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Original article

The clinical use of longitudinal bio-electrical impedance vector analysis in assessing stabilization of children with severe acute malnutrition

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SUMMARY

Background & aims: Severe Acute Malnutrition (SAM) in children is determined using anthropometry. However, bio-electrical impedance (BI) analysis could improve the estimation of altered body composition linked to edema and/or loss of lean body mass in children with SAM. We aimed to assess: 1) the changes in BI parameters during clinical stabilization and 2) whether BI parameters add prognostic value for clinical outcome beyond the use of anthropometry.

Methods: This prospective observational study enrolled children, aged 6–60 months, that were admitted at Queen Elizabeth Central Hospital in Blantyre, Malawi, for complicated SAM (i.e., having either severe wasting or edematous SAM with a complicating illness). Height, weight, mid-upper arm circumference (MUAC), and BI were measured on admission and after clinical stabilization. BI measures were derived from height-adjusted indices of resistance (R/H), reactance (Xc/H), and phase angle (PA) and considered to reflect body fluids and soft tissue in BI vector analysis (BIVA).

Results: We studied 183 children with SAM (55% edematous; age 23.0 ± 12.0 months; 54% male) and 42 community participants (age 20.1 ± 12.3 months; male 62%). Compared to community participants, the BIVA of children with edematous SAM were short with low PA and positioned low on the hydration axis which reflects severe fluid retention. In contrast, children with severe wasting had elongated vectors with a PA that was higher than children with edematous SAM but lower than community participants. Their BIVA position fell within the top right quadrant linked to leanness and dehydration. BIVA from severely wasted and edematous SAM patients differed between groups and from community children both at admission and after stabilization ($p < 0.001$). Vector position shifted during treatment only in children with edematous SAM ($p < 0.001$) and showed a upward translation suggestive of fluid loss. While PA was lower in children with SAM, PA did not contribute more than anthropometry alone towards explaining mortality, length of stay, or time-to-discharge or time-to-mortality. The variability and heterogeneity in BI measures was high and their overall added predictive value for prognosis of individual children was low.

Conclusions: BIVA did not add prognostic value over using anthropometry alone to predict clinical outcome. Several implementation challenges need to be optimized. Thus, in low-resource settings, the

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routine use of BI in the management of pediatric malnutrition is questionable without improved implementation.

Abbreviations

AIC	Akaike information criterion
AUC	Area Under the Curve
BER	Balanced Error Rate
BI	Bio-electrical impedance
BIVA	Bio-electrical impedance vector analysis
CV	Coefficient of Variation
HAZ	Length/height-for-age z-score
HIV	Human Immunodeficiency Virus
MUAC	Mid-upper arm circumference
NRU	Nutrition Rehabilitation Unit
PA	Phase angle
Xc/H	height-adjusted reactance
PLS-DA	Partial Least Square Discriminant analysis
Xc	Reactance
R	Resistance
R/H	Height-adjusted resistance
ROC	Receiver operating characteristic
RUTF	Ready-to-use therapeutic food
SAM	Severe acute malnutrition
WAZ	Weight-for-age z-score
WHZ	Weight-for-height z-score
WHO	World Health Organization

1. Introduction

Severe acute malnutrition (SAM) in children remains a major global health problem, and both reducing childhood mortality and ending malnutrition are specifically targeted by the Sustainable Development Goals [1,2]. Nearly half (45%) of global under-five mortality is related to under-nutrition and most of these children live in sub-Saharan Africa and Southeast Asia [3]. Despite adherence to WHO protocols [4], the case fatality rate of children hospitalized with SAM has remained unacceptably high at 10–25% [5]. Thus, current SAM management and methods for identifying children most at risk need to be improved [3,6,7].

WHO standards define SAM as either: 1) non-edematous with a weight-for-height z-score (WHZ) below −3 standard deviation (SD) or a mid-upper arm circumference (MUAC) of less than 115 mm; 2) edematous SAM with the presence of bilateral pitting edema, a condition of fluid retention linked to early childhood malnutrition or 3) mixed phenotype with the presence of both wasting and edema [8]. Current management strategies are 'blanket approaches' that disregard the different presentations of SAM and their associated clinical risk [4]. In general, edematous SAM is linked to higher morbidity and mortality [4,9], but the prevalence of underlying pathologies such as Human Immunodeficiency Virus (HIV) has changed the risk profiles associated with the different SAM phenotypes. Recent studies have shown children with non-edematous SAM to be more vulnerable in certain contexts (e.g., children with HIV and severe wasting have the highest mortality risk) [10,11].

In the 1960s, the four-surface electrode technique to measure bioelectrical impedance (BI) was introduced as a non-invasive and inexpensive method of estimating body composition [12,13]. BI analysis has since been implemented as a clinical assessment tool in high resource settings [12–14]. However, due to the variety of devices and methodologies [15], standardized and longitudinal BI measurements are recommended for clinical use [16]. BI is an indirect measure of body composition that is calculated from body resistance (R) and reactance (Xc), which are derived from changes in a small alternating electrical current when passed through the body [17,18]. R and Xc are together thought to reflect cell membranes and extra- and intra-cellular fluid and electrolytes, and their combination is termed 'body-impedance' [12]. Body-impedance can reliably estimate total body water and fat free mass in healthy individuals but requires population and disease-specific equations [19]. For accuracy, the predictive equations should be adapted depending on differences in hydration which varies with ethnicity, age, illness, and body-size [15,20]. However, BI measures can also be interpreted using BI vector analysis (BIVA) as developed by Piccoli et al. [21,22]. In theory, this method can differentiate hydration from cell mass and, thus can monitor hydration status and changes in muscle mass [23]. BIVA evaluates differences in R-Xc vectors which are defined by the bivariate vector of height-adjusted R (R/H) and Xc (Xc/H) [21] and phase angle (PA) which is the arc tangent relation of Xc/H on R/H converted to degrees [24]. PA reflects the phase shift between the current and voltage that results from the electrochemical membrane [25] and is associated with both cell membrane integrity, cell size, and cell mass and also with tissue resistance which depends on lean tissue and hydration status [26,27]. A low PA is associated with several diseases and higher mortality risk [13] and the use of clinical cut-off values have been suggested to identify children at risk of poor health outcome [28,29].

In addition to estimating body composition or hydration status, components of BIVA have been proposed to be useful prognostic markers in two high-resource studies examining children with renal disease or undergoing hematopoietic stem cell transplantation [30,31]. Also, Girma et al. showed that Xc/H correlated with serum calcium and chloride in malnourished children while R/H correlated with albumin [32]. Although the study was cross-sectional with a small sample size, results suggested that R/H could be used to monitor nutritional recovery.

This prospective study aimed to assess whether BIVA parameters: 1) change during hospitalization in children with severe wasting or edematous SAM, and 2) add a prognostic value to predict clinical outcome, compared to using anthropometry alone.

2. Materials and methods

2.1. Study design and setting

This prospective, observational study was conducted within the framework of the 'F75 trial', a multicenter, randomized, double-blind intervention trial (ClinicalTrials.gov: NCT02246296). Briefly, this study aimed to determine whether stabilization of

malnourished children could be improved by a re-formulation of F75 milk. For the trial, children with SAM were randomized to receive either the WHO recommended standard F75 milk or a modified iso-caloric formulation, which contained more triglycerides but less carbohydrates. The main trial was conducted in Malawi at the Nutrition Rehabilitation Unit (NRU) in the Pediatric Department of Queen Elizabeth Central Hospital in Blantyre. A total of 320 patients were enrolled between December 2014 and December 2015 [33]. The BI analysis sub-study recruited patients between February 2015 and December 2015. The study was approved by the Malawi College of Medicine Research and Ethics Committee (COMREC no P.03/14/1540) and conducted according to guidelines of Good Clinical Practice, which are based on the principles of the Declaration of Helsinki [34].

2.2. Participants

For the F75 trial, children admitted with complicated SAM (i.e. having SAM, as defined by WHO standards (see above), together with signs of severe illness or poor appetite) [4,35] were screened for eligibility. Children were excluded if parental consent was not obtained or had known allergies to milk products. For the BI sub-study, children between 6 and 60 months were included and additional exclusion criteria were: 1) presence of open skin lesions on hands or feet that would impede electrode positioning, 2) inability to stretch limbs due to cerebral palsy (CP), and 3) significant body asymmetry such as amputations, unilateral hemiparesis, and neuromuscular conditions causing localized changes in perfusion or tissue atrophy [14]. BI sub-study participants were enrolled during weekdays and office hours; sample size was a convenience sample that was not calculated a priori. To establish expected norms, 42 community children were also recruited and measured using the same procedures and equipment. These participants were: between 6 and 60 months of age, from the same communities, being treated if known to have HIV or tuberculosis, without acute illness requiring hospitalization according to WHO and national guidelines and without a history of hospital admission within the last 14 days.

2.3. Inpatient care

The standard clinical care for children with SAM consists of three distinct phases: stabilization, transition, and rehabilitation. A child with SAM admitted to hospital is first given F75, a low protein milk with reduced caloric energy (80–100 kcal/kg/day) and is treated for clinical 'danger signs'. Once stabilized, a child is transitioned to either ready-to-use therapeutic foods (RUTF) or a milk formula known as F100 depending on the child's capability to drink/eat. Compared to F75, RUTF and F100 have higher energy density and protein content. When clinically stable, a child enters the 'rehabilitation phase' and if able to finish RUTF feeds the patient is discharged from hospital and referred to outpatient programs.

