

# Frailty Index to Measure Health Status in People with Systemic Sclerosis

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**ABSTRACT. Objective.** To develop and validate, as a measure of overall health status, a Frailty Index (FI) for patients (n = 1372) in the Canadian Scleroderma Research Group (CSRG) Registry.

**Methods.** Forty-four items were selected from the CSRG database as health deficits and recoded using FI criteria. To test construct validity, we compared measurement properties of the CSRG-FI to other FI, and related it to measures of damage, age, and time since diagnosis. To test criterion validity, we compared the baseline FI to that at last recorded visit and to mortality.

**Results.** The mean CSRG-FI was 0.33 with a sub-maximal limit of 0.67. In patients with diffuse disease, the mean was 0.38(SD 0.14); in patients with limited disease, the mean was 0.31(SD 0.13). The CSRG-FI was weakly (but significantly) correlated with the Rodnan Skin Score (r = 0.28 in people with diffuse disease; 0.18 with limited) and moderately with the Physician Assessment of Damage (r = 0.51 for both limited and diffuse). The risk of death increased with higher FI scores and with higher physician ratings of damage. The area under the receiver operating characteristic curve for the baseline FI in relation to death was 0.75, higher than for other measures (range: 0.57–0.67).

**Conclusion.** The FI quantifies overall health status in people with scleroderma and predicts mortality. Whether the FI might help with decisions about who might best be served by more aggressive treatment, such as bone marrow transplantation, needs to be evaluated. (J Rheumatol First Release March 1 2014; doi:10.3899/jrheum.130182)

Key indexing terms:

SCLERODERMA                      FRAILTY                      FRAILTY INDEX                      SYSTEMIC SCLEROSIS

As the population ages, so too does the prevalence of scleroderma<sup>1</sup>. This is both because autoimmune disorders become more common with age, and because advances in treatment mean that more people with scleroderma are living longer. Ageing itself reflects the accumulation of subcellular deficits, which arise in a diverse set of interactions between stochastic, damage-driven mechanisms and genetically specified pathways that influence longevity; such deficits commonly scale up to become manifest clinically (or detectable by laboratory methods)<sup>2</sup>. Although people with scleroderma might be expected to accumulate

more deficits than do others of the same age, not everyone at the same age with scleroderma has the same level of need. This partly reflects disease activity and degree of damage, and partly reflects the variable health status of people of the same age. This increased vulnerability to adverse outcomes of people of the same age is a wider phenomenon, broadly known as frailty<sup>3</sup>.

The need to identify people at greatest risk means that frailty is a topic of growing interest across a wide range of medical literature<sup>4,5</sup>. Even so, its precise operational definition has yet to be settled. Two approaches are recog-

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*For a list of CSRG members see Appendix 1.*

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nized<sup>6</sup>. One views frailty as a specific syndrome typically associated with wasting, and consisting in weight loss, impaired strength, reduced activities, slow gait speed, and exhaustion<sup>7</sup>. Another sees frailty as arising in relation to the accumulation of a wide variety of health deficits: people with few deficits are relatively fit; those with many things wrong are frail. Inasmuch as deficits can accumulate across the adult lifespan, frailty in this light is seen as a problem not just of the aged, but of the ageing process itself<sup>8</sup>.

Systemic sclerosis (SSc) is an example of an illness that affects many organ systems, with problems that can accumulate across the adult lifespan in some people, and much more rapidly in others<sup>9,10,11,12,13,14,15</sup>. Many people live decades with SSc<sup>14</sup>, but mortality risk is high<sup>15</sup>; our central hypothesis is that such variable health trajectories can be seen as another face of variable vulnerability in relation to deficit accumulation. If so, evaluating frailty as deficit accumulation might assist in understanding the variable health status of adults with SSc, so we evaluated the properties of a frailty index (FI) in the Canadian Scleroderma Research Group (CSRG) database. Our goals were to: (1) assess the feasibility of employing a standard procedure to calculate an FI from the CSRG database, and (2) assess the validity of the CSRG-FI.

