					
38.	**Diagnosis SAM made at**	1=clinic	2=CHC	3= district hospital	4=admission	5= ward	
39.	**Presenting complaint**	1=diarrhoea	2=cough	3= poor weight gain	4= fever		
		5= otitis media	6=difficulty breathing	**7=pallor**	9=other		
40.	**Duration of presenting complaint**	**_____days**					
41.	**Duration of illness (unwell)**	**_____days**					

Emergency unit

42.	**Triage tool**	1= ETAT	2=SATS	3=none	
43.	**Admitting Dr**	1= medical intern	2=Com serve	3=MO	4=Specialist
44.	**Time seen by nurse: _____h_____**	**Time seen by Dr: _____h_____**	**Ward admission time: _____h_____**		
45.	**Vitals**	1=HR ___	2=RR _____	3= HGT ____	4=$SP0_2$ ____	5=Temp_____
46.	**Neurological status**	1=alert	2=lethargic	3=decrease LOC	4=convulsions	5=coma	781= ND
47.	**Airway & breathing**	1=normal	2=cyanosed	3=severe respiratory distress	781=ND	
48.	**Circulation**	1=normal	2=CRT> 3s	3=weak pulse volume	4= cold peripheries	781= ND
49.	**Dehydration**	1= absent	2=severe dehydration	3=some dehydration	4= no dehydration	781= ND

Admission area case management

Sx/signs		Present	Checked by Dr	Managed	Appropriate Mx		
50.	**Hypothermia**	**1=Yes 2=No**	**1=Yes 2=No**	**1=Yes 2=No**	1=appropriate	2=poorly managed	781=ND
51.	**Hypoglycaemia**	**1=Yes 2=No**	**1=Yes 2=No**	**1=Yes 2=No**	1=appropriate	2=poorly managed	781=ND
52.	**Dehydration**	**1=Yes 2=No**	**1=Yes 2=No**	**1=Yes 2=No**	1=appropriate	2=poorly managed	781=ND

WARD 10 STEPS OF SAM Rx

		0-24 hrs									25-48hrs								
		done	**checked**				**Mx**				**done**	**checked**				**Mx**			
56.	**Blood sugar**	1=Yes 2=No	1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	781 =ND	1=Yes 2=No	1=A	2=P	3=Pr	81 =ND	1=A	2=P	3=Pr	781= ND
57.	**Temperature**	1=Yes 2=No	1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	781 =ND		1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	781= ND
58.	**Rehydration**	1-Yes 2=No	1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	78 1=ND		1=A	2=P	3=Pr	9=ND	1=A	2=P	3=Pr	781=N D
59.	**Feeds**	Given	1=A		2=P		3=Pr		781=ND		Given	1=A		2=P		3=Pr		781=ND	
60.	**Antibiotics**	Given	1=A		2=P		3=Pr		781=ND		Given	1=A		2=P		3=Pr		781=ND	

61.	**Kcl**	Given	1=A	2=P	3=Pr	781=ND	Given	1=A	2=P	3=Pr	781=ND
62.	**Supplements**	Given	1=A	2=P	3=Pr	781=ND	Given	1=A	2=P	3=Pr	781=ND

Other orders > 1week		**Done**	**Carried out**			
63.	**Catch-up growth monitoring**	**1=Yes 2=No**	1=A	2=P	3=Pr	781=ND
64.	**Stimulation**	**1=Yes 2=No**	1=A	2=P	3=Pr	781=ND
65.	**Discharge plan**	**1=Yes 2=No**	1=A	2=P	3=Pr	781=ND

A=appropriate P=partial Pr=poor ND=no details

Investigations

		On admission	**24-72 hours**	**Highest of any results**	**Lowest of any results**	**Last blood results taken**
66.	**Wcc**					
67.	**Hb**					
68.	**CRP**					
69.	**Na**					
70.	**K**					
71.	**Urea**					
72.	**Creatinine**					
73.	**Calcium**					
74.	**Magnesium**					
75.	**Phosphate**					
76.	**ALT**					
77.	**AST**					
78.	**Bilirubin**					
79.	**Albumin**					

Once off investigation

80.	**HIV test: a=DNA PCR b=Rapid**	1=positive	2=negative	3= indeterminant	4= unknown	5= not tested		
81.	**Mantoux**	1=positive	2=negative	3=not done	781=ND			
82.	**Sputum GXP**	1=M.TB detected RIF sensitive	2= M. TB detected RIF resistant	3= M. TB not detected	4=Insufficient specimen	5= Patient already on treatment on admission	6=not done but indicated	
83.	**Urine dipstick**	**1=nitrites 2= leukocytes 3=normal 4= not done 781=ND**						
84.	**Urine MCS**	1=positive 2=negative b) if positive organism cultured: _____						
85.	**CSF**	1= cells	2= chemistry	3=ADA	4=MCS	5= India ink	6=cryptococcal antigen	7= bacterial antigen	781=ND
86.	**Blood culture**	1= positive	2= negative	3= not done	781=ND			
87.	**CXR**							

Child PIP data: modifiable factors for death

88.	**Home**	1=caregiver did not recognize danger signs/severity of illness 2=traditional remedy given from traditional healer, with negative effect on child 3=child not provided with adequate food at home 4=caregiver took child to clinic infrequently 5=child not assessed and managed for HIV/AIDS 9= other(state)
89.	**Referring facility**	1=Inadequate referral letter from referring facility 2= inappropriate care or late referral from GP 3= Delayed arrival of ambulance at referring facility 4= Child not monitored correctly in ambulance 5=inadequate notes on transit care 9=other
90.	**Clinic/outpatient**	1= caregiver didn't bring RTHC 2=IMCI not used 3=Danger signs missed @clinic/OPD 4=Delayed referral of child with danger signs 5=severity of dehydration incorrectly assessed 9=other

91.	**Admissions**	1=primary caregiver not present 2=inadequate Hx taken 3=child not triaged 4= inadequate assessment of shock 5= no handover of critically ill child from admitting Dr to the ward Dr 9=other
92.	**Ward**	1= RTHC info not present in child's folder 2=insufficient notes on clinical care in ward 3=inadequate review of child with severe dehydration 4=inadequate monitoring of blood glucose in ward 5=inadequate Hx taken 9=other

Outcome

	Death	1=Yes 2=No				
93.	**If death, time of death**	_____ hours since admission				
94.	**Immediate cause of death**	1=Diarrhoea	2=pneumonia	3=sepsis	4=heart failure from fluid overload	5=meningitis
		6=malaria	7= acute kidney injury	8=severe acidosis	9=anaemia	10=re-feeding syndrome
		99=other(state)				
95.	**Underlying cause of death**	1=SAM	2=AIDS	3=TB	99=other(state)	
96.	**Other conditions contributing to death**	1=cerebral palsy 2=congenital abnormality				
97.	**Complications on the day of death**	1=hypoglycaemia	2=septic shock	3=hypothermia	4=hypovolaemic	9=other

Appendix B: Study protocol

DETERMINANTS OF MORTALITY IN CHILDREN YOUNGER THAN FIVE YEARS ADMITTED WITH SEVERE ACUTE MALNUTRITION TO THREE HOSPITALS IN VHEMBE DISTRICT, LIMPOPO.

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Towards Fulfilment of MSc in Child Health (Community Paediatrics)

SCHOOL OF CLINICAL MEDICINE

FACULTY OF HEALTH SCIENCES

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ABBREVIATIONS

Child PIP: Child Problem Identification Programme

CoMMiC: Committee on Morbidity and Mortality in Children under 5 years

CRP: C-reactive protein

DCST: district clinical specialist team

DHIS: district health information system

HIV: human immunodeficiency virus

MUAC: mid upper arm circumference

SA: South Africa

SAM: severe acute malnutrition

TB: tuberculosis

TX: Texas

WHO: World Health Organization

Table of Contents

1 INTRODUCTION

1.1 Background

Malnutrition remains a global concern and contributes significantly to childhood mortality.[1] Childhood undernutrition is listed by the World Health Organization (WHO) as a major health problem globally.[2] It contributes to almost half of all mortality in children under the age of 5 years.[3,4] As an adult effect of childhood undernutrition can still be evident as intellectual impairment and increased risk of diseases, which in turn lead to sub-optimal work capacity.[2] Severe acute malnutrition (SAM) affects about 25-35 million under-5 children globally. Of these 13 million live in sub-Saharan Africa and it is estimated that 1 million die every year in the sub-Saharan Africa alone.[5] According to the 2017 joint child malnutrition estimates, 52 million children below the age of 5 years (7.7%) were said to be wasted globally and 14 million of these were found in Africa.[6] The prevalence of severe wasting were estimated at 2.8, 2.2, 2.4 and 1.0% in developing countries, Africa, sub–Saharan Africa and southern Africa respectively.[6] This translates to 1.5 million in southern Africa alone.

