Bioelectrical impedance vector analysis for nutritional status assessment in systemic sclerosis and association with disease characteristics

Marco Di Battista, Simone Barsotti, Alessia Monaco, Alessandra Rossi, Alessandra Della Rossa*, Marta Mosca

Rheumatology Unit, University of Pisa, Pisa, Italy

* Corresponding author: via Roma 67, Pisa, 56123, Italy; email: a.dellarossa@ao-pisa.toscana.it

Key indexing terms: Systemic sclerosis, Bioelectrical impedance, Malnutrition, Nutritional status

Founding: none

Conflict of interest: none

Authors' list:

M. Di Battista, MD (ORCID ID 0000-0002-4788-5729)

S. Barsotti, MD, PhD (ORCID ID 0000-0002-4864-4505)

A. Monaco, MD

A. Rossi, MD

A. Della Rossa, MD, PhD

M. Mosca, MD, PhD, Prof (ORCID ID 0000-0001-5937-4574)

Running title: BIVA in SSc malnutrition

Abstract

Objective: To use bioelectrical impedance vector analysis (BIVA) in a cohort of systemic sclerosis (SSc) patients 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) or only symptomatic (n.15), and with 50 healthy controls (HC).

Results: SSc patients presented significantly lower values of phase angle (PhA), basal metabolic rate (BMR), body cellular mass (BCM) and an increase in extracellular water (ECW) ($p<0.01$ for all) than HC, unlike body mass index (BMI). No significant differences were found between SSc and OCAD. Among SSc patients, age directly correlated with ECW ($\rho=0.342$; $p=0.015$) and inversely with PhA ($\rho=-0.366$; $p=0.009$). Female sex, anaemia, hypoalbuminemia, reflux and early satiety/abdominal distension associated with relevant alterations in BIVA results. BIVA parameters were significantly different when cardiopulmonary and microvascular involvement was present. Four patients died during the study: they had significantly ($p\leq0.01$) lower PhA, BMR and BCM, with an increased ECW.

Conclusions: 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 parameters might represent a surrogate marker of damage accrual that leads to malnutrition, thus playing a leading role in the prognostic stratification of SSc patients.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease which can affect different organs and whose pathogenesis is due to vascular abnormalities, autoimmune activation and fibrosis (1). Malnutrition is one of the most important complication reported in this disease, with a prevalence ranging from about 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 manifestations, which can be found in up to 90% of patients (3) adversely affecting their quality of life (4). Indeed, each region of the gastrointestinal tract can adversely affect the intake of nutrients and their absorption, as can occur with oral microstomia and xerostomia, oesophageal dysmotility with reflux and dysphagia, gastric dysmotility with delayed emptying and early satiety, small intestinal bacterial overgrowth with diarrhoea (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.

Body mass index (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 on 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, that is why it was developed bioelectrical impedance vector analysis (BIVA), a 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 (ssSSc), 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, 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 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).

Subjects with neoplastic co-morbidities 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 the written informed consent to publish the material.

Clinical variables

At the enrolment time, data were collected through medical history, medical records and physical examination. Data included:

- 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 anti-centromere – ACA, anti-topoisomerase I – Scl70 and positivity only for anti-nuclear 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 gastrointestinal signs and symptoms (microstomia, xerostomia, reflux, oesophageal dilatation at x-ray or CT imaging, reflux oesophagitis at esophagogastroduodenoscopy, dysphagia, early satiety and abdominal distension, constipation, diarrhoea, faecal incontinence). Skin involvement was evaluated with modified Rodnan Skin Score (mRSS) (16). Additionally, patients completed the UCLA GIT 2.0 questionnaire (17);

- Laboratory parameters potentially associated with nutritional status, as serum haemoglobin (normal value >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 the evaluation patients were apyretic and had not taken 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, Florence, Italy)* which applies alternating sinusoidal electric current of 800 μÅ 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, Florence, Italy*). The phase angle (PhA) is a parameter that describes the relationship between nutrition and hydration status and low values are considered index 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 software, USA). Given that BIVA values were not normally distributed, especially when grouped according to the clinical parameters included in the study, data were analyzed with non-parametric test

(Wilcoxon rank-sum test and Mann-Whitney test) and Spearman's R for correlation between values. P values of less than 0.05 were considered statistically significant.

Results

Patients

Fifty SSc patients were enrolled for this study, along with the same number of HC matched for age and sex. 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 lcSSc subset, ACA positivity and a capillaroscopic SSc-PDM late pattern. GI symptoms were mainly characterized by reflux (90%), oesophageal dilatation (84%) and dysphagia (56%). Anaemia was the most common laboratory abnormality (30%), whereas the main specific organ involvement concerned ILD (52%) and DUs history (68%). Mean total GIT score was 0.67 ±0.5. Clinical characteristics of the SSc group are reported in Table 1.