BI measures were taken at hospital admission and after stabilization (i.e. on the first day of transition). All children admitted to the NRU had a thick blood film examined for parasitemia, hematocrit counts, and were offered a rapid HIV antibody test with appropriate pre- and post-counselling. HIV tests were also performed for community participants.

2.4. Data collection

Weight was measured using a digital scale (Marsden Portable Digital Baby Scale - Class III MS-4101). The height of children under 24 months was measured in supine position using length boards, whereas stadiometers were used for older children. Edema was scored based on the WHO grading system (i.e., +, edema in lower limbs only; ++, edema present in upper body; +++, edema, progressed to impact arms and face) [35]. Anthropometry, i.e. WHZ, weight-for-age z-score (WAZ) or length/height-for-age z-score (HAZ), were calculated using WHO 2006 references. BI was measured using a Bioelectrical Impedance Analyzer (Bodystat QuadScan4000) at 50 kHz. As per manufacturer's instructions, four self-adhesive disposable electrodes provided by manufacturer were attached in a standard tetrapolar position (see Supplemental Fig. 1). The two distal electrodes, one on the dorsal side of the hand next to the metacarpal-phalangeal joint and the other on the foot next to the metatarsal-phalangeal joint, were connected to injection leads. The two proximal electrodes were connected to measuring leads and positioned on the forearm and leg. A spacing of > 5.5 cm was maintained between the distant and proximal electrodes. This positioning has been recommended to prevent interactions between electrodes [30,36,37]. To ensure a supine position with legs and arms extended, research staff guided mothers to verbally support their child and use distraction methods (e.g., watching cartoons at bedside). Care was taken that children were well positioned, untouched by mothers, and not in contact with conductive materials (e.g., bed frame). Measurements were taken in triplicates, but tests were repeated up to 5 times if the variance in R or Xc was above 5%. The coefficient of variation (CV) for PA was evaluated when cleaning the database and if above 10% either the discrepant replicate was identified and removed, or the measurement was rejected as unreliable.

2.5. Statistical methods

Data were collected on standardized proforma's, entered in a database and analyzed with Stata (Release 13) [38] and R (Version 3.4.0). Differences in baseline characteristics of participants were assessed using Fisher exact test, or logistic regression. As children with severe wasting or edematous SAM display different clinical and biochemical characteristics, we conducted sub-analyses. For BI, we used logistic regression to analyze group differences at admission and logistic mixed effects models to evaluate changes between admission and after stabilization while accounting for repeated measures within subjects. Linear relationships between anthropometric variables and BI measures were evaluated with Pearson's correlation test.

As described by Piccoli, A. et al. [21], analysis was performed using open source BIVA software (Piccoli A, Pastori G: BIVA software. Department of Medical and Surgical Sciences, University of Padova, Padova, Italy, 2002, available at E-mail: apiccoli@unipd.it). Differences were tested between: 1) patients with severe wasting or edematous SAM on admission; and 2) admission and after clinical stabilization. R/H and Xc/H, were plotted with ellipses indicating the 95% confidence area of the mean as previously described [39]. Differences in independent multivariate means were tested using Hotelling's t^2 test (e.g. between severe wasting and edematous SAM or survival and mortality) whereas paired Hotelling's t^2 test was used to evaluate changes between patients at admission and after stabilization. This test is a multivariate extension of the Student's t-test and $p < 0.05$ was considered significant. Shifts in BIVA were interpreted as previously described [39,40]. PA and the prevalence of low PA (i.e., $< 2.8^\circ$) was analyzed for differences between groups, edema status, duration of hospital stay and mortality using either Fisher's exact test, logistic or Poisson regression. To further illustrate the contribution of BIA towards explaining mortality and duration of hospital stay, we compared 4 linear models: 1) a base model including edema status and WHZ; 2) the base model with R/H; 3) the base model with Xc/H; 4) the base

model with PA. These models and their variables were evaluated using R^2, partial R^2, and Akaike information criterion (AIC).

Pearson's correlation test was used to relate PA, R/H and Xc/H and anthropometry (i.e. WHZ, WAZ, and MUAC). To compare the prognostic value of anthropometry alone or in combination with BIVA parameters including PA, R/H and Xc/H, we conducted Partial Least Squares discriminant analysis (PLS-DA) using the mixOmics package. Values were offset by 10, log transformed, mean centered, and scaled. Multilevel PLS-DA was used to compare admission and nutritional stabilization to account for repeated measures within patients. The discriminative power of the PLS-DA models to classify groups was assessed using the balanced error rate (BER) based on centroid distance obtained from leave-one-out cross-validation. Receiver operating characteristic (ROC) curves and associated area under the curve (AUC) are presented to indicate specificity and sensitivity. Finally, competitive risk analysis was conducted using cmprsk and survCompetingRisk R packages to relate WHZ, and PA to the competing censoring risks of either time-to-discharge or time-to-death.

3. Results

Between December 2014 and December 2015, 183 patients with SAM were recruited for the BI sub-study (see flow chart in Supplemental Fig. 2). Anthropometry and BI were successfully conducted on admission in 174 children (severe wasting n = 80 and edematous SAM n = 94), and in 148 patients after clinical stabilization (severe wasting n = 72 and edematous SAM n = 76), with 147 children (severe wasting n = 68 and edematous SAM n = 79) having both time points. One participant at admission and seven after stabilization were removed based on high CV of PA. The CVs for BI variables are presented in Supplemental Table 1. Overall mortality in patients with SAM was 17% and thirteen occurred before clinical stabilization (Total deaths, n = 31: severe wasting, n = 17, and edematous SAM, n = 14). Baseline characteristics are provided in Table 1 separated by edema status while Supplemental Table 2 also splits participants by survival status. Children with edematous SAM were older ($p = 0.002$) and less likely to be HIV positive (16% vs. 38% in children with severe wasting, $p < 0.001$). Anthropometry and BI were also measured in 42 children selected to represent the community. Their anthropometry tended to be normal based on WHO growth standards; but did show some degree of stunting with an average HAZ of −1.7 ± 1.3.

BI values at admission and after stabilization are shown in Table 2 split by edema status, and in Supplemental Table 3 split by survival status. The BIVA plot presents individual's data overlaid with group multivariate means of R/H and Xc/H at both time points (Fig. 1). To ease interpretation, the BIVA positions are contextualized within the 50th, 75th and 95th percentile ellipses of community participants and presented overlaid by the quadrants and directions of the major axis of hydration and the minor axis of soft tissue mass (Fig. 2A). Compared to community participants, children with edematous SAM had lower PA (2.3 ± 1.4° vs. 3.8 ± 0.8°, $p < 0.001$) and significantly shorter BIVA vectors linked to lower R/H and Xc/H (802 ± 272 Ω/m vs. 937 ± 127 Ω/m, $p = 0.005$, and 33.2 ± 20.6 Ω/m vs. 61.1 ± 11.6 Ω/m, $p < 0.001$, respectively). As expected, the BIVA vectors of these children were positioned in the bottom right quadrant linked to fluid retention (Fig. 2A). In contrast, compared to community participants, children with severe wasting had lower PA (2.9 ± 1.0° vs. 3.8 ± 0.8°, $p < 0.001$) but higher R/H (1247 ± 245 Ω/m vs. 937 ± 127 Ω/m, $p < 0.001$). Thus, these children present with elongated vectors positioned at the top right quadrant just beyond the 95th percentile of community participants, a position associated with leanness and reduced body fluid (Fig. 2A). Based on Hotelling's t^2-test, the BIVA vectors from patients with severe wasting and edematous SAM differed both at admission and after stabilization ($p < 0.001$, Fig. 1) and both groups also differed from controls at each time point ($p < 0.001$). Following treatment, BIVA vectors of children with edematous SAM showed an upwards translation ($p < 0.001$) with associated differences in R/H (802 ± 272 Ω/m vs. 934 ± 263 Ω/m, $p = 0.0024$) and Xc/H (33.2 ± 20.6 Ω/m vs. 41.6 ± 22.9 Ω/m, $p < 0.017$) but without significant change in PA. This shift would reflect fluid loss during treatment as the vectors moved up along the major hydration axis (Fig. 2A). In contrast, the BIVA vectors of children with severe wasting did not change between admission and after stabilization ($p = 0.73$) (Fig. 1).

To better contextualized our findings, we compared our data with BIVA reported from different or similar populations (Table 3 and Fig. 2B). These include the works of Piccoli, A. and his team in normal adults or with conditions associated with or without edema [41–43]; as well as in normal infants and children [36,37]. We also included other studies looking at groups of healthy infants [44], and non-European children that are either healthy, with severe wasting or with edematous SAM [19,32,45,46]. Our data aligns well with these reported findings. The BIVA from children with severe wasting at both time points are comparable to those of other children with severe wasting (Fig. 2B, sW and sW′ vs. groups 11, 12,

Table 1
Patient characteristics of children with edematous or non-edematous SAM on admission and community controls.