In South Africa, in the financial year 2015-16, the case fatality rate for SAM was 8.9%, some 1380 deaths of the 15 537 admissions of children with SAM, according to the District Health Barometer.[7] The Child Problem Identification Programme (Child PIP) revealed that one third of child deaths is attributable to severe malnutrition. [8] Although many provinces described a decline in SAM deaths, Limpopo in the same financial year, had a higher case fatality attributable to SAM (11.6%) and Vhembe district in the same province had a 13% case fatality rate.[7] Mortality was higher in the lower socio–economic quantiles.[7]

Although South Africa offers free health services to children under the age of 6 years, transport availability and cost are still key barriers in accessing healthcare.[8] Inappropriate use of the Road to Health growth chart to classify child nutritional status has also been associated with a negative outcome of children with SAM.[8]

Differences in SAM mortality rates observed may be related to the extent of illness and anthropometric compromise, comorbid conditions such as HIV, delayed presentation and referrals, substandard case management, socio-demographic factors and health system factors and in the way clinical guidelines are being used.[9-15] Although studies on contributors to SAM mortality in hospital have been carried out in various African settings, [10] few emanate

from South Africa. Information on determinants of mortality among severely malnourished children is essential to improve quality of care.[16]

1.2 Literature review

Malnutrition is a multifactorial disease. Severely malnourished children present with many complications and comorbid conditions which predispose them to death if not identified early and treated promptly. Different studies done in some African countries identified blood transfusion, administration of intravenous fluids, sepsis and electrolyte imbalance, amongst others, as predictors of poor outcome. [4,5,10] Critical condition at presentation was also implicated as a predictor of poor outcome.[15,17]

A retrospective cohort study of 500 children in South Ethiopia with SAM found that the admission type of SAM was associated with mortality, while comorbid disease did not influence mortality.[18] Children readmitted for SAM were more likely to die than the first-time admissions. Altered level of consciousness, presence of oral thrush, low mid-upper arm circumference (MUAC) and caregiver report of severity of illness were stated as factors contributing to death among children with SAM in another study.[19] Another study conducted in Ethiopia found a clinical variables to be independent predictors of mortality, including altered pulse rate, temperature, anaemia, shock and hypoglycemia.[20] These independent predictors were also identified in a cross sectional study done in the same country by the same author.[21] A South African study, found hypothermia within 72 hours of admission was a strong predictor of death. Severity of illness as well as delayed presentation was also associated with poor outcomes.[15]

An Ethiopian cohort study found age of less than 24 months and the type of health facility in which the children received care were independent predictors of mortality.[20] Skin lesions were associated with higher odds of dying in children with SAM during a study which was conducted in Burkina Faso.[22]

Lower MUAC at admission was also significant contributor to mortality in this study population.[22] Low MUAC as a significant contributor of death was a similar finding in a study which was conducted in Nigeria.[23] A cross sectional study in India found that MUAC of less than 11.5 cm was a better predictor of death among children aged 1 and 5 years admitted with SAM compared to MUAC more than 11.5 cm.[24]

In Zambia, TB was a significant contributor to death among the malnourished children admitted in hospitals in settings with high prevalence of HIV and TB. [25] These findings were also in keeping with a study that was conducted in South Africa.[26] In Uganda, it was noted that certain co–morbid conditions resulted in higher mortality e.g. septicaemia, severe pneumonia, TB and severe anemia.[9]Another Ugandan study identified the same risk factors but also found hypothermia and HIV as factors associated with mortality in children with SAM. [27] Children with comorbid HIV infection were more likely to die from SAM compared to their counterparts.[26-30]

Mismanagement of complicated SAM was found to be a major contributor to mortality in these children - 50% of deaths were recorded in the first 48 hours of admission.[12,13,31,32] A study conducted in Uganda found that administration of blood and intravenous fluids were associated with increased mortality.[9] In an Ethiopian study, children who did not receive antibiotics were also at higher risk of mortality.[13]

A South African study conducted in a tertiary hospital found that liver impairment, very low serum phosphate levels and a positive blood culture were associated with increased risk of dying .[15] In a Burkina Faso study, hypokalaemia and hyponatraemia in children with SAM were found to contribute to death. Rytter found that SAM children with hypophosphataemia on day 2 of admission and elevated plasma CRP (≥15) on admission had high risk of mortality compared to those with lower values.[19]

A number of studies investigated the timing of death in children with SAM. A Kenyan study found that 60% of SAM death occurred in the first 72 hours 40% of deaths occurred in the first 24 hours and just over half (53%) within 48 hours of admission.[33] A Zambian study reported a mortality of 93.2%, 88.7% and 29% in 1 week and 48 hours and 24 hours of admission in severely malnourished children.[29] The high mortality in the first 48 hours of admission is not surprising as most children have many complications that needed stabilization at this period. A South African study found that 81% of deaths occurred during the first 24 hours of admission and overall mortality was 29%.[15] Severity of illness at presentation and delayed presentation contributed to the high early mortality in this setting.[15,17]

1.3 Justification for study

Many children admitted to Vhembe hospitals die as a result of severe acute malnutrition. The district still had a child mortality rate secondary to SAM (13%) that is much higher than the

national (7%) and the international mortality target (5%). There is no local study that has described the determinants of mortality in children admitted with severe acute malnutrition. Information generated by this study will be used to assist health workers within the health setting to better recognise and manage children with SAM, to reduce the risk of dying.

1.4 Aim of study

To determine factors contributing to mortality in severely malnourished children younger than 5 years admitted at selected hospitals in Vhembe district, Limpopo.

1.5 Study Objectives

Primary objective

To compare demographic, family, socio-economic, clinical and laboratory factors in children with severe acute malnutrition who died with those who survived

Secondary objectives

- To describe risk factors for death in severely malnourished children
- To describe the care and management of children with severe acute malnutrition
- To distinguish factors associated with early (< 24 hours) versus late mortality in severely malnourished children

2 STUDY METHODS

2.1 Setting of the Study

Vhembe district is one of the five districts of Limpopo province. The district is largely rural with approximately 774 villages and covers 21 407 square kilometres of land. It is the northernmost district of the country and shares its northern border with Zimbabwe and Botswana. Children under-5 years constitute 13% of the total population in the district.

The three hospitals purposively chosen for the study are Tshilidzini, Donald Fraser and Malamulele. Tshilidzini Regional Hospital, is the only regional hospital within the district. It receives referrals from 6 district hospitals namely Donald Fraser, Malamulele, Elim, Siloam and Musina. The district has three paediatrician who are based at the regional hospital who undertake outreach visits once weekly to the district hospital. Vhembe does not have a district paediatrician as part of the district clinical specialist team (DCST).

2.2 Study design

This will be a retrospective study, involving patient record review.

2.3 Definition of severe acute malnutrition

Severe acute malnutrition in children aged 6 months to 59 months is defined by WHO by the presence of (i) bilateral pedal oedema, or (ii) a weight for height/length below -3 z score, or (iii) a mid-upper arm circumference below 115 mm.[2]

2.4 Study Population

Children 6 months to 5 years of age admitted with severe acute malnutrition at Tshilidzini Regional Hospital, Donald Fraser Hospital, and Malamulele Hospital.

2.5 Study sample

All children under the age of 5 years who were admitted between January 2016 and June 2018 with severe acute malnutrition will form part of the study sample. There will not be any sampling. The admission record and head count book will be used to identify children eligible for the study.

2.6 Sample size

Based on the district health information system (DHIS) data there were 365 children admitted in 2015 at the three hospitals and 353 in 2016. It is anticipated that about 50% of the hospital records will be available (extractable), as a minimum. Thus, the likely sample size will be about 300 children with severe acute malnutrition. For a sample size of 300 children, assuming a 11.5% mortality in children with SAM over this period (based on DHIS data), it will be possible to identify a 18% or higher difference in any mortality risk factor, with a power of 80% and an alpha (p-value) of 0.05.

2.7 Inclusion and exclusion criteria

Any child aged 6 months to 5 years meeting the definition of SAM will be included. There are no exclusion criteria. Children with chronic disorders, disabilities or congenital abnormalities will not be excluded.

2.8 Study period

The study will enrol all children admitted with severe acute malnutrition in the selected hospitals from January 2016 to June 2018.

3 DATA COLLECTION, PROCESSING AND ANALYSIS

3.1 Data collection and management

Admission and discharge registers will be consulted to ascertain total numbers of children admitted and discharged with SAM. Only children who meet the study definition of SAM will be enrolled. Data will be collected from patients' medical records and an in-facility Child Problem Identification Programme (Child PIP) form using a structured data collection tool.

