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DOI:

[10.3899/jrheum.181338](https://doi.org/10.3899/jrheum.181338)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Gordon, C 2019, 'Construction of a frailty index as a novel health measure in systemic lupus erythematosus', *The Journal of Rheumatology*, vol. 46, no. 5, 181338. <https://doi.org/10.3899/jrheum.181338>

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Checked for eligibility: 01/04/2019

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The Journal of Rheumatology Apr 2019, jrheum.181338]; DOI: 10.3899/jrheum.181338 is available online at: <http://www.jrheum.org/content/early/2019/04/09/jrheum.181338>

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

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Key Indexing Terms: Systemic lupus erythematosus, Outcome assessment, Cohort studies

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Funding support:

Funding for this work was provided by the Nova Scotia Health Authority Research Fund.

Dr. Sang-Cheol Bae's work was supported in part by_NRF-2017M3A9B4050335, Republic of Korea.

Dr. Caroline Gordon's work was supported by Lupus UK and the NIHR /Wellcome Trust Clinical Research Facility

The Montreal General Hospital Lupus Clinic is partially supported by the Singer Family Fund for Lupus Research.

Dr. Clarke holds The Arthritis Society Chair in Rheumatic Diseases at the University of Calgary.

Dr. Paul R. Fortin presently holds a tier 1 Canada Research Chair on Systemic Autoimmune Rheumatic Diseases at Université Laval, and part of this work was done while he was still holding a Distinguished Senior Investigator of The Arthritis Society.

Dr. Bruce is a National Institute for Health Research (NIHR) Senior Investigator and is supported by Arthritis Research UK, the NIHR Manchester Biomedical Centre and the NIHR/Wellcome Trust Manchester Clinical Research Facility. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Dr Isenberg and Dr Rahman are supported by and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Center.

The Hopkins Lupus Cohort is supported by the NIH (grant AR43727 and 69572).

Dr. Mary Anne Dooley's work was supported by the NIH (grant RR00046).

Dr. Ramsey-Goldman's work was supported by the NIH (grants 5UL1TR001422-02, formerly 8UL1TR000150 and UL-1RR-025741, K24-AR-02318, and P60AR064464 formerly P60-AR-48098).

Dr. Ruiz-Irastorza is supported by the Department of Education, Universities and Research of the Basque Government.

Dr. Soren Jacobsen is supported by the Danish Rheumatism Association (A3865) and the Novo Nordisk Foundation (A05990).

Dr. John G. Hanly is supported by the Canadian Institutes of Health Research (grant MOP-88526)

Disclosure statement: The authors have declared no conflicts of interest.

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Running title: Frailty index in SLE

Word count (text only, not including abstract): 3,504

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.

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 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 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 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.

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 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 ≤ 0.03), relatively less fit ($0.03 < \text{SLICC-FI} \leq 0.10$), least fit ($0.10 < \text{SLICC-FI} \leq 0.21$), 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% 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 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.

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 ($SLICC-FI \leq 0.03$). These individuals were combined with the relatively less fit patients ($0.03 < SLICC-FI \leq 0.10$) 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 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 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.

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 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 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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