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Prediction of damage accrual in systemic lupus erythematosus using the Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI)

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ABSTRACT

Objective: The Systemic Lupus International Collaborating Clinics (SLICC) frailty index (FI) has been shown to predict mortality, but its association with other important outcomes is unknown. We examined the association of baseline SLICC-FI values with damage accrual in the SLICC inception cohort.

Methods: The baseline visit was defined as the first at which both organ damage (SLICC/ACR Damage Index [SDI]) and health-related quality of life (Short-Form 36 [SF-36]) were assessed. Baseline SLICC-FI scores were calculated. Damage accrual was measured by the increase in SDI between the baseline assessment and the last study visit. Multivariable negative binomial regression estimated the association between baseline SLICC-FI values and the rate of increase in the SDI during follow-up, adjusting for relevant demographic and clinical characteristics.

Results: The 1549 SLE patients eligible for this analysis were mostly female (88.7%) with mean (standard deviation, SD) age 35.7 (13.3) years and median (interquartile range) disease duration 1.2 (0.9-1.5) years at baseline. Mean (SD) baseline SLICC-FI was 0.17 (0.08) with a range of 0-0.51. Over a mean (SD) follow-up of 7.2 (3.7) years, 653 patients (42.2%) had an increase in SDI. Higher baseline SLICC-FI values (per 0.05 increment) were associated with higher rates of increase in the SDI during follow-up (Incidence Rate Ratio [IRR] 1.19; 95% CI 1.13-1.25), after adjusting for age, sex, ethnicity/region, education, baseline SLEDAI-2K, baseline SDI, and baseline use of corticosteroids, antimalarials, and immunosuppressives.

Conclusion: The SLICC-FI predicts damage accrual in incident SLE, which further supports the SLICC-FI as a valid health measure in SLE.

The clinical course of systemic lupus erythematosus (SLE) is variable and challenging to predict. In geriatric medicine(1) and other disciplines(2-5), susceptibility to adverse outcomes is quantified using the construct of frailty, defined as increased vulnerability due to diminished ability to respond to physiologic stressors(6). One approach to operationalizing frailty is through a frailty index (FI)(7), which measures the accumulation of health deficits across multiple systems(8). Individuals with few deficits are considered relatively fit, while those with more health problems are considered increasingly frail(9). The validity of the FI approach is well-established in non-lupus populations(7,10-13). Recently, in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort, we constructed the first FI for SLE patients(14) and demonstrated an association between higher SLICC-FI values and increased mortality risk(15).

Organ damage is a core disease domain in SLE(16). It is evaluated using the SLICC/American College of Rheumatology (ACR) Damage Index (SDI)(17), which measures damage occurring after the diagnosis of SLE, regardless of attribution(17,18). Among SLE patients, higher SDI scores are associated with increased mortality(19-24), higher healthcare costs(25), greater activity limitations(26), and lower health-related quality of life(19,27). As organ damage accumulates at different rates in individual patients(20), predicting which SLE patients are likely to experience greater damage accrual would be valuable.

We hypothesized that the SLICC-FI would identify which SLE patients are most likely to accumulate organ damage over time. The primary objective of this study was to estimate the association between baseline SLICC-FI values and the rate of damage accrual in the SLICC

inception cohort. Preexisting organ damage also predicts future damage in SLE(19,20). Therefore, a secondary aim was to compare the predictive validity of baseline SLICC-FI and baseline SDI scores for subsequent damage accrual.

PATIENTS 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, an inception cohort of SLE patients was recruited from 31 SLICC sites in Europe, Asia, and North America. In total, 1826 SLE patients were enrolled within 15 months of SLE diagnosis(28). Data were collected per a standardized protocol, submitted to the coordinating centres at the University of Toronto (Toronto, ON, Canada) and Dalhousie University (Halifax, NS, Canada), and entered into centralized databases. The study was approved by the Institutional Research Ethics Boards of all participating centres and all participants provided written informed consent.

Clinical and laboratory assessments: Patients were evaluated at enrolment and annually for the following variables: demographic features (age, sex, race/ethnicity, and years of post-secondary education); physical measurements (blood pressure, height and weight); medications (corticosteroids, antimalarials, and immunosuppressives); individual ACR classification criteria for SLE(28); medical comorbidities; neuropsychiatric events(29,30); SLE disease activity [SLE Disease Activity Index 2000 (SLEDAI-2K)(31)]; cumulative organ damage [SLICC/ACR Damage Index (SDI)(17)]; and health-related quality of life [Medical Outcomes Study Short-Form 36 (SF-36)(32)]. Pertinent laboratory investigations were performed locally at each

visit(19). Antibodies to cardiolipin, β-2-glycoprotein I, and the lupus anticoagulant were measured at a central laboratory at the Oklahoma Medical Research Foundation as previously described(33).

