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Bioelectrical Impedance Vector Analysis for Nutritional Status Assessment in Systemic Sclerosis and Association With Disease Characteristics

Marco Di Battista[1], Simone Barsotti[1], Alessia Monaco[1], Alessandra Rossi[1], Alessandra Della Rossa[1], and Marta Mosca[1]

ABSTRACT. ***Objective***. To use bioelectrical impedance vector analysis (BIVA) in a cohort of patients with systemic sclerosis (SSc) in order to assess their nutritional status in comparison to other groups of patients and to find any correlation with clinical characteristics and outcome of the disease.

Methods. We retrospectively collected data from 50 SSc patients who underwent BIVA for clinical suspicion of malnutrition and compared them with patients affected by other chronic autoimmune rheumatic diseases (OCAD, n = 27) and those who were only symptomatic of malnutrition but without autoimmune features (n = 15), and with 50 healthy controls (HC).

Results. Patients with SSc presented significantly lower values of phase angle (PhA), basal metabolic rate (BMR), and body cellular mass (BCM), and an increase in extracellular water (ECW; $P < 0.01$ for all) than HC; instead, there were no significant differences for BMI. No significant differences were found between SSc and OCAD. Among patients with SSc, age directly correlated with ECW ($\rho = 0.342$, $P = 0.015$) and inversely with PhA ($\rho = -0.366$, $P = 0.009$). Female sex, anemia, hypoalbuminemia, reflux, and early satiety/abdominal distension associated with relevant alterations in BIVA results. BIVA variables were significantly different when cardiopulmonary and microvascular involvement was present. Four patients died during the study: they had significantly ($P \leq 0.01$) lower PhA, BMR, and BCM, with an increased ECW.

Conclusion. BIVA, unlike BMI, allowed an accurate characterization of SSc patients at risk of malnutrition, correlating with serological malnutrition markers, with SSc-specific organ manifestations (cardiopulmonary involvement and microvascular damage), and with mortality. BIVA variables might represent a surrogate marker of damage accrual that leads to malnutrition, thus playing a leading role in the prognostic stratification of SSc patients.

Key Indexing Terms: bioelectrical impedance, malnutrition, nutritional status, systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune disease that can affect different organs and whose pathogenesis is due to vascular abnormalities, autoimmune activation, and fibrosis[1]. Malnutrition is one of the most important complications reported in this disease, with a prevalence ranging approximately from 10% to 50%, a variation that can be explained by the use of different assessment tools[2].

Among the multiple factors that can contribute to the development of nutritional impairment in SSc (e.g., both skin and visceral involvement and mood disturbances), an important role is played by gastrointestinal (GI) manifestations, which can be found in up to 90% of patients[3], adversely affecting their quality of life[4]. Indeed, each region of the GI tract can adversely affect the intake of nutrients and their absorption, as can occur with oral microstomia and xerostomia, esophageal dysmotility with reflux and dysphagia, gastric dysmotility with delayed emptying and early satiety, and small intestinal bacterial overgrowth with diarrhea[5].

It was widely shown that malnutrition in SSc is associated with a reduced quality of life[6] and with an increased morbidity and mortality[7,8], thus making accurate malnutrition assessment a very important issue.

BMI is certainly one of the most widespread methods used to assess malnutrition, but it has been shown to have various limitations, whereas bioelectrical impedance analysis (BIA) is proposed as a reliable, low-cost, quick, and bedside method[2]. Through the use of a weak electric current applied to the patient's body, it is in fact possible to measure resistance (R) and reactance (Xc). These values are subsequently used in prediction equations in order to obtain information on body composition, for example, the percentage of fat mass (FM) and fat-free mass (FFM)[9]. However, BIA predictive equations could lead to errors in the elderly and in comorbid states, which is why the bioelectrical impedance vector analysis (BIVA) was developed, a

[1]*M. Di Battista, MD, S. Barsotti, MD, PhD, A. Monaco, MD, A. Rossi, MD, A. Della Rossa, MD, PhD, M. Mosca, MD, PhD, Professor, Rheumatology Unit, University of Pisa, Pisa, Italy.*

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Address correspondence to Alessandra Della Rossa, via Roma 67, Pisa, 56123, Italy. Email: a.dellarossa@ao-pisa.toscana.it.