	Control	SAM	*p*	Severe wasting	Edematous	*p*
	n = 42	n = 183		n = 86	n = 97	
Male sex, n (%)	26 (62)	99 (54)	0.39	46 (53)	53 (55)	0.88
HIV reactive[a], n (%)	2 (6)	47 (26)	<0.01	32 (38)	15 (16)	<0.001
Age, mon	20.1 ± 12.3	23 ± 12	0.17	20 ± 12.5	25.6 ± 11	<0.01
Height-for-age, z-score	−1.7 ± 1.3	−3.4 ± 1.5	<0.0001	−3.7 ± 1.5	−3.2 ± 1.5	0.020
Weight-for-age, z-score	−0.9 ± 1.1	−3.8 ± 1.6	<0.0001	−4.7 ± 1.1	−3.1 ± 1.6	<0.0001
Weight-for-height, z-score	0.0 ± 1.2	−3.0 ± 1.8	<0.0001	−4.0 ± 1.1	−2.0 ± 1.8	<0.0001
MUAC, cm	14.3 ± 1.3	11.4 ± 1.7	<0.0001	10.4 ± 1.2	12.2 ± 1.7	<0.0001
Time to stabilization, days	–	3.3 ± 2	–	3.2 ± 1.8	3.5 ± 2.2	0.26
Duration of admission, days[b]	–	5.6 ± 3.3	–	5.3 ± 3	5.9 ± 3.5	0.29
Time to death, days	–	6.5 ± 4.2	–	7.1 ± 5.1	5.8 ± 3	0.40
Death, n (%)	–	31 (17)	–	17 (20)	14 (14)	0.43

Data in cell are mean ± SD or n (%). Significance test performed with either Fisher's exact test or logistic regression as appropriate. Significance, $p < 0.5$. MUAC, mid upper arm circumference; SAM, severe acute malnutrition.

[a] 3 SAM patients with unknown HIV status. 7 Community Controls with unknown HIV status.

[b] Duration of admission in patients that survived.

Table 2
Bio-electrical impedance values of community children and patients with either severe wasting or edematous SAM on admission and after stabilization.

		Admission						Stabilization					
	Controls[a]	SAM[b]	$p^{a,b}$	Severe wasting[c]	Edematous[d]	$p^{c,d}$	$p^{a,c}$	$p^{a,d}$	SAM[e]	Severe wasting[f]	Edematous[g]	$p^{f,g}$	$p^{a,f}$	$p^{a,g}$	$p^{c,f}$	$p^{d,g}$
	N = 42	n = 174		n = 80	n = 94				n = 148	N = 72	n = 76					
Resistance, ohm	715 ± 73	737 ± 237	0.57	885 ± 184	610 ± 201	<0.0001	<0.0001	<0.01	782 ± 198	861 ± 175	708 ± 191	<0.0001	<0.0001	0.81	0.38	<0.01
Reactance, ohm	47.2 ± 11.2	34.3 ± 18.2	<0.0001	44.9 ± 14.7	25.2 ± 16	<0.0001	0.38	<0.0001	39.5 ± 19.2	48.1 ± 18.6	31.3 ± 16.1	<0.0001	0.76	<0.0001	0.29	0.020
Phase angle, degree	3.8 ± 0.8	2.6 ± 1.3	<0.0001	2.9 ± 1	2.3 ± 1.4	<0.01	<0.0001	<0.0001	2.8 ± 1.1	3.2 ± 1.1	2.5 ± 1	<0.001	<0.01	<0.0001	0.14	0.36
Resistance index, ohm/m	937 ± 127	1007 ± 342	0.2	1247 ± 245	802 ± 272	<0.0001	<0.0001	<0.01	1073 ± 281	1219 ± 219	934 ± 263	<0.0001	<0.0001	0.94	0.42	<0.01
Reactance index, ohm/m	61.1 ± 11.6	47.1 ± 25.4	<0.0001	63.4 ± 20.3	33.2 ± 20.6	<0.0001	0.5	<0.0001	54.6 ± 27.8	68.2 ± 26	41.6 ± 22.9	<0.0001	0.098	<0.0001	0.25	0.017

Bio-electrical impedance values were measured at 50 kHz, resistance (R/H) and reactance (Xc/H) indices are derived from values divided by height in m. Data are presented as mean ± SD and logistic regression was used to assess group differences and mixed effect logistic regression was used to compare admission and stabilization while accounting for repeated measures within subjects. Significance, p < 0.05. SAM, severe acute malnutrition.

[a] Control group.
[b] SAM at admission.
[c] Severe wasting at admission.
[d] edematous SAM at admission.
[e] SAM at stabilization.
[f] Severe wasting at stabilization.
[g] edematous SAM at stabilization.

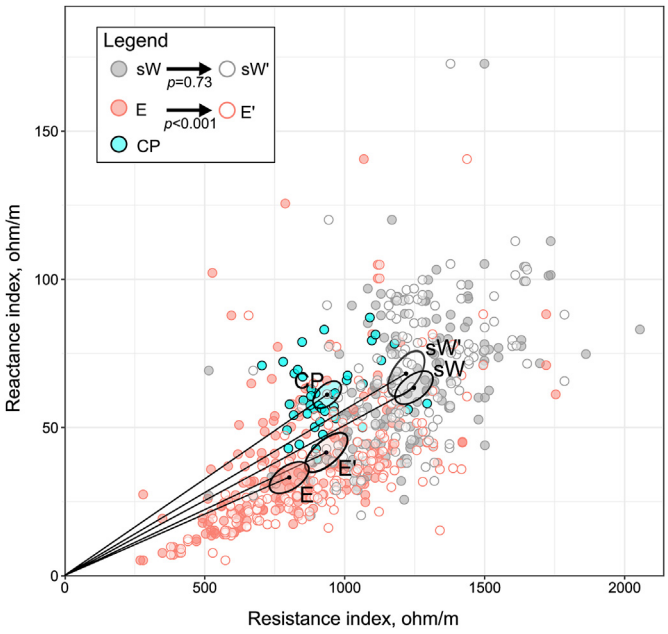

Fig. 1. Bioelectrical impedance vector analysis (BIVA) in children hospitalized with SAM at admission and after their clinical stabilization. Circles indicate R/H plotted against Xc/H of each patient colour coded by group as per legend: E, edematous SAM (coral); sW, severe wasting (grey); CP, community participants (cyan); solid circles are from admission and open circles from after stabilization. The multivariate mean and 95% confidence area for each group is represented by a black central dot and shaded ellipse (i.e., dark coral, edematous SAM at admission; pale coral, edematous SAM after clinical stabilization; dark grey, severe wasting at admission; pale grey, severe wasting after clinical stabilization; cyan, community participants). BIVA vectors are drawn in black linking the zero x-y intercept to the group means at each time point. Shifts in R/Xc positions can be interpreted as detailed in Supplementary Fig. 1. Significance of shifts between time points were tested with paired Hotelling's t^2 test; significance threshold, $p < 0.05$. Abbreviations: R/H, height-adjusted resistance; SAM, severe acute malnutrition; Xc/H, height-adjusted reactance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and 13). Also, those with edematous SAM (E and E′) compare to other children with this presentation (i.e., groups 14 and 15). The spread of BIVA positions from various groups of community children likely reflects differences in age, ethnicity and methodology (CP vs. 4, 5, 6, 7, 8, and 9 as well as group 10 which are children classified as recovered from SAM).

Separated by group (i.e., community participants, severe wasting or edematous SAM), anthropometry (WHZ, WAZ and MUAC) tended to showed a negative relationship with R/H, and Xc/H (shown on admission in Table 4 and after stabilization in Supplemental Table 4). The relationships were however strongest in edematous SAM, and Xc/H did not correlate with anthropometry of children with severe wasting. PA showed the weakest overall correlation and tended to present a differential relationship depending on edema status. These patterns within groups were similar at admission and after stabilization. However, the expected correlations were more apparent when analyzing children split only by having edema or not, i.e., across a broader spectrum of anthropometry as opposed to within each group separately. For example, Fig. 3 presents the correlation patterns between WAZ and the BI values of children based on edema status. While a difference in mean exists, the correlation direction and strength were similar for R/H, but Xc/H showed a negative relationship only in children with edema, and the positive relationship between WHZ and PA was only seen in those without edema.

Subsequently, we used PLS-DA models to evaluate: 1) the correlation between anthropometry (i.e., WHZ, WAZ, HAZ, and