## MATERIALS AND METHODS

*Design and setting.* This is a secondary analysis of longitudinal data collected by the CSRG, a national research collaboration based in Montréal, Québec. Patients in the CSRG Registry are recruited from 15 centers across Canada and must have a diagnosis of either limited or diffuse scleroderma as determined by the recruiting rheumatologist, be > 18 years of age at the time of recruitment and fluent in either English or French. Patients are seen yearly. The baseline visit was between 2004 and 2012. Details of the registry have been published elsewhere<sup>12,13,14,16,17</sup>. As of June 26, 2012, the dataset consisted of 1372 patients.

*Assessing the feasibility of constructing an FI in the CSRG database.* An FI can be developed according to a standard procedure for selecting items and calculating the resulting scores<sup>18</sup>. The procedure for this is as follows: first, potential health deficits are identified. Here, the CSRG database contained 211 items available from a self-report questionnaire and a clinical evaluation. Items were selected if they met standard criteria to be a health deficit. A single health deficit can be any symptom, sign, functional impairment, or laboratory abnormality that meets the criteria of being: associated with age; associated with an adverse outcome, present in at least 1%, but not more than 80% of the sample; and present in 95% of participants (i.e., containing < 5% missing data)<sup>18,19</sup>. Next, any set of health deficits included in an FI must cover several organ systems. In addition, it is worth noting that even though an FI can include comorbidities, it must also contain more items than only comorbid illnesses, and so, for example, typically includes information about function and mobility<sup>18,19</sup>. Finally, the individual health deficits are combined to produce an FI score. For individual patients, their FI score is the proportion, between 0 and 1, of the number of health deficits present in them in relation to the number of health deficits considered. Here, for example, with 44 items from the CSRG qualifying as health deficits, a person in whom 22 were recorded as present would have an FI of  $22/44 = 0.50$ . The FI developed from the CSRG database (the CSRG-FI; Appendix 2) was created from disease specific variables, as well as more general health measures from function, mood, fatigue, and sleep scales. The CSRG database contains the PHQ-9 depression scale<sup>20</sup>, the FACIT fatigue

scale<sup>21</sup>, and the 8-item version of the PROMIS sleep scale<sup>22</sup>. We added laboratory and measurement data on target organ damage (Appendix 2). Each health deficit was calculated using established cut points, assigned a score between 0 and 1. In most cases, variables were binary, with a score of 0 representing no deficit, and 1 representing the deficit fully expressed. For trichotomous variables, a score of 0.5 was assigned to midpoint values.

*Validation strategy.* We followed a tripartite approach to validation, considering each of content, construct, and criterion validity<sup>23</sup>. Content validity is inherent in the use of items from known scleroderma scales. Their selection and combination followed a well established procedure<sup>18</sup>, satisfying the requirement that items included in a measure make sense on their face. To test construct validity, we first compared the properties of the CSRG-FI with those known to obtain in other FI. For example, we were interested in knowing the relationship with age. Note that in population-based studies from developed countries, the slope of the relationship to age is about 3% per year on a log scale; by contrast, in clinical and institutional samples, this is attenuated, usually to about 1% per year<sup>24</sup>. Further, a consistent feature of the FI approach is the presence of a submaximal limit: 99% of people have an FI value < 0.7<sup>25</sup>. For comparison with other measures used in scleroderma studies, we correlated the CSRG-FI with the Rodnan Skin Score<sup>26</sup> and the Physician Global Assessment of Damage<sup>27,28</sup> (“On a 10-point scale, where 0 = no damage and 10 = most damage, how much damage do you think that the patient has from his/her scleroderma?”). We used linear regression to evaluate the relationship between the CSRG and age and time since diagnosis. Recognizing that, on average, people with diffuse scleroderma should have more deficits than those with limited scleroderma, we also compared CSRG-FI scores by scleroderma type. To evaluate the statistical significance of differences arising in relation to our objectives, differences in proportions were tested using chi-square, and in means using t test or 2-way ANOVA. The most rigorous form of validation is criterion validity. There are 2 accepted types of criterion validity: comparison with a reference standard and predictive validity<sup>23</sup>. The lacking of a reference standard (often also known as a “gold standard”) was one of the factors that motivated the creation of the CSRG Registry<sup>12</sup>. To evaluate the predictive validity of the CSRG-FI, we focused on predicting 2 outcomes, using the baseline CSRG-FI values: future health status, and mortality risk. Predicting future health status was done by evaluating the association between the baseline CSRG-FI and the final recorded visit CSRG-FI. To evaluate mortality prediction, we calculated the areas under the Receiver Operating Characteristic (ROC) curves for the baseline CSRG-FI and compared these with the Physician Global Assessment and Rodnan Skin Severity Scores. Likewise, to look at change in the mortality hazard rates associated with increments in the various test scores we first tested the assumption of proportionality with a log-minus-log-plus plot and then used Cox proportional hazards model. In these analyses, for each measure, and for covariates, we used baseline visit data.