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tool where R and Xc are normalized per height and are plotted as a bivariate vector[10]. BIVA provides a semiquantitative evaluation of patient's hydration status and cell mass, representing a better predictor of nutritional status in all types of patients, from the elderly to those with short bowel syndrome[11,12].

So far, no data about the use of BIVA in SSc have been published. The aim of this study is to apply BIVA in SSc patients in order to assess their nutritional status and any correlation with clinical characteristics and outcome of the disease, also evaluating the differences with the general population and with other states of illness.

MATERIALS AND METHODS

Patients. Adult patients fulfilling 2013 European League against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for SSc[13] who were requested a nutritional evaluation between March 2016 and March 2019 at the Rheumatology Unit of the University of Pisa were enrolled for this retrospective cross-sectional observational study. They were further classified on the basis of the degree of skin involvement in sine scleroderma, and limited (lcSSc) and diffuse cutaneous (dcSSc) groups according to LeRoy classification[14]. Patients were sent for nutritional evaluation because they had at least one of the following signs and symptoms: progressive weight loss, dyspepsia and dysphagia, loss of appetite, or clinical suspicion of malnutrition. As control groups, we included a cohort of healthy controls (HC) matched for age and sex, and a group of patients with the same signs and symptoms but without a diagnosis of SSc. This latter group was further divided in patients with other chronic autoimmune rheumatic diseases (OCAD) and subjects who only presented the aforementioned symptoms without any OCAD (only symptomatic [OS] group).

Subjects with neoplastic comorbidities or other chronic diseases (e.g., inflammatory bowel disease, chronic kidney disease) that could compromise nutritional status by themselves were excluded.

Full ethical approval was obtained from the local ethical committee (Comitato Etico Area Vasta Nord Ovest, approval number 15464). Each patient voluntarily agreed to participate and gave written informed consent to publish the material.

Clinical variables. At the time of enrollment, data were collected through medical history, medical records, and physical examination. Data included the following:

- Anthropometric measurements to calculate BMI (values < 18.5 kg/m^2 were considered underweight);
- Clinical features including
  - Capillaroscopic pattern according to Cutolo[15],
  - Autoantibody profile (distinguishing between anticentromere [ACA], Scl70 [antitopoisomerase I] and positivity only for antinuclear antibodies [ANA]),
  - Specific organ involvement: interstitial lung disease (ILD); pulmonary arterial hypertension (PAH); ongoing digital ulcers (DUs) or history of DUs; heart, muscle or joint involvement. Particular attention was paid to GI signs and symptoms (microstomia, xerostomia, reflux, esophageal dilatation at radiograph or computed tomography [CT] imaging, reflux esophagitis at esophagogastroduodenoscopy, dysphagia, early satiety and abdominal distension, constipation, diarrhea, fecal incontinence). Skin involvement was evaluated with the modified Rodnan skin score (mRSS)[16]. Additionally, patients completed the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (GIT) 2.0 questionnaire[17].
- Laboratory variables potentially associated with nutritional status, as serum hemoglobin (normal values [NV] > 11.5 g/dL for women and > 13.0 g/dL for men), albumin (NV > 3.5 g/dL), total protein (NV > 6.0 g/dL), creatinine (NV > 0.5 mg/dL for women and > 0.7 mg/dL for men), and total cholesterol (NV < 200 mg/dL).

Assessment of nutritional status. At the time of evaluation, patients were apyretic and had not consumed alcoholic beverages or carried out physical activity in the previous 12 hours. After lying on an examination table for 5 minutes, whole-body bioimpedance was performed using BIA101 BIVA (Akern), which applies alternating sinusoidal electric currents of 800 μA at an operating frequency of 50 kHz. BIVA measurements were carried out using tetrapolar configuration as described by Lukaski, *et al*[18]. R and Xc were recorded for each patient, normalized for height and then compared with the tolerance ellipses of the reference population, thus allowing body composition evaluation[19]. FM, FFM, total body water (TBW), extracellular water (ECW), body cell mass (BCM), basal metabolic rate (BMR), and extracellular mass (ECM)/BCM ratio (an early index of protein catabolism) were then predicted using Bodygram Plus software (Akern). The phase angle (PhA) is a variable that describes the relationship between nutrition and hydration status, and low values are considered indicative of a pathologically impaired nutritional status[9,20].