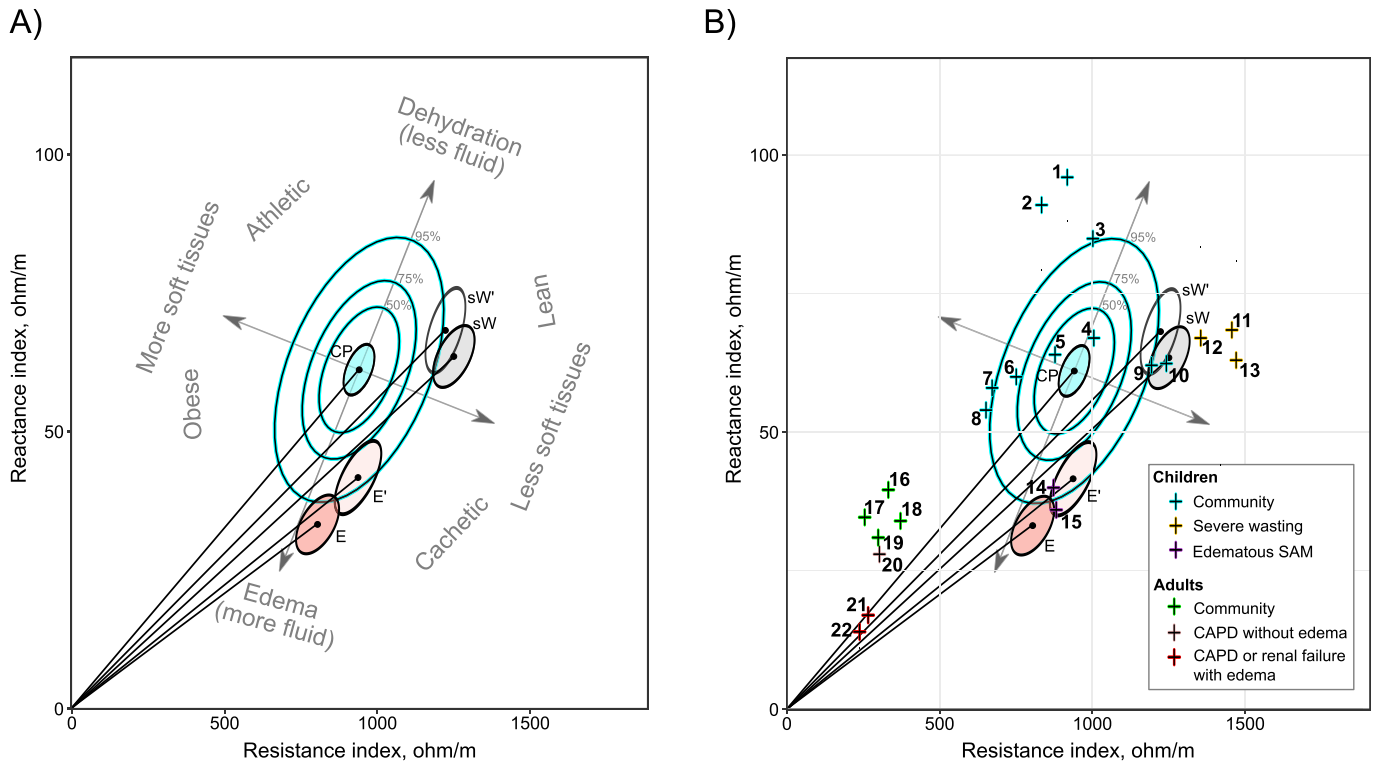

Fig. 2. Interpretation and contextualization of bioelectrical impedance vector analysis (BIVA) in children hospitalized with SAM at admission and after clinical stabilization. A) Interpretation of BIVA vector positions and shifts based on description from Piccoli and et al. (2002). The confidence ellipse of the bivariate mean for community participant is indicated in cyan while the rings show their 50th, 75th, and 95th percentile. BIVA vectors from children with SAM can be ranked following the orthogonal directions of the major and minor axis of this confidence ellipse (indicated by grey arrows and grey interpretive descriptions). Different positions along these axes can reflect combined changes in both hydration and tissue mass. Vector displacements parallel to the major axis indicate progressive changes in tissue hydration that range from edema at the bottom left pole where BIVA of children with edematous SAM at admission (E, dark coral) and after stabilization (E′, pale coral) are positioned; to "normal hydration" within the 75th percentile and then towards dehydration. BIVA of children with severe wasting at admission (sW, dark grey) and after discharge (sW′, light grey) position just beyond the 95th percentile towards the lean quadrant. Vector displacements parallel to the minor axis indicate level of cell mass in soft tissues and both phenotypes of SAM tend towards less soft tissue mass positioning in either the lean or cachectic quadrants. The multivariate mean and 95% confidence area for each group is represented by a black central dot and shaded ellipse. BIVA vectors are drawn in black linking the zero x-y intercept to the group means at each time point. B) Contextualization of BIVA in children hospitalized with SAM compared to BIVA reported in other populations. As per detailed in associated Table 3, the cross points and associated numerical keys indicate the positions of the mean BIVA from specific populations reported in the literature while general categorization of compared populations are indicated as per colour legend. Abbreviations: R/H, height-adjusted resistance; SAM, severe acute malnutrition; Xc/H, height-adjusted reactance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

MUAC) and BI variables (i.e., R/H, Xc/H and PA) and 2) their collective capacity to distinguish groups (Fig. 4). The anthropometric variables of WHZ, WAZ, and MUAC were highly correlated as indicated by their relatively parallel directional arrows (Fig. 4A). Using only anthropometry, groups separated mainly along Variate 1, i.e., the first composite variable summarizing 78% of the variance of the 4 anthropometric measures (Fig. 4B). The PLS-DA ROC curves indicate that anthropometry alone can distinguish children with SAM from community participants, and the different types of SAM (Black line in Fig. 4E-G: severe wasting vs. edematous SAM, AUC 0.82; severe wasting vs. community participants, AUC 1.0; edematous SAM vs. community participants, AUC 0.89). We then evaluated if combining anthropometry with BI variables would improve classification. Adding R/H, Xc/H and PA improved classification between children with edematous SAM and community participants (Grey line in Fig. 4E-G: severe wasting vs. edematous SAM, AUC 0.88; severe wasting vs. community participants, AUC 1.0; edematous SAM vs. community participants, AUC 0.98). The centroid distance BER for component-1 was 0.33 for the PLS-DA model using only anthropometry and was 0.29 when combining anthropometry and BI variables. However, these gains were marginal and error rates may be underestimated as we used "leave one out" cross-validation due to the sample sizes of the sub analyses.

Since BIVA vectors were so different between severe wasting and edematous SAM, we conducted a stratified analysis to relate BIVA vector changes and mortality. BIVA at admission in children with severe wasting did not differ between children that survived or died ($p = 0.55$) (Supplemental Fig. 3A). However, in edematous SAM, BIVA was associated with mortality ($p = 0.009$) but this subgroup was small ($n = 14$) and the effect was driven by 3 outliers with high Xc/H and PA (Supplemental Fig. 3B). R/H and Xc/H but not PA were lower at admission in children with high (+++) edema scores (i.e., 33/94 (35%) of edema cases) ($p < 0.0001$, Supplemental Fig. 3C). While BIVA of children with varying levels of clinically scored edema seemed to position along the expected major hydration axis, considerable overlap was found between children scored with low, moderate, or high edema (+, ++, +++). We also ran PLS-DA models to assess whether admission BI variables and anthropometry can better identify children at high risk of mortality over using anthropometry alone. The combined model including BI variables and anthropometry did not improve classification of mortality (died vs. survived: AUC = 0.73 with only anthropometry vs. AUC = 0.72

Table 3
Bio-electrical indices in children and adults that are healthy or with specific conditions.

Reference	Legend key	Condition	Edema	Sex	Population	Age Group	Age	n =	Resistance index (ohm/m)	Reactance index (ohm/m)	PA (degrees)	Instrument
Redondo-del-Río M.P. et al. Am J Hum Biol (2019); 31:e23244	1	Community	no	F	Spanish	Newborns	1.2 ± 0.8 days	75	918 ± 108	96 ± 23	5.95 ± 1.23	BIA-101, RJL/Akern Systems, USA
	2	Community	no	M	Spanish	Newborns	1.1 ± 0.8 days	79	834 ± 98	91 ± 35	6.26 ± 2.11	BIA-101, RJL/Akern Systems, USA
Piccoli, A. et al., Nutrition (2002); 18(5): 383-7	3	Community	no	mixed	Italian	Newborns	1–7 days[a]	163	1002 ± 128	85 ± 27	4.9 ± 1.5	BIA-101, RJL/Akern Systems, USA
Girma T. et al. Clinical Nutrition (2018); 37:701–705	4	Community	no	mixed	Ethiopian	Children	2.3 ± 1.3	80	1005 ± 196	67 ± 8	3.8 ± 0.7	Quadscan 4000, Bodystat, UK
	5	Community	no	mixed	Ethiopian	Children	3.2 (1.8–6.8)[b]	120	878 ± 246	64 ± 8	4.3 ± 1.0	Quadscan 4000, Bodystat, UK
De Palo T. et al. Nutrition (2000); 16:417–424	6	Community	no	mixed	Italian	Children	2–3[a]	115	751 ± 75	60 ± 10	4.6 ± 0.7	BIA-101, RJL/Akern Systems, USA
	7	Community	no	mixed	Italian	Children	4–5[a]	220	672 ± 72	58 ± 8	5.0 ± 0.6	BIA-101, RJL/Akern Systems, USA
Nguyen P.H. et al. British Journal of Nutrition (2020); 07:1–25	8	Community	no	mixed	Vietnamese	Children	6.2 ± 1.0	119	652 ± 72	54 ± 6	–	Seca mBCA 525 multifrequency BIA, USA*
Kangas S.T. et al., Clinical Nutrition (2020); in press	9	Community	no	mixed	Burkinabè	Children	1.1 ± 0.8	97	1198 ± 173	62.2 ± 9	3.1 ± 0.9	Nutriguard S, DataInput, Germany
	10	SAM Recovered	no	mixed	Burkinabè	Children	1.3 ± 0.7	452	1243 ± 150	62.6 ± 10.8	2.9 ± 0.6	Nutriguard S, DataInput, Germany
	11	SAM Admission	no	mixed	Burkinabè	Children	1.2 ± 0.8	259	1461 ± 219	68.9 ± 16.5	2.7 ± 0.5	Nutriguard S, DataInput, Germany
Girma T. et al. Clinical Nutrition (2016); 35:713–717	12	SAM	no	mixed	Ethiopian	Children	4 (2.2–5)[b]	16	1355 ± 375	67 ± 22	–	Quadscan 4000, Bodystat, UK
	13	SAM	no	mixed	Ethiopian	Children	2.3 ± 1.5	15	1471 ± 224	63 ± 23	2.4 ± 0.8	Quadscan 4000, Bodystat, UK
	14	SAM	yes	mixed	Ethiopian	Children	3 (2.5–4)[b]	19	873 ± 234	40 ± 18	–	Quadscan 4000, Bodystat, UK
Girma T. et al. Clinical Nutrition (2018); 37:701–705	15	SAM	yes	mixed	Ethiopian	Children	2.9 ± 2	40	882 ± 314	36 ± 19	2.1 ± 0.6	Quadscan 4000, Bodystat, UK
Marini, E. et al. Clinical Nutrition (2020); 39(2):447-454	16	Athletes	no	M	Portuguese	Adult	21.5 ± 5.0	139	256 ± 31	35 ± 5	7.7 ± 0.8	BIA 101 Anniversary, Akern, Italy
	17	Athletes	no	F	Portuguese	Adult	20.7 ± 5.1	63	332 ± 41	40 ± 6	6.8 ± 0.8	BIA 101 Anniversary, Akern, Italy
Piccoli A. et al. Am J Clin Nutr (1995); 61:269	18	Community	no	F	Italian	Adult	50 [15–85][c]	372	372 ± 49	34 ± 8	–	BIA-101, RJL/Akern Systems, USA
	19	Community	no	M	Italian	Adult	48 [15–85][c]	354	299 ± 43	31 ± 7	–	BIA-101, RJL/Akern Systems, USA
Piccoli A. et al. Kidney International (2004); 65: 1050–1063	20	Continuous ambulatory peritoneal dialysis	no	M	Italian	Adult	59 ± 14	77	303 ± 44.9	28 ± 6	5.32 ± 1.1	BIA-101, RJL/Akern Systems, USA
	21	Continuous ambulatory peritoneal dialysis	yes	M	Italian	Adult	64 ± 12	29	266 ± 57	17 ± 3	3.79 ± 0.9	BIA-101, RJL/Akern Systems, USA
Piccoli A. et al. International Journal of Obesity (1998); 22: 97-104	22	Chronic renal failure or nephrotic syndrome	yes	M	Italian	Adult	50 ± 14	25	238 ± 48	14 ± 5	3.4 ± 1.1	BIA-109, RJL/Akern Systems, USA