Information of interest, including demographic characteristics, family details, triage and clinical presentations, ward case management, laboratory markers, comorbid conditions and child outcome status, will be gathered and form part of the analysis (see Appendices A, B and C). Variables to be considered were obtained from a literature review. The Child PIP forms completed for deaths that occurred during the study period will be reviewed to determine modifiable factors that have contributed to hospital mortality of children with severe acute malnutrition in the selected hospitals. Once participants are enrolled, they will remain in the study even if their records are incomplete or if the parents signed refusal of hospital treatment forms, prompting premature (early) discharge. The researcher will be solely responsible for collecting the data.

3.2 Statistical analysis

All data collected will be coded, cleaned and entered into a Microsoft Excel spreadsheet for analysis. STATA 13 software (StataCorp. College Station, Texas, USA) will be used to analyse data. Descriptive and inferential statistic will be used to achieve study objectives. The chi–square test will be used to compare categorical variables; for example, proportion of children who died compared to survived, with leucocytosis. For normally distributed data, a t–test for continuous variables will be used; for example, mean CRP of children who died compared to survived. Non-parametric tests will be used when appropriate. A p-value < 0.05 will be considered significant. The results will be summarized in tables and graphs.

3.3 Limitations of the study

Children not identified by a doctor or nurse as having SAM (on admission and/or in the ward) will not be enrolled into the study, since they will not appear in the admission book (measurement bias). Thus, less severely ill children with SAM may be missed.

There might be missing information in the patients' medical records (information bias).

Since many records might not be found, this will not be a truly consecutive sample (sampling bias), although the intention is to have a consecutive sample.

4 ETHICAL CONSIDERATIONS

Ethical clearance will be sought from the Committee for Research in Human Subjects at the University of the Witwatersrand. The protocol will also be submitted to the Limpopo provincial Department of Health research committee for permission to undertake the study. Permission to conduct the study will also be sought from the Vhembe district authority and the individual hospitals involved in the study. No participant consent is required as this is a retrospective study using medical records. However, all individual identifiers will be removed when extracting data to maintain confidentiality.

5 PROJECT MANAGEMENT AND BUDGET

5.1 Timelines

A Gant chart of the study timelines is shown below:

	2017			2018												2019						
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Proposal development																						
Submission to postgraduate assessor group																						
Ethics approval																						
Data Collection Process																						
Data analysis																						
Writing chapters																						
Submit the First Draft																						
Submission of thesis																						

5.2 Plan for utilization and dissemination of results

Results will be analysed and submitted to the University of the Witwatersrand in partial fulfilment of the requirement for award of degree of MSc Child Health (Community Paediatrics) degree. The results of the study will also be disseminated to Tshilidzini Regional Hospital, Donald Fraser Hospital and Malamulele Hospital and the manuscript will be submitted for publication in a local peer reviewed journal.

5.3 Budget

Item	Description	Amount
Travelling	Traveling from Tshilidzini Hospital to Malamulele and Donald Fraser hospitals for data collection @ R3.30 per km x 30 km x 10 trips x 2 hospitals	R2,112.00
Stationery and printing	300 questionnaires x 4 pages x 30c per page	R360.00
	Total	R2472.

The cost of the project will be covered by the researcher. A grant will the sought from the University of the Witwatersrand medical research fund.

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Appendices

Appendix A

Data collection sheet (Determinants of mortality in children admitted with SAM)

Study reference details

10.	**Study No**					
11.	**Hospital name**	1=Tshilidzini	2= Malamulele	3=Donald Fraser		
12.	**DOA**	/ /201_				
13.	**Admission type**	1= New	2= Readmission			
14.	**DOD**	/ /201__				
15.	**Status**	1=Discharge	2=Death	3=Transfer	4= RHT	9=Other
16.	**Length of hospital stay**	_____ days				
17.	**Case definition**	1=Wt/length (ht)	2=MUAC	3=nutritional oedema		

Child demographic details

18.	**Age**	_____ months	**10.**	Residential area_____					**11.**	Nearest clinic_____	
12.	**Caregiver**	1=mother	2=father	3=granny	4= aunt	5=uncle	6=older sibling	7=other relatives	9=other	**13.**	**Attending day care Centre** 1=Yes 2=No

Anthropometry (admission)

14.	**Wt**	kg	**15.**	**Height**	cm	**16.**	**MUAC**	cm
17.	**Wt/age z-score**		**18.**	**Ht/age z-score**		**19.**	**Wt/Ht z-score**	
20.	**Oedema on admission**	1=Yes 2=No 3=unknown						

Family details

21.	**Mother**	1=Alive			2=Dead	
	(a)Age	_____Years				
	(b) Marital status	1=Single	2=Married	3=Separated	4=Unknown	9=Other _____
	(c) Occupation	1=Employed	2=Unemployed	3=Farmer	4=Salesman	9=Other _____
	(d) Highest level achieved	1=None	2= Grade_____	3= Tertiary education	4= unknown	9=Other _____
22.	**Father**	1=Alive	2=Dead	3=Unknown		
	(d) Age	_____Years				
	(e) Marital status	1=Single	2=Married	3=Separated	4=Unknown	9=Other
	(f) Occupation	1=Employed	2=Unemployed	3=Farmer	4=Salesman	9=Other
	(d) Highest level achieved	1=None	2= Grade_____	3= Tertiary education	4= unknown	9=Other
23.	**Primary caregiver (if not mother)**					
	(a)Relationship with child	1= Grandmother	2= Grandfather	3= Aunt	4= Uncle	5= Older sibling	6= cousin	7= other relatives	9=other
	(b)Age	_____Years				
	(c)Sex	1= Female	2= Male			
	(d)Marital status	1=Single	2=Married	3=Separated	4=Unknown	9=Other
	(e)Occupation	1=Employed	2=Unemployed	3=Farmer	4=Salesman	9=Other
	(f)Highest level achieved	1=None	2= Grade_____	3= Tertiary education	4= unknown	9=Other
24.	**Siblings**	Total no.	How many dead			

	Ages	**1_____months**	**2_____**	**3**	**4_____**	**5_____**
		6_____ 7_____				

Feeding practices

25.	**Was the child ever breastfed/still breastfeeding?**	1=Yes	2=No	3= Never	**781=ND**	**26.**	**Total duration of Breastfeeding** _____months						
27.	**How long was child Exclusively Breastfed**	_____months		**28.**	**Complimentary feeds initiated at** _____months								
29.	**Current diet**	1=Vegetables		2=Green leaves		3=Fruits		4=Red meat		5=chicken		6=liver	7=egg
		8=fish		9=other		10=maas		11=Tea		12=bread			13=Pap
		14=Cow's milk		15=soft porridge									

Past medical history

30.	**HIV**	(a)Positive 1=Yes 2=No	(b)If positive, on HAART? 1=Yes 2=No 3=defaulted	(c) HIV exposed 1=Yes 2=No	(d)Received PMTCT 1=Yes 2=No 781=ND
31.	**TB**	(a)=is there TB contact in the last 12 months? 1= Yes 2=No (b)= is the child currently on TB Rx? 1=Yes 2=No			
32.	**Was the child ever admitted to hospital before?**	1=Yes 2= No If yes, how many times? __			
33.	**Immunization**	1=Up to date	2=Missed immunization	3=Not immunized	781=ND
34.	**Previous illnesses**	1= Cerebral palsy	2=Congenital abnormality	3=Chronic disease(s) (state: a=HIV b=Chronic lung disease c=malignancy)	9=other

Current hospitalization

35.	**Referral from**	1=clinic		2=CHC		3=district hospital		4=self-referral		9=other			
36.	**Brought by**	1=mother	2=father	3=granny	4=aunt	5=uncle	6=older sibling	7=other relative	9=other				
37.	**Consulted traditional healer**	1=Yes	2=No										
38.	**Diagnosis SAM made at**	1=clinic		2=CHC		3= district hospital		4=admission		5= ward			
39.	**Presenting complaint**	1=diarrhoea		2=cough		3= poor weight gain		4= fever					
		5= otitis media		6=difficulty breathing		**7=pallor**		9=other					
40.	**Duration of presenting complaint**	**_____days**											
41.	**Duration of illness (unwell)**	**_____days**											