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 spondiloarthritis, 1 with Behçet syndrome and 1 with mixed connective tissue disease), mostly females (85.2%) and with a mean age of 57.8 ±13.3 years, whereas 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 gender were found.

Comparisons between groups

Comparing the obtained values between the different groups, BIVA revealed that SSc patients presented a significant reduction in PhA, BMR, BCM and FFM values than HC, in addition to an increase in ECW

and ECM/BCM ratio. No statistically significant differences were found neither between SSc and HC as regards the BMI, nor between SSc and OCAD as regards all the parameters examined. SSc patients instead had significantly higher BMI, FM and TBW values than the OS group. No significant differences were found between OCAD and OS, instead when these two groups were 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 parameters between SSc and the other groups are reported in Table 2.

Relationships between parameters and SSc characteristics

Analysing 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 also 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 OS group. 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 three different skin subsets, both lcSSc and dcSSc groups presented a significant reduction of BMI (respectively $p=0.022$ and $p=0.015$), FFM ($p=0.026$ and $p=0.017$) and TBW ($p=0.017$ and $p=0.021$) in comparison to ssSSc. No relevant dissimilarities were found between lcSSc and dcSSc subsets. Furthermore, 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 ($p=0.026$). Analysing autoantibody profile, no relevant dissimilarities were found among ACA, Scl70 and only ANA subgroups. From laboratory investigations it emerged that anaemia and hypoalbuminemia were significantly associated

with alterations in BMI, BMR, BCM, FFM and TBW; hypoalbuminemia also associates with impaired PhA and ECW, as shown in Table 3. No significant relationships were found regarding hypoproteinemia, hypocreatininemia and hypercholesterolemia.

Among gastrointestinal 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 parameters 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 (ρ=-0.332; p=0.039).

Four patients died in the post-enrolment 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 (See Table 4), whereas BMI showed no relevant associations.

Discussion

Knowledge about nutritional status and body composition in SSc is still limited. We analysed a cohort of SSc patients with clinical suspicion of malnutrition, assessing BMI and performing BIVA. We compared them with healthy subjects and with patients with the same suspicion, either affected by other chronic autoimmune diseases or not. BIVA, unlike BMI, showed that SSc patients had several significant differences in comparison to HC e OS groups, whereas SSc and OCAD were substantially equivalent. Furthermore, we sought to find out any relevant association between the examined parameters and the clinical-laboratory characteristics of the disease. The results obtained with BIVA in SSc patients

correlated with female sex and serological malnutrition markers (haemoglobin and albumin). Moreover, BIVA parameters were found to be remarkably associated with cardiopulmonary involvement (ILD, PAH and heart involvement) and microvascular damage (DUs and late capillaroscopic pattern). Finally, the sub-analysis on the deceased patients allowed to highlight some significantly more impaired BIVA parameters that could act as prognostic stratifiers.

Malnutrition affects hydration and cell masses, impairing body's 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 also in rheumatic diseases. For example, in RA BIA proved to be the method of choice for assessing nutritional status (24), whereas BIVA was useful to detect 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 had not yet been applied in SSc patients.

Comparing the examined variables between the groups in our study, it first clearly emerged the presence of significant differences for several BIVA parameters between SSc patients and HC, whereas there was 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 it appears noteworthy the absence of such differences between SSc and OCAD. This data would suggest that, for the same risk of malnutrition, the presence of

a chronic autoimmune rheumatic disease by itself impacts this condition regardless of whether SSc, IIM, SLE or UCTD, even if obviously the percentage of patients at risk of malnutrition changes considerably among the various chronic autoimmune rheumatic diseases.

It also clearly emerged that age correlates inversely with PhA, which is in agreement with 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 the increasing of age we have not observed a decrease in BCM, whereas a significant increase in ECW has occurred.

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

The disease characteristics that best reflected in our cohort a significant alteration of BIVA parameters were female sex, reflux and early satiety/abdominal distension among gastrointestinal symptoms, anaemia and hypoalbuminemia among laboratory findings. When BIVA results were analysed in relationship with SSc-specific organ involvement, several strong associations were found. The presence of DUs was in fact associated with significant alterations of almost all BIVA parameters. Interestingly, most of them still remained when considering DUs history and late pattern at capillaroscopy, thus reinforcing the concept of how microvascular damage deeply affects the body composition of patients. 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 with 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 a SSc patient with normal BMI, the presence of one or more of the aforementioned clinical-laboratory features could represent a red flag and the use of BIVA can concretely lead to the detection of an impaired nutritional status.