Statistical analysis. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS, version 22.0, IBM Corp.). Given that BIVA values were not normally distributed, especially when grouped according to the clinical variables included in the study, data were analyzed with nonparametric tests (Wilcoxon rank-sum test and Mann-Whitney *U* test) and Spearman R for correlation between values. P values < 0.05 were considered statistically significant.

RESULTS

Patients. Fifty patients with SSc were enrolled for this study, along with the same number of HC matched for age and sex. Clinical characteristics of the SSc group are reported in Table 1. They were mostly females (92%), with a mean age of 61.1 ± 12.5 years and a mean disease duration of 13 ± 10 years. About half of the patients presented with lcSSc, ACA positivity, and a capillaroscopic late scleroderma pattern. GI symptoms were mainly characterized by reflux (90%), esophageal dilatation (84%), and dysphagia (56%). Anemia was the most common laboratory abnormality (30%), whereas the main specific organ involvement concerned ILD (52%) and DU history (68%). The mean total GIT score was 0.67 ± 0.5.

The OCAD group included 27 patients (7 with systemic lupus erythematosus [SLE], 6 with undifferentiated connective tissue disease [UCTD], 6 with idiopathic inflammatory myopathy [IIM], 3 with rheumatoid arthritis [RA], 3 with spondyloarthritis [SpA], 1 with Behçet disease [BD], and 1 with mixed connective tissue disease), mostly females (85.2%), and with a mean age of 57.8 ± 13.3 years, whereas the OS group consisted of 15 subjects, 86.7% of which were female, and with a mean age of 58 ± 17.3 years. In the analysis between patient groups, no statistically significant differences with respect to age and sex were found.

Comparisons between groups. Comparing the obtained values between the different groups, BIVA revealed that patients with SSc presented a significant reduction in PhA, BMR, BCM, and FFM values compared with HC, in addition to an increase in ECW and ECM/BCM ratio. No statistically significant differences were found between SSc and HC for BMI, nor between SSc and OCAD for all the variables examined. Instead, patients with SSc had significantly higher BMI, FM, and TBW values than the OS group. No significant differences were found between OCAD and OS; instead, when these 2 groups were

Table 1. Epidemiologic, clinical, and laboratory characteristics of the SSc group (n = 50).

	n (%) or mean ± SD
Female	46 (92)
Age, yrs, mean ± SD	61.1 ± 12.5
Disease duration, yrs, mean ± SD	13 ± 10
Sine scleroderma	6 (12)
lcSSc	26 (52)
dcSSc	18 (36)
Autoantibody profile	
Only ANA	7 (14)
ACA	28 (56)
Scl70	15 (30)
Capillaroscopic pattern	
Early	9 (18)
Active	17 (34)
Late	24 (48)
Gastrointestinal symptoms	
Microstomia	16 (32)
Xerostomia	23 (46)
Dysphagia	28 (56)
Reflux	45 (90)
Esophageal dilatation	42 (84)
Esophagitis	21 (42)
Early satiety/abdominal distension	16 (32)
Constipation	17 (34)
Diarrhea	13 (26)
Fecal incontinence	8 (16)
Laboratory variables	
Anemia	15 (30)
Hypoalbuminemia	9 (18)
Hypoproteinemia	3 (6)
Hypocreatininemia	4 (8)
Hypercholesterolemia	5 (10)
Specific organ involvement	
DU ongoing	14 (28)
DU history	34 (68)
ILD	26 (52)
PAH	7 (14)
Heart involvement	6 (12)
Muscle involvement	3 (6)
Joint involvement	10 (20)

ACA: anticentromere antibody; ANA: antinuclear antibody; dcSSc: diffuse cutaneous SSc; DU: digital ulcer; ILD: interstitial lung disease; lcSSc: limited cutaneous SSc; PAH: pulmonary arterial hypertension; Scl70: antitopoisomerase I; SSc: systemic sclerosis.

compared with HC, a significant difference ($P < 0.001$) was found for all the variables examined. Statistical comparisons of the medians of BMI and BIVA variables between SSc and the other groups are reported in Table 2.