Emergency unit

42.	**Triage tool**	1= ETAT		2=SATS		3=none			
43.	**Admitting Dr**	1= medical intern		2=Com serve		3=MO		4=Specialist	
44.	**Time seen by nurse: _____h_____**	**Time seen by Dr: _____h_____**				**Ward admission time: _____h_____**			
45.	**Vitals**	1=HR ___	2=RR _____	3= HGT ____	4=SPO_2 ____	5=Temp_____			
46.	**Neurological status**	1=alert	2=lethargic	3=decrease LOC	4=convulsions	5=coma	781= ND		
47.	**Airway & breathing**	1=normal	2=cyanosed	3=severe respiratory distress	781=ND				
48.	**Circulation**	1=normal	2=CRT> 3s	3=weak pulse volume	4= cold peripheries	781= ND			
49.	**Dehydration**	1= absent	2=severe dehydration	3=some dehydration	4= no dehydration	781= ND			

Admission area case management

Sx/signs		**Checked by Dr**	**Present**	**Managed**	**Appropriate Mx**			
50.	**Hypothermia**	**1=Yes 2=No**	**1=Yes 2=No**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND
51.	**Hypoglycaemia**	**1=Yes 2=No**	**1=Yes 2=No**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND
52.	**Dehydration**	**1=Yes 2=No**	**1=Yes 2=No**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND

		Given	**Standard met**			
53.	**Antibiotics**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND
54.	**Supplements**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND
55.	**Fluids**	**1=Yes 2=No**	1=appropriate	2=partial	3=poor	781=ND

WARD 10 STEPS OF SAM Rx

		0-24 hrs									25-48hrs								
		done	checked				Mx				done	checked				Mx			
56.	Blood sugar	1=Yes 2=No	1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	781 =ND	1=Yes 2=No	1=A	2=P	3=Pr	81 =ND	1=A	2=P	3=Pr	781=ND
57.	Temperature	1=Yes 2=No	1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	781 =ND		1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	781=ND
58.	Rehydration	1-Yes 2=No	1=A	2=P	3=Pr	781 =ND	1=A	2=P	3=Pr	78 1=ND		1=A	2=P	3=Pr	9=ND	1=A	2=P	3=Pr	781=ND
59.	Feeds	Given	1=A		2=P		3=Pr		781=ND		Given	1=A		2=P		3=Pr		781=ND	
60.	Antibiotics	Given	1=A		2=P		3=Pr		781=ND		Given	1=A		2=P		3=Pr		781=ND	
61.	Kcl	Given	1=A		2=P		3=Pr		781=ND		Given	1=A		2=P		3=Pr		781=ND	
62.	Supplements	Given	1=A		2=P		3=Pr		781=ND		Given	1=A		2=P		3=Pr		781=ND	

Other orders > 1week		Done	Carried out			
63.	Catch-up growth monitoring	1=Yes 2=No	1=A	2=P	3=Pr	781=ND
64.	Stimulation	1=Yes 2=No	1=A	2=P	3=Pr	781=ND
65.	Discharge plan	1=Yes 2=No	1=A	2=P	3=Pr	781=ND

A=appropriate P=partial Pr=poor ND=no details

Investigations

		On admission	24-72 hours	Highest	lowest	Last
66.	Wcc					
67.	Hb					
68.	CRP					
69.	Na					
70.	K					
71.	Urea					
72.	Creatinine					
73.	Calcium					
74.	Magnesium					
75.	Phosphate					
76.	ALT					
77.	AST					
78.	Bilirubin					
79.	Albumin					

Once off investigation

80.	HIV test: a=DNA PCR b=Rapid	1=positive	2=negative	3= indeterminant	4= unknown	5= not tested	
81.	Mantoux	1=positive	2=negative	3=not done	781=ND		
82.	Sputum GXP	1=M.TB detected RIF sensitive	2= M. TB detected RIF resistant	3= M. TB not detected	4=Insufficient specimen	5= Patient already on treatment on admission	6=not done but indicated
83.	Urine dipstick	1=nitrites 2= leukocytes 3=normal 4= not done 781=ND					
84.	Urine MCS	1=positive 2=negative b) if positive organism cultured: _____					
85.	CSF	1= cells	2= chemistry	3=ADA	4=MCS	5= India ink	6=cryptococcal antigen	7= bacterial antigen	781=ND
86.	Blood culture	1= positive	2= negative	3= not done	4= not indicated	781=ND	
87.	CXR						

Child PIP data: modifiable factors for death

88.	**Home**	1=caregiver did not recognize danger signs/severity of illness 2=traditional remedy given from traditional healer, with negative effect on child 3=child not provided with adequate food at home 4=caregiver took child to clinic infrequently 5=child not assessed and managed for HIV/AIDS 9= other(state)
89.	**Referring facility**	1=Inadequate referral letter from referring facility 2= inappropriate care or late referral from GP 3= Delayed arrival of ambulance at referring facility 4= Child not monitored correctly in ambulance 5=inadequate notes on transit care 9=other
90.	**Clinic/outpatient**	1= caregiver didn't bring RTHC 2=IMCI not used 3=Danger signs missed @clinic/OPD 4=Delayed referral of child with danger signs 5=severity of dehydration incorrectly assessed 9=other
91.	**Admissions**	1=primary caregiver not present 2=inadequate Hx taken 3=child not triaged 4= inadequate assessment of shock 5= no handover of critically ill child from admitting Dr to the ward Dr 9=other
92.	**Ward**	1= RTHC info not present in child's folder 2=insufficient notes on clinical care in ward 3=inadequate review of child with severe dehydration 4=inadequate monitoring of blood glucose in ward 5=inadequate Hx taken 9=other

Outcome

	Death	1=Yes 2=No						
93.	**If death, time of death**	_____ hours						
94.	**Immediate cause of death**	1=Diarrhoea		2=pneumonia	3=sepsis	4=heart failure from fluid overload		5=meningitis
		6=malaria		7= acute kidney injury	8=severe acidosis	9=anaemia		10=re-feeding syndrome
		99=other(state)						
95.	**Underlying cause of death**	1=SAM	2=AIDS	3=TB	99=other(state)			
96.	**Other conditions contributing to death**	1=cerebral palsy 2=cleft palate and cleft lip and palate						
97.	**Complications on the day of death**	1=hypoglycaemia		2=septic shock	3=hypothermia	4=hypovolaemic		9=other

Appendix B

Compliance with WHO 10 steps management protocol for SAM

	Prevention	Treatment
Hypoglycaemia -dextrostix <3 mmol/l	2 hourly feeds, day and night	If child is conscious, give 50 ml bolus of 10% glucose orally or by nasogastric (NG) tube. Then feed starter F-75 every 30 min. for two hours Unconscious child, IV 10% glucose (5ml/kg), followed by 50ml of 10% glucose or sucrose by Ng tube. Then give starter F-75 as above
Hypothermia -axillary temperature is <35.0°C Or -rectal temperature is <35.5°C (<95.9oF):	- feed two-hourly, start on admission -child sleep with mother/caregiver at night for warmth -keep child covered and dry - check for hypoglycaemia whenever hypothermia is found	-Re-warm the child: either clothe the child, cover with a warmed blanket and place a heater nearby - antibiotics
Dehydration and shock	Shock General principles of resuscitation Administer O_2 15ml/kg/hr of either ½ DD or R/L with 5% dextrose or 0.45% saline + 5% dextrose	Dehydration ReSoMal 5ml/kg every 30 min first hr If still dehydrated 5-10ml/kg/hr in alternate hrs with F-75 - Hydration checks ½ hrly for first 2hrs then hourly
Blood transfusion	Indication: Hb < 4 or <6 with respiratory distress	-To be given within 24hrs of admission - whole blood 10 ml/kg body weight slowly over 3 hours • furosemide 1 mg/kg IV at the start of the transfusion
Electrolytes	extra potassium 3-4 mmol/kg/d • extra magnesium 0.4-0.6 mmol/kg/d • when rehydrating, give low sodium rehydration fluid (e.g. ReSoMal) • prepare food without salt	
Infection	Ampicillin 50 mg/kg IM/IV 6-hourly for 2 days, then oral amoxycillin for 5 days AND • Gentamicin 7.5 mg/kg IM/IV once daily for 7 days	
Micronutrients	Only if child not on ready-made WHO feeds i.e. F-75/100/RUFT	
Cautious feeding	F-75 100-135kcal/kg/day 2hourly for 48 hours	
Catch-up growth	F-100 and RUTF increase each successive feed by 10 ml until some feed remains	
Stimulation	Play therapy is intended to develop language skills and motor activities aided by simple toys. It should take place in a loving, relaxed and stimulating environment.	
Prepare for D/C	Criteria for discharge: good appetite, no oedema, good weight gain for 5 consecutive days.	
HIV management	-Start ARV after stabilization of metabolic complications and sepsis -Give high dose Vit A on admission	

Source: extracted from 2013 WHO guideline updates on management of severe acute malnutrition in infants and children.[2]