Legend Key indicates the BIVA position in Supplemental Fig. 2B; reported bio-electrical impedance values measured at 50 kHz using tetrapolar electrode positioning. Resistance (R/H) and reactance (Xc/H) indices were derived from BI measures divided by height in m. BIA data are presented as mean ± SD; Age is presented as mean ± SD in years, unless indicated.

* Note multifrequency BIA machine measured at 50 kHz may not be directly comparable to 50 kHz measurements obtained from single frequency machines. SAM, severe acute malnutrition; PA, phase angle.

[a] Age range.

[b] Median (IQR).

[c] Median [range].

Table 4
Correlations between bio-electrical impedance indices and anthropometry at hospital admission of children with severe acute malnutrition with either severe wasting or edema.

Admission		SAM patients				Severe wasting				Edematous				Controls			
		r (95% CI)	df	R^2	*p*	r (95% CI)	df	R^2	*p*	r (95% CI)	df	R^2	*p*	r (95% CI)	df	R^2	*p*
Resistance index, ohm/m	Weight-for-height, z-score	−0.64 (−0.72,-0.54)	172	0.4	<0.0001	−0.21 (−0.41,0.01)	78	0.04	0.061	−0.54 (−0.67,-0.38)	92	0.3	<0.0001	−0.38 (−0.61,-0.09)	40	0.14	0.013
	Weight-for-age, z-score	−0.52 (−0.62,-0.4)	172	0.27	<0.0001	−0.07 (−0.28,0.15)	78	0	0.55	−0.42 (−0.57,-0.23)	92	0.17	<0.0001	−0.4 (−0.63,-0.11)	40	0.16	<0.01
	MUAC, cm	−0.49 (−0.6,-0.37)	172	0.24	<0.0001	−0.02 (−0.24,0.2)	78	0	0.84	−0.39 (−0.55,-0.2)	92	0.15	<0.001	−0.15 (−0.44,0.16)	40	0.02	0.33
Reactance index, ohm/m	Weight-for-height, z-score	−0.51 (−0.61,-0.39)	172	0.26	<0.0001	0.07 (−0.15,0.29)	78	0.01	0.53	−0.38 (−0.54,-0.19)	92	0.15	<0.001	−0.1 (−0.39,0.21)	40	0.01	0.52
	Weight-for-age, z-score	−0.45 (−0.56,-0.32)	172	0.2	<0.0001	0.08 (−0.14,0.3)	78	0.01	0.46	−0.33 (−0.5,-0.13)	92	0.11	<0.01	−0.19 (−0.47,0.12)	40	0.04	0.23
	MUAC, cm	−0.41 (−0.53,-0.28)	172	0.17	<0.0001	0.12 (−0.1,0.33)	78	0.01	0.29	−0.28 (−0.46,-0.09)	92	0.08	<0.01	0.25 (−0.05,0.52)	40	0.06	0.1
Phase angle, degree	Weight-for-height, z-score	−0.22 (−0.36,-0.08)	172	0.05	<0.01	0.23 (0.01,0.42)	78	0.05	0.044	−0.12 (−0.31,0.09)	92	0.01	0.26	0.08 (−0.23,0.38)	40	0.01	0.61
	Weight-for-age, z-score	−0.24 (−0.38,-0.1)	172	0.06	<0.01	0.13 (−0.09,0.34)	78	0.02	0.24	−0.16 (−0.35,0.04)	92	0.03	0.12	−0.01 (−0.32,0.29)	40	0	0.93
	MUAC, cm	−0.21 (−0.35,-0.07)	172	0.05	<0.01	0.13 (−0.09,0.34)	78	0.02	0.23	−0.12 (−0.31,0.09)	92	0.01	0.26	0.35 (0.06,0.59)	40	0.13	0.021

Bio-electrical impedance values were measured at 50 kHz, resistance (R/H) and reactance (Xc/H) indices are derived from values divided by height in m. Correlation (r) was assessed with Pearson product–moment correlation; for this, BIA values were log transformed. CI is 95% confidence interval; df is degrees of freedom (n-2); R^2 is the coefficient of determination. Significance, $p < 0.05$. MUAC, mid upper arm circumference; SAM, severe acute malnutrition.

with anthropometry and BI combined) (Supplemental Fig. 4). We also performed this analysis stratified by edema status (edematous SAM died vs. survived: AUC = 0.71 and BER = 0.46 with only anthropometry vs. AUC = 0.66 and BER = 0.40 with anthropometry and BI combined; severe wasting died vs. survived: AUC = 0.66 and BER = 0.31 with only anthropometry vs. AUC = 0.70 and BER = 0.31 with anthropometry and BI combined). We also ran PLS-DA models to assess whether admission BI values can either alone or in combination with anthropometry better characterize children with diarrhea and associated dehydration (data not shown). The classification error rates were high, and AUC values ranged between 0.45 and 0.49, i.e. low and not better than random, suggesting that BI variables would not help identify diarrhea or grading its' severity. Together, these results suggest that BI measures would not significantly improve the identification of children with SAM or identify those at high risk of mortality beyond the information captured by clinical observation and anthropometry.

Given the reported prognostic values of a low PA (i.e., <2.8°), we evaluated whether prevalence differed between groups. We found that 117/174 (67%) children with SAM had a low PA, compared to only 4/42 (7%) in community children ($p < 0.0001$). Prevalence did not differ in children with SAM that survived compared to those that died (98/143 (69%) vs. 19/31 (61%), $p = 0.53$). However, children with edema had higher prevalence of low PA than those without (78/94 (83%) vs. 39/80 (49%), $p < 0.0001$) but differences were not found in relation to mortality in either sub-group. To further evaluate the contribution of BIA towards explaining mortality, we compared 4 linear models (Supplemental Table 5). The overall adjusted R^2 of the base model (Model 1) was low (0.09) and was only slightly improved (0.11) by adding PA (Model 4). The partial R^2 of WHZ was always higher than any BI measure and model fit was not significantly different between the base model (Model 1) and that with PA included (Model 4, AIC 151 vs. 153, $p = 0.053$). Similar findings are detailed for duration of hospital stay (Supplemental Table 5). We then evaluated the association between edema status, WHZ and PA and time-to-discharge or time-to-death. We conducted competitive risk analysis and present the cumulative incidence function for outcomes of mortality or discharge split by children with a PA either above or below 2.8° (Supplemental Table 6 and Supplemental Fig. 5). Time-to-discharge (Grey's test, $p = 0.49$) or time-to-death (Grey's test, $p = 0.48$) did not differ between these groups. These analyses were also conducted stratified by edema and results were similar. We also tested the association between either time-to-death or time-to-discharge with WHZ (Model 1), PA (Model 2) and both variables (Model 3) while adjusting for edema status. Only WHZ was associated with time-to-event distribution while PA showed a trend (Supplemental Table 6). These results suggest that WHZ and PA are associated with time-to-death or time-to-discharge but that WHZ is sufficient to explain the relationship in children with SAM.

4. Discussion

This study is the first to show how BIVA change together with 'classic' anthropometry throughout nutritional recovery of children with complicated SAM. We conducted different analyses, including Piccolis' BIVA method [39], linear models and PLS-DA, and found that BIVA, as currently implemented, did not add significant prognostic value to the diagnosis or prognosis of children with complicated SAM treated in low resource settings.