*Data analysis.* Data were analyzed using MATLAB R2010b, version 7.11, and PASW Statistics, version 18.0. Ethics data collection under the CSRG was approved at McGill University (Montreal, Quebec) and at all participating sites. All patients provided written, informed consent. Permission for these secondary analyses was granted by the Research Ethics Committee of the Capital District Health Authority.

## RESULTS

*Cohort at baseline and feasibility of constructing the FI.* Most study participants in each of the limited and diffuse scleroderma types were white women. Except for blood pressure, patients with diffuse disease tended to have worse health measures at baseline than did patients with limited cutaneous disease (Table 1). Of the 211 potential health deficits, most (N = 167) were excluded due to missing data. Of the remaining 44 items with < 5% missing data, each met

Table 1. Clinical and demographic characteristics of patients at the time of their baseline visit, by scleroderma type.

Characteristic	Limited	Diffuse
CSRG-FI, mean (SD)	0.31 (0.13)	0.38 (0.14)
Age, yrs, mean (SD)	58.5 (11.5)	54.6 (12.1)
Female, %	91.0	81.0
Physician assessed damage, mean (SD)	2.9 (2.1)	4.3 (2.2)
Rodnan Skin Score, mean (SD)	5.8 (5.2)	18.1 (10.5)
Hospitalized past year, %	12.2	13.3
Pulmonary hypertension, %	14.5	18.1
Diffusing capacity, mean (SD)	70.8 (20.1)	67.4 (21.7)
Creatinine, mean (SD)	79.7 (52.9)	82.9 (69.5)
Tender joint count, mean (SD)	2.6 (6.4)	3.5 (7.7)
Swollen joint count, mean (SD)	1.1 (3.9)	1.3 (4.7)
Blood pressure, mean (SD)	125/73 (19/10)	123/72 (20/11)
Scleroderma renal crisis, %	2.1	7.2
Ethnic background, %		
White	85.3	79.5
Black	0.6	2.0
Aboriginal	4.1	7.6
Asian	1.1	2.6
Other	12.0	15.5

CSRG-FI: Canadian Scleroderma Research Group-Frailty Index.

all criteria for being a health deficit. As a group, they covered several organ systems. As detailed in Appendix 2, they included items on comorbidity, impairments, health attitude, affect, and function. The mean CSRG-FI for the group was 0.33 (SD 0.14). A baseline CSRG-FI could be calculated for 1260 of 1372 participants. Of the total, 293 dropped out or were lost to followup before study end. Compared to those on whom data are complete [mean age 55.9 years (12.0); 86.5% women; CSRG-FI = 0.33 (0.13)], people who dropped out were older [mean 59.5 years (13.4)], more often women (92.1%), and less frail [mean FI-CSRG 0.29 (0.13)].

**Validation of the CSRG-FI.** In the construct validity analysis, as expected, older people had higher CSRG-FI values than did younger people, and those that had been admitted to the hospital in the last year had higher CSRG-FI than those who had not. On average, older people had more health deficits than younger people, so that the mean value of the CSRG-FI increased with age. Even so, reflecting that some young people with scleroderma can be very ill, this relationship was nonlinear, and the fit of the data was not improved by log transformation. Overall, the 99% limit was approximately 0.67, but the maximum recorded value was higher in diffuse (CSRG-FI = 0.70) than in limited scleroderma (CSRG-FI = 0.62). Similarly, patients with diffuse cutaneous disease had a higher mean CSRG-FI than did patients with limited scleroderma, even though they were 4 years younger on average (Table 1). The FI was slightly, but not significantly, higher in people with tender joints (0.37; SD 0.13) than in those without tender joints (0.31; SD 0.14).