Appendix C

South African standard treatment guidelines for SAM

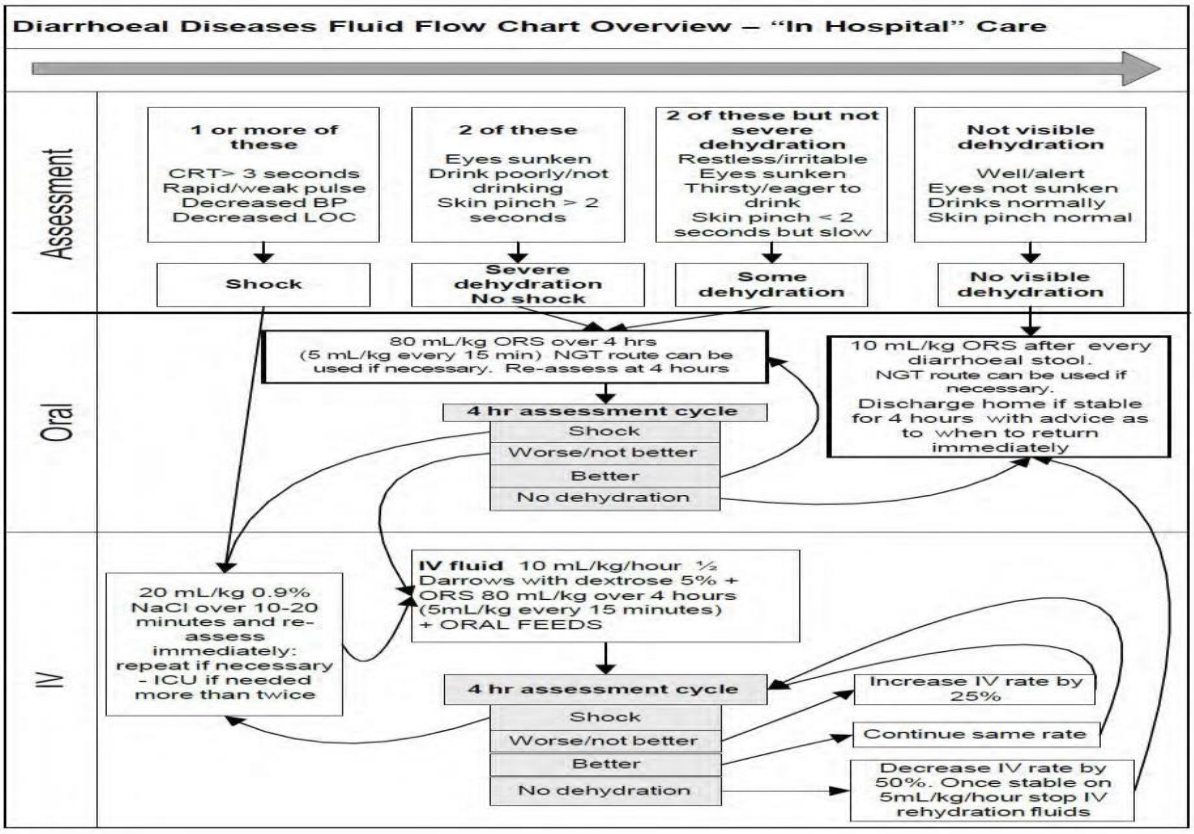
	Prevention	Treatment
Hypoglycaemia	-Feed child with severe acute malnutrition immediately (within 30 minutes of presentation) and then ensure every feed is given by day and at night. -Test blood glucose level 3 hourly in severely ill child for first 24 hours and until stable	Asymptomatic hypoglycaemia: blood glucose < 3 mmol/L in asymptomatic child: Stabilization/F75 formula, oral, 15 mL/kg. **OR** Dextrose, 10%, oral, 10 mL/kg. Check blood glucose after 30 minutes. Target blood sugar=3 mmol/L. If symptomatic or persistent hypoglycaemia: Dextrose, 10%, IV, 5 mL/kg. **OR** Neonatal maintenance solution, IV, 5 mL/kg. Change feeds to 2 hourly if hypoglycaemia has occurred
Hypothermia	Care for child in a warm area, i.e. 25–30ºC room temperature Avoid exposure e.g. bathing. Feed immediately and 2–3 hourly as this provides energy to generate heat. Allow child to sleep with mother/caregiver at night for warmth. Check axillary (underarm) temperature, 3 hourly	Check temperature 2-hourly until > 36.5ºC. Consider and treat for infection and sepsis Kangaroo care Place heater nearby
Dehydration	Flow chart of diarrhoea appendix D	
Electrolytes	If the formula is made without combined mineral and vitamin complex**, add**: Potassium chloride solution, 25–50 mg/kg/dose, oral, 8 hourly until oedema subsides: If < 10 kg: 250 mg. If > 10 kg: 500 mg. Trace element mix, oral, daily: If < 10 kg: 2.5 mL. If > 10 kg: 5 mL. If **OR** Magnesium sulphate 50%, oral, 0.2 mL/kg as a once daily dose for at least 2 weeks. The IV preparation can be given orally	

Infection	Child with no complications: Amoxicillin, oral, 30 mg/kg/dose 8 hourly for 5 days. SAM with complications: Ampicillin, IV/IM, 50 mg/kg 6 hourly for 7 days. and Gentamicin, IV, 6 mg/kg once daily for 7 days. If the child is severely ill or fails to improve after 48hours: Ceftriaxone, IV/IM, 50 mg/kg/dose once daily. If meningitis suspected: use 80 mg/kg/dose Intestinal worm infestation Treat after the acute phase: Children 1–2 years of age: Mebendazole, oral, 100 mg 12 hourly for three days. Children > 2 years: Mebendazole, oral, 500 mg as a single dose.
micronutrients	Vitamin A, oral, as a single dose Age Dose No. of capsules Infants < 6 months: 50 000 IU 1 capsule Infants 6–11 months: 100 000 IU 1 capsule Children 12 months to 5 years: 200 000 IU 1 capsule All children with clinical signs of severe vitamin A deficiency (eye changes: xerophthalmia, corneal ulceration, Bitot's spots, corneal clouding) and severe measles: Vitamin A, oral, 3 doses If on feeds with combined mineral and vitamin complex: Folic acid, oral, 2.5 mg as a single dose. If not on feeds with combined mineral and vitamin complex: Folic acid, oral, 2.5 mg as a single daily dose and Multivitamin, oral, 5 mL as a single daily dose
Anaemia	blood transfusion, if: Symptomatic anaemia (Hb 4 g/dL). **OR** If there is respiratory distress with a ≤ Hb 6. Packed red cells, IV, 5 mL/kg administered over 3 hours. PLUS**,** Furosemide, IV, 1 mg/kg at the start of the transfusion. Repeat if severe anaemia or respiratory distress persist When child is gaining weight and oedema has resolved: Iron, oral, 2 mg/kg elemental iron per dose 8 hourly with meals for 2 months
Cautious feeding	Give "F75/stabilising feed" at 130 mL/kg/day divided into 3 hourly feeds If danger signs, hypothermia or hypoglycaemia present, feed the same daily volume but divided into 2 hourly feeds
Catch-up growth	F100 formula. increase the volume by 10 mL/feed until some formula remains unfinished, usually ± 200 mL/kg/day.
Stimulation	Involve occupational therapist, if available, for structured play
Prepare for D/C	Discharge criteria: good appetite, no infection, no oedema, continuous good weight gain for last 5 days, playful and alert, and all preparation in place for discharge
HIV management	Once the child enters the rehabilitative phase, commence antiretroviral therapy without delay if HIV infected

Source: extracted from 2013 and 2017 hospital level paediatrics STG&EML for South Africa.[34,35]

Appendix D

Flow chart for correction of dehydration in diarrhoeal disease



Source[34]

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Appendix C Ethics clearance certificate and permission letters

R 14/49 Dr D Mudzielwana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M181051

NAME: (Principal Investigator)	Dr D Mudzielwana
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Division of Community Paediatics Medical School University
PROJECT TITLE:	Determinants of mortality in children younger than five years admitted with severe acute malnutrition to three hospitals in Vhembe district, Limpopo
DATE CONSIDERED:	26/10/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor H Saloojee and Ms T Malwela
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/02/2019

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 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised 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 to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore reports, and re-certification will be due early in the month of October each ye[illegible]. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigato[illegible] Signat[illegible] Date 01 - 02-2019

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

Enquiries: Stander SS (015 293 6650) Ref: LP201811 003

Mudzielwana D , Dr
University of WITS

Greetings,

RE: Determinants of mortality in children younger than five years admitted with severe acute malnutrition to three hospitals in Vhembe District, Limpopo

I, Permission to conduct the above mentioned study is hereby granted,

2. Kindly be informed that:-

- Research must be loaded on the NHRD site (http://nhrd.hst.prgza) by the researcher.
- Further arrangement should be made with the targeted institutions, after consultation with the District Executive Manager.
- In the course of your study there should be no action that disrupts the services or incur any cost on the Department.
- After completion of the study, it is mandatory that the findings should be submitted to the Department to serve as a resource,
- The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible
- The above approval is valid for a 3 year period [e] If the proposal has been amended, a new approval should be sought from the Department of Health.
- Kindly note, that the Department can withdraw the approval at any time

Your cooperation will be highly appreciated.