Analysing the data of the four dead SSc patients, it was possible to identify a significant alteration of some BIVA parameters, 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 parameter can reflect an increase in extracellular fluids and/or the destruction of cell membranes, consequently indicating a worse cellular functions. In our cohort PhA values had a negative correlation with age and a significant association with hypoalbuminemia, late capillaroscopic pattern, history of DUs, ILD, PAH, and heart involvement. All these elements suggest that PhA can reliably reflect an impaired functionality of the organism, 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, anaemia, hypoalbuminemia, presence and history of DUs, ILD and PAH. Thus a strong association is outlined between the reduction of the cellular pool of the organism and of 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 parameters, 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 malnutrition is a major issue in SSc and its diagnosis and management are still challenging, the use of an easy and accurate tool like BIVA can provide a great help. BMI should not be used in the assessment of malnutrition in SSc, since it proved to be unreliable and not related to mortality. BIVA, which is the more accurate version of BIA, showed instead 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 SSc patients, in order to early diagnose the forms of subclinical malnutrition. A further conceivable step could be the focusing on early nutritional interventions on the basis of BIVA parameters, to test the hypothesis that the prompt intervention on 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 this bias of selection and due to 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 who applied BIA in SSc consecutive patients. Nonetheless, when analysing 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 at the variation of patient's nutritional status.

In conclusion, we showed how in SSc BIVA alterations correlate with serological malnutrition markers (haemoglobin 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 SSc patients.

Further studies on the application of BIVA in SSc are needed in order to increase the knowledge on this easy and reliable method, and consequently be able to significantly improve the early diagnosis and the management of malnutrition in SSc patients.

References

1. Barsotti S, Orlandi M, Codullo V, Di Battista M, Lepri G, Della Rossa A, et al. One year in review 2019: Systemic sclerosis. Clin Exp Rheumatol Suppl. 2019;37:3-14.

2. Spanjer MJ, Bultink IEM, de van der Schueren MAE, Voskuy AE. Prevalence of malnutrition and validation of bioelectrical impedance analysis for the assessment of body composition in patients with systemic sclerosis. Rheumatology. 2017;56:1008–12.

3. Thoua NM, Bunce C, Brough G, Forbes A, Emmanuel A V., Denton CP. Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre. Rheumatology. 2010;49:1770–5.

4. Johnson SR, Glaman DD, Schentag CT, Lee P. Quality of life and functional status in systemic sclerosis compared to other rheumatic diseases. J Rheumatol. 2006;33:1117-22.

5. Harrison E, Herrick AL, Mclaughlin JT, Lal S. Malnutrition in systemic sclerosis. Rheumatology. 2012;51:1747–56.

6. Preis E, Franz K, Siegert E, Makowka A, March C, Riemekasten G, et al. The impact of malnutrition on quality of life in patients with systemic sclerosis. Eur J Clin Nutr. 2018;72:504–10.

7. Cereda E, Codullo V, Klersy C, Breda S, Crippa A, Rava ML, et al. Disease-related nutritional risk and mortality in systemic sclerosis. Clin Nutr. 2014;33:558–61.

8. Krause L, Becker MO, Brueckner CS, Bellinghausen CJ, Becker C, Schneider U, et al. Nutritional status as marker for disease activity and severity predicting mortality in patients with systemic sclerosis. Ann Rheum Dis. 2010;69:1951–7.

9. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis - Part I: Review of principles and methods. Clin Nutr. 2004;23:1226–43.

10. Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis - Clinical relevance and applicability of impedance parameters. Clin Nutr. 2012;31:854–61.

11. Norman K, Smoliner C, Valentini L, Lochs H, Pirlich M. Is bioelectrical impedance vector analysis of value in the elderly with malnutrition and impaired functionality? Nutrition. 2007;23:564–9.

12. Fassini PG, Nicoletti CF, Pfrimer K, Nonino CB, Marchini JS, Ferriolli E. Bioelectrical impedance vector analysis as a useful predictor of nutritional status in patients with short bowel syndrome. Clin Nutr. 2017;36:1117–21.

13. Van Den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: An american college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum. 2013;65:2737–47.

14. Carwile LeRoy E, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): Classification, subsets and pathogenesis. J Rheumatol. 1988;15:202–5.

15. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol. 2000;27:155–60.

16. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017;2:11-18.

17. Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Reliability and validity of UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) Instrument. Arthritis Rheumatol. 2009;61:1257–63.

18. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr. 1985;41:810-7.

19. Buffa R, Saragat B, Cabras S, Rinaldi AC, Marini E. Accuracy of specific BIVA for the assessment of body composition in the United States population. PLoS One. 2013;8:e58533 (E-pub ahead of print).

20. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis - Part II: Utilization in clinical practice. Clin Nutr. 2004;23:1430–53.

21. 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;68:1234-40.

22. Redondo-del-Río MP, Camina-Martín MA, Moya-Gago L, de-la-Cruz-Marcos S, Malafarina V, de-Mateo-Silleras B. Vector bioimpedance detects situations of malnutrition not identified by the indicators commonly used in geriatric nutritional assessment: A pilot study. Exp Gerontol. 2016;85:108–11.

