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Clinical and Biochemical Markers of Risk in Uncomplicated Severe Acute Malnutrition

Trenton Dailey-Chwalibóg, MPH, PhD,[a,b,c] Michael Freemark, MD,[d,e] Michael Muehlbauer, PhD,[e] Dominique Roberfroid, MD, PhD,[c,f,g] Issa A. Kemokai, BSN,[h] Md. Rayhan Mostak, MSc, MPH,[i,j] Md. Abdul Alim, MBBS, MPH,[k] Murad Md. Shamsher Tabris Khan, MBBS,[k] Md. Abul Hashem Khan, MBBS,[l] Luke Bawo, MPH,[m] Nelson K. Dunbar, MPH,[m] Curtis H. Taylor, BSc,[n] Helene Fouillet, PhD,[b] Jean-Francois Huneau, PhD,[b] Patrick Kolsteren, MD, PhD,[c] Benjamin Guesdon, PhD[a]

abstract

BACKGROUND AND OBJECTIVES: Use of mid–upper arm circumference (MUAC) as a single screening tool for severe acute malnutrition (SAM) assumes that children with a low weight-for-height *z* score (WHZ) and normal MUAC have lower risks of morbidity and mortality. However, the pathophysiology and functional severity associated with different anthropometric phenotypes of SAM have never been well characterized. We compared clinical characteristics, biochemical features, and health and nutrition histories of nonedematous children with SAM who had (1) low WHZ only, (2) both low WHZ and low MUAC, or (3) low MUAC only.

METHODS: In Bangladesh, Burkina Faso, and Liberia, we conducted a multicentric cohort study in uncomplicated, nonedematous children with SAM and low MUAC only (n = 161), low WHZ only (n = 138), or a combination of low MUAC and low WHZ (n = 152). Alongside routine anthropometric measurements, we collected a wide range of critical indicators of clinical and nutritional status and viability; these included serum leptin, an adipocytokine negatively associated with mortality risk in SAM.

RESULTS: Median leptin levels at diagnosis were lower in children with low WHZ only (215.8 pg/mL; $P < .001$) and in those with combined WHZ and MUAC deficits (180.1 pg/mL; $P < .001$) than in children with low MUAC only (331.50 pg/mL). The same pattern emerged on a wide range of clinical indicators, including signs of severe wasting, dehydration, serum ferritin levels, and caretaker-reported health deterioration, and was replicated across study sites.

CONCLUSIONS: Illustrative of the likely heterogeneous functional severity of the different anthropometric phenotypes of SAM, our results confirm the need to retain low WHZ as an independent diagnostic criterion.

[a]*Department of Expertise and Advocacy, Action Contre la Faim, Paris, France;* [b]*Université Paris-Saclay, AgroParisTech, INRAE, UMR PNCA, 75005, Paris, France;* [c]*Department of Food Technology, Safety, and Health, Ghent University, Ghent, Belgium;* [d]*Division of Pediatric Endocrinology and Diabetes, Duke University Medical Center, Durham, North Carolina;* [e]*Duke Molecular Physiology Institute, Duke University Medical Center, Durham, North Carolina;* [f]*Belgian Health Care Knowledge Centre, Brussels, Belgium;* [g]*Medicine Department, Faculty of Medicine, University of Namur, Namur, Belgium;* [h]*Action Contre la Faim, Monrovia, Liberia;* [i]*Action Contre la Faim, Dhaka, Bangladesh;* [j]*Palli Karma-Sahayak Foundation, Dhaka, Bangladesh;* [k]*National Nutrition Service, Institute of Public Health Nutrition, Dhaka, Bangladesh;* [l]*Community Based Health Care, Dhaka, Bangladesh;* [m]*Ministry of Health, Monrovia, Liberia; and* [n]*Pacific Institute for Research and Evaluation, University of Liberia, Monrovia, Liberia*

Dr Dailey-Chwalibóg conceptualized and designed the study, wrote the original study protocol, supervised recruitment, collected, analyzed, and interpreted data, produced figures, and drafted the original manuscript; Dr Guesdon conceptualized and designed the study, cowrote the study protocol, collected and interpreted the data, and provided major input into the drafting and revision of the manuscript; Drs Freemark, Huneau, and Kolsteren conceptualized and designed the study, cowrote the study protocol, interpreted the data, and provided major input into (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Use of mid–upper arm circumference (MUAC) as a single assessment tool for severe acute malnutrition assumes that children with low weight-for-height *z* scores are at lower risk for morbidity and mortality than children with low MUAC. This assumption has never been tested directly.

WHAT THIS STUDY ADDS: Malnourished children with low weight-for-height *z* scores have deficits in nutritional status, hydration, and iron balance as or more severe than those in children with low MUAC and have lower levels of leptin, a marker of mortality risk in severe acute malnutrition.

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Severe acute malnutrition (SAM) in young children (aged 6–59 months) is a life-threatening condition requiring urgent referral for intensive medico-nutritional care. Current recommendations for diagnosis of SAM are based either on a weight-for-height *z* score (WHZ) <-3 SDs from the reference median, a mid–upper arm circumference (MUAC) <115 mm, and/or bilateral pitting edema.[1,2] By the nature of these recommendations, nonedematous children with SAM segregate into 1 of 3 distinct anthropometric phenotypes: (1) low WHZ only (WHZ <-3 and MUAC ≥ 115 mm), (2) both low WHZ and low MUAC (WHZ <-3 and MUAC <115 mm), and (3) low MUAC only (WHZ -3 and MUAC <115 mm). In a recent meta-analysis compiling data from representative surveys it was found that only 16% of children classified as having SAM had both low WHZ and low MUAC.[3] In other words, most children with SAM in the community present with either low WHZ or low MUAC. This means that adoption of a single criterion for diagnosis effectively excludes from treatment the large number of children who have SAM as defined by using the alternative anthropometric criterion.

