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Construction of a frailty index as a novel health measure in systemic lupus erythematosus

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Abstract

Objective. To construct a frailty index (FI) as a measure of vulnerability to adverse outcomes among patients with SLE, using data from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort.

Methods. The SLICC inception cohort consists of recently diagnosed SLE patients followed annually with clinical and laboratory assessments. For this analysis, the baseline visit was defined as the first study visit at which sufficient information was available for construction of a frailty index. Following a standard procedure, variables from the SLICC database were evaluated as potential health deficits. Selected health deficits were then used to generate a SLICC frailty index (SLICC-FI). The prevalence of frailty in the baseline dataset was evaluated using established cut points for FI values.

Results. The 1683 SLE patients (92.1% of the overall cohort) eligible for inclusion in the baseline dataset were mostly female (89%) with mean (SD) age 35.7 (13.4) years and mean (SD) disease duration 18.8 (15.7) months at baseline. Of 222 variables, 48 met criteria for inclusion in the SLICC-FI. Mean (SD) SLICC-FI was 0.17 (0.08) with a range from 0 to 0.51. At baseline, 27.1% (95% CI 25.0%-29.2%) of patients were classified as frail, based on SLICC-FI values greater than 0.21.

Conclusion. The SLICC inception cohort permits feasible construction of an FI for use in patients with SLE. Even in a relatively young cohort of SLE patients, frailty was common. The SLICC-FI may be a useful tool for identifying SLE patients who are most vulnerable to adverse outcomes but validation of this index is required prior to its use.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with diverse manifestations and an unpredictable clinical course(1). Despite advances in diagnosis and treatment(2), many SLE patients accumulate organ damage(3) and the mortality risk remains high(4,5). Given this variability in health trajectories, it would be advantageous to identify those SLE patients at increased risk for adverse outcomes. However, instruments that accurately predict long-term outcomes in SLE are limited(6).

In geriatric medicine(7), and increasingly in other disciplines(8-13), differences in susceptibility to adverse outcomes are quantified using the construct of frailty, defined as a state of increased vulnerability due to degradation of homeostatic mechanisms, resulting in diminished ability to respond to physiologic stressors(14). Although often linked to advanced age, frailty can be observed across the life course(15), including among individuals with acquired vulnerability states(16,17).

Two different conceptual approaches inform the measurement of frailty(18). One approach uses rules-based tools, where specific criteria must be met to classify an individual as frail(18). The most common example of this approach is the Fried frailty phenotype, which defines frailty as a clinical syndrome with at least three of five specific health deficits: weight loss, exhaustion, physical inactivity, slow walking speed, and reduced grip strength(19).

The second approach to measuring frailty is the frailty index (FI)(20), which conceptualizes frailty as a loss of physiologic reserve arising from the accumulation of health deficits across

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multiple systems(21). Individuals who possess few deficits are considered relatively fit, while those with an increasing number of health problems are considered increasingly frail(18). Prior studies have consistently shown an association between higher FI values and increased risk of negative health outcomes, including hospitalizations, morbidity, and mortality(15,22-24). Although utilized in many different clinical contexts(22,23,25), the deficit accumulation approach has yet to be applied in SLE.

Health deficits in SLE may occur due to the disease, its treatment, other comorbidities, or ageing. Evaluating frailty through deficit accumulation could improve our understanding of the heterogeneous health outcomes in SLE. The aim of the present study was to employ the deficit accumulation approach to construct an FI as a novel health measure in SLE, using data from an international inception cohort. Future studies are required to validate the SLICC-FI, including its predictive validity for adverse health outcomes.

Materials and Methods

Data source. This was a secondary analysis of longitudinal data from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort. SLICC comprises 52 investigators at 43 academic centres in 16 countries. From 1999 to 2011, a cohort of 1826 recently-diagnosed SLE patients was recruited from 31 SLICC sites in Europe, Asia, and North America. Patients were enrolled within 15 months of SLE diagnosis, based on ≥4 revised American College of Rheumatology (ACR) classification criteria for SLE(26). At enrolment and annually thereafter, data were collected per a standardized protocol, submitted to the coordinating centres at the University of Toronto (Toronto, Ontario, Canada) and Dalhousie University (Halifax, Nova

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Scotia, Canada), and entered into centralized databases. The study was approved by the Institutional Research Ethics Boards of the Nova Scotia Health Authority central zone (# 1020396) and of participating centres in accordance with the Declaration of Helsinki's guidelines for research in humans. All participants provided written informed consent.