Relationship between variables and SSc characteristics. Analyzing the relationship between the results obtained and the clinical characteristics of SSc group, it emerged that age was directly correlated to ECW ($\rho = 0.342$, $P = 0.015$) and inversely to PhA ($\rho = -0.366$, $P = 0.009$). These same correlations were found in OCAD (ECW $\rho = 0.443$, $P = 0.021$; PhA $\rho = -0.482$, $P = 0.011$) and in HC (ECW $\rho = 0.398$, $P = 0.005$; PhA $\rho = -0.386$, $P = 0.006$) groups. In addition, age inversely correlated with BMR in OCAD ($\rho = -0.396$, $P = 0.041$), whereas it directly correlated with ECM/BCM in HC ($\rho = 0.374$, $P = 0.008$). No correlations were found regarding age and the results obtained in the OS group (data not shown).

Disease duration showed a direct correlation with FM ($\rho = 0.285$, $P = 0.045$). Female patients had significant lower values of BMR, BCM, FFM, and TBW, as reported in Table 3. Among the 3 different skin subsets, both the lcSSc and dcSSc groups presented a significant reduction of BMI ($P = 0.022$ and $P = 0.015$, respectively), FFM ($P = 0.026$ and $P = 0.017$), and TBW ($P = 0.017$ and $P = 0.021$) in comparison to the sine scleroderma group. No relevant dissimilarities were found between lcSSc and dcSSc subsets. Further, mRSS was inversely correlated with BMI ($\rho = -0.363$, $P = 0.048$).

Nailfold capillaroscopy provided significant differences between late and active patterns, having the former lower PhA ($P = 0.032$) and BMR ($P = 0.024$) and higher ECW ($P = 0.026$). Analyzing autoantibody profile, no relevant dissimilarities were found among ACA, Scl70, and ANA-only subgroups. From laboratory investigations, it emerged that anemia and hypoalbuminemia were significantly associated with alterations in BMI, BMR, BCM, FFM, and TBW; hypoalbuminemia also associated with impaired PhA and ECW, as shown in Table 3. No significant relationships were found regarding hypoproteinemia, hypocreatininemia, and hypercholesterolemia.

Among GI signs and symptoms, only reflux and early satiety/abdominal distension were associated with significant alterations in BMI and BIVA results. The statistical associations between the examined variables and SSc-specific organ involvement are reported in Table 3. The UCLA GIT 2.0 questionnaire presented exclusively an inverse correlation between the reflux domain and TBW ($\rho = -0.332$, $P = 0.039$).

Four patients died in the postenrollment period from SSc-related causes. Comparing their results with those of the other SSc patients, it emerged that the deceased had a significant reduction in the median values of PhA, BMR, and BCM, together with a significant increase in the median ECW (Table 4), whereas BMI showed no relevant associations.

DISCUSSION

Knowledge about nutritional status and body composition in SSc is still limited. We analyzed a cohort of SSc patients with clinical suspicion of malnutrition, assessing BMI and performing BIVA. We compared them with healthy subjects and patients suspected of malnutrition who had either OCAD or did not show any autoimmune feature (OS group). BIVA, unlike BMI, showed that patients with SSc had several significant differences in comparison to HC and OS groups, whereas SSc and OCAD were substantially equivalent. Further, we sought to find out any relevant association between the examined variables and the clinical/laboratory characteristics of the disease. The results obtained with BIVA in SSc patients correlated with female sex and serological malnutrition markers (hemoglobin and albumin). Moreover, BIVA variables were found to be remarkably associated with cardiopulmonary involvement (ILD,

Table 2. Statistical comparison of BIVA variables and BMI between SSc and the other groups.

	SSc, n = 50	OCAD, n = 27	OS, n = 15	HC, n = 50
BMI, kg/m²	23.5 (9.2)	18.8 (9.1)	17.8 (4.3)**	25.2 (7.3)
PhA, degrees	3.8 (1.3)	3.6 (1.1)	3.7 (0.8)	4.5 (0.7)**
BMR, kcal	1231 (226)	1204 (68)	1202 (102)	1368 (116)**
BCM, kg/m	10.3 (4.4)	9.6 (1.9)	9.6 (2.4)	13.1 (2.4)**
FFM, kg/m	26.6 (5.1)	25.1 (3.5)	24.2 (3.2)	28.6 (4.6)*
FM, kg/m	10.2 (10)	4.9 (10.3)	6.4 (4.6)**	12.7 (10.1)
TBW, L/m	20.8 (5)	19.2 (4)	17.9 (1.6)*	21.1 (3.3)
ECW (% on TBW)	58.7 (10.5)	60.6 (8.5)	59.4 (6)	53.5 (5.2)**
ECM/BCM	1.5 (0.8)	1.6 (0.6)	1.5 (0.4)	1.2 (0.2)**