Despite this, some program experts advocate using only MUAC or edema to identify children in need of intensive medico-nutritional intervention.[4,5] They argue that abandoning WHZ enhances feasibility and scale-up and improves coverage and impact of SAM management programs. This controversial position, contradicting World Health Organization (WHO) recommendations, is linked to an important clinical assumption: that nonedematous children with low WHZ but MUAC >115 mm are at lower risk for morbidity and mortality than children with low MUAC.[4] This assumption has played an instrumental role in popularizing the use of MUAC as a single assessment tool for identification of infants and children with SAM and in the abandonment of WHZ by practitioners and agencies supporting SAM management services.[6]

However, the pathophysiology and functional severity associated with different anthropometric phenotypes of SAM have never been well characterized, and it is unclear if low WHZ and low MUAC reflect differences in morbidity and mortality risk and need for treatment. Indeed, the WHO and scientific community have repeatedly called for investigation into the pathophysiology and functional severity linked to anthropometric phenotype.[1,3,7,8] The aim of the OptiDiag study was to characterize health and nutrition status, pathophysiology, and functional severity linked to anthropometric phenotype in children with SAM. To that end, we compared the clinical characteristics, biochemical features, and health and nutrition histories of nonedematous children with SAM who had (1) low WHZ only, (2) both low WHZ and low MUAC, or (3) low MUAC only.

We chose serum leptin as our primary outcome measure and marker of risk of mortality on the basis of our comprehensive hormonal and metabolic profile of Ugandan children with SAM, which revealed that hypoleptinemia at time of hospital admission was a robust biochemical predictor of acute mortality.[9] This association was recently confirmed in a study of hospitalized Kenyan children with SAM, in which the authors reported that predischarge hypoleptinemia was among the strongest determinants of death post discharge.[10]

METHODS

Study Design

The OptiDiag study followed a multicentric design and was conducted in Bangladesh, Burkina Faso, and Liberia. We present here data obtained at the time of enrollment, before therapeutic refeeding was begun.

Setting

The geographic, demographic, and epidemiological profiles of the study areas are detailed in the Supplemental Information.

Participants

Children with SAM were identified and referred to treatment by active and passive screening by community health workers and health staff (see Supplemental Information). Nonedematous, uncomplicated children with SAM aged 6 to 59 months were recruited into the study at the time of admission to therapeutic feeding programs. Exclusion criteria were bilateral pitting edema; medical complications requiring inpatient care, including inability to drink or breastfeed, bloody diarrhea, uncontrolled vomiting, convulsions, lethargy, or unconsciousness; known peanut and/or milk allergies; congenital malformations that affect food intake; and plans to leave the catchment area within the next 6 months.

Our recruitment process (Supplemental Information) was aimed at ensuring a balanced representation of each anthropometric phenotype over the 1-year implementation period to account for seasonal variability.

Variables

Anthropometric measurements were taken in duplicate and followed standard WHO recommendations for children in this age group (Supplemental Information).[11,12] WHZ and height-for-age *z* scores (HAZ) were calculated by using WHO growth standards.[13]

Leptin levels were compared among the 3 experimental groups and interpreted in comparison to levels in normal, healthy infants and

TABLE 1 Demographic and Anthropometric Characteristics on Admission

Characteristic	WHZ Only (n = 138)	Both WHZ and MUAC (n = 152)	MUAC Only (n = 161)
Study site,[a] % (n)			
Bangladesh (n = 142)	34.5 (49)	31.7 (45)	33.8 (48)
Burkina Faso (n =165)	20.1 (48)	32.1 (53)	38.8 (64)
Liberia (n = 144)	28.5 (41)	37.5 (54)	34.0 (49)
Age, mo, median (IQR)	15.5 (10.55 to 25.61)	10.2 (7.36 to 16.47)	8.0 (6.71 to 11.8)
6–11, % (n)	33.3 (46)	61.2 (93)	76.4 (123)
12–23, % (n)	36.9 (51)	29.6 (45)	21.1 (32)
24–59, % (n)	29.7 (41)	9.2 (14)	3.7 (6)
Male sex, % (n)	68.1 (94)	44.7 (68)	32.9 (53)
Anthropometry			
WHZ, median (IQR)	−3.33 (−3.7 to −3.16)	−3.54 (−3.98 to −3.25)	−2.38 (−2.69 to −1.88)
MUAC, mm, median (IQR)	120 (117 to 124)	111 (107 to 113)	113 (110 to 114)
HAZ, mean ± SD	−1.82 ± 1.31	−2.46 ± 1.44	−2.72 ± 1.33
HAZ <−3, % (n)	16.7 (23)	34.2 (52)	40.4 (65)
SSRZ, median (IQR)	−0.06 (−0.59 to 0.39)	0.18 (−0.35 to 0.51)	0.14 (−0.30 to 0.52)
Longer legs,[b] % (n)	41.3 (57)	31.3 (46)	28.3 (45)

Values are % (n) for categorical variables, means ± SDs for continuous variables with a normal distribution, or medians (IQRs) for continuous variables with a skewed distribution.
[a] Percentages in these lines reflect proportions of each phenotype per country.
[b] Lowest tertile of SSRZ.

children.[14] We also compared the percentage of children in each group with serum leptin levels <35 pg/mL because this cutoff had high predictive value for mortality among hospitalized patients with SAM.[9,10]

We measured retinol-binding protein (RBP), serum ferritin, and soluble transferrin receptor (sTfR) as biomarkers of vitamin A and iron status. Because RBP and ferritin are known to inaccurately reflect nutrition status in the presence of subclinical inflammation, correction factors were calculated to adjust their values.[15] Thresholds for defining abnormal biochemical parameters in blood are described in the Supplemental Information.

All analytes were measured by using enzyme-linked immunosorbent assays and, with rare exception, were performed in duplicate.

During clinical examinations, nurses measured vital signs, including temperature and heart and respiratory rates. Presence or absence of respiratory infection and changes in skin and hair were recorded. Visible severe wasting, pneumonia, hydration state, and clinical evidence of vitamin A and iron deficiencies were assessed by using WHO guidelines for the integrated management of childhood illness (IMCI) and the WHO Training Course on the Management of Severe Malnutrition: Principles of Care.[16,17]

Caretakers were asked to report recent changes in their children's general state of health, body weight, and food intake.

Study Size

The study was exploratory in nature. Therefore, we employed the general rule of thumb that a minimum sample size of 30 is sufficient for normal approximation.[18] To account for possible difficulties in collecting biological samples, this number was increased to a minimum of 50 patients per anthropometric phenotype in each study site.