23 Marini E, Buffa R, Saragat B, Coin A, Toffanello ED, Berton L, et al. The potential of classic and specific bioelectrical impedance vector analysis for the assessment of sarcopenia and sarcopenic obesity. Clin Interv Aging. 2012;7:585–91.

24. Konijn NPC, Van Tuyl LHD, Bultink IEM, Lems WF, Earthman CP, Van Bokhorst-De Van Der Schueren MAE. Making the invisible visible: Bioelectrical impedance analysis demonstrates

unfavourable body composition in rheumatoid arthritis patients in clinical practice. Scand J Rheumatol. 2014;43:273–8.

25. Santillán-Díaz C, Ramírez-Sánchez N, Espinosa-Morales R, Orea-Tejeda A, Llorente L, Rodríguez-Guevara G, et al. Prevalence of rheumatoid cachexia assessed by bioelectrical impedance vector analysis and its relation with physical function. Clin Rheumatol. 2018;37:607–14.

26. Wojteczek A, Dardzińska JA, Małgorzewicz S, Gruszecka A, Zdrojewski Z. Prevalence of malnutrition in systemic sclerosis patients assessed by different diagnostic tools. Clin Rheumatol. 2020;39:227–32.

27. Siegert E, March C, Otten L, Makowka A, Preis E, Buttgereit F, et al. Prevalence of sarcopenia in systemic sclerosis: Assessing body composition and functional disability in patients with systemic sclerosis. Nutrition. 2018;55:51–5.

28. Baron M, Hudson M, Steele R, Pope J, Markland J, Robinson D, et al. Malnutrition is common in systemic sclerosis: Results from the Canadian Scleroderma Research Group database. J Rheumatol. 2009;36:2737–43.

29. Slee A, Birch D, Stokoe D. Bioelectrical impedance vector analysis, phase-angle assessment and relationship with malnutrition risk in a cohort of frail older hospital patients in the United Kingdom. Nutrition. 2015;31:132–7.

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

Female	46 (92%)
Mean age ±SD years	61.1 ±12.5
Mean disease duration ±SD years	13 ±10
- ssSSc	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 symptomatology	
Microstomia	16 (32%)
Xerostomia	23 (46%)
Dysphagia	28 (56%)

Reflux	45 (90%)
Oesophageal dilatation	42 (84%)
Oesophagitis	21 (42%)
Early satiety / abdominal distension	16 (32%)
Constipation	17 (34%)
Diarrhoea	13 (26%)
Faecal incontinence	8 (16%)
Laboratory parameters	
Anaemia	15 (30%)
Hypoalbuminemia	9 (18%)
Hypoproteinemia	3 (6%)
Hypocreatininemia	4 (8%)
Hypercholesterolemia	5 (10%)
Specific organ involvement	
DUs ongoing	14 (28%)
DUs history	34 (68%)
ILD	26 (52%)
PAH	7 (14%)
Heart involvement	6 (12%)
Muscle involvement	3 (6%)

Joint involvement	10 (20%)

ssSSc: sine scleroderma; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ANA: antinuclear antibodies; ACA: anti-centromere antibodies; Scl70: anti-topoisomerase I antibodies; DU: digital ulcer; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

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

Median (IQR)	**SSc** (n=50)	**OCAD** (n=27)	**OS** (n=15)	**HC** (n=50)
BMI (kg/m^2)	23.5 (9.2)	18.8 (9.1)	17.8 (4.3)**	25.2 (7.3)
PhA (°)	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)**

Significative comparisons were signalled with asterisks (*p<0.05; **p<0.01).

OCAD: other chronic autoimmune diseases; OS: only symptomatic; HC: healthy controls; BMI: body mass index; PhA: phase angle; BMR: basal metabolic rate; BCM: body cellular mass; FFM: fat-free mass; FM: fat mass; TBW: total body water; ECW: extracellular water; ECM/BCM: extracellular mass/BCM.

Table 3. Significant associations for clinical and laboratory features.

Median (IQR)		**BMI** (kg/m^2)	**PhA** (°)	**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**		
Anaemia	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**		
DUs 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**		
DUs 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.

BMI: body mass index; PhA: phase angle; BMR: basal metabolic rate; BCM: body cellular mass; FFM: fat-free mass; FM: fat mass; TBW: total body water; ECW: extracellular water; ECM/BCM: extracellular mass/BCM; DU: digital ulcer; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

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

Median (IQR)	**Dead** (n=4)	**Alive** (n=46)	p
PhA (°)	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

PhA: phase angle; BMR: basal metabolic rate; BCM: body cellular mass; ECW: extracellular water; TBW: total body water.