Similar results were seen in relation to swollen joints (0.37; SD 0.14 vs 0.32 vs 0.14); note that neither of these were items in the CSRG-FI. The correlation between the Rodnan Skin Score and the CSRG-FI was 0.28 in people with diffuse scleroderma and 0.18 in those with limited disease. The correlation between the physician assessed damage score and the CSRG-FI was the same (0.51) in people with diffuse and in those with limited scleroderma. For criterion validation, the risk of death increased with increasing values of the baseline CSRG-FI scores and with the physician assessed damage scores (Figure 1). In the ROC curve analyses (using baseline visit data), the area under the curve (AUC) for the FI was 0.75 in those with diffuse disease. By contrast, the AUC for the physician assessed damage score was 0.67. The AUC for limited disease were not significantly different: 0.70 versus 0.71, respectively. Each was significantly higher than the Rodnan Skin Score (e.g., AUC = 0.57 for diffuse) and age (AUC = 0.56). In the proportional hazards analysis, controlled for age and sex, each of the CSRG-FI (HR = 1.68, 1.50–1.87,  $p < 0.001$ ), the physician assessed damage (HR = 1.35, 1.27–1.43,  $p < 0.001$ ), and the skin score (HR = 1.03, 1.02–1.05,  $p < 0.001$ ) predicted mortality when considered individually, but when combined, only the FI and physician assessed damage (and age) remained significant (Table 2). In relation to the final recorded visit scores, the mean CSRG-FI of the people with diffuse disease who died was 0.50 (SD 0.13), compared with 0.34 (SD 0.13) in those with diffuse disease who lived ( $p < 0.01$ ). Likewise, in people with limited disease, the mean CSRG-FI score was 0.41 (SD 0.13) in those who died versus 0.29 (SD 0.12) in those who survived ( $p < 0.01$ ). Physician assessed damage scores for people with diffuse disease who died were 6.4 (SD 2.3), compared with 4.4 (SD 2.1) in those with diffuse disease who lived ( $p < 0.01$ ). Similarly, in people with limited disease, the physician assessed damage score in decedents was 5.2 (SD 2.7) compared with 2.9 (SD 1.9) in survivors ( $p = 0.02$ ).

## DISCUSSION

Using data from the multicenter Canadian Scleroderma Research Group database, we were able to create an FI for people with scleroderma. The resulting CSRG-FI showed good construct and criterion validity. The CSRG-FI was correlated with physician assessments of disease severity, but was more highly associated with the risk of death. The mean CSRG-FI scores were also higher in patients with diffuse scleroderma than in patients with limited scleroderma. Most important, regardless of age, disease type, or time since diagnosis, the risk of death was higher with higher FI scores.

Our data must be interpreted with caution. With 1372 participants, the numbers become small for some clinically useful levels of disaggregation. Even so, this is the largest database for individuals with scleroderma in Canada, and an