Statistical Methods

Characteristics of the study population were summarized as percentages, means ± SDs, or medians and interquartile ranges (IQRs) if not normally distributed. Differences in clinical features, health and nutritional histories, and biochemical data among the 3 phenotypes were assessed by using χ^2 and Kruskal-Wallis tests; when statistical differences were detected ($P < .05$), we compared the following groups: (1) WHZ only versus MUAC only; (2) both low WHZ and low MUAC versus MUAC only, which tests the effect of adding low WHZ to low MUAC; and (3) all MUAC (MUAC <115 mm with or without WHZ <–3) versus children with low WHZ alone, who would be denied eligibility to SAM treatment under a program abandoning the use of WHZ as an

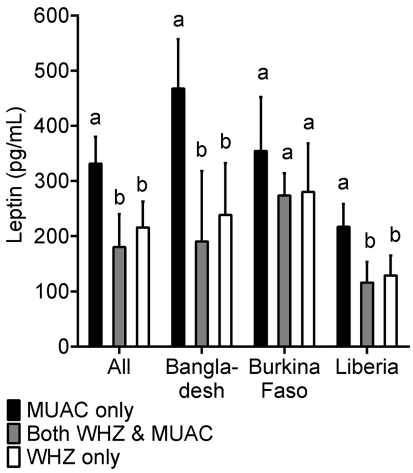

FIGURE 1
Median leptin levels (picograms per milliliter) with IQRs by anthropometric phenotype, combined and by country. Different letters, by site, signify statistical difference at $P < .05$.

TABLE 2 Biochemical Features, Urinalysis, Clinical Characteristics, and Health and Nutrition Histories at Admission

	WHZ Only (n = 138)	Both WHZ and MUAC (n = 152)	MUAC Only (n = 161)	P[a]
Biochemical features				
Serum leptin, pg/mL, median (IQR)	215.80 (122.0 to 346.6)	180.10 (87.7 to 346.8)	331.50 (159.0 to 560.1)	<.001
Serum leptin <35 pg/mL, % (n)	5 (7)	9 (14)	3 (5)	.07
APPs				
AGP, g/L, median (IQR)	1.25 (0.83 to 1.69)	1.25 (0.88 to 1.82)	1.13 (0.79 to 1.81)	.41
AGP >1 mg/L, % (n)	66 (85)	66 (94)	56 (87)	.13
CRP, mg/L, median (IQR)	1.51 (0.50–12.44)	1.655 (0.63 to 8.29)	2.67 (0.68 to 10.14)	.25
CRP >5 mg/L, % (n)	34 (44)	32 (45)	38 (59)	.49
AGP >1 mg/L and/or CRP >5 mg/L, % (n)	67 (86)	69 (98)	62 (96)	.46
Iron deficiency				
Body iron stores, mg/kg body weight, median (IQR)	5.99 (1.82 to 8.17)	5.68 (1.8 to 8.34)	4.56 (1.87 to 7.92)	.23
Body iron stores <0 mg/kg body weight, % (n)	25 (32)	17 (24)	14 (21)	.04
Adjusted serum ferritin, μL/L, median (IQR)	27.74 (8.77 to 48.44)	33.99 (16.42 to 67.71)	33.60 (15.93 to 54.27)	.04
Adjusted serum ferritin level <12 μg/L, % (n)	30 (39)	18 (26)	19 (29)	.03
sTfR, mg/L, median (IQR)	8.34 (6.91 to 11.24)	8.8 (8.8 to 11.65)	8.7 (7.21 to 12.96)	.41
sTfR level >8.3 mg/L, % (n)	52 (67)	54 (76)	57 (88)	.70
Vitamin A insufficiency or deficiency				
Adjusted RBP, μmol/L, median (IQR)	1.01 (0.77 to 1.24)	0.98 (0.78 to 1.22)	1 (0.77 to 1.25)	.99
Adjusted RBP level <1.05 μmol/L, % (n)	55 (71)	58 (83)	56 (87)	.88
Adjusted RBP level <0.7 μmol/L, % (n)	20 (25)	15 (22)	19 (29)	.64
Urinalysis, % (n/N)				
Ascorbic acid excretion, ≥0.2 g/L (20 mg/dL)	44 (39/88)	53 (49/92)	48 (41/86)	.48
Bilirubinuria, ≥15 μmol/L (1 mg/dL)	19 (17/88)	18 (17/92)	6 (5/86)	.03
Hematuria, ≥5–10 erythrocytes per μL	9 (8/88)	17 (15/90)	19 (16/86)	.17
Glycosuria, ≥2.8 mol/L (50 mg/dL)	1 (1/88)	3 (3/91)	1 (1/85)	.48
Ketonuria, ≥1 mmol/L (10mg/dL)	16 (14/88)	8 (7/92)	5 (4/84)	.19
Leukocyturia, ≥25 leukocytes per μL	14 (12/88)	30 (28/92)	22 (19/85)	.03
Nitrituria	25 (22/88)	31 (28/91)	40 (34/86)	.12
Proteinuria	8 (7/88)	10 (9/92)	8 (7/85)	.90
Urobilinogenuria, ≥35 μmol/L (2 mg/dL)	3 (3/88)	1 (1/92)	1 (1/86)	.43
Clinical features, % (n/N)				
Cough or difficult breathing				
Cough	48 (66)	56 (85)	45 (73)	.15
Nasal discharge	31 (43/137)	37 (56)	28 (45)	.24
Tachypnea[b]	17 (24)	25 (38)	21 (34)	.29
Difficult breathing	4 (6)	9 (13)	4 (7)	.19
Subcostal indrawing	2 (3)	2 (3)	1 (2)	.81
Stridor	1 (2)	3 (4)	4 (7)	.32
WHO IMCI recommendations: pneumonia or severe pneumonia	19 (26/137)	28 (42)	24 (39)	.22
Dehydration				
Slow or very slow skin pinch	17 (15/90)	21 (21/99)	4 (4/97)	.002
Sunken eyes	32 (29/90)	30 (30/99)	14 (14/97)	.008
Restlessness and/or irritability	8 (7/90)	16 (16/99)	3 (3/97)	.006
WHO IMCI recommendations: some or severe dehydration	18 (16/89)	22 (22/99)	6 (6/96)	.006
Dermatosis	9 (12)	18 (27)	7 (12)	—
Hair changes	9 (13)	4 (6/150)	7 (11/157)	.18
Iron deficiency				
Conjunctival and/or palmar pallor	34 (47)	41 (62/151)	27 (43)	.03
Fever	15 (21)	18 (28)	18 (29)	.74
Malaria	8 (11/136)	14 (20/148)	21 (33/157)	.007
Visible severe wasting				
Visible ribs	67 (60/90)	76 (75/99)	53 (51/97)	.003
Loose skin on arms or thighs	14 (19/90)	24 (37/99)	9 (14/97)	<.001
Visible back ribs or shoulder bones	58 (52/90)	69 (68/99)	46 (45/97)	.004
Flesh missing or folds of skin on buttocks and/or baggy pants	6 (5/90)	17 (17/99)	3 (3/97)	<.001
WHO IMCI recommendations: severe or extreme wasting	67 (60/90)	77 (76/99)	57 (55/97)	.01
Recent health and nutritional histories, caretaker reported, % (n/N)				
Eaten less[c]	49 (67)	38 (58)	37 (59)	.08
Health status deterioration[d]	42 (58)	43 (65)	29 (47)	.02
Weight loss[e]	63 (87)	62 (94)	52 (83/160)	.09
Any 1[f]	75 (104)	72 (109)	6 (100)	.04