Clinical assessments. Demographic features included age, sex, race/ethnicity, geographic location, and years of post-secondary education. Corticosteroid, antimalarial, and immunosuppressive use was documented. Medical comorbidities prior to SLE diagnosis and between follow-up visits were recorded. The revised ACR classification criteria for SLE(26) and neuropsychiatric events(27) were documented at enrolment and between follow-up visits(28). SLE disease activity was measured using the SLE Disease Activity Index 2000 (SLEDAI-2K)(29), cumulative organ damage using the SLICC/ACR Damage Index (SDI)(30), and health-related quality of life using the Medical Outcomes Survey Short-Form 36 (SF-36)(31). Blood pressure (in mmHg), height (in metres), and weight (in kilograms) were also recorded.

Laboratory data. Investigations for the assessment of SLE disease activity and organ damage were performed at each visit: anti-double-stranded DNA, C3 and C4, serum creatinine, urinalysis, fasting glucose, lipid profile, and inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]).

Standard procedure for FI construction. An FI can be constructed from any existing health dataset using a standard procedure described by Searle et al. **(Table 1)**(20). These methods have been shown to be valid and reliable(15,22,23,32-34). Briefly, potential health deficits are first

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identified. A health deficit is any symptom, physical sign, disease process, functional impairment, or laboratory abnormality that is acquired, associated with adverse health outcomes, and associated with chronological age(20,35). If deficits are either too infrequent or too common, they are unlikely to provide meaningful information in an FI, and are respectively combined or excluded(20,35). Finally, if a single item is missing values for >5% of individuals, it is excluded(20,35).

The totality of health deficits in an FI must represent several organ systems. Of note, frailty not only captures irreversible damage, but also measures an individual's potential for recovery. Therefore, an FI also includes measures of function and mobility(20,35). Finally, an FI requires a minimum of 30-40 health deficits to produce stable and precise estimates of frailty(22,33,35,36).

Each health deficit is assigned a score from 0 to 1, with 0 representing no deficit and 1 representing the deficit fully expressed(20). Health deficit scores are combined to produce an FI score between 0 and 1, calculated as the sum of deficit scores for an individual divided by the total number of deficits considered(20,35).

Establishing a baseline dataset for SLICC-FI construction. Given the importance of the SDI and the SF-36 for the construction of the SLICC-FI, each patient's baseline visit was defined as the first at which both an SDI and an SF-36 were completed. Patients were excluded if they had never had an SDI recorded, never had an SF-36 recorded, or never had both instruments recorded at the same visit.

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Selecting health deficits for the SLICC-FI. Potential health deficits were evaluated using the criteria in **Table 1**. Variables judged to be innate, as opposed to acquired, were excluded. Age-relatedness was assessed by reviewing the literature to determine whether each variable is observed more frequently with increasing age in SLE populations. While a health deficit should generally increase in prevalence with increasing age, this relationship may not exist for all deficits, in part due to survivor effects(20). Variables were retained in the SLICC-FI even if there was attenuation of this relationship at advanced ages.

The association of each health deficit with increased risk of adverse health outcomes in SLE was also determined through literature review. Variables not clearly associated with adverse outcomes were excluded. If literature specific to SLE was not available, evidence from the general population was sought and extrapolated to SLE populations.

Next, variables were evaluated for duplications. Items were excluded from the SLICC-FI if they represented constructs that were already better-accounted for by another variable in the database. Where appropriate, multiple related variables were combined to produce single health deficits. Variables whose prevalence in the dataset was <1% were excluded if there were no similar deficits with which they could be reasonably combined. Finally, variables were excluded if their prevalence in the dataset was >80%, or if there were missing values for >5% of observations.

Coding of individual health deficits for the SLICC-FI. Binary variables were assigned a score of 0 (absence of the deficit) or 1 (presence of the deficit). Ordinal variables were coded by

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converting the number of possible ranks into equally-spaced scores ranging from 0 to 1. Continuous variables were coded using established cut points from the SLE literature.

SLICC-FI calculation. Individual health deficit scores were combined to produce a SLICC-FI score for each patient. For example, with 48 health deficits in the SLICC-FI, an individual in whom 24 of these deficits were fully present would have a SLICC-FI score of 24/48=0.50. SLICC-FI scores were not calculated for individuals with missing values for >20% of health deficits(36).