Similar to Girma et al. [32], we found BIVA vectors to be shorter and with lower PA in children with edematous SAM compared to

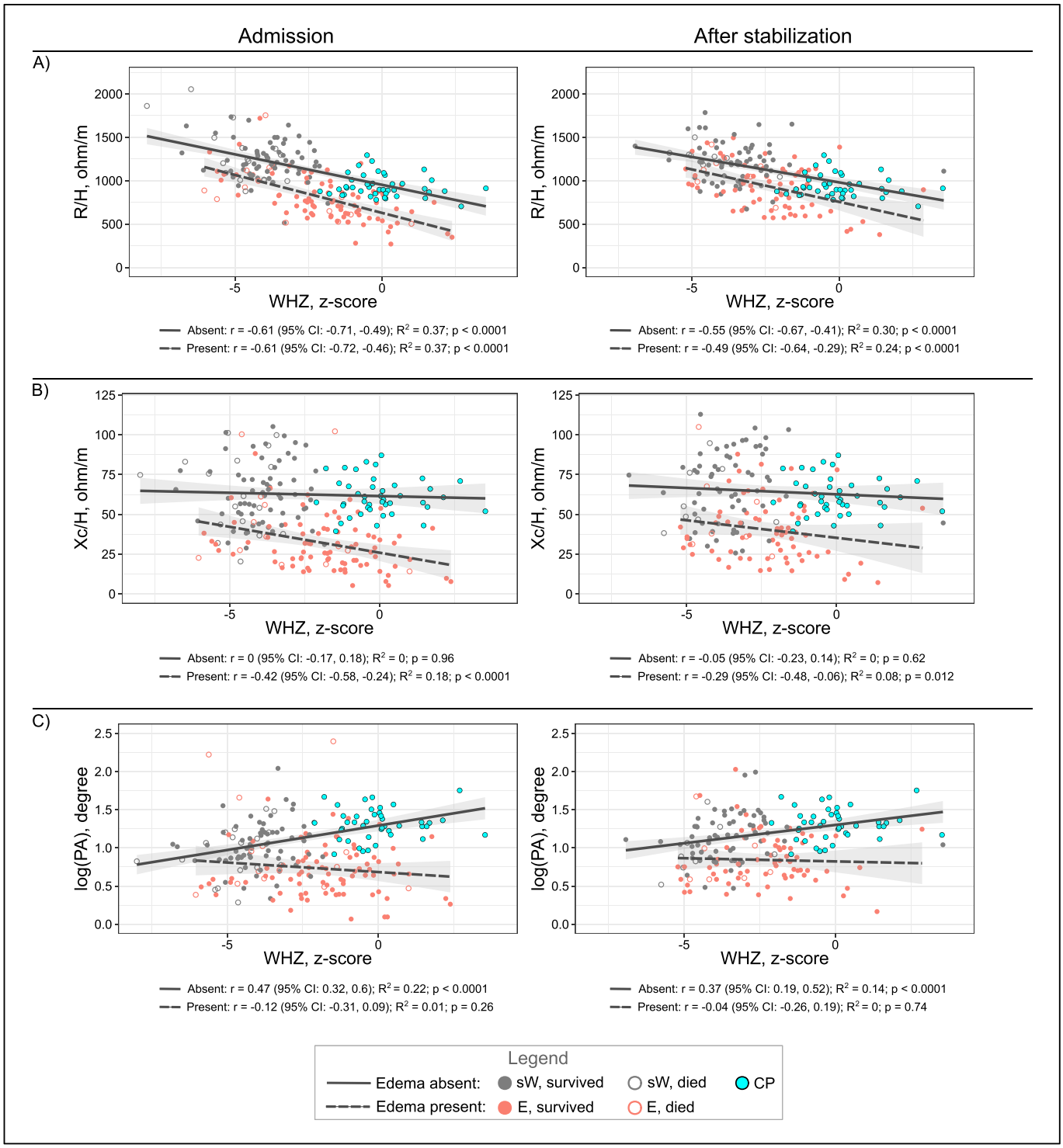

Fig. 3. Correlation between WHZ and indices of resistance (A), reactance (B) and phase angle (C) at admission and after stabilization in children with or without edema. Colours code groups is as per legend: E, edematous SAM (coral); sW, severe wasting (grey); CP, community participants (cyan) where solid circles are from patients that survived and open circles are from patients that died. Linear relationship between anthropometric variables and BI measures were evaluated with Pearson's correlation test. Significance threshold, $p < 0.05$. Abbreviations: PA, phase angle; R/H, height-adjusted resistance; SAM, severe acute malnutrition; Xc/H, height-adjusted reactance; WHZ, weight-for-height z score. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

community children or those with severe wasting. The group mean of edematous SAM aligned as expected towards the bottom major axis of hydration just beyond the 95th percentile of community children, a position associated with severe edema [30,47]. While children with the highest clinical edema score tended to have the shortest BIVA vectors, the gradation across the hydration axis did

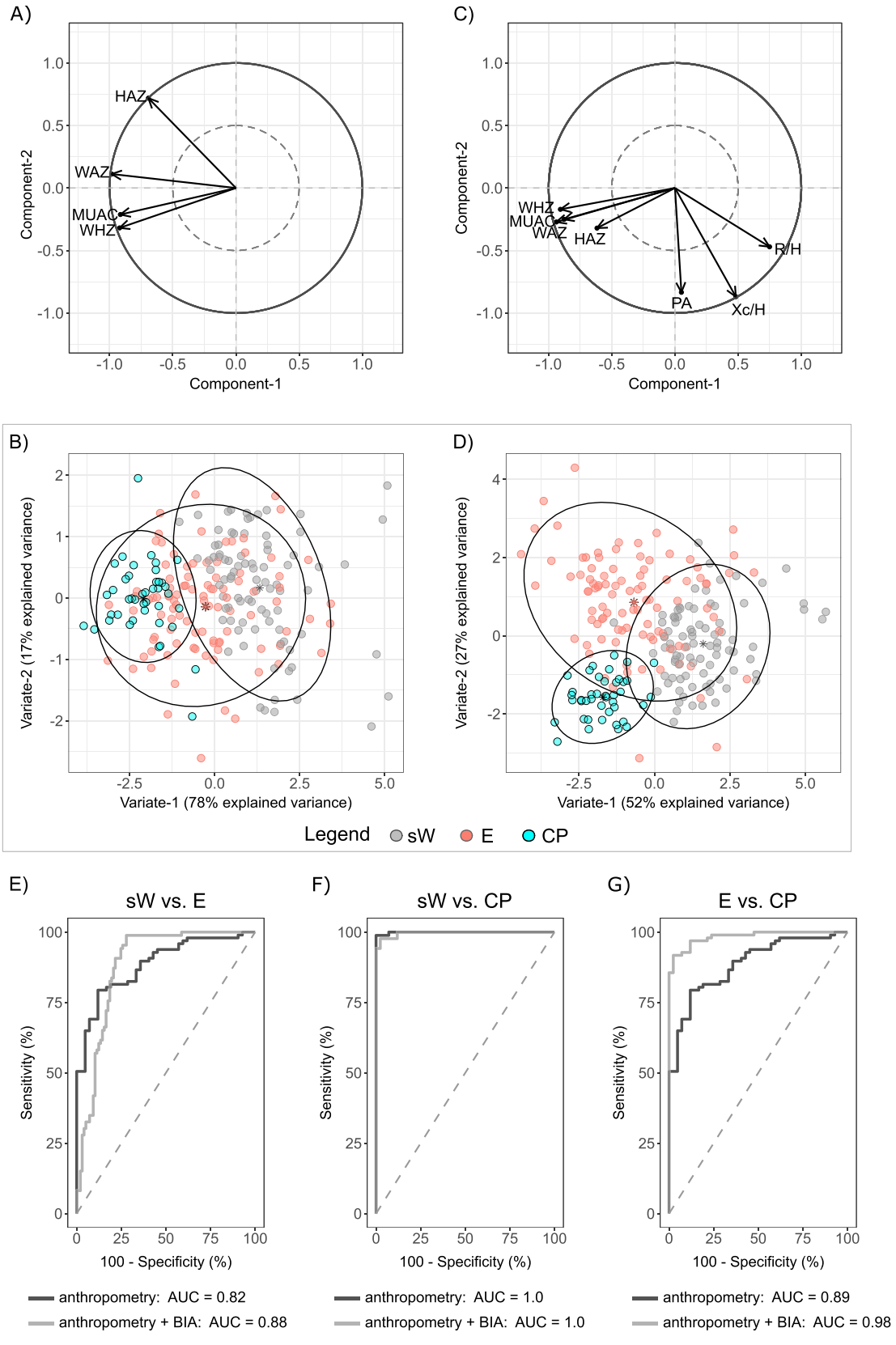

Fig. 4. Partial least squares discriminant analysis (PLS-DA) of anthropometry with or without measures of bioelectrical impedance (BI) in children hospitalized with different SAM subtypes at admission and in community participants. Correlation PLS-DA plots demonstrate that the anthropometric variables are highly intercorrelated here represented by the parallel direction of the vectors of anthropometry (A) but that BI measures show an orthogonal relationship to the vectors of anthropometry which suggests lower correlation with these variables (B). Two-dimensional PLS-DA score plots reveal that group separation achieved with anthropometry alone (B) is not significantly improved when BI values are included as only community participants show further separation along the second PLS-DA variate which is mainly loaded by BI variables (D). The group centroids are depicted by stars and ellipses represent the 95% confidence area. Colour coding is as per legend: E, edematous SAM (coral); SW, severe wasting (grey); CP, community participants (cyan). ROC

not necessarily reflect clinical scoring of high, moderate, low edema. The BIVA of children with edematous SAM did elongate along the hydration vector after stabilization which would reflect their overall fluid loss during treatment. However, it remains unclear if their vector position would stabilize with higher PA towards that of community participants or continue to lengthen towards those of children with severe wasting.

Children with severe wasting have elongated BIVA vectors with low PA that localize within the top right "lean" quadrant just beyond the 95th percentile of community children, a position suggestive of both dehydration and malnutrition [47]. However, their BIVA does not migrate between admission and after clinical stabilization; thus, changes in body composition are not observed within this timeframe.