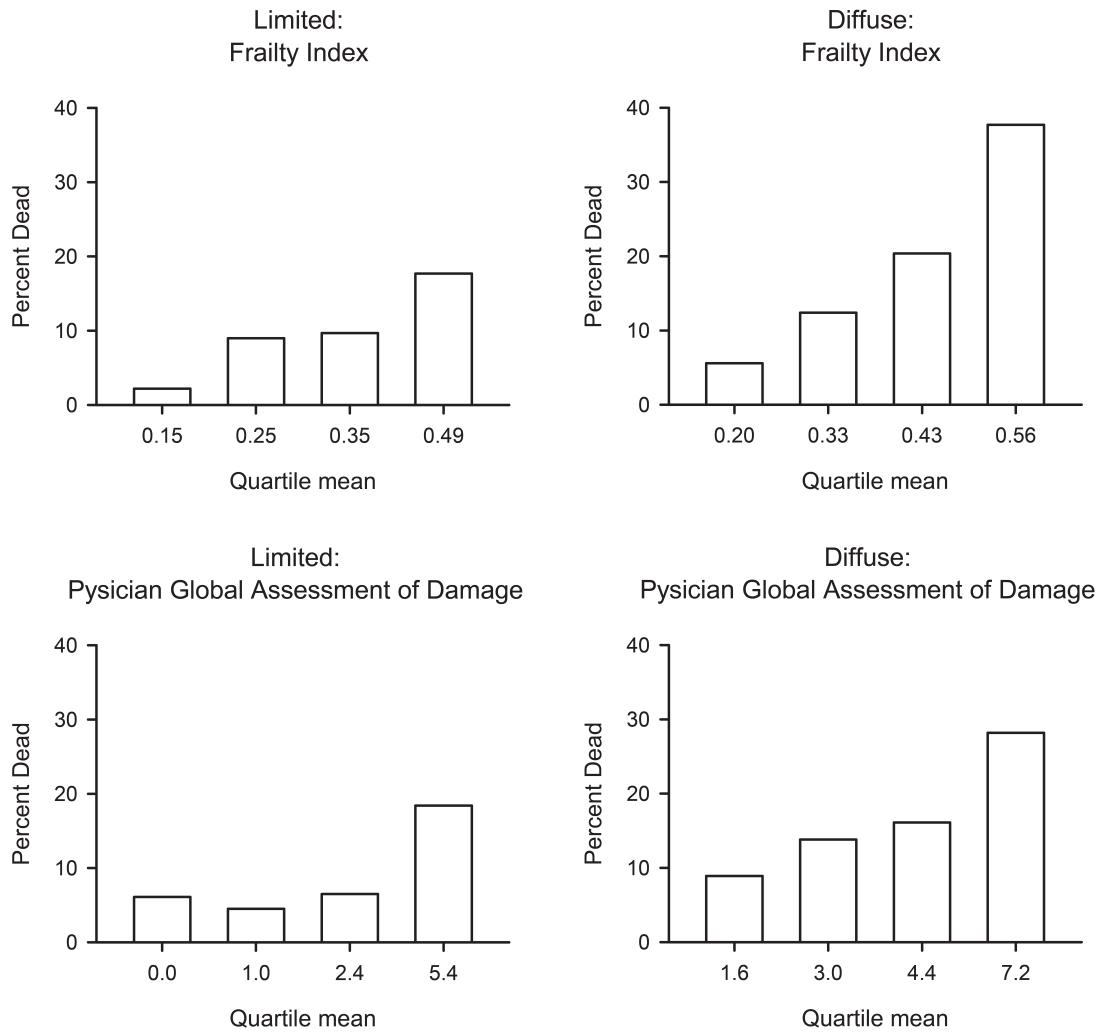


Figure 1. Risk of death increased with worsening disease as measured by the frailty index and physician global assessment of damage.

Table 2. Cox proportional Hazards model for patients at the time of their baseline visit.

Measure	Beta Coefficient	Standard Error	Hazard Ratio	95% CI
Age	0.04	0.01	1.04	1.03–1.06
CSRG-Frailty Index Score	0.32	0.07	1.38	1.21–1.58
Physician Assessed Damage Score	0.19	0.04	1.21	1.12–1.31

CSRG: Canadian Scleroderma Research Group.

ongoing national effort that enrolls about 175 patients annually and contributes information about a range of important topics<sup>12,13,16,17</sup>. Similarly, as a sample of people referred to subspecialty clinics, the database is not representative of the population, but this too is a necessary condition, given that the low prevalence of scleroderma (4 to 489 cases per million individuals)<sup>1,9</sup> makes representative studies

impractical. Similarly, although longitudinal, this study incorporates people enrolled at varying points in their disease course, resulting in considerable variability in baseline health status. Modeling longitudinal effects in such a circumstance is a particular challenge, especially when exposures have a nonlinear distribution and nonlinear impact on outcomes<sup>1</sup>. With the data to hand, we used a

typical compromise of considering only baseline scores in the ROC and proportional hazards analysis; initial longitudinal analysis showed that the rate at which the FI might change may be important, but this will require a larger dataset and nonlinear models for further evaluation. Patients were only seen once a year, which is a limitation for individuals with accelerated disease, although for most of the study participants this was not an issue. The mortality rate was low (12%) making estimates associated with death more challenging. In this regard a common and troubling clinical problem is how to identify people with diffuse scleroderma who are at a high risk of death (such that early aggressive immunotherapy or experimental therapies might be considered). Here, of 142 people diagnosed with diffuse systemic sclerosis and an estimated disease duration less than 3 years, 25 (17%) died. Considering their baseline CSRG-FI scores, only modest differences between the 2 groups were observed: people who died within 3 years had a mean CSRG-FI equal to 0.44 (SD 0.13) compared with those who survived, in whom the mean score equalled 0.36 (SD 0.13). This might reflect that not all disease activity conveys equal risk. Considering trajectories, the mean CSRG-FI in those who died (last visit mean = 0.47; SD 0.13) was higher than at baseline, whereas in those who survived it was in fact slightly lower than their baseline score (next visit CSRG-FI score = 0.35; SD 0.14).