Values are expressed as median (IQR). Significant comparisons were signalled with asterisks (*$P < 0.05$; **$P < 0.01$). BCM: body cellular mass; BIVA: bioelectrical impedance vector analysis; BMR: basal metabolic rate; ECM: extracellular mass; ECW: extracellular water; FFM: fat-free mass; FM: fat mass; HC: healthy controls; OCAD: other chronic autoimmune diseases; OS: only symptomatic; PhA: phase angle; SSc: systemic sclerosis; TBW: total body water.

Table 3. Significant associations for clinical and laboratory features.

		BMI, kg/m²	PhA, degrees	BMR, kcal	BCM, kg/m	FFM, kg/m	FM, kg/m	TBW (L/m)	ECW (% TBW)	ECM/ BCM
Female	No			1510 (347)	15.1 (6.1)	33.7 (32)		25.4 (5.4)		
	Yes			1212 (223)	10.1 (4.4)	26.1 (4.8)		20.7 (4.4)		
	P			**0.004**	**0.015**	**0.001**		**0.019**		
Anemia	No	25.1 (7.8)		1262 (187)	11 (3.9)	28 (5.1)		21.3 (4.3)		
	Yes	20 (4.4)		1137 (189)	8.3 (4.6)	23.4 (3.9)		18.8 (3.7)		
	P	**0.02**		**0.022**	**0.021**	**0.005**		**0.017**		
Hypoalbuminemia	No	25.1 (8.5)	4.1 (0.5)	1288 (177)	11.3 (3.6)	27.9 (4.8)		21.3 (4.2)	56.2 (7.8)	
	Yes	20.5 (4.9)	3.2 (1.3)	1115 (183)	8.3 (4.8)	23.3 (1)		17.3 (3.6)	63.3 (13.7)	
	P	**0.037**	**0.004**	**< 0.001**	**0.018**	**0.003**		**0.008**	**0.005**	
Reflux	No	29.7 (8.1)					18.5 (12)			
	Yes	22.9 (8)					10.1 (9)			
	P	**0.024**					**0.024**			
Early satiety/abdominal distension	No	24.5 (9.2)				28 (5.2)	12 (10.7)	21.5 (4.2)		
	Yes	20 (7.1)				23.5 (5.3)	8.2 (5.8)	17.7 (4.5)		
	P	**0.001**				**0.004**	**0.008**	**0.002**		
DU ongoing	No	25.9 (7.6)		1262 (178)	10.9 (3.4)	28 (4.1)	14.1 (9.5)	21.5 (4.2)		
	Yes	18.9 (6)		1141 (242)	9.1 (6.8)	23.2 (3.1)	7.7 (5.4)	17.8 (4.2)		
	P	**< 0.001**		**0.004**	**0.034**	**0.001**	**0.001**	**0.001**		
DU history	No	27.1 (7.4)	4.4 (1.1)	1355 (198)	12.7 (3.5)				54.3 (7.9)	
	Yes	22.3 (8.1)	3.6 (1.3)	1196 (162)	9.8 (3.2)				59.9 (10.4)	
	P	**0.037**	**0.031**	**0.013**	**0.015**				**0.048**	
ILD	No	26 (8.7)	4.2 (0.8)	1314 (168)	11.6 (3.1)	28.1 (3.6)		21.6 (3.8)	55.6 (5.5)	1.4 (0.4)
	Yes	21.8 (7.4)	3.2 (1.4)	1141 (177)	9 (3.7)	24 (4.3)		18.8 (4.6)	62.7 (11.8)	1.8 (0.9)
	P	**0.004**	**0.013**	**0.001**	**0.008**	**< 0.001**		**0.004**	**0.013**	**0.031**
PAH	No		3.8 (1.3)	1245 (215)	10.6 (4.1)				58.4 (9.2)	1.4 (0.6)
	Yes		3 (1.5)	1128 (233)	8.3 (5.2)				65.4 (16.1)	2 (2.8)
	P		**0.005**	**0.016**	**0.016**				**0.005**	**0.011**
Heart	No	24 (9.2)	3.9 (1.2)		10.6 (4.3)				57.6 (9.5)	1.4 (0.7)
	Yes	20.1 (7.3)	3 (1.7)		7.9 (5.8)				64.9 (17.3)	2 (2.6)
	P	**0.039**	**0.03**		**0.045**				**0.025**	**0.042**

Spaces were left blank when no statistical significance was reached. No significant associations were found for muscle and joint involvement. Values are expressed as median (IQR) unless otherwise specified. BCM: body cellular mass; BMR: basal metabolic rate; DU: digital ulcer; ECM: extracellular mass; ECW: extracellular water; FFM: fat-free mass; FM: fat mass; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; PhA: phase angle; TBW: total body water.