Statistical analysis. Descriptive statistics were calculated for demographic and clinical characteristics. For quantitative variables, measures of central tendency (means and medians) and dispersion (standard deviations and interquartile ranges) were reported, as appropriate. For categorical variables, absolute and relative frequencies were reported. Descriptive statistics were calculated for SLICC-FI values and the distribution of SLICC-FI scores was visualized. Using cut-points derived in the general population(15,37,38), we classified patients as robust (SLICC-FI $\leq$0.03), relatively less fit (0.03< SLICC-FI $\leq$0.10), least fit (0.10< SLICC-FI $\leq$0.21), or frail (SLICC-FI >0.21) and reported the prevalence of frailty with 95% confidence intervals (CI).

To evaluate for bias due to varying SLE disease durations, analyses were repeated in patients with baseline assessments within two years of SLE diagnosis. Finally, to evaluate the impact of a given variable on the SLICC-FI, an iterative, re-sampling procedure was used(20,39). One hundred iterations were performed where each iteration calculated SLICC-FI values using 80%

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of health deficits and then re-evaluated the descriptive statistics of the SLICC-FI. Data analysis was conducted using STATA-IC Version 14 (StataCorp, TX, USA).

Results

Patient characteristics. There were 1683 patients (92.2% of cohort) with study visits at which both the SDI and SF-36 were recorded. The first such visit was included in our baseline dataset and, for most patients, this occurred early in their disease course (1390/1683 patients [82.6%] within two years of SLE diagnosis). Demographic and clinical characteristics are shown in **Table 2**.

Excluded patients. 143 patients (7.8% of cohort) were excluded, most (n=90) of whom had a single visit within six months of diagnosis, which precluded scoring the SDI. Other reasons for exclusion were: no SF-36 recorded (n=32), no SDI recorded (n=6), and no visit with both SF-36 and SDI recorded (n=15). At enrolment, excluded patients were similar to non-excluded patients in age, sex, education, SLE disease activity, and SLE manifestations (data not shown). Hispanic patients were more likely to be excluded compared to patients of other races/ethnicities, largely due to higher rates of missing SF-36 data and early loss to follow-up (data not shown).

SLICC-FI construction – selection of health deficits. Of the 222 candidate variables identified as potential health deficits **(Figure 1)**, 18 were excluded for failing to meet the first three health deficit criteria (**Table 1**) and 46 were excluded as duplicates. The remaining 158 SLICC variables were used to construct health deficits. There were 36 variables that were directly converted into 36 health deficits. In other cases, several variables representing varying aspects of

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the same condition were combined to create a single health deficit. For example, the health deficit "Coronary Artery Disease", defined as "Any history of angina, myocardial infarction, or coronary revascularization ever", used information from 12 different variables. Thus, information from the remaining 122 variables was combined to form 32 health deficits. In total, 68 distinct health deficits were generated for further evaluation. Of these, 9 were excluded due to low baseline prevalence (<1%), one due to high baseline prevalence (>80%), and 10 due to missing data in >5% of observations. Forty-eight health deficits met all required criteria for inclusion in the SLICC-FI.

SLICC-FI construction –health deficit coding. The majority of SLICC-FI health deficits were binary, with values of either 0 or 1. Examples included "Diabetes" and "Active Nephritis". Ordinal health deficits included those derived from the SF-36. For example, for "Self-Rated Health", the self-reported SF-36 responses were coded as "Excellent=0", "Very Good=0.25", "Good=0.5", "Fair=0.75", "Poor=1". For continuous variables, existing literature was used to define clinically significant cut-points. For example, the "Body Mass Index" cut-points were derived from published data regarding the association between BMI and mortality in the general population ("BMI 18.5-25.0 = 0"; BMI 25.0-30.0 = 0.5"; "BMI <18.5 or BMI >30 = 1")(40).

The SLICC-FI. Of the 48 health deficits in the SLICC-FI (**Table 3)**, 14 were related to organ damage, before or after the diagnosis of SLE (e.g. congestive heart failure and chronic kidney disease). Another 14 deficits reflected active inflammation (e.g. serositis and inflammatory arthritis), while 6 items reflected comorbid conditions (e.g. hypertension and obesity). Finally, there were 14 variables related to function, mobility, health attitude, and mental health.

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SLICC-FI values. SLICC-FI scores were calculated for 1682 patients in the baseline dataset. In one patient, a SLICC-FI score could not be calculated due to missing data for 12 (25%) health deficits. The distribution of baseline SLICC-FI scores (**Figure 2)** ranged from 0 to 0.51, with a median (I.Q.R.) of 0.16 (0.11–0.22) and a mean (S.D.) of 0.17 (0.08).