Head of Department _____ Date _____

Private Bag .X9302 Polokwane
Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.
Website: http/www.timpopo.gov.za

The heartland of Southern Africa Development is about people!

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH
VHEMBE DISTRICT

Ref: S5/6
Enq: Muvari MME
Date: 04 February 2019

Dear : Mudzielwana D

PERMISSION TO CONDUCT RESEARCH

…….

l . The above matter bears reference

2. Your letter received on the 04/01/2019 requesting for permission to conduct research in our facilities is hereby acknowledged

3, The District has no objection to your request.

4. Permission is therefore granted for the research to be conducted within Vhembe District.

5. You are requested to make a presentation of your findings after completion to the District.

6. You are however to make the necessary arrangements with the facilities concerned.

7. Wishing you success in your research in the Vhembe health facilities.

…… ……

CHIEF DIRECTOR DATE

Private Bag X5009 THOHOYANDOU 0950
OLD parliamentary Building Tel (015) 9621000 (Health) (015) 962 4958 (Social Dev) Fax (015) 962 2274/4623
Old Parliamentary Building Tel: (015) 962 1848, (015) 962 1852, (015) 962 1754, (015) 962 100112/3/415/6 Fax (015) 962 2373, (015) 962 227

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

MALAMULELE HOSPITAL

REF : S 4/5
ENQ . Siwela T.S
DATE : 01/03/2019

TO WHOM IT MAY CONCERN

SUBJECT: PERMISSION TO CONDUCT A RESEARCH: DAKALO MUDZIELWANA

l . This serves to acknowledge the receipt your application to conduct a research study at Malamulele hospital and the research topic is "Determination of Mortality in Children younger than five years admitted with Severe Acute Malnutrition to three hospitals in Vhembe District, Limpopo Province"

2. The permission to conduct the study in question is recommended since it has all the required documents such as: the application letter, research proposal, Training institutions Ethical clearance certificate, Provincial and District offices approvals as prescribed by departmental circular no 24 of 2015.

3. Hopping for an effective cooperation between the participants of this research

Thank you

.....
CHIEF EXECUTIVE OFFICER
MALAMULELE HOSPITAL

07/03/2019
DATE

DEPARTMENT OF HEALTH
MALAMULELE HOSPITAL, P/BAG X9245
MALAMULELE, 0982
07 MAR 2019
REGISTRY

CONFIDENTIAL

Malamulele Hospital Private Bag x9245 Malamulele 0982
Tel: (015) 851 0026/1020/1017/1019 Fax: (015) 851 0620
The heartland of Southern Africa – Development is about people! !

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH
DONALD FRASER HOSPITAL

Ref: 4/2/2
Enquiries: Mphephu V.F
Cell No: 072 1880 436
Ext. 9306/ 9348
15/02/2019

To: DR Mudzielwana Dakalo
P. O Box 273
Makonde
0984

Re: Permission to Conduct Research Study

Topic: Determinants of mortality in children younger than five years admitted with severe acute malnutrition to three hospitals in Vhembe district, Limpopo.

1. The above matter refers.
2. Permission to conduct the above mentioned study is hereby granted.
3. Kindly be informed that:-
    - In the course of study there should be no action that disrupts the service.
    - You are to give report to quality assurance manager of Donald Fraser Hospital after the completion of the study at Donald Fraser Hospital.
    - After completion of the study, a copy should be submitted to our institution to serve as resources.
    - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
    - You are therefore requested to contact nursing audit office number 5, OPD basement for logistics arrangements.
4. Please bring along the following documents.
    - Permission latter granted from department of health.
    - Permission granted from educational institution.
    - This letter.

LIMPOPO PROVINCE
DONALD FRASER HOSPITAL
2019 -02- 15
PRIVATE BAG X1172
0971 VHUFULI
DEPARTMENT OF HEALTH

Hoping you will find this in order.

Chief Executive Officer

15/2/2019
Date

Private bag x1172, VHUFULI 0971
Tel +27 15 963 1778/9, 015 963 179/2. Fax +27 015 963 1796 cell: 27 83 248 0184

Appendix D Submission guidelines to PLOS ONE
Style and Format

File format Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected.

LaTeX manuscripts must be submitted as PDFs. Read the LaTeX guidelines.

Length Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information.

We encourage you to present and discuss your findings concisely.

Font Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.

Headings Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.

Layout and spacing Manuscript text should be double-spaced.

Do not format text in multiple columns.

Page and line numbers Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).

Footnotes Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.

Language Manuscripts must be submitted in English.

You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.

Abbreviations Define abbreviations upon first appearance in the text.

Do not use non-standard abbreviations unless they appear at least three times in the text.

Keep abbreviations to a minimum.

Reference style PLOS uses "Vancouver" style, as outlined in the ICMJE sample references.

See reference formatting examples and additional instructions below.

Equations We recommend using MathType for display and inline equations, as it will provide the most reliable outcome. If this is not possible, Equation Editor or Microsoft's Insert→Equation function is acceptable.

Avoid using MathType, Equation Editor, or the Insert→Equation function to insert single variables (e.g., "$a^2 + b^2 = c^2$"), Greek or other symbols (e.g., β, Δ, or ′ [prime]), or mathematical operators (e.g., x, ≥, or ±) in running text. Wherever possible, insert single symbols as normal text with the correct Unicode (hex) values.

Do not use MathType, Equation Editor, or the Insert→Equation function for only a portion of an equation. Rather, ensure that the entire equation is included. Equations should not contain a mix of different equation tools. Avoid "hybrid" inline or display equations, in which part is text and part is MathType, or part is MathType, and part is Equation Editor.

Nomenclature Use correct and established nomenclature wherever possible.

Units of measurement Use SI units. If you do not use these exclusively, provide the SI value in parentheses after each value. Read more about SI units.

Drugs Provide the Recommended International Non-Proprietary Name (rINN).

Species names Write in italics (e.g., Homo sapiens). Write out in full the genus and species, both in the title of the manuscript and at the first mention of an organism in a paper. After first mention, the first letter of the genus name followed by the full species name may be used (e.g., H. sapiens).

Genes, mutations, genotypes, and alleles Write in italics. Use the recommended name by consulting the appropriate genetic nomenclature database (e.g., HGNC for human genes; we strongly recommend using this tool to check against previously approved names). It is sometimes advisable to indicate the synonyms for the gene the first time it appears in the text. Gene prefixes such as those used for oncogenes or cellular localization should be shown in roman typeface (e.g., v-fes, c-MYC).

Allergens The systematic allergen nomenclature of the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee should be used for manuscripts that include the description or use of allergenic proteins. For manuscripts describing new allergens, the systematic name of the allergen should be approved by the WHO/IUIS Allergen Nomenclature Sub-Committee prior to manuscript publication. Examples of the systematic allergen nomenclature can be found at the WHO/IUIS Allergen Nomenclature site.

Copyediting manuscripts

Prior to submission, authors who believe their manuscripts would benefit from professional editing are encouraged to use language-editing and copyediting services. Obtaining this service

is the responsibility of the author and should be done before initial submission. These services can be found on the web using search terms like “scientific editing service” or “manuscript editing service.”

Submissions are not copyedited before publication.

Submissions that do not meet the PLOS ONE publication criterion for language standards may be rejected.

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section, the following elements are required, in order:

- Title page: List title, authors, and affiliations as first page of manuscript
- Abstract
- Introduction

Middle sectionthe following elements can be renamed as needed and presented in any order:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

Ending section, the following elements are required, in order:

- Acknowledgments
- References
- Supporting information captions (if applicable)

Other elements • Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately.

- Tables are inserted immediately after the first paragraph in which they are cited.
- Supporting information files are uploaded separately.

Refer to our downloadable sample files to ensure that your submission meets our formatting requirements:

- Download sample title, author list, and affiliations page (PDF)
- Download sample manuscript body (PDF)

Viewing Figures and Supporting Information in the compiled submission PDF

The compiled submission PDF includes low-resolution preview images of the figures after the reference list. The function of these previews is to allow you to download the entire submission as quickly as possible. Click the link at the top of each preview page to download a high-resolution version of each figure. Links to download Supporting Information files are also available after the reference list.

Parts of a Submission

Title

Include a full title and a short title for the manuscript.