A proinflammatory state is often seen in many patients with frailty, especially increased IL-6<sup>29,30</sup>, which has also been implicated in systemic sclerosis<sup>31,32</sup>. Although an FI has been used to evaluate frailty in immunosenescence<sup>29</sup> and vaccination<sup>33</sup> studies, this is the first study to develop an FI for scleroderma patients. The correlation of the CSRG-FI with the 17-item modified Rodnan Skin Score is consistent with other reports of higher skin scores being associated with poor prognosis<sup>34,35,36</sup>. Our study showed that although the modified Rodnan Skin Score predicted mortality in an age and sex adjusted model, the CSRG-FI is a better predictor. Other studies have shown that decreasing skin scores are associated with a lower risk of death<sup>35</sup>. The low correlation between the modified Rodnan Skin Score and CSRG-FI is most likely related to mechanisms of disease: those who survive will eventually see skin involvement decrease. Patients with limited disease generally show late skin thickening, which stays constant at a relatively low modified Rodnan Skin Score. Patients with diffuse scleroderma who survive their first 10 years with the disease will most likely die with their disease, not from it<sup>37</sup>. Other scales have been created to measure scleroderma severity, although as noted none has yet enjoyed widespread clinical use<sup>1,12</sup>. The CSRG-FI covers 9 organ systems, as well as mood and fatigue. As a more holistic measure of health, and not just a measure of disease severity, the CSRG-FI may aid in characterizing older scleroderma samples, as older adults in particular have other grounds on which to accumulate

important health deficits. In this regard, it is worth considering that any FI works because it allows for the impact of small cumulative effects, which on their own might not meet a threshold for being statistically significant, but which might still provide information of value<sup>38</sup>. Our data also contribute to a broader understanding of frailty and its impact on healthcare. Although most studies have focused on older adults, it is clear that frailty can be detected across the lifespan<sup>39</sup>. Here, as in another recent study<sup>40</sup>, we expand that understanding to demonstrate its use in a disease that affects not just older adults, even though we note that older adults are a growing constituency of rheumatology clinics<sup>41</sup>. Even so, whereas the other measures were scored at the patient interview, the FI-CSRG is presented here for the first time. Its clinical utility will require prospective evaluation in a setting in which the scores could be made available to treating physicians at the time that they were seeing patients. We found that the FI was higher (0.33) than would be expected in a general population, where the median value is 0.03<sup>39</sup>. Even so, the 99% maximum limit value (0.67) did not exceed the 99% limit reported in a large number of other settings<sup>24,38,42,43,44</sup>. This is an important finding worth confirming in a clinical cohort, i.e., that there appears to be a biological limit to the number of health deficits that an individual can accumulate. The outcomes of people close to the limit will be of particular interest as the cohort expands, and as longer followup periods are recorded.

That small effects can aggregate to produce large ones is well established in domains such as information theory and signal processing. It has been adapted in a variety of healthcare settings<sup>19,40,42,43,44,45</sup>. In evaluating cumulative small effects, the FI can offer important insights. For example, an FI made up only of items not known to be associated with dementia proved to be a powerful risk factor for dementia, even trumping known traditional risk factors<sup>46</sup>. This has led to the suggestion that the epidemiology of late life cognitive disorders might need to be reevaluated<sup>47</sup>. Just as diseases present differently in people who have many illnesses, so too might risk factors operate in ways that need reconsideration (a point that might have special relevance in multisystem diseases like scleroderma, especially as survival improves). For now, using an FI appears justified by integrating useful, available information that is otherwise gathered in severity scoring systems. Whether that proposition holds more generally, or extends to a reevaluation of risk factors, will require additional cross-validation, both in the growing CSRG database, and by other groups. If it holds, then it would be possible to consider whether an FI might help with decisions about who might best be served by more aggressive treatment, such as bone marrow transplantation.