TABLE 2 Continued

	WHZ Only (n = 138)	Both WHZ and MUAC (n = 152)	MUAC Only (n = 161)	P^a
Any 2[g]	57 (79)	48 (73)	41% (65/160)	.02
Diarrhea	22 (31)	27 (40/150)	21 (33/159)	.45
Vomiting	13 (18/135)	23 (34/149)	16 (25/158)	.09
Fever	54 (74/136)	60 (89/148)	50 (78/157)	.19
Cough and/or difficult breathing	45 (62)	47 (71/150)	44 (70/159)	.84
Any 1[h]	70 (95/136)	77 (114/149)	68 (108/159)	.22
Any 2[i]	47 (64/135)	52 (77/148)	41 (65/157)	.18

Values are % (n) (n lower than N indicates missing data) or median (IQR). AGP, α-1-acid glycoprotein; APP, acute phase protein; CRP, C-reactive protein; —, not applicable.

[a] For 3-group comparison (WHZ only, both WHZ and MUAC, and MUAC only) by Pearson's χ^2 test (or Fisher's exact tests for small sample sizes) for categorical data and Kruskal-Wallis tests for skewed continuous data.

[b] 50 breaths per minute in children 2–12 mo of age and >40 breaths per minute in children ≥1 y of age.

[c] Eaten a lot less or quite a lot less food.

[d] Much less or a great deal less healthy than usual.

[e] Lost a lot or quite a lot of weight.

[f] Any 1 of the 3 above mentioned indicators.

[g] Any 2 of the 3 above mentioned indicators.

[h] Any 1 of the 4 above mentioned indicators.

[i] Any 2 of the 4 above mentioned indicators.

independent criterion of detection and admission.

Construction of bivariate and multivariate logistic models is described in the Supplemental Information. Confounding and/or effect modification by site, age, sex, severe stunting, and presence of a low sitting/standing ratio z score (SSRZ) was assessed.[19] All analyses were performed by using Stata version 13 (Stata Corp, College Station, TX); P values <.05 were considered statistically significant.

RESULTS

A total of 473 patients were recruited between March 2017 and June 2018. Refusal of caregivers for participation of their children in the study was rare. Twenty-two patients (4.7%) were excluded from analysis because of inclusion error: 4 patients (0.9%) were younger than 6 months at the time of admission, and 18 patients (3.8%) were only moderately malnourished. The distribution of patients across phenotype groups was as follows: 138 (30.6%), low WHZ only; 152 (33.7%), both low WHZ and low MUAC; 161 (35.7%), low MUAC only. In total, 142 patients were from Bangladesh, 165 were from Burkina Faso, and 144 were from Liberia. Each of the 3 phenotypes represented approximately one-third of the sample size in each study site; there was no statistically significant difference (P = .681 from Pearson's χ^2 test) in phenotype proportion among study sites (Table 1).

Statistically significant differences in age, sex, stunting, and SSRZ were detected among phenotypes (Table 1). Compared with children with low WHZ only, children with low MUAC only were younger, more stunted, and more often girls and had a lower

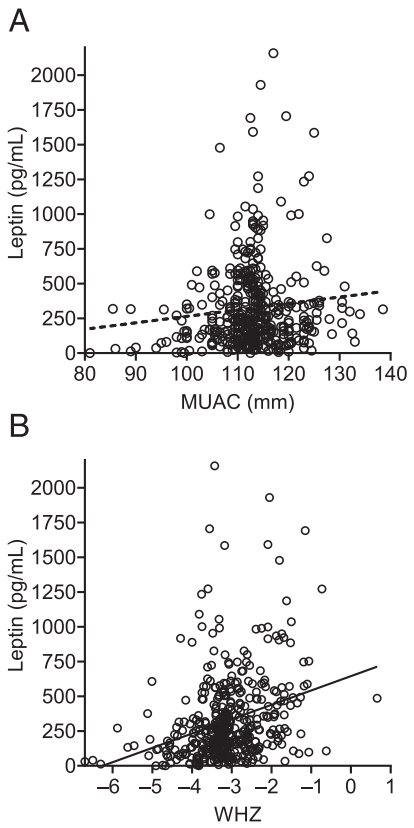

FIGURE 2
Correlation of serum leptin with A, MUAC (r = 0.10, P = .032), and B, WHZ (r = 0.29, P < .0001) as assessed by linear regression.

TABLE 3 Unadjusted and Adjusted Median Serum Leptin and Serum Ferritin by Comparison

	Comparison 1					Comparison 2					Comparison 3				
	WHZ Only		MUAC Only		*P*	MUAC Only		Both WHZ and MUAC		*P*	WHZ Only		All MUAC		*P*
	Median	95% CI	Median	95% CI		Median	95% CI	Median	95% CI		Median	95% CI	Median	95% CI	
Serum leptin, pg/mL															
Unadjusted median[a]	215.8	122.0–346.6	331.5	159.0–560.1	<.001	331.5	159.0–560.1	180.1	87.7–346.8	<.001	215.8	122.0–346.6	245.8	117.0–482.0	.21
Adjusted median	232.1	193.9–263.0	372.8	226.4–380.0	<.001	352.0	229.8–414.3	217.6	133.2–238.0	<.001	220.1	193.9–309.0	262.0	223.0–331.4	.21
Serum ferritin, μL/L															
Unadjusted median[a]	27.7	8.8–48.4	33.6	15.9–54.3	.06	33.6	15.9–54.3	34.0	16.4–67.7	.49	27.7	8.8–48.4	33.9	16.1–60.2	.02
Adjusted median	31.9	7.1–34.4	32.9	24.0–51.0	.83	31.1	27.4–34.9	34.3	30.6–38.6	.40	22.3	18.3–26.7	33.8	33.3–37.8	.02

Adjusted for age, sex, stunting, SSRZ, and country.