Title	Length	Guidelines	Examples
Full title	250 characters	Specific, descriptive, concise, and comprehensible to readers outside the field	Impact of cigarette smoke exposure on innate immunity: A Caenorhabditis elegans model Solar drinking water disinfection (SODIS) to reduce childhood diarrhoea in rural Bolivia: A cluster-randomized, controlled trial
Short title	100 characters	State the topic of the study	Cigarette smoke exposure and innate immunity SODIS and childhood diarrhoea

Titles should be written in sentence case (only the first word of the text, proper nouns, and genus names are capitalized). Avoid specialist abbreviations if possible. For clinical trials, systematic reviews, or meta-analyses, the subtitle should include the study design.

Author list

Authorship requirements

All authors must meet the criteria for authorship as outlined in the authorship policy. Those who contributed to the work but do not meet the criteria for authorship can be mentioned in the Acknowledgments. Read more about Acknowledgments.

The corresponding author must provide an ORCID iD at the time of submission by entering it in the user profile in the submission system. Read more about ORCID.

Author names and affiliations

Enter author names on the title page of the manuscript and in the online submission system.

On the title page, write author names in the following order:

- First name (or initials, if used)
- Middle name (or initials, if used)
- Last name (surname, family name)

Each author on the list must have an affiliation. The affiliation includes department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country. Authors have the option to include a current address in addition to the address of their affiliation at the time of the study. The current address should be listed in the byline and clearly labeled "current address." At a minimum, the address must include the author's current institution, city, and country.

If an author has multiple affiliations, enter all affiliations on the title page only. In the submission system, enter only the preferred or primary affiliation. Author affiliations will be listed in the typeset PDF article in the same order that authors are listed in the submission.

Author names will be published exactly as they appear in the manuscript file. Please double-check the information carefully to make sure it is correct.

Corresponding author

The submitting author is automatically designated as the corresponding author in the submission system. The corresponding author is the primary contact for the journal office and the only author able to view or change the manuscript while it is under editorial consideration.

The corresponding author role may be transferred to another coauthor. However, note that transferring the corresponding author role also transfers access to the manuscript. (To designate a new corresponding author while the manuscript is still under consideration, watch the video tutorial below.)

Only one corresponding author can be designated in the submission system, but this does not restrict the number of corresponding authors that may be listed on the article in the event of publication. Whoever is designated as a corresponding author on the title page of the

manuscript file will be listed as such upon publication. Include an email address for each corresponding author listed on the title page of the manuscript.

How to select a new corresponding author in Editorial Manager

Consortia and group authorship

If a manuscript is submitted on behalf of a consortium or group, include its name in the manuscript byline. Do not add it to the author list in the submission system. You may include the full list of members in the Acknowledgments or in a supporting information file.

PubMed only indexes individual consortium or group author members listed in the article byline. If included, these individuals must qualify for authorship according to our criteria.

Read the group authorship policy.

Author contributions

Provide at minimum one contribution for each author in the submission system. Use the CRediT taxonomy to describe each contribution. Read the policy and the full list of roles.

Contributions will be published with the final article, and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and we expect that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

PLOS ONE will contact all authors by email at submission to ensure that they are aware of the submission.

Cover letter

Upload a cover letter as a separate file in the online system. The length limit is 1 page.

The cover letter should include the following information:

- Summarize the study's contribution to the scientific literature
- Relate the study to previously published work
- Specify the type of article (for example, research article, systematic review, meta-analysis, clinical trial)
- Describe any prior interactions with PLOS regarding the submitted manuscript
- Suggest appropriate Academic Editors to handle your manuscript (see the full list of Academic Editors)

- List any opposed reviewers

IMPORTANT: Do not include requests to reduce or waive publication fees in the cover letter. This information will be entered separately in the online submission system.

Read about publication fee assistance.

Title page

The title, authors, and affiliations should all be included on a title page as the first page of the manuscript file.

Download our sample title, author list, and affiliations page (PDF)

Abstract

The Abstract comes after the title page in the manuscript file. The abstract text is also entered in a separate field in the submission system.

The Abstract should:

- Describe the main objective(s) of the study
- Explain how the study was done, including any model organisms used, without methodological detail
- Summarize the most important results and their significance
- Not exceed 300 words

Abstracts should not include:

- Citations
- Abbreviations, if possible

Introduction

The introduction should:

- Provide background that puts the manuscript into context and allows readers outside the field to understand the purpose and significance of the study
- Define the problem addressed and why it is important
- Include a brief review of the key literature

- Note any relevant controversies or disagreements in the field
- Conclude with a brief statement of the overall aim of the work and a comment about whether that aim was achieved

Materials and Methods

The Materials and Methods section should provide enough detail to allow suitably skilled investigators to fully replicate your study. Specific information and/or protocols for new methods should be included in detail. If materials, methods, and protocols are well established, authors may cite articles where those protocols are described in detail, but the submission should include sufficient information to be understood independent of these references.

Supporting reproducibility with protocols

To enhance the reproducibility of your results, we recommend and encourage you to make your protocols public. There are several options:

Protocols associated with Research Articles

Protocol documents may be uploaded as Supporting Information or linked from the Methods section of the article. For laboratory protocols, we recommend protocols.io. Include the DOI link in the Methods section of your manuscript using the following format: http://dx.doi.org/10.17504/protocols.io. [PROTOCOL DOI]. This allows editors and reviewers to consult the detailed step-by-step protocol when evaluating your manuscript. You can choose to keep the protocol private on the protocols.io platform until your article is published—at which time it will be published automatically.

Protocols published in their own right

PLOS ONE offers two options for publishing stand-alone protocol articles: Lab Protocols that describe verified methodologies and Study Protocols that describe detailed plans and proposals for research projects. Specific guidelines apply to the submission of Lab Protocol and Study Protocol manuscripts. Read the detailed instructions for submitting Lab Protocols and Study Protocols.

Results, Discussion, Conclusions

These sections may all be separate or may be combined to create a mixed Results/Discussion section (commonly labeled “Results and Discussion”) or a mixed Discussion/Conclusions section (commonly labeled “Discussion”). These sections may be further divided into subsections, each with a concise subheading, as appropriate. These sections have no word limit, but the language should be clear and concise.

Together, these sections should describe the results of the experiments, the interpretation of these results, and the conclusions that can be drawn.

Authors should explain how the results relate to the hypothesis presented as the basis of the study and provide a succinct explanation of the implications of the findings, particularly in relation to previous related studies and potential future directions for research.

PLOS ONE editorial decisions do not rely on perceived significance or impact, so authors should avoid overstating their conclusions. See the PLOS ONE Criteria for Publication for more information.

Acknowledgments

Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution.

Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.

PLOS journals publicly acknowledge the indispensable efforts of our editors and reviewers on an annual basis. To ensure equitable recognition and avoid any appearance of partiality, do not include editors or peer reviewers—named or unnamed—in the Acknowledgments.

Do not include funding sources in the Acknowledgments or anywhere else in the manuscript file. Funding information should only be entered in the financial disclosure section of the submission system.

References

Any and all available works can be cited in the reference list. Acceptable sources include:

- Published or accepted manuscripts
- Manuscripts on preprint servers, providing the manuscript has a citable DOI or arXiv URL.

Do not cite the following sources in the reference list:

- Unavailable and unpublished work, including manuscripts that have been submitted but not yet accepted (e.g., "unpublished work," "data not shown"). Instead, include those data as supplementary material or deposit the data in a publicly available database.
- Personal communications (these should be supported by a letter from the relevant authors but not included in the reference list)

References are listed at the end of the manuscript and numbered in the order that they appear in the text. In the text, cite the reference number in square brackets (e.g., "We used the techniques developed by our colleagues [19] to analyze the data"). PLOS uses the numbered citation (citation-sequence) method and first six authors, et al.

Do not include citations in abstracts.

Make sure the parts of the manuscript are in the correct order before ordering the citations.

Formatting references

Because all references will be linked electronically as much as possible to the papers they cite, proper formatting of the references is crucial.

PLOS uses the reference style outlined by the International Committee of Medical Journal Editors (ICMJE), also referred to as the "Vancouver" style. Example formats are listed below. Additional examples are in the ICMJE sample references.

A reference management tool, EndNote, offers a current style file that can assist you with the formatting of your references. If you have problems with any reference management program, please contact the source company's technical support.

Journal name abbreviations should be those found in the National Center for Biotechnology Information (NCBI) databases.

Source Format

Published articles Hou WR, Hou YL, Wu GF, Song Y, Su XL, Sun B, et al. cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpL9) of the giant panda (Ailuropoda melanoleuca). Genet Mol Res. 2011;10: 1576-1588.