Table 4. Comparison between deceased SSc patients and the rest of the group.

	Deceased, n = 4	Alive, n = 46	*P*
PhA, degrees	2.4 (1.5)	3.8 (1.2)	0.007
BMR, kcal	1018 (269)	1243 (211)	0.007
BCM, kg/m	6.2 (6.2)	10.6 (4.1)	0.01
ECW (% TBW)	71.8 (17.1)	58.4 (9.2)	0.006

Values are expressed as median (IQR) unless otherwise indicated. BCM: body cellular mass; BMR: basal metabolic rate; ECW: extracellular water; PhA: phase angle; SSc: systemic sclerosis; TBW: total body water.

PAH, and heart involvement) and microvascular damage (DU and late capillaroscopic pattern). Finally, the subanalysis on the deceased patients highlighted some significantly more impaired BIVA variables that could act as prognostic stratifiers.

Malnutrition affects hydration and cell masses, impairing body composition and functional status, ultimately leading to abnormalities that can be detected by BIA and its more accurate version, BIVA[21]. These are cheap, quick, and bedside methods that have widely demonstrated great reliability in the evaluation of body compartment changes and nutritional status in the most fragile subjects, such as the elderly[22] and sarcopenic patients[23]. These tools have found their own field of application in rheumatic diseases as well. For example, in RA, BIA proved to be the method of choice for assessing nutritional status[24], whereas BIVA was useful in detecting rheumatoid cachexia[25]. Some studies used BIA in SSc, aiming to assess nutritional status and malnutrition[8,26] or the presence of sarcopenia[27]. So far, BIVA has not yet been applied in patients with SSc.

Comparing the examined variables between the groups in our study clearly revealed the presence of significant differences for several BIVA variables between SSc patients and HC, as well as a lack of such a difference when considering BMI. This failure of the BMI to differentiate SSc patients with clinical suspicion of malnutrition from healthy subjects reinforces even more what was observed by Baron, *et al* in the Canadian Scleroderma Research Group Registry, where the BMI had a similar distribution between a large cohort of SSc patients (in which 18% were at risk of malnutrition) and the general population[28]. In the comparison between the remaining groups, predictable significant differences arose between SSc and OS, whereas the absence of such differences between SSc and OCAD appears noteworthy. These data would suggest that, for patients with the same risk of malnutrition, the presence of CAD affects this condition regardless of the subtype (e.g., SSc, IIM, SLE, or UCTD), even if the percentage of patients at risk of malnutrition changes considerably among the various CAD.

It also clearly emerged that age correlated inversely with PhA, which supports what has already been stated in other important studies on BIVA in the elderly[29]. However, our SSc cohort differs from the latter because with increasing age, we did not observe a decrease in BCM, whereas a significant increase in ECW occurred.

Evaluating the possible relationships between the assessed variables and the clinical characteristics within the SSc group, BIVA has provided results that strengthen the relevance of skin involvement, as a milder impaired nutritional status was described in sine sclerodema among skin subsets.

In our cohort, the disease characteristics that best reflected a significant alteration of BIVA variables were female sex, reflux and early satiety/abdominal distension among GI symptoms, and anemia and hypoalbuminemia among laboratory findings. When BIVA results were analyzed in relationship with SSc-specific organ involvement, several strong associations were found. The presence of DU was in fact associated with significant alterations of almost all BIVA variables. Interestingly, most of them remained when considering DU history and late pattern at capillaroscopy, thus reinforcing the concept of how microvascular damage deeply affects body composition. Regarding ILD, widespread and strong associations were also found: in particular, it is noteworthy how the reduction of BCM and the parallel increase in ECM/BCM ratio is likely linked to the increased fibrotic component detectable in ILD (which increases ECM values). Finally, BIVA allowed a detailed characterization of the nutritional impairment found in patients with PAH and heart involvement. This study highlighted how some clinical features are more important than others when evaluating an impaired nutritional status. Nevertheless, it is conceivable that SSc-specific organ damage and BIVA alterations are mutually influenced.