[a] The Wilcoxon rank test is used to test for equality of medians when the unadjusted median is presented.

proportion of body length in the legs. Children with both low WHZ and low MUAC fell in the range between children with either low WHZ or low MUAC.

Biochemical data, clinical features, and health and nutritional histories among phenotypes at admission are shown in Table 2. Significant differences were observed and prompted pairwise comparisons, beginning with leptin, the primary outcome measure. Unadjusted and adjusted analyses of continuous data are presented in Table 3. Unadjusted bivariate pairwise analyses of categorical data are presented in Table 4 and adjusted multivariate models that included age, sex, stunting, proportion of body length in the legs, and country as covariates are presented in Table 5.

Among the 3 anthropometric phenotypes, median serum leptin levels were lowest in patients with both low WHZ and low MUAC (180.10 pg/mL; IQR, 87.7 to 346.8), followed by those with low WHZ only (215.80 pg/mL; IQR, 122.0 to 362.6), and was highest in those with low MUAC only (331.50 pg/mL; IQR, 159.0 to 560.1). Unadjusted and adjusted models for pairwise comparisons confirmed the statistical significance of the observed differences between the patients with low MUAC only and the 2 other groups (Table 3). As illustrated in Fig 1, this pattern was consistent across the 3 study sites. There were relatively few children with severe hypoleptinemia (≤35 pg/mL); however, the proportions of children with leptin levels below this cutoff followed a similar trend, with the highest rate of severe hypoleptinemia in children with both low WHZ and low MUAC (Table 2). Leptin levels among all patients correlated far more strongly with WHZ (r = 0.287, $P < .001$) than with MUAC (r = 0.102, P = .03; Fig 2).

Similar patterns were found for a wide range of clinical and biochemical indicators of nutritional deficit, hydration, and iron balance, as well as caretaker-reported changes in nutritional and health status (Table 4). Conversely, children with low MUAC only were 3 times more likely to present with malarial infection (unadjusted odds ratio [UOR], 0.33; P = .003) than children with low WHZ only.

Relative to the combined cohort of all children with low MUAC (MUAC <115 mm with and without WHZ <−3), children with low WHZ only presented with comparable deficits in most clinical and biochemical indicators. For example, median serum leptin levels were not statistically different between these 2 phenotypes (Tables 4 and 5). However, children with low WHZ alone had lower body iron stores and comparable or higher rates of visible severe wasting and dehydration (Table 4).

Additional clinical indicators are presented in Supplemental Table 6. Unadjusted and adjusted analyses of continuous and categorical data, corrected for false discovery rates, are presented in Supplemental Tables 7–9.

DISCUSSION

The pathophysiology and functional severity associated with different anthropometric phenotypes of SAM have heretofore not been well characterized.[8] Yet policy makers and government stakeholders need robust scientific evidence to generate evidence-based guidelines to appropriately target and prioritize malnourished children for treatment. Although the WHO recommends measurement of both WHZ and MUAC for assessment of SAM, the use of MUAC as a single anthropometric assessment tool for case finding and admission to therapeutic feeding programs and the abandonment of

TABLE 4 Unadjusted, Bivariate Logistic Regression Analysis by Comparison

	Comparison 1: WHZ Only Versus MUAC Only			Comparison 2: Both WHZ and MUAC Versus MUAC Only			Comparison 3: All MUAC Versus WHZ Only		
	UOR	95% CIs	*P*	UOR	95% CIs	*P*	UOR	95% CIs	*P*
Biochemical features									
Iron deficiency									
Body iron stores <0 mg/kg body weight	2.11	1.15–3.88	.02	1.29	0.68–2.43	.44	0.54	0.32–0.90	.02
Adjusted serum ferritin level <12 μg/L	1.89	1.09–3.28	.03	0.97	0.54–1.74	.91	0.52	0.32–0.84	.007
Urinalysis									
Bilirubinuria, ≥15 μmol/L (1 mg/dL)	3.88	1.36–11.05	.01	3.67	1.29–10.45	.02	0.59	0.29–1.18	.13
Leukocyturia, ≥25 leukocytes per μL	0.55	0.25–1.21	.14	1.52	0.77–2.99	.23	2.29	1.14–4.58	.02
Clinical features									
Slow or very slow skin pinch	4.65	1.48–14.60	.009	6.26	2.06–19.01	.001	0.73	0.36–1.47	.38
Sunken eyes	2.82	1.37–5.78	.005	2.58	1.27–5.24	.009	0.61	0.35–1.06	.08
Restlessness and/or irritability	2.64	0.66–10.55	.17	6.04	1.70–21.46	.006	1.27	0.51–3.15	.60
WHO IMCI recommendations: some or severe dehydration	3.29	1.22–8.83	.02	4.29	1.65–11.11	.003	0.76	0.39–1.50	.44
Dermatosis	1.18	0.51–2.72	.69	2.68	1.31–5.51	.007	1.49	0.76–2.95	.25
Iron deficiency									
Conjunctival and/or palmar pallor	1.42	0.86–2.33	.17	1.91	1.19–3.08	.008	0.98	0.64–1.50	.93
Malaria	0.33	0.16–0.68	.003	0.59	0.32–1.08	.09	2.39	1.21–4.74	.01
Visible severe wasting									
Visible ribs	1.80	1.00–3.26	.05	2.82	1.53–5.18	.001	0.61	0.35–1.06	.08
Loose skin on arms or thighs	1.59	0.74–3.39	.23	3.54	1.76–7.11	<.001	1.27	0.51–3.15	.60
Visible back ribs or shoulder bones	1.65	0.92–2.94	.09	2.64	1.47–4.73	.001	0.76	0.39–1.50	.44
Flesh missing or folds of skin on buttocks and/or baggy pants	1.84	0.43–7.95	.41	6.50	1.84–22.96	.004	1.93	0.70–5.32	.20
WHO IMCI recommendations: severe or extreme wasting	1.53	0.84–2.77	.16	2.52	1.36–4.67	.003	1.01	0.59–1.71	.98
Recent health and nutritional histories (caretaker reported)									
Health status deterioration	1.76	1.09–2.84	.02	1.74	1.08–2.79	.02	0.77	0.51–1.16	.21
Any 1[a]	1.87	1.13–3.08	.03	1.55	0.96–2.49	.07	0.66	0.42–1.03	.07
Any 2[b]	1.96	1.23–3.11	.004	1.35	0.86–2.11	.19	0.59	0.40–0.89	.01

CI, confidence interval.

[a] Any 1 of the following: eaten a lot less or quite a lot less food, much less or a great deal less healthy than usual, and lost a lot or quite a lot of weight.