Based on SLICC-FI values >0.21, 27.1% (95% CI 25.0%-29.2%) of SLE patients were classified as frail at baseline (**Table 4**). The prevalence of frailty increased with increasing age, from 19.3% (95% CI 16.4%-22.6%) among patients <30 years of age, to 28.1% (95% CI 24.6%-31.8%) for patients aged 30-45 years, and 38.5% (95% CI 33.7%-43.5%) among patients aged 45 years or older. Very few patients (n=28; 1.7%) were classified as robust (SLICC-FI ≤0.03). These individuals were combined with the relatively less fit patients (0.03< SLICC-FI ≤0.10) into a single category ("Relatively Fit").

Compared to the relatively fittest patients, those who were classified as frail were older, less well-educated, and more likely to be current smokers (**Table 4**). There was a trend towards a higher prevalence of frailty among women (27.5%; 95% CI 25.3%-29.9%) compared to men (23.7%; 95% CI 17.8%-30.4%). There was also a trend towards shorter SLE disease duration among frail patients when compared to relatively fit patients (**Table 4**).

Sensitivity analysis. Our results were similar when only patients with baseline assessments within two years of SLE diagnosis (n=1390) were considered (data not shown). Finally, SLICC-FI scores showed little sensitivity to which health deficits were included. In 100 iterations where

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the SLICC-FI was recalculated using 80% of the 48 total deficits selected at random, the descriptive statistics and distribution of SLICC-FI scores were largely unchanged.

Discussion

In this secondary analysis of data from the SLICC inception cohort, we have demonstrated the feasibility of constructing the first FI for patients with SLE. We have described the process for constructing the SLICC-FI in detail, including the selection of health deficits, and how these deficits were operationalized to calculate SLICC-FI values. We found a high prevalence of frailty among SLE patients, the majority of whom were early in their disease course. A similar approach can be applied to investigate frailty in other SLE cohorts. However, additional studies are needed to demonstrate the validity of the SLICC-FI, including its association with the risk of future adverse health outcomes.

The process for constructing the SLICC-FI has many strengths. First, we followed a standard protocol(20) to derive health deficits and their cut points from existing instruments that are well-validated in SLE. With 48 items, the number of health deficits in the SLICC-FI is sufficient to provide stable and reliable estimates of frailty(22,33,35,36). Last, the deficits in the SLICC-FI cover multiple organ systems and embrace both fixed and reversible health domains(20).

That many small effects can aggregate to produce larger ones is well-recognized in other disciplines. Applying this principle in medicine allows for the cumulative impact of multiple small deficits, which individually might not be statistically or clinically significant(41). Some may be concerned about redundancy within the SLICC-FI, and desire a more parsimonious list

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of items. However, each item contributes additional information, regardless of the correlation between them. One strength of the deficit accumulation approach to quantifying vulnerability is its ability to embrace the complexity of human systems, by placing less emphasis on specific items, and instead focusing on the overall impact of multiple health problems(18). Indeed, similar to the results of prior work in other populations(20,37), our sensitivity analysis demonstrated that SLICC-FI scores were not driven by a small number of specific variables, but reflected the global effect of deficit accumulation.

The relationships that exist between deficits within the SLICC-FI are critical to its performance(20). For example, the equal weighting of transient ischemic attacks (TIAs) and debilitating strokes in the "Cerebrovascular Disease" health deficit may appear to lack face validity, as these events clearly differ in their impact on overall health. However, an individual with a disabling stroke is more likely to have additional deficits related to their functional performance that will be reflected in their SLICC-FI score. Thus, including deficits related to functional status ensures that the health impact of different medical problems is accurately represented. Furthermore, the potential reversibility of such deficits means that individuals may transition in and out of a frail state during follow-up, enabling the SLICC-FI to capture improvements in a patient's status over time and distinguishing this instrument from the SDI(30). Future work will examine the trajectories of SLICC-FI values during follow-up. Given that frailty is potentially treatable(7), the SLICC-FI may be useful as an outcome measure for future intervention studies.

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An alternative conceptual approach to the measurement of frailty is the Fried frailty phenotype(19), which was recently evaluated in a prevalent cohort of 152 women with SLE(42). In this study, 20% of the sample was classified as frail(42). The presence of frailty was associated with increased risk of functional decline and mortality(42), emphasizing its relevance in SLE. However, the authors also found that two of the five components of the frailty phenotype, as defined in geriatric medicine, had limited utility in SLE(42), suggesting that measures with more relevance in SLE may be needed to better quantify frailty in this population.