Construction of the SLICC-FI: The procedure for SLICC-FI construction is described in detail elsewhere(14). Briefly, we established a baseline dataset of 1683 patients, consisting of the first visit at which both the SDI and SF-36 had been completed. Variables were included in the SLICC-FI if they met the standard criteria for a health deficit, defined as any symptom, disease process, functional impairment, or laboratory abnormality that is: (i) acquired, (ii) associated with chronological age, (iii) associated with adverse health outcomes, (iv) present in ≥1% and ≤80% of the sample, and (v) having non-missing values for ≥95% of the sample(7). Of 222 candidate variables, 48 health deficits met inclusion criteria, spanning multiple organ systems and incorporating organ damage, disease activity, comorbidities, and functional status(14). For each of the 48 health deficits, patients were assigned a score between 0 (complete absence of the deficit) and 1 (deficit fully present) using definitions from the SLE literature(17,28,29,31,32). More detailed information can be found in the **supplementary file**.

Calculation of baseline SLICC-FI scores: A baseline SLICC-FI score was calculated for each patient as the sum of their individual health deficit scores divided by the total number of deficits. For example, an individual in whom 12 of the 48 health deficits in the SLICC-FI are fully present at baseline would have a baseline SLICC-FI score of 12/48=0.25. Each additional health deficit increases the SLICC-FI by 0.021.

Measurement of organ damage accrual: To measure damage accrual, we calculated the change in SDI during follow-up for each patient by subtracting their baseline SDI score from their SDI score at last follow-up. Patients with no follow-up assessments after their baseline visit (N=134) were excluded.

Statistical analysis: Descriptive statistics were calculated for baseline demographic and clinical characteristics, baseline SLICC-FI values and change in SDI values during follow-up. Using a frailty cut-off value established in non-SLE populations(12,34,35), we compared the rate of change in SDI scores between patients classified as frail at baseline (SLICC-FI >0.21) versus those who were not (SLICC-FI ≤0.21). We also compared rates of damage accrual between those with organ damage (SDI >0) at baseline versus those without (SDI=0).

We initially fit Poisson regression models for the change in SDI scores during follow-up, using likelihood ratio tests to evaluate for overdispersion. However, all Poisson models demonstrated overdispersion, and therefore negative binomial models were fit instead. To account for differential patient follow-up, we considered the rate of change in SDI as the outcome of interest by including follow-up time (patient-years) as an offset. All models were evaluated for goodness-of-fit and assessed for multicollinearity between independent variables.

First, a univariable model was constructed with baseline SLICC-FI (per 0.05 increase) as the independent variable. To identify potential confounders of the relationship between the baseline SLICC-FI and damage accrual, we considered baseline demographic and clinical variables associated with damage accrual in SLE(19,20). Univariable models for rate of change in SDI were constructed for each potential confounder.

A multivariable model for the rate of damage accrual included the baseline SLICC-FI, as well as any potentially confounding variables with *p*-values <0.1 in univariable analyses. Similarly, univariable and multivariable models were constructed for the rate of damage accrual with 1) baseline SDI scores (per one-unit increase) as the independent variable of interest; and 2) both baseline SLICC-FI and SDI scores as independent variables in the same model. We then used likelihood ratio tests to compare the multivariable model containing both baseline SLICC-FI and SDI scores to the multivariable models containing 1) the baseline SLICC-FI alone and 2) the baseline SDI alone. We compared the relative performance of these alternative models using the Akaike information criterion (AIC), with smaller AIC values indicating better predictive quality. Data analysis was conducted using STATA-IC Version 14 (StataCorp, TX, USA).

Sensitivity analyses: The SLICC-FI contains health deficits which overlap with items captured by the SDI. To determine the relationship between baseline SLICC-FI scores and damage accrual independent of the baseline SDI, we repeated the above analyses after removing overlapping SDI items from the SLICC-FI and recalculating SLICC-FI scores using the remaining 33 health deficits. We investigated whether the SLICC-FI could predict damage accrual in patients without baseline damage by reassessing the association of baseline SLICC-FI scores with the rate of change in the SDI in a subgroup of patients without baseline damage (SDI=0).

To address differential follow-up, we selected different follow-up time cut-points, based approximately on the 10^{th} (2.5 years), 25^{th} (5 years), 50^{th} (7.5 years), 75^{th} (10 years), and 90^{th} (12.5 years) percentiles in the dataset. We then repeated the above analyses separately for patients with follow-up time above versus below each cut-point.

RESULTS

Baseline patient characteristics: There were 1549 patients (92.0% of the baseline dataset) with ≥1 follow-up visit such that two data points were available to model change in SDI scores. Baseline demographic and clinical characteristics are shown in **Table 1**. Median (interquartile range, IQR) SLE disease duration at baseline was 1.2 (0.9-1.5) years and most patients (n=1300 [83.9%]) had their baseline visit within two years of SLE diagnosis.