[b] Any 2 of the following: eaten a lot less or quite a lot less food, much less or a great deal less healthy than usual, and lost a lot or quite a lot of weight.

WHZ are increasingly promoted and applied.[4–6] This is in part because children presenting with WHZ <–3 but MUAC ≥ 115 mm have been assumed to be at lower risks of morbidity and mortality than children with low MUAC.[4] By characterizing the clinical and biochemical features of separate cohorts of children with low WHZ alone, low MUAC alone, and both low WHZ and low MUAC, we take a novel approach to addressing this controversy.

We present 3 new observations of clinical import; results were consistent across all 3 countries, lending credibility to our findings. First, a range of clinical and biochemical indicators reveal that children with low WHZ alone have deficits in nutritional status, hydration, and iron balance equal to or more severe than those in children with low MUAC alone, and they have lower levels of leptin, a critical marker of mortality risk in SAM.[9,10] The only complication detected more frequently in children with low MUAC only than in those with low WHZ only was malaria prevalence, a finding consistent with observations made in a previous study.[20] Second, children with both low WHZ and low MUAC have the most severe nutritional deficits and lowest leptin levels, suggesting that they are at highest risks of acute and postdischarge morbidity and death. Finally, children with low WHZ alone display vulnerabilities at least as great as the combined cohort of all children with low MUAC.

In previous investigations[9,21] we suggested potential mechanisms that may explain the relationship between hypoleptinemia and mortality in SAM. Leptin is produced by white adipocytes, and its levels in circulation reflect the mass of subcutaneous and, to a lesser extent, visceral white adipose tissue. A low level of leptin suggests white adipose tissue depletion. Because white adipose tissue represents the major bodily storage form of mobilizable energy, a low level of leptin likely reflects a deficiency of body energy stores. Under conditions of severe malnutrition and other severe illnesses and stress, a lack of white adipose tissue may limit the ability to sustain energy production for cardiopulmonary function and gluconeogenesis and thereby increase the risk of death.[9,10,21] Leptin also promotes immune cell development

TABLE 5 Adjusted, Multivariate Logistic Regression Analysis by Comparison

	Comparison 1: WHZ Only Versus MUAC Only			Comparison 2: Both WHZ and MUAC Versus MUAC Only			Comparison 3: All MUAC Versus WHZ Only		
	aOR	95% CIs	*P*	aOR	95% CIs	*P*	aOR	95% CIs	*P*
Biochemical features									
Iron deficiency									
Body iron stores <0 mg/kg body weight	2.25	1.10–4.60	.03	1.29	0.68–2.44	.43	0.50	0.28–0.90	.02
Adjusted serum ferritin level <12 μg/L	2.13	1.11–4.09	.02	0.97	0.54–1.75	.92	0.35	0.21–0.60	<.001
Urinalysis									
Bilirubinuria, ≥15 μmol/L (1 mg/dL)	2.51	0.67–9.36	.17	3.96	1.38–11.42	.01	0.61	0.31–1.24	.17
Leukocyturia, ≥25 leukocytes per μL	0.55	0.25–1.21	.14	1.46	0.73–2.91	.29	1.77	0.86–3.66	.12
Clinical features									
Slow or very slow skin pinch	4.58	1.45–14.39	.009	6.36	2.09–19.35	.001	0.74	0.37–1.48	.39
Sunken eyes	2.88	1.22–6.76	.02	2.58	1.25–5.34	.01	0.57	0.32–1.00	.05
Restlessness and/or irritability	1.78	0.42–7.52	.44	6.72	1.86–24.30	.004	1.06	0.41–2.76	.90
WHO IMCI recommendations: some or severe dehydration	2.51	0.90–6.97	.08	4.29	1.65–11.12	.003	0.76	0.39–1.49	.43
Dermatosis	1.25	0.54–2.92	.61	4.56	1.72–12.10	.002	3.43	0.95–12.46	.06
Clinical iron deficiency									
Conjunctival and/or palmar pallor	1.42	0.86–2.33	.14	1.93	1.20–3.12	.008	0.99	0.65–1.52	.97
Malaria	0.24	0.10–0.56	.001	0.58	0.31–1.06	.08	2.34	1.18–4.65	.02
Visible severe wasting									
Visible ribs	2.44	0.73–8.20	.15	10.00	2.71–36.85	.005	0.59	0.20–1.74	.34
Loose skin on arms or thighs	1.78	0.74–4.27	.21	3.66	1.81–7.40	<.001	1.13	0.60–2.11	.71
Visible back ribs or shoulder bones	2.88	1.07–7.81	.04	8.36	2.98–23.44	<.001	0.79	0.32–1.91	.60
Flesh missing or folds of skin on buttocks and/or baggy pants	2.04	0.46–9.00	.35	6.46	1.81–23.02	.004	1.25	0.43–3.63	.68
WHO IMCI recommendations: severe or extreme wasting	1.28	0.51–3.25	.60	9.17	2.48–33.87	.009	0.64	0.21–1.95	.47
Recent health and nutrition history (caretaker reported)									
Recent health deterioration	1.79	1.11–2.91	.02	5.73	1.91–17.25	.002	0.75	0.50–1.14	.18
Any 1[a]	1.29	0.53–3.15	.57	1.55	0.93–2.58	.09	0.86	0.40–1.88	.71
Any 2[b]	1.13	0.55–2.36	.74	6.12	2.17–17.27	.006	0.93	0.52–1.66	.80

Adjusted for age, sex, stunting, SSRZ and/or country. aOR, adjusted odds ratio.

[a] Any 1 of the following: eaten a lot less or quite a lot less food, much less or a great deal less healthy than usual, and lost a lot or quite a lot of weight.