With respect to serologic profile, the absence of differences among autoantibody subgroups can be explained by the fact that other SSc-specific autoantibodies associated with peculiar clinical phenotypes (e.g., anti-RNA polymerase III) were not investigated in this study.

Hence, when there is the suspicion of malnutrition in an SSc patient with normal BMI, the presence of 1 or more of the aforementioned clinical/laboratory features could represent a red flag, and the use of BIVA can lead concretely to the detection of an impaired nutritional status.

Analyzing the data of the 4 deceased SSc patients, it was possible to identify a significant alteration of some BIVA variables, namely PhA, BMR, BCM, and ECW. Therefore, unlike BMI, BIVA showed a predictive association with mortality. Higher PhA values indicate higher cellularity, membrane integrity, and better cellular function, whereas the reduction of this variable can reflect an increase in extracellular fluids and/or the destruction of cell membranes, consequently indicating worse cellular function. In our cohort, PhA values had a negative correlation with age and a significant association with hypoalbuminemia; late capillaroscopic pattern; history of DU, ILD, PAH; and heart involvement. All these elements suggest that PhA can reliably reflect an impaired functionality, and that lower values can be predictors of SSc-related mortality. This is in accordance with the findings of Krause, *et al*, who described the important predictive value that PhA has in SSc mortality, in association with the unreliability of BMI[8]. Interestingly, in our cohort, both BMR and BCM shared a significant reduction for the same clinical features: female sex; anemia; hypoalbuminemia; presence; and history of DU, ILD, and PAH. Thus, a strong association is outlined between the reduction of the cellular

pool of the organism and the basal metabolism, both induced by the aforementioned elements and a more impaired nutritional status, which, in the most severe cases, is a predictor of mortality. All these observations point to the concept that BIVA variables, and especially PhA, given its remarkable correlation with age and mortality, may reflect the accrual of damage during the course of the disease.

To the best of our knowledge, this is the first study to have applied BIVA in SSc. Since a major issue in SSc is malnutrition and its diagnosis and management are still challenging, the use of an easy and accurate tool like BIVA can provide great help. BMI should not be used in the assessment of malnutrition in SSc, since it proved to be unreliable and was not related to mortality. BIVA, which is the more accurate version of BIA, instead showed several strong associations with the various clinical characteristics of SSc and revealed a predictive role in mortality. BIVA should therefore be considered the method of choice when approaching malnutrition in SSc. Given these relevant qualities, it could be proposed to use BIVA routinely in the evaluation of patients with SSc for the early diagnosis of subclinical malnutrition. A further conceivable step could be focusing on early nutritional interventions on the basis of BIVA variables, to test the hypothesis that the prompt intervention in nutritional status may improve disease outcome.

The main limitation of our study is the selection of patients, which was not consecutive but occurred when a clinical suspicion of malnutrition was present; however, the assessment of the prevalence of malnutrition was not a purpose of this study. Due to selection bias and the fact that BIVA was never used in SSc, it was not possible to make comparisons between our cohort and the other few cohorts present in the literature in which BIA was applied in SSc consecutive patients. Nonetheless, when analyzing the results obtained in 2010 by Krause, *et al* applying BIA in 124 SSc patients[8], we share the common finding that PhA values are a reliable index of malnutrition and a good predictor of SSc-related mortality, whereas BMI values are quite unreliable. Since this is not a prospective study, we could not assess any sensitivity to change of BIVA results with the variation of patients' nutritional status.

In conclusion, we showed how in SSc, BIVA alterations correlate with serological malnutrition markers (hemoglobin and albumin), with various organ-specific SSc manifestations (cardiopulmonary involvement and microvascular damage) and, noticeably, with mortality. In this regard, BIVA may represent a useful instrument for grading damage accrual and therefore could also play a role in the prognostic stratification of patients with SSc. Further studies on the application of BIVA in SSc are needed in order to increase the knowledge about this easy and reliable method, and consequently, to significantly improve the early diagnosis and management of malnutrition in patients with SSc.

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