At the baseline assessment, SLICC-FI values ranged from 0.004 to 0.510, with a median (IQR) of 0.16 (0.11–0.22) and a mean (standard deviation, SD) of 0.17 (0.08). In total, 422 patients (27.2%) were classified as frail at baseline (SLICC-FI >0.21). There were 370 patients (23.9%) with preexisting organ damage (SDI > 0) at baseline and 1179 patients (76.1%) without baseline organ damage (SDI=0). Baseline SLICC-FI scores were higher among patients with baseline organ damage (mean baseline SLICC-FI = 0.203) compared to those without damage at baseline (mean baseline SLICC-FI = 0.155), and this difference was statistically significant (t-test p-value < 0.0001).

Excluded patients: 134 patients (8.0% of baseline dataset) were excluded from this analysis. One patient was excluded due to insufficient baseline data for calculation of a baseline SLICC-FI score. The remaining 133 patients were excluded due to lack of available follow-up data to model changes in SDI scores. Eight patients died prior to their next follow-up visit, while 125 patients were lost to clinic follow-up. There were no significant baseline differences between excluded and non-excluded patients with respect to age, sex, education level, marital status, cigarette smoking, SLEDAI-2K scores, therapeutic exposures, or specific SLE manifestations

(data not shown). There were differences between excluded and non-excluded patients based on race/ethnicity, which were largely explained by a higher proportion of excluded patients at study sites within the Unites States (data not shown). SLE disease duration at baseline was longer among excluded patients (median 15.6 months versus 14.0 months among non-excluded patients; p-value = 0.003). Baseline SDI scores were slightly higher among excluded patients (mean 0.54 versus 0.40 among non-excluded patients; p-value = 0.05). However, this difference in baseline SDI values was no longer statistically significant after accounting for differences in baseline disease duration.

Organ damage accrual: Over a mean (SD) follow-up of 7.2 (3.7) years and 11,189 patient-years, there were 896 patients (57.8%) with no change in SDI score. There were 332 patients (21.4%) with an SDI increase of one, 178 patients (11.5%) with an increase of two, and 143 patients (9.2%) with an increase of ≥3 points during follow-up.

Baseline SLICC-FI and organ damage accrual: Patients classified as frail at baseline demonstrated a rate of increase in SDI per patient-year of follow-up that was twice the rate observed among patients who were classified as non-frail (Incidence Rate Ratio [IRR] 1.98, 95% Confidence Interval [CI] 1.68-2.34). Patients with damage at baseline (SDI>0) demonstrated a higher rate of change in SDI scores during follow-up compared to patients without baseline organ damage (IRR 1.70, 95% CI 1.43-2.01).

Unadjusted models for organ damage accrual: In unadjusted analysis, each 0.05 increase in baseline SLICC-FI was associated with a 26% increase in the rate of change in the SDI (IRR

1.26, 95% CI 1.20-1.33). Similarly, each one-point increase in baseline SDI was associated with a 31% increase in the rate of subsequent damage accrual (IRR 1.31, 95% CI 1.20-1.43). When baseline SLICC-FI (IRR 1.23, 95% CI 1.17-1.30) and baseline SDI (IRR 1.19, 95% CI 1.09-1.31) scores were included in the same model, both measures maintained independent associations with the rate of damage accrual.

Identifying other factors associated with damage accrual in univariate analysis: Older age, male sex, steroid use, immunosuppressive use, and higher disease activity (SLEDAI-2K) at baseline were associated with a higher rate of increase in SDI scores during follow-up **(Table 2)**. Antimalarial use and post-secondary education at baseline were associated with lower rates of damage accrual **(Table 2)**. There were also differences in the rate of increase in the SDI based on race/ethnicity and geographic region **(Table 2)**. As the effects of race/ethnicity and geographic region could not be evaluated independent of one another, a combined ethnicity/region variable was created for multivariable analysis.

Multivariable models for organ damage accrual: The relationship between the baseline SLICC-FI and the rate of increase in the SDI during follow-up remained largely unchanged following multivariable adjustment **(Table 3-Model 1)**. Each 0.05 increase in the baseline SLICC-FI was associated with a 20% increase in the rate of subsequent damage accrual (IRR 1.20, 95% CI 1.14-1.27), after adjusting for baseline age, sex, steroid use, antimalarial use, immunosuppressive use, ethnicity/location, post-secondary education, and SLEDAI-2K.

Baseline SDI scores also remained significantly associated with the rate of further damage accrual after multivariable adjustment **(Table 3-Model 2)**. In the multivariable model including both the baseline SLICC-FI and baseline SDI as independent variables, both measures maintained statistically significant associations with the rate of increase in the SDI per patient-year of follow-up **(Table 3-Model 3)**. Compared to the models containing either the baseline SLICC-FI or the baseline SDI alone, the model containing both baseline SLICC-FI and SDI scores was superior for predicting the rate of subsequent damage accrual (**Table 3**). In particular, the addition of the baseline SLICC-FI