[b] Any 2 of the following: eaten a lot less or quite a lot less food, much less or a great deal less healthy than usual, and lost a lot or quite a lot of weight.

and function; a lack of leptin production or action in patients with mutations in leptin or the leptin receptor is associated with increased risks of infection.[22,23] Thus, hypoleptinemia in infants and children with SAM may impair immune function and predispose them to mortality from sepsis and other major infectious diseases.[24–26]

Our study has some limitations. First, heterogeneity in screening processes among study sites likely contributed to slight differences in age range, anthropometric deficits, and clinical profiles between countries. The active screening network in Bangladesh was highly developed, and a majority of participants there were identified in their communities. In Liberia, a majority of participants were identified by passive screening during medical management. Only in Burkina Faso were participants passively screened during growth monitoring activities. Yet active community screening, growth monitoring and promotion, and passive screening are all major routes that lead children with SAM to medical care. We consider heterogeneities between study sites to reflect the widespread variability of screening procedures used for SAM and in fact validate the generalizability of our results. Second, our study was focused on uncomplicated SAM. Recommendations that propose the abandonment of the use of WHZ as an independent detection and admission criterion have thus far not been applied to inpatient management of complicated SAM. To avoid selection bias in recruiting patients, we conducted our study in primary health care units, where uncomplicated cases are routinely managed, rather than in hospitals. In these settings, we had to rely on low-invasive procedures, such as capillary blood sampling. The limitation of blood volume precluded us from measuring potentially valuable analytes, including albumin, micronutrients, and amino acids. Finally, leptin levels may decrease with time since feeding.[27] In our study, children were assessed in the morning and were administered an appetite test and/or food challenge as per routine procedures ~1.5 hours before blood sampling. Therefore, we think it unlikely that differences in time since feeding explain the striking differences in leptin levels among the various groups.

Previous analyses of receiver operating characteristic curves in unselected cohorts of children, in community settings where treatment of SAM was not available, revealed that MUAC has greater discriminatory performance for subsequent mortality than WHZ.[28] This observation has been used by some investigators as a rationale for prioritizing low MUAC and discounting or omitting low WHZ for identification and management of SAM.[4] Receiver operating characteristic curves, however, do not quantify relative risk of death or even probability of death of children below specific cutoffs. To assess this more precisely, we recently calculated mortality hazard ratios associated with different phenotypes of SAM in available data sets of past community cohort studies.[29] We found similar hazard ratios in malnourished children with low MUAC only and low WHZ only and higher mortality risk in children with combined deficits. Importantly, these findings from unselected and untreated cohorts of children are supported by the few clinical studies that compared the vulnerability of different subpopulations of children with SAM on admission to treatment[20,30] and by a recent reanalysis of case fatality rates observed in large historical cohorts of malnourished patients.[31] Moreover, WHO experts have noted that the association between absolute MUAC and mortality is subject to age bias (younger children have lower MUAC and higher risks of death) and have questioned its causal relationship with mortality risk.[32] The results reported here are consistent with and extend previous findings: compared with children with low MUAC, children with low WHZ have lower leptin levels and higher rates of severe iron deficiency, dehydration, and visible signs of severe wasting, all of which are associated with higher risks of acute and postdischarge mortality. In our study, all patients were carefully managed with WHO recommendations, regardless of anthropometric criteria. As expected in well-treated, uncomplicated SAM, short-term mortality was low; 1 death occurred in the group with low WHZ only; a second was in the group with both low WHZ and low MUAC.

Together, these observations indicate that malnourished children with low WHZ require intensive nutritional assessment and intervention, even if MUAC exceeds 115 mm. Highest priority should be assigned to children with combined deficits in WHZ and MUAC, who are at greatest risk of life-threatening illness and death. It is clear now that abandonment of WHZ as a diagnostic criterion for SAM effectively excludes from treatment a large number of children with high risks of morbidity and mortality.[33] The analyses of representative survey data indicate that children with low WHZ only may represent >40% of the SAM caseload in most countries, with higher proportions in high-burden and acute-crisis contexts[3,34]; increasing the MUAC threshold for admission would increase the number of these children who would be eligible for treatment but would dramatically increase the program target at the expense of specificity.[35] In summary, the weight of evidence suggests that both WHZ and MUAC should be measured in all children evaluated for malnutrition.

CONCLUSIONS

A research priority should be to harness technological capacity to develop innovative diagnostic methods to identify children with low WHZ in the community. Until then, both WHZ and MUAC should be retained as independent diagnostic criteria for SAM, in line with WHO recommendations.

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ABBREVIATIONS

HAZ: height-for-age *z* score
IMCI: Integrated Management of Childhood Illness
IQR: interquartile range
MUAC: mid–upper arm circumference
RBP: retinol-binding protein
SAM: severe acute malnutrition
SSRZ: sitting/standing ratio *z* score
sTfR: soluble transferrin receptor
UOR: unadjusted odds ratio
WHO: World Health Organization
WHZ: weight-for-height *z* score

the drafting and revision of the manuscript; Mr Kemokai and Mr Mostak provided major input into the design of the study, supervised recruitment, collected data, provided extensive database support, analyzed the data, and revised the manuscript for important intellectual content; Drs Alim, M.M.S.T. Khan, and M.A.H. Khan, Mr Bawo, Mr Dunbar, and Mr Taylor provided major input into the design and implementation of the study, supervised recruitment, and revised the manuscript for important intellectual content; Dr Fouillet conceptualized and designed the study, cowrote the protocol, and revised the manuscript for important intellectual content; Dr Roberfroid provided extensive database support, analyzed and interpreted the data, and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols. The data will be made available after publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted

to Dr Benjamin Guesdon at bguesdon@actioncontrelafaim.org.

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Address correspondence to Dr. Trenton Dailey-Chwalibóg, Department of Food Technology, Safety, and Health, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium. E-mail: trenton@dailey-chwalibog.com