On average, both children with edematous SAM and wasting had lower PA than community children and low PA is reported to be associated with poor clinical outcome [28,29,48,49]. However, based on fit criteria, the models we tested did not suggest PA to contribute more than anthropometry alone towards explaining mortality, duration of hospital stay or time-to-mortality or time-to-discharge. Furthermore, these models only explained a small proportion of variance ($R^2 < 0.15$). We also compared the classification performance of PLS-DA models that combined all anthropometric variables with or without additional BI parameters. This showed that anthropometry alone had predictive value to classify children into nutritional groups and that the gain of adding BI parameters was, if any, small. Thus, the value over real time clinical examination remains unclear. BI also did not add prognostic value with regards to clinical outcomes. Similar results were shown by Roche et al. [50] where BIVA in hospitalized children with heterogeneous and complex conditions did not show predictive value toward length of stay or complications. However, given the outlier pattern, a small subgroup of children with edematous SAM may present with strongly deviant BIVA that could relate to higher mortality risk in this particular subgroup.

Overall, BI measures negatively correlate with anthropometry as reported by Girma et al. [32]. However, we show that these correlation patterns depend on edema status; where stronger relationships are apparent in children with edematous SAM, and weaker relationships ($r < |0.25|$) are seen in children with severe wasting. Thus, the body composition of severely wasted children likely combined with dehydration may be at the extremes of BIVA sensitivity.

Together, this highlights that BIVA interpretation, sensitivity and usefulness may depend on underlying conditions and SAM phenotypes. Although BIA has been in use for over 4 decades, the required population and disease-specific equations to estimate fat mass and lean body mass have not yet been developed for children with SAM or complicated SAM [19] and the different phenotypes likely require specific consideration. Complications common in SAM such as systemic inflammation can change tissue hydration, and permeability [47] and thus impact the relationship and interpretation of BI measures. As done in other populations [51], estimating total body water and the extracellular-to-intracellular water ratio would be of interest for children with edematous SAM. With improved implementation, BIA could help track the resolution of edema for research purposes or indicate if malnourished children achieve with longer treatment similar estimates of fat and lean body mass to those of community children. Therefore, pediatric BI data over a spectrum of nutritional status and underlying complications would be required to facilitate the clinical interpretation of BIVA in children with SAM living in low resource settings.

Also, an analytical variant of BIVA has been proposed: specific BIVA [52] and this method has been shown to be more accurate in estimating the relative proportion of fat mass in adults. Based on the assumption of Ohm's law that body impedance is affected by cross-sectional area, specific BIVA is thought to better normalize parameters for differences in proportion and body size by using not only height but also cross-sectional measures of the arm, waist, and calf [52]. This approach may be relevant for SAM, since wasting (narrow limbs) and stunting (altered limb-to-body ratios) are thought to contribute disproportionally to body impedance [53,54]. Finally, normalizing BI values by height adds variability, since height/length is challenging to measure accurately in young children. Using specific BIVA together with a robust measure of pediatric height could improve the clinical usefulness of BIVA in children with SAM.

Finally, several critical factors influence BI measurements that are difficult to ensure in young malnourished children, especially in low resource settings. This includes fasting time, optimal hydration, voiding before analysis, maintaining body position, rest time before testing, minimizing movement of the child, room temperature, and standardizing time of measurement [55]. Also, this study used a traditional electrode position that has been questioned in small body-sized infants [55–57]. Our average group CV was around 2% with eight measurement rejected as being higher CV than 10% in PA. The Quad4000 BodyStat manufacturer state that CVs of 1% or less is achievable in children as per recommended protocol. Perhaps, our younger population with small body size and severe conditions compound the above listed factors that influence BI measures. For example, high variance of PA and BI variables has been discussed in ill malnourished adults with cancer [58], and in healthy infants [44,57]. Also, as reviewed in Rinaldi, S. et al. [59], the use of PA has not been validated for clinical use in diseased adults with no established guidelines or cut-offs for malnutrition screening or assessment. The use of single frequency analysis (i.e., 50 kHz) has now been evaluated as less useful than a multi-frequency approach [55]. These methodological, standardization and implementation issues faced when conducting BIA are more challenging in the young [60], and likely more so in stunted, and wasted or edematous children with complicated SAM. This further supports our conclusions of not currently recommending the routine clinical use of BIA in low resource settings.

This is the first large prospective longitudinal study reporting BI changes in children hospitalized with complicated SAM. BIVA has inherent limitations and high variability when applied to children with SAM, especially considering their heterogenous underlying conditions. While BIVA can help understand differences in body composition of groups, we do not recommend its' use to guide clinical management of specific children. It would have been useful to measure BI at discharge and possibly beyond to assess whether the BIVA of children with SAM tend to stabilize overtime towards community levels. If the clinical use of BIVA in low-resource settings is to be pursued, the method should be further optimized for use in children with SAM.

curves for the discrimination of groups based on PLS-DA using only anthropometric measures (black line) compared to using both anthropometry and BI variables (grey line) are presented to distinguish groups of children with severe wasting or edematous SAM (E), severe wasting or community participants (F) and edematous SAM or community participants (G). Abbreviations: BI, bioelectrical impedance; HAZ, height-for-age z-scores; MUAC, mid-upper arm circumference; ROC, receiver operating characteristic; SAM, severe acute malnutrition; WAZ, weight-for-height z-scores; WHZ, weight-for-height z-scores. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

5. Conclusion

BIVA vectors differed significantly between groups of children with severe wasting or edematous SAM and reflected the accepted interpretation of BIVA vector positions (i.e., edema at bottom left quadrant vs. lean and dehydrated at top right). However, the added values for risk assessment of an individual child over clinical examination and anthropometry is unclear, especially considering the high variability and heterogeneity. Fluid loss can be followed with physical examination, clinical scoring, and anthropometric indicators. Based on our results, the current implementation of BI analysis does not add enough prognostic value to justify the costs in time and resources required for clinical use in the care of ill hospitalized children with SAM.

Statement of authorship

RHB, MBvH, RHJB and WV were involved in the conception and design of the study. RHB, EC, KC and JK contributed to acquisition of the data. RHB, CB, LP, DB, RHJB and WV analyzed and interpreted the data and wrote up the final manuscript. MBvH, EC, KC and JK contributed to revising the manuscript critically for important intellectual content. All co-authors reviewed the draft manuscript and accepted the final version to be submitted.

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Conflict of interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.09.031.

References

[1] Bhutta ZA, Berkley JA, Bandsma RHJ, Kerac M, Trehan I, Briend A. Severe childhood malnutrition. Nat Rev Dis Primers 2017;Sep 21(3):17067.
[2] United Nations (UN). United Nations Sustainable Development [Internet] [cited 2019 Nov 1], https://www.un.org/sustainabledevelopment/.
[3] UN-IGME. Levels and trends in child mortality report 2018 | United Nations Population Division | Department of Economic and Social Affairs [Internet]. United Nations; 2018 [cited 2019 Nov 1], https://www.un.org/en/development/desa/population/publications/mortality/child-mortality-report-2017.asp.
[4] World Health Organization. Guideline. Updates on the management of severe acute malnutrition in infants and children, vol. 115. Geneva: World Health Organization; 2013.
[5] Hossain M, Chisti MJ, Hossain MI, Mahfuz M, Islam MM, Ahmed T. Efficacy of World Health Organization guideline in facility-based reduction of mortality in severely malnourished children from low and middle income countries: a systematic review and meta-analysis. J Paediatr Child Health 2017;53(5):474–9.
[6] Heikens GT, Bunn J, Amadi B, Manary M, Chhagan M, Berkley JA, et al., Blantyre Working Group. Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence. Lancet 2008;371(9620):1305–7.
[7] Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al., Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382(9890):427–51.
[8] WHO. WHO child growth standards and the identification of severe acute malnutrition in infants and children [Internet]. WHO; 2018 [cited 2020 Aug 21]; Available from: http://www.who.int/nutrition/publications/severemalnutrition/9789241598163/en/.
[9] Bartels RH, Meyer SL, Stehmann TA, Bourdon C, Bandsma RHJ, Voskuijl WP. Both exocrine pancreatic insufficiency and signs of pancreatic inflammation are prevalent in children with complicated severe acute malnutrition: an observational study. J Pediatr 2016;Jul(174):165–70.
[10] Kerac M, Bunn J, Chagaluka G, Bahwere P, Tomkins A, Collins S, et al. Follow-up of post-discharge growth and mortality after treatment for severe acute malnutrition (FuSAM study): a prospective cohort study. PloS One 2014;9(6):e96030.
[11] Munthali T, Jacobs C, Sitali L, Dambe R, Michelo C. Mortality and morbidity patterns in under-five children with severe acute malnutrition (SAM) in Zambia: a five-year retrospective review of hospital-based records (2009-2013). Arch Public Health 2015;73(1):23.
[12] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al., ESPEN Working Group. Bioelectrical impedance analysis - Part I: review of principles and methods. Clin Nutr 2004;23(5):1226–43.
[13] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al., ESPEN Working Group. Bioelectrical impedance analysis - Part II: utilization in clinical practice. Clin Nutr 2004;23(6):1430–53.
[14] Statement NI of HTAC. Bioelectrical impedance analysis in body composition measurement [Internet] Nutrition 1996 Nov;12(11–12):749–59. https://linkinghub.elsevier.com/retrieve/pii/S0899900797851799.
[15] Talma H, Chinapaw MJM, Bakker B, Hirasing RA, Terwee CB, Altenburg TM. Bioelectrical impedance analysis to estimate body composition in children and adolescents: a systematic review and evidence appraisal of validity, responsiveness, reliability and measurement error. Obes Rev 2013;14(11):895–905.
[16] Haverkort EB, Reijven PLM, Binnekade JM, de Van Der Schueren MAE, Earthman CP, Gouma DJ, et al. Bioelectrical impedance analysis to estimate body composition in surgical and oncological patients: a systematic review. Eur J Clin Nutr 2015;69(1):3–13.
[17] Foster KR. Whole-body impedance what does it measure?. 1996.
[18] Baumgartner RN. Bioelectric impedance phase angle and body composition. 1988.
[19] Girma T, Kæstel P, Workeneh N, Mølgaard C, Eaton S, Andersen GS, et al. Bioimpedance index for measurement of total body water in severely malnourished children: assessing the effect of nutritional oedema. Clin Nutr 2016;35(3):713–7.
[20] Silva AM, Fields DA, Sardinha LB. A PRISMA-driven systematic review of predictive equations for assessing fat and fat-free mass in healthy children and adolescents using multicomponent molecular models as the reference method. J Obes 2013;2013(148696).
[21] Piccoli A, Rossi B, Pillon L, Bucciante G. A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. Kidney Int 1994;46(2):534–9.
[22] Piccoli A. Patterns of bioelectrical impedance vector analysis: learning from electrocardiography and forgetting electric circuit models. Nutrition 2002;18(6):520–1.
[23] Norman K, Smoliner C, Kilbert A, Valentini L, Lochs H, Pirlich M. Disease-related malnutrition but not underweight by BMI is reflected by disturbed electric tissue properties in the bioelectrical impedance vector analysis. Br J Nutr 2008;100(3):590–5.
[24] Colín-Ramírez E, Castillo-Martínez L, Orea-Tejeda A, Vázquez-Durán M, Rodríguez AE, Keirns-Davis C. Bioelectrical impedance phase angle as a prognostic marker in chronic heart failure. Nutrition 2012;28(9):901–5.
[25] Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance phase angle and body composition. Am J Clin Nutr 1988;48(1):16–23.
[26] Kyle UG, Earthman CP, Pichard C, Coss-Bu JA. Body composition during growth in children: limitations and perspectives of bioelectrical impedance analysis. Eur J Clin Nutr 2015;69(12):1298–305.
[27] Anja BW, Danielzik S, Dörhöfer RP, Later W, Wiese S, Müller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. J Parenter Enteral Nutr 2006;30(4):309–16.
[28] Zamberlan P, Feferbaum R, Doria Filho U, Brunow de Carvalho W, Figueiredo Delgado A. Bioelectrical impedance phase Angle and morbidity and mortality in critically ill children. Nutr Clin Pract 2019;34(1):163–71.
[29] Marino LV, Meyer R, Johnson M, Newell C, Johnstone C, Magee A, et al. Bioimpedance spectroscopy measurements of phase angle and height for age are predictive of outcome in children following surgery for congenital heart disease. Clin Nutr 2018;37(4):1430–6.