Devaraju P, Gulati R, Antony PT, Mithun CB, Negi VS. Susceptibility to SLE in South Indian Tamils may be influenced by genetic selection pressure on TLR2 and TLR9 genes. Mol Immunol. 2014 Nov 22. pii: S0161-5890(14)00313-7. doi: 10.1016/j.molimm.2014.11.005.

Note: A DOI number for the full-text article is acceptable as an alternative to or in addition to traditional volume and page numbers. When providing a DOI, adhere to the format in the example above with both the label and full DOI included at the end of the reference (doi: 10.1016/j.molimm.2014.11.005). Do not provide a shortened DOI or the URL.

Accepted, unpublished articles Same as published articles, but substitute "Forthcoming" for page numbers or DOI.

Online articles Huynen MMTE, Martens P, Hilderlink HBM. The health impacts of globalisation: a conceptual framework. Global Health. 2005;1: 14. Available from: http://www.globalizationandhealth.com/content/1/1/14

Books Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.

Book chapters Hansen B. New York City epidemics and history for the public. In: Harden VA, Risse GB, editors. AIDS and the historian. Bethesda: National Institutes of Health; 1991. pp. 21-28.

Deposited articles (preprints, e-prints, or arXiv) Krick T, Shub DA, Verstraete N, Ferreiro DU, Alonso LG, Shub M, et al. Amino acid metabolism conflicts with protein diversity. arXiv:1403.3301v1 [Preprint]. 2014 [cited 2014 March 17]. Available from: https://128.84.21.199/abs/1403.3301v1

Kording KP, Mensh B. Ten simple rules for structuring papers. BioRxiv [Preprint]. 2016 bioRxiv 088278 [posted 2016 Nov 28; revised 2016 Dec 14; revised 2016 Dec 15; cited 2017 Feb 9]: [12 p.]. Available from: https://www.biorxiv.org/content/10.1101/088278v5 doi: 10.1101/088278

Published media (print or online newspapers and magazine articles) Fountain H. For Already Vulnerable Penguins, Study Finds Climate Change Is Another Danger. The New York Times. 2014 Jan 29 [Cited 2014 March 17]. Available from: http://www.nytimes.com/2014/01/30/science/earth/climate-change-taking-toll-on-penguins-study-finds.html

New media (blogs, web sites, or other written works) Allen L. Announcing PLOS Blogs. 2010 Sep 1 [cited 17 March 2014]. In: PLOS Blogs [Internet]. San Francisco: PLOS 2006 -. [about 2 screens]. Available from: http://blogs.plos.org/plos/2010/09/announcing-plos-blogs/.

Masters' theses or doctoral dissertations Wells A. Exploring the development of the independent, electronic, scholarly journal. M.Sc. Thesis, The University of Sheffield. 1999. Available from: http://cumincad.scix.net/cgi-bin/works/Show?2e09

Databases and repositories (Figshare, arXiv) Roberts SB. QPX Genome Browser Feature Tracks; 2013 [cited 2013 Oct 5]. Database: figshare [Internet]. Available from: http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214

Multimedia (videos, movies, or TV shows) Hitchcock A, producer and director. Rear Window [Film]; 1954. Los Angeles: MGM.

Supporting information

Authors can submit essential supporting files and multimedia files along with their manuscripts. All supporting information will be subject to peer review. All file types can be submitted, but files must be smaller than 20 MB in size.

Authors may use almost any description as the item name for a supporting information file as long as it contains an “S” and number. For example, “S1 Appendix” and “S2 Appendix,” “S1 Table” and “S2 Table,” and so forth.

Supporting information files are published exactly as provided and are not copyedited.

Supporting information captions

List supporting information captions at the end of the manuscript file. Do not submit captions in a separate file.

The file number and name are required in a caption, and we highly recommend including a one-line title as well. You may also include a legend in your caption, but it is not required.

Example caption

S1 Text. Title is strongly recommended. Legend is optional.

In-text citations

We recommend that you cite supporting information in the manuscript text, but this is not a requirement. If you cite supporting information in the text, citations do not need to be in numerical order.

Read the supporting information guidelines for more details about submitting supporting information and multimedia files.

Figures and tables

Figures

Do not include figures in the main manuscript file. Each figure must be prepared and submitted as an individual file.

Cite figures in ascending numeric order at first appearance in the manuscript file.

Read the guidelines for figures and requirements for reporting blot and gel results.

Figure captions

Figure captions must be inserted in the text of the manuscript, immediately following the paragraph in which the figure is first cited (read order). Do not include captions as part of the figure files themselves or submit them in a separate document.

At a minimum, include the following in your figure captions:

• A figure label with Arabic numerals, and “Figure” abbreviated to “Fig” (e.g., Fig 1, Fig 2, Fig 3, etc). Match the label of your figure with the name of the file uploaded at submission (e.g., a figure citation of “Fig 1” must refer to a figure file named “Fig1.tif”).

- A concise, descriptive title

The caption may also include a legend as needed.

Read more about figure captions.

Tables

Cite tables in ascending numeric order upon first appearance in the manuscript file.

Place each table in your manuscript file directly after the paragraph in which it is first cited (read order). Do not submit your tables in separate files.

Tables require a label (e.g., “Table 1”) and brief descriptive title to be placed above the table. Place legends, footnotes, and other text below the table.

Read the guidelines for tables.

Statistical reporting

Manuscripts submitted to PLOS ONE are expected to report statistical methods in sufficient detail for others to replicate the analysis performed. Ensure that results are rigorously reported in accordance with community standards and that the statistical methods employed are appropriate for the study design.

Consult the following resources for additional guidance:

- SAMPL guidelines, for general guidance on statistical reporting
- PLOS ONE guidelines, for clinical trials requirements
- PLOS ONE guidelines, for systematic review and meta-analysis requirements
- EQUATOR, for specific reporting guidelines for a range of other study types

Reporting of statistical methods

In the methods, include a section on statistical analysis that reports a detailed description of the statistical methods. In this section:

- List the name and version of any software package used, alongside any relevant references
- Describe the technical details or procedures required to reproduce the analysis
- Provide the repository identifier for any code used in the analysis (See our code-sharing policy.)

Statistical reporting guidelines:

- Identify research design and independent variables as being between- or within-subjects

- For pre-processed data:

o Describe any analysis carried out to confirm the data meets the assumptions of the analysis performed (e.g. linearity, co-linearity, normality of the distribution).

o If data were transformed include this information, with a reason for doing so and a description of the transformation performed

- Provide details of how outliers were treated and your analysis, both with the full dataset and with the outliers removed

- If relevant, describe how missing/excluded data were handled

- Define the threshold for significance (alpha)

- If appropriate, provide sample sizes, along with a description of how they were determined. If a sample size calculation was performed, specify the inputs for power, effect size and alpha. Where relevant, report the number of independent replications for each experiment.

- For analyses of variance (ANOVAs), detail any post hoc tests that were performed

- Include details of any corrections applied to account for multiple comparisons. If corrections were not applied, include a justification for not doing so

- Describe all options for statistical procedures. For example, if t-tests were performed, state whether these were one- or two-tailed. Include details of the type of t-test conducted (e.g. one sample, within-/between-subjects).

- For step-wise multiple regression analyses:

o Report the alpha level used

o Discuss whether the variables were assessed for collinearity and interaction

o Describe the variable selection process by which the final model was developed (e.g., forward-stepwise; best subset). See SAMPL guidelines.

- For Bayesian analysis explain the choice of prior trial probabilities and how they were selected. Markov chain Monte Carlo settings should be reported.

Reporting of statistical results

Results must be rigorously and appropriately reported, in keeping with community standards.

- Units of measurement. Clearly define measurement units in all tables and figures.

- Properties of distribution. It should be clear from the text which measures of variance (standard deviation, standard error of the mean, confidence intervals) and central tendency (mean, median) are being presented.

- Regression analyses. Include the full results of any regression analysis performed as a supplementary file. Include all estimated regression coefficients, their standard error, p-values, and confidence intervals, as well as the measures of goodness of fit.

- Reporting parameters. Test statistics (F/t/r) and associated degrees of freedom should be provided. Effect sizes and confidence intervals should be reported where appropriate. If percentages are provided, the numerator and denominator should also be given.

- P-values. Report exact p-values for all values greater than or equal to 0.001. P-values less than 0.001 may be expressed as $p < 0.001$, or as exponentials in studies of genetic associations.

- Displaying data in plots. Format plots so that they accurately depict the sample distribution. 3D effects in plots can bias and hinder interpretation of values, so avoid them in cases where regular plots are sufficient to display the data.

- Open data. As explained in PLOS's Data Policy, be sure to make individual data points, underlying graphs and summary statistics available at the time of publication. Data can be deposited in a repository or included within the Supporting Information files.