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#### APPENDIX 1.

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#### APPENDIX 2. Canadian Scleroderma Research Group Frailty Index to measure health status in patients with systemic sclerosis.

Label	Scores	Notes
Vascular	No = 0 Yes = 1	History of peripheral vascular disease
Joint	No = 0 Yes = 1	Joint involvement
Gastrointestinal	No = 0 Yes = 1	Gastrointestinal involvement
Cardiorespiratory	None = 0 Any = 1	Asthma, COPD, heart failure
Renal	None = 0 Any = 1	Medications for blood pressure, kidney function, need for dialysis, and kidney transplantation
Neurological	None = 0 Any = 1	History of entrapment neuropathies or any other peripheral neuropathies
Other vascular	None = 0 Any = 1	Coronary artery disease
Other	None = 0 Any = 1	Alzheimer's disease (or another form of dementia); cirrhosis, or serious liver damage; leukemia or polycythemia vera; lymphoma; skin cancer; cancer (other than skin cancer, leukemia or lymphoma); AIDS
Hospital visit	None = 0 Any = 1	Stay overnight in hospital due to scleroderma; either for rehabilitation or acute care
Malignancies	None = 0 Any = 1	Solid tumors
Body mass index	18.5–25 = 0 <18.5 = 1 >25 = 1	
Blood pressure	≤ 140/90 = 0 >140/90 = 1	
Oral	No = 0 Yes = 1	Apthous ulcers, xerostomia
Respiratory	No = 0 Yes = 1	Difficulties breathing
Telangiectasia	No = 0 Yes = 1	Presence of telangiectasia
Upper body	No = 0 Yes = 1	Upper body calcinosis
Neurological examination	No = 0 Yes = 1	Abnormal findings upon physical examination
Raynaud	No = 0 Yes = 1	History of Raynaud's phenomenon in the past month
Global assessment	0–4 = 0 5–10 = 1	Physician global assessment of activity and change in status
Depression	I = 0 A = 0.5 D = 1	Validated measure used in physician assessment
Dressing	I = 0 A = 0.5 D = 1	

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APPENDIX 2. Continued

Label	Scores	Notes
Arising	I = 0 A = 0.5 D = 1	
Eating	I = 0 A = 0.5 D = 1	Cut meat, lift a glass, open milk
Walking	I = 0 A = 0.5 D = 1	
Aids 1	None = 0 Any = 1	Walking aids
Hygiene	I = 0 A = 0.5 D = 1	
Reach	I = 0 A = 0.5 D = 1	
Grip	I = 0 A = 0.5 D = 1	Open doors, jars, taps
General activities	I = 0 A = 0.5 D = 1	Shopping, chores
Aids 2	None = 0 Any = 1	Reaching aids, sitting aids
Self-rated health	Excellent/very good/good = 0 fair = 0.5 poor = 1	As measured by questionnaire in patient survey
Vigorous activities	I = 0 A = 0.5 D = 1	Running, lifting, strenuous sports
Moderate activities	I = 0 A = 0.5 D = 1	Moving furniture, vacuuming, bowling
Lifting groceries	I = 0 A = 0.5 D = 1	
Stair use	I = 0 A = 0.5 D = 1	1 flight
Kneeling	I = 0 A = 0.5 D = 1	
Walking 100 meters	I = 0 A = 0.5 D = 1	
Hospitalization	<50 = 0 >50 = 1	Number of times the patient has been to the hospital in the last year
Fatigue	>30 = 0 ≤ 30 = 1	Self-assessment of fatigue
Sleep	≥ 40 = 0 < 40 = 1	Self-assessment of sleep quality
Serum creatinine	≤ 110 = 0 >110 = 1	
Diffusing capacity	≥ 60% = 0 < 60% = 1	
Pulmonary hypertension	No = 0 Yes = 1	Pulmonary artery systolic pressure ≥ 36 mmHg by right heart catheterization or by ECHO
History of scleroderma renal crisis	No = 0 Yes = 1	

I: independent; A: needs assistance/minimal difficulty; D: dependent on help from others; COPD: chronic obstructive pulmonary disease; AIDS: acquired immunodeficiency syndrome; ECHO: echocardiography.