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REFERENCES

1. World Health Organization; United Nations Children's Fund. WHO child growth standards and the identification of severe acute malnutrition in infants and children: a joint statement by the World Health Organization and the United Nations Children's Fund. 2009. Available at: www.who.int/nutrition/publications/severemalnutrition/9789241598163/en/. Accessed April 27, 2019
2. World Health Organization. Guideline: updates on the management of severe acute malnutrition in infants and children. 2013. Available at: www.ncbi.nlm.nih.gov/books/NBK190328/. Accessed April 27, 2019
3. Grellety E, Golden MH. Weight-for-height and mid-upper-arm circumference should be used independently to diagnose acute malnutrition: policy implications. *BMC Nutr*. 2016;2:10
4. Briend A, Alvarez J-L, Avril N, et al. Low mid-upper arm circumference identifies children with a high risk of death who should be the priority target for treatment. *BMC Nutr*. 2016;2(1):63
5. Council of Research and Technical Advice on Acute Malnutrition. Recommendation on the use of mid-upper arm circumference (MUAC) in the community: a statement from the Council of Research & Technical Advice on Acute Malnutrition (CORTASAM). 2018. Available at: http://static1.squarespace.com/static/58da81cdd1758e39ca705526/t/5bf80b5a0ebbe88c33842f13/1542982496317/MUAC_statement_only_1.pdf. Accessed April 14, 2020
6. Woodhead S, Rio D, Zagre N. Regional perspectives on simplified approaches for the management of children with acute malnutrition: West and Central Africa. 2019. Available at: https://www.ennonline.net/attachments/3185/FEX-60-Web_final_33-35.pdf. Accessed April 14, 2020
7. Roberfroid D, Hammami N, Lachat C, et al. Utilization of mid-upper arm circumference versus weight-for-height in nutritional rehabilitation programmes: a systematic review of evidence. 2013. Available at: https://www.who.int/nutrition/publications/guidelines/updates_management_SAM_infantandchildren_review1.pdf. Accessed April 14, 2020
8. World Health Organization. Global action plan on child wasting: a framework for action to accelerate progress in preventing and managing child wasting and the achievement of the sustainable development goals. 2020. Available at: www.who.int/who-documents-detail/global-action-plan-on-child-wasting-a-framework-for-action. Accessed April 14, 2020
9. Bartz S, Mody A, Hornik C, et al. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. *J Clin Endocrinol Metab*. 2014;99(6):2128–2137
10. Njunge JM, Gwela A, Kibinge NK, et al. Biomarkers of post-discharge mortality among children with complicated severe acute malnutrition. *Sci Rep*. 2019;9(1):5981
11. World Health Organization; United Nations Children's Fund. Recommendations for data collection, analysis and reporting on anthropometric indicators in children under 5 years old. 2019. Available at: https://www.who.int/nutrition/publications/anthropometry-data-quality-report/en/. Accessed August 19, 2019
12. Cashin K, Oot L. Guide to anthropometry: a practical tool for program planners, managers, and implementers. 2018. Available at:

https://www.fantaproject.org/sites/default/files/resources/FANTA-Anthropometry-Guide-May2018.pdf. Accessed April 14, 2020

13. WHO Multicentre Growth Reference Study Group. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. 2006. Available at: https://www.who.int/childgrowth/standards/technical_report/en/. Accessed April 27, 2019
14. Savino F, Rossi L, Benetti S, Petrucci E, Sorrenti M, Silvestro L. Serum reference values for leptin in healthy infants. *PLoS One*. 2014;9(11):e113024
15. Thurnham DI. Interactions between nutrition and immune function: using inflammation biomarkers to interpret micronutrient status. *Proc Nutr Soc*. 2014;73(1):1–8
16. World Health Organization. Handbook: IMCI integrated management of childhood illness. 2005. Available at: http://apps.who.int/iris/handle/10665/42939. Accessed April 22, 2019
17. World Health Organization. Training course on the management of severe malnutrition. 2002. Available at: www.who.int/nutrition/publications/severemalnutrition/training_inpatient_MSM/en/. Accessed March 11, 2016
18. Ross SM. Distributions of Sampling Statistics. In: Ross SM, ed. *Introductory Statistics*, 4th ed. Cambridge, MA: Academic Press; 2017:297–328
19. Roberfroid D, Huybregts L, Lachat C, Vrijens F, Kolsteren P, Guesdon B. Inconsistent diagnosis of acute malnutrition by weight-for-height and mid-upper arm circumference: contributors in 16 cross-sectional surveys from South Sudan, the Philippines, Chad, and Bangladesh. *Nutr J*. 2015;14:86
20. Isanaka S, Guesdon B, Labar AS, Hanson K, Langendorf C, Grais RF. Comparison of clinical characteristics and treatment outcomes of children selected for treatment of severe acute malnutrition using mid upper arm circumference and/or weight-for-height z-score. *PLoS One*. 2015;10(9):e0137606
21. Mody A, Bartz S, Hornik CP, et al. Effects of HIV infection on the metabolic and hormonal status of children with severe acute malnutrition. *PLoS One*. 2014;9(7):e102233
22. Duggal P, Guo X, Haque R, et al. A mutation in the leptin receptor is associated with Entamoeba histolytica infection in children. *J Clin Invest*. 2011;121(3):1191–1198
23. Maurya R, Bhattacharya P, Dey R, Nakhasi HL. Leptin functions in infectious diseases. *Front Immunol*. 2018;9:2741
24. Saucillo DC, Gerriets VA, Sheng J, Rathmell JC, Maciver NJ. Leptin metabolically licenses T cells for activation to link nutrition and immunity. *J Immunol*. 2014;192(1):136–144
25. Cohen S, Danzaki K, MacIver NJ. Nutritional effects on T-cell immunometabolism. *Eur J Immunol*. 2017;47(2):225–235
26. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. *Front Immunol*. 2018;9:1055
27. Levitt Katz LE, Abraham M, Johansen L, Jawad AF. Leptin levels decline steadily during prolonged fasting in lean children. *J Pediatr*. 2006;149(6):798–802
28. Pelletier DL. The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research. *J Nutr*. 1994;124(suppl 10):2047S–2081S
29. Schwinger C, Golden MH, Grellety E, Roberfroid D, Guesdon B. Severe acute malnutrition and mortality in children in the community: Comparison of indicators in a multi-country pooled analysis. *PLoS One*. 2019;14(8):e0219745
30. Berkley J, Mwangi I, Griffiths K, et al. Assessment of severe malnutrition among hospitalized children in rural Kenya: comparison of weight for height and mid upper arm circumference. *JAMA*. 2005;294(5):591–597
31. Grellety E, Golden MH. Severely malnourished children with a low weight-for-height have a higher mortality than those with a low mid-upper-arm-circumference: I. Empirical data demonstrates Simpson's paradox. *Nutr J*. 2018;17(1):79
32. de Onis M, Yip R, Mei Z. The development of MUAC-for-age reference data recommended by a WHO expert committee. *Bull World Health Organ*. 1997;75(1):11–18
33. Grellety E, Golden MH. Severely malnourished children with a low weight-for-height have a higher mortality than those with a low mid-upper-arm-circumference: III. Effect of case-load on malnutrition related mortality- policy implications. *Nutr J*. 2018;17(1):81
34. Bilukha O, Leidman E. Concordance between the estimates of wasting measured by weight-for-height and by mid-upper arm circumference for classification of severity of nutrition crisis: analysis of population-representative surveys from humanitarian settings. *BMC Nutr*. 2018;4(1):24
35. Guesdon B, Couture A, Pantchova D, Bilukha O. Potential consequences of expanded MUAC-only programs on targeting of acutely malnourished children and ready-to-use-therapeutic-food allocation: lessons from cross-sectional surveys. *BMC Nutr*. 2020;6:5