There are several other challenges associated with applying the frailty phenotype in SLE that are overcome using the deficit accumulation approach. First, the frailty phenotype requires physical performance data(18,19,42) that is not routinely collected in SLE and is unavailable in the SLICC inception cohort. In contrast, the variables in the SLICC-FI are derived from existing, validated instruments that are commonly used in SLE cohorts and rheumatology clinics, allowing the SLICC-FI to be easily implemented in other clinical and research settings. Another limitation of the frailty phenotype is its lack of granularity, as individuals are assigned to one of three risk categories(18,19). Meanwhile, the SLICC-FI identifies a full spectrum of vulnerability, and studies using this approach in other populations have demonstrated a dose-response relationship between FI values and risk of adverse outcomes(20,22,23,33). Finally, with only five variables included in the frailty phenotype, modifying how the phenotypic criteria are defined can alter the prevalence estimates for frailty considerably(43). In contrast, the properties of the FI remain remarkably consistent regardless of the number or type of variables included(20,22-24,33). While the FI and the frailty phenotype have shown reasonable agreement in geriatric populations(34,37), it is unclear whether this correlation exists in SLE. Future work

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should investigate agreement between the SLICC-FI and the Fried phenotype for the identification of frailty in SLE.

In our study, 27.1% of patients were classified as frail. This is higher than expected for similarly-aged individuals in the general population(15,32,44). For example, among SLE patients less than 30 years of age, 19.3% were classified as frail, compared with an estimated frailty prevalence of 2.0% among Canadian adults in the same age group(15). SLICC-FI values (mean FI 0.17) were substantially lower than FI scores reported in other clinical cohorts, including patients with HIV (mean FI 0.31)(22) and systemic sclerosis (mean FI 0.33)(23). This could be partially explained by the higher mean age in these other cohorts, as deficits accumulate with increasing age(35). Overall, our findings support those of prior studies in non-lupus populations that have demonstrated older age, female sex, lower educational attainment, and cigarette smoking to be associated with higher prevalence of frailty(15,20,33).

There is biologically plausible to our findings. The link between chronic inflammation and frailty is well-established, with elevated markers of systemic inflammation observed among frail older adults compared with those who are not frail(45). Furthermore, certain inflammatory cytokines, such as IL-6, have been implicated in the pathogenesis of both frailty and SLE(45,46). While more work is required to fully elucidate the role of immune dysregulation in the development of frailty, this could represent a potential mechanism for accelerated aging in SLE.

Our study has important limitations. Due to missing data, we were unable to calculate SLICC-FI scores at enrolment for some patients. Despite this, 82.6% of eligible patients had their baseline

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assessment for SLICC-FI construction within two years of SLE diagnosis. Second, our sample size is small compared with some other FI studies(15,20,33), but is still sufficient for FI construction(23). Third, we used FI cut-points derived from general population samples to estimate the prevalence of frailty in our dataset(15,37,38). It is possible that a different cut-off for SLICC-FI scores should be used to define phenotypic frailty in SLE. This is an area for future research. Last, we have constructed the SLICC-FI in a cohort of relatively young, recently-diagnosed SLE patients. It remains unclear whether these findings can be generalized to older patients with longstanding SLE. Prior to use, validation of the SLICC-FI is required including external validation in prevalent SLE cohorts and its association with the risk of future adverse health outcomes.

In conclusion, evaluating frailty through deficit accumulation provides a novel approach to the quantification of vulnerability among SLE patients. We identified a high prevalence of frailty among SLE patients, which warrants additional investigation. The SLICC-FI requires validation prior to its use as a tool to identify SLE patients who are at increased risk for adverse outcomes.