[30] Bozzetto S, Piccoli A, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. Pediatr Nephrol 2010;25(2):329–34.
[31] Farias CLA, Campos DJ, Bonfin CMS, Vilela RM. Phase angle from BIA as a prognostic and nutritional status tool for children and adolescents undergoing hematopoietic stem cell transplantation. Clin Nutr 2013;32(3):420–5.
[32] Girma T, Hother Nielsen AL, Kæstel P, Abdissa A, Michaelsen KF, Friis H, et al. Biochemical and anthropometric correlates of bio-electrical impedance parameters in severely malnourished children: a cross-sectional study. Clin Nutr 2018;37(2):701–5.
[33] Bandsma RHJ, Voskuijl W, Chimwezi E, Fegan G, Briend A, Thitiri J, et al. A reduced-carbohydrate and lactose-free formulation for stabilization among hospitalized children with severe acute malnutrition: a double-blind, randomized controlled trial. PLoS Med 2019;16(2):e1002747.
[34] World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191–4.
[35] WHO child growth standards and the identification of severe acute malnutrition in infants and children. WHO. World Health Organization; 2018 [cited 2020 Aug 21], www.who.int/childgrowth/standards.
[36] Piccoli A, Fanos V, Peruzzi L, Schena S, Pizzini C, Borgione S, et al. Reference values of the bioelectrical impedance vector in neonates in the first week after birth. Nutrition 2002;18(5):383–7.
[37] de Palo T, Messina G, Edefonti A, Perfumo F, Pisanello L, Peruzzi L, et al. Normal values of the bioelectrical impedance vector in childhood and puberty. Nutrition 2000;16(6):417–24.
[38] StataCorp. Stata statistical software: release, vol. 13. Texas: College Station; 2013.
[39] Piccoli A, Pastori G. BIVA software. 2002.
[40] Piccoli A. Bioelectric impedance measurement for fluid status assessment. Fluid Overload: Diagnosis and Management. In: Ronco C, et al., editors. Contrib Nephrol, 164. Basel: Karger; 2010. p. 143–52. http://www.ncbi.nlm.nih.gov/pubmed/20428000.
[41] Piccoli A, Italian CAPD-BIA Study Group. Bioelectric impedance vector distribution in peritoneal dialysis patients with different hydration status. Kidney Int 2004 Mar;65(3):1050–63.
[42] Piccoli A, Brunani A, Savia G, Pillon L, Favaro E, Berselli ME, et al. Discriminating between body fat and fluid changes in the obese adult using bioimpedance vector analysis. Int J Obes 1998;22(2):97–104.
[43] Piccoli A, Nigrelli S, Caberlotto A, Bottazzo S, Rossi B, Pillon L, et al. Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. Am J Clin Nutr 1995;61(2):269–70.
[44] Redondo-del-Río MP, Escribano-García C, Camina-Martín MA, Caserío-Carbonero S, Cancho-Candela R, De-Mateo-Silleras B. Bioelectrical impedance vector values in a Spanish healthy newborn population for nutritional assessment. Am J Hum Biol 2019;31(3):e23244.
[45] Nguyen PH, Young MF, Khuong LQ, Ramakrishnan U, Martorell R, Hoffman DJ. Development of population-specific prediction equations for bioelectrical impedance analyses in Vietnamese children. Br J Nutr 2020;Jul(3):1–8.
[46] Kangas ST, Kaestel P, Salpéteur C, Nikièma V, Talley L, Briend A, et al. Body composition during outpatient treatment of severe acute malnutrition: results from a randomised trial testing different doses of ready-to-use therapeutic foods. Clin Nutr 2020 Nov;39(11):3426–33.
[47] Lukaski HC, Kyle UG, Kondrup J. Assessment of adult malnutrition and prognosis with bioelectrical impedance analysis: phase angle and impedance ratio. Curr Opin Clin Nutr Metab Care 2017;20(5):330–9.
[48] Kyle UG, Genton L, Pichard C. Low phase angle determined by bioelectrical impedance analysis is associated with malnutrition and nutritional risk at hospital admission. Clin Nutr 2013;32(2):294–9.
[49] Buffa R, Mereu E, Comandini O, Ibanez ME, Marini E. Bioelectrical impedance vector analysis (BIVA) for the assessment of two-compartment body composition. Eur J Clin Nutr 2014;68(11):1234–40.
[50] Roche S, Lara-Pompa NE, Macdonald S, Fawbert K, Valente J, Williams JE, et al. Bioelectric impedance vector analysis (BIVA) in hospitalised children; predictors and associations with clinical outcomes. Eur J Clin Nutr 2019;73(10):1431–40.
[51] Marini E, Campa F, Buffa R, Stagi S, Matias CN, Toselli S, et al. Phase angle and bioelectrical impedance vector analysis in the evaluation of body composition in athletes. Clin Nutr 2020;39(2):447–54.
[52] Buffa R, Mereu E, Succa V, Latini V, Marini E. Specific BIVA recognizes variation of body mass and body composition: two related but different facets of nutritional status. Nutrition 2017;Mar(35):1–5.
[53] Fuller N, Fewtrell M, Dewit O, Elia M, Wells J. Segmental bioelectrical impedance analysis in children aged 8-12 y: 1. The assessment of whole-body composition. Int J Obes 2002;26(5):684–91.
[54] Martins PA, Hoffman DJ, Fernandes MTB, Nascimento CR, Roberts SB, Sesso R, et al. Stunted children gain less lean body mass and more fat mass than their non-stunted counterparts: a prospective study. Br J Nutr 2004;92(5):819–25.
[55] Brantlov S, Ward LC, Jødal L, Rittig S, Lange A. Critical factors and their impact on bioelectrical impedance analysis in children: a review. J Med Eng Technol 2017;41(1):22–35.
[56] Savino F, Cresi F, Grasso G, Oggero R, Silvestro L. The biagram vector: a graphical relation between reactance and phase Angle measured by bioelectrical analysis in infants. Ann Nutr Metabol 2004;48(2):84–9.
[57] Savino F, Grasso G, Cresi F, Oggero R, Silvestro L. Bioelectrical impedance vector distribution in the first year of life. Nutrition 2003;19(6):492–6.
[58] Grundmann O, Yoon SL, Williams JJ. The value of bioelectrical impedance analysis and phase angle in the evaluation of malnutrition and quality of life in cancer patients - a comprehensive review. Eur J Clin Nutr 2015;69(12):1290–7.
[59] Rinaldi S, Gilliland J, O'Connor C, Chesworth B, Madill J. Is phase angle an appropriate indicator of malnutrition in different disease states? A systematic review. Clin Nutr ESPEN 2019;Feb(29):1–14.
[60] Brantlov S, Jødal L, Lange A, Rittig S, Ward LC. Standardisation of bioelectrical impedance analysis for the estimation of body composition in healthy paediatric populations: a systematic review. J Med Eng Technol 2017;41(6):460–79.