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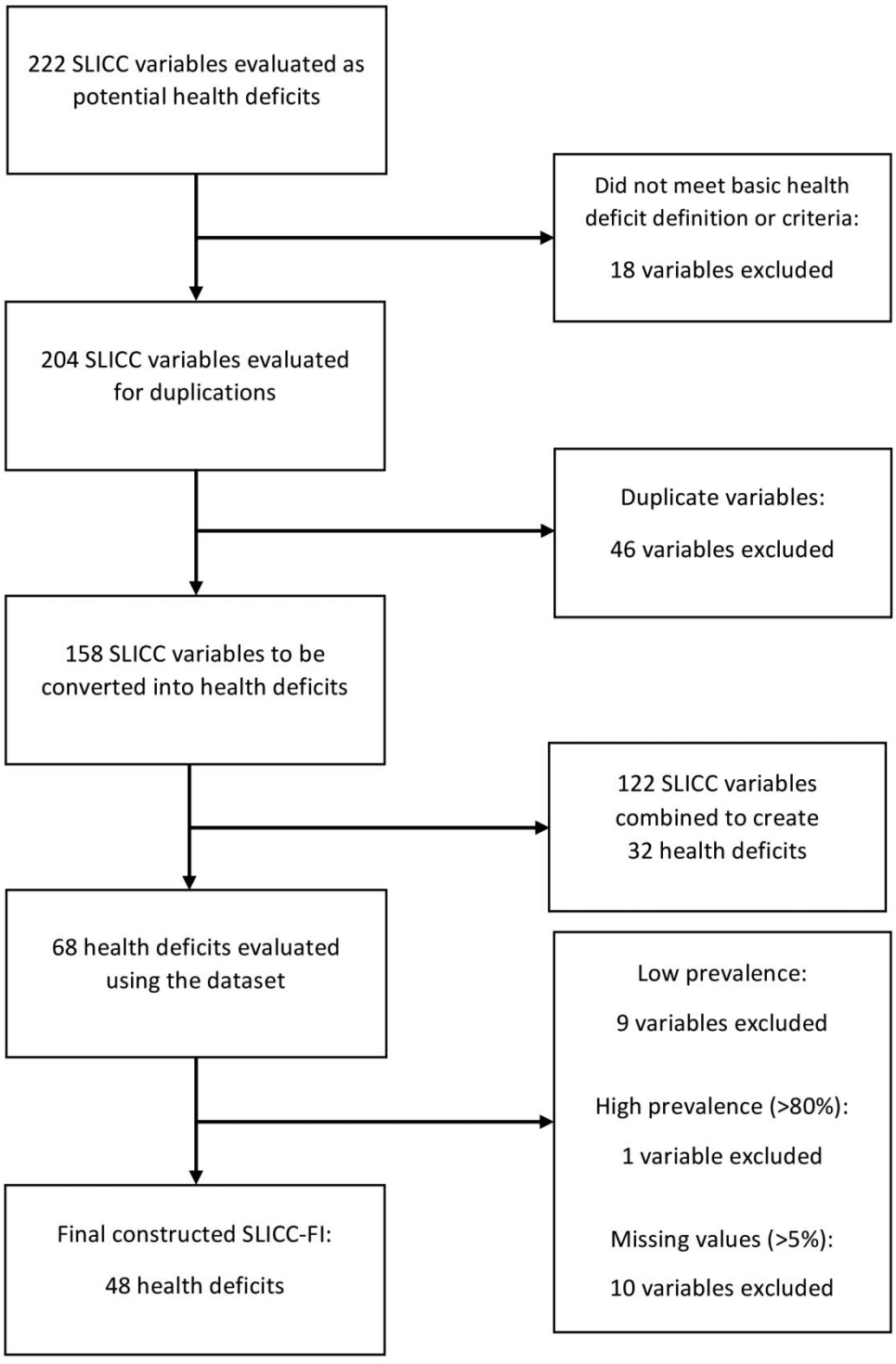
Figure 1. Flow diagram of the evaluation of SLICC variables for inclusion as health deficits in the SLICC-FI.



Systemic Lupus International Collaborating Clinics (SLICC); Frailty Index (FI).

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Figure 2. Distribution of SLICC-FI values among 1682 SLE patients in the baseline dataset.

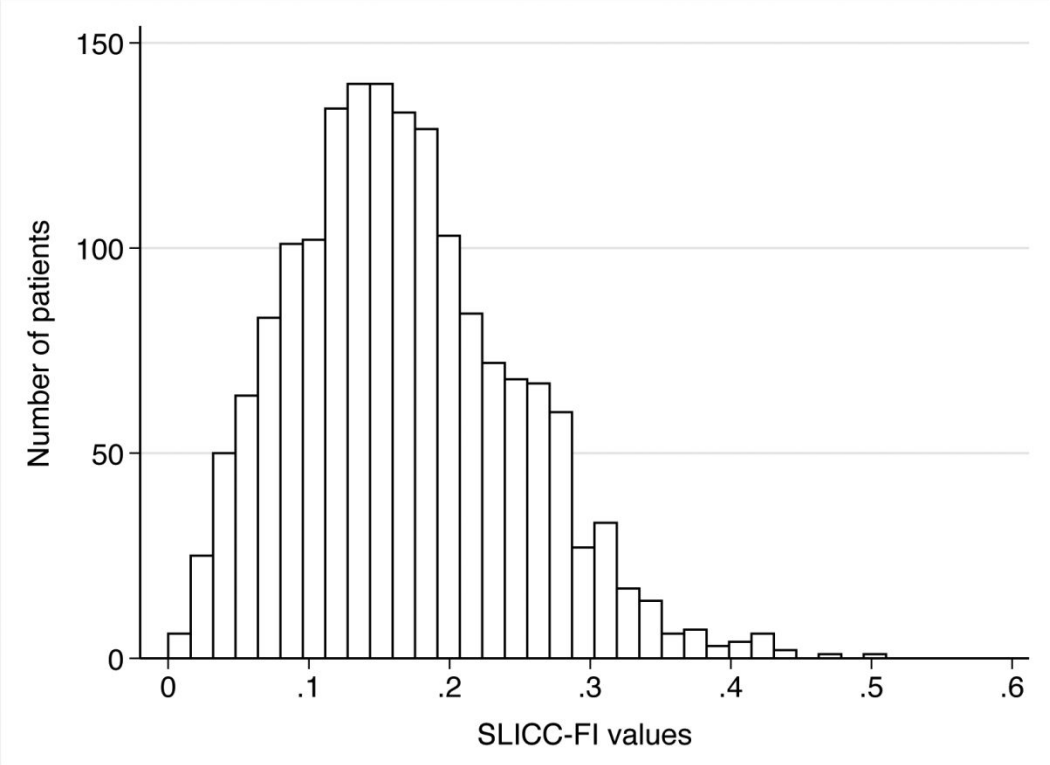

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Table 1. Standard criteria for the identification of health deficits for inclusion in a frailty index.

Health deficit definition
Any symptom, physical sign, disease process, functional impairment, or laboratory/radiographic abnormality
Criteria to be met by each individual health deficit
1. Must be acquired, as opposed to innate 2. Must be associated with an adverse health outcome 3. Prevalence should generally increase with increasing chronological age 4. Must be present in at least 1%, but not more than 80% of the sample 5. Must have non-missing values for at least 95% of the sample
Criteria to be met by the overall set of health deficits
1. Must cover a range of physiologic organ systems 2. Must include integrated variables indicative of repair potential, including measures of function and mobility 3. Must include at least 30-40 deficits in total

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Table 2. Baseline characteristics of SLICC inception cohort patients included in the dataset for SLICC-FI construction (n=1683).

Variables	Descriptive statistics
Patient age at baseline (years)	
Mean (S.D.)	35.7 (13.4)
Sex	
Female, n (%)	1493 (88.7)
Male, n (%)	190 (11.3)
Race/Ethnicity	
Caucasian, n (%)	834 (49.6)
African ancestry, n (%)	280 (16.6)
Asian, n (%)	260 (15.5)
Hispanic, n (%)	248 (14.7)
Other, n (%)	61 (3.6)
Geographic location	
United States, n (%)	467 (27.7)
Canada, n (%)	395 (23.5)
Mexico, n (%)	197 (11.7)
Europe, n (%)	461 (27.4)
Asia, n (%)	163 (9.7)
Education	
Post-secondary education, n (%)	847 (50.3)
Missing, n (%)	22 (1.3)
Cigarette smoking	
Current smoking, n (%)	242 (14.4)
SLE disease duration at baseline (months)	
Median (I.Q.R.)	14.0 (10.7-18.4)
SLEDAI-2K at baseline	
Median (I.Q.R.)	2 (0-6)
SLICC/ACR Damage Index (SDI) at baseline	
Baseline SDI = 0, n (%)	1270 (75.5)
Medication use	
Corticosteroids, n (%)	1179 (70.1)
Antimalarials, n (%)	1149 (68.3)
Immunosuppressives, n (%)	681 (40.5)

S.D. = standard deviation; I.Q.R. = interquartile range; SLICC = Systemic Lupus International Collaborating Clinics; FI = frailty index; SLEDAI-2K = SLE disease activity index 2000.

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Table 3. Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI) health deficits.

Health Deficit	Scoring System
Diabetes	No = 0; Yes = 1
Malignancy	No = 0; Yes = 1
Coronary artery disease	No = 0; Yes = 1
Congestive heart failure	No = 0; Yes = 1
Peripheral vascular disease	No = 0; Yes = 1
Cerebrovascular disease	No = 0; Yes = 1
Chronic kidney disease	None = 0; Stage 1 = 0.2; Stage 2 = 0.4; Stage 3 = 0.6; Stage 4 = 0.8; Stage 5 = 1
Deforming or erosive arthritis	No = 0; Yes = 1
Venous thromboembolism	No = 0; Yes = 1
Pulmonary disease	No = 0; Yes = 1
Gastrointestinal disease	No = 0; Yes = 1
Osteoporosis / Avascular necrosis	No = 0; Yes = 1
Ocular manifestations related to SLE	No = 0; Yes = 1
SLE myocarditis/endocarditis	No = 0; Yes = 1
Cognitive impairment	No = 0; Yes = 1
Seizures & seizure disorders	No = 0; Yes = 1
Altered mental status	No = 0; Yes = 1
Neuropathy	No = 0; Yes = 1
Other neuropsychiatric manifestations	No = 0; Yes = 1
Active nephritis	No = 0; Yes = 1
Active nephrotic syndrome	No = 0; Yes = 1
Active serositis	No = 0; Yes = 1
Active inflammatory arthritis	No = 0; Yes = 1
Active inflammatory rash	No = 0; Yes = 1
Active mucosal ulcers	No = 0; Yes = 1
Alopecia	No = 0; Yes (acute) = 0.5; Yes (chronic) = 1
Active vasculitis	No = 0; Yes = 1
Hematologic disorder	No = 0; Yes = 1
Immunologic disorder	No = 0; Yes = 1
Complement levels	Normal/high = 0; Low & negative dsDNA = 0.5; Low & positive dsDNA = 1
Sjogren's syndrome	No = 0; Yes = 1
Hypothyroidism	No = 0; Yes = 1
Hypertension	No = 0; Yes = 1
Body mass index (BMI)	BMI 18.5 – 24.9 kg/m^2 = 0; BMI 25 – 29.9 kg/m^2 = 0.5; BMI $\geq$ 30 kg/m^2 = 1
Mood disorder	No = 0; Yes = 1
Anxiety disorder	No = 0; Yes = 1
Headache disorder	No = 0; Yes = 1
Self-rated health	Excellent = 0; Very good=0.25; Good = 0.5; Fair = 0.75; Poor = 1
Self-reported deterioration in health	Better or same = 0; Somewhat worse = 0.5; Much worse = 1
Vigorous activities	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Moderate activities	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Lifting/carrying groceries	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Climbing stairs	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Bending, kneeling, or stooping	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Walking 100 metres	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Bathing or dressing	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1
Self-rated fatigue	None = 0; A little = 0.2; Some = 0.4; Moderate = 0.6; Most = 0.8; Always = 1
Self-rated pain	None = 0; Very mild = 0.2; Mild = 0.4; Moderate = 0.6; Severe = 0.8; Very severe = 1

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Table 4. Demographic characteristics of SLE patients, stratified by baseline health status [a] (n=1682).

	Missing, n (%)	Relatively fit (SLICC-FI ≤0.10)	Least fit (0.10 < FI ≤ 0.21)	Frail (SLICC-FI > 0.21)
Sample size, n	-	352	874	456
Baseline SLICC-FI, Mean (S.D.)	-	0.07 (0.02)	0.15 (0.03)	0.27 (0.05)
Age at baseline (years), Mean (S.D.)	-	32.1 (11.7)	35.1 (13.1)	39.6 (14.1)
Sex ratio (female / male)	-	6.18	8.10	9.13
Postsecondary education, % (95% CI)	22 (1.3)	52.6 (47.2-57.9)	55.9 (52.5-59.2)	40.5 (35.9-45.2)
Current smoking, % (95% CI)	1 (0.06)	11.1 (8.0-14.8)	12.9 (10.8-15.4)	19.7 (16.2-23.7)
SLE disease duration (months), Median (I.Q.R)	-	16.7 (14.0-26.3)	13.6 (10.3-18.1)	12.5 (9.1-16.1)

S.D. = standard deviation; I.Q.R. = interquartile range; 95% CI = 95% confidence interval; SLICC = Systemic Lupus International Collaborating Clinics; FI = Frailty Index.

[a] Health status categories based on established FI cut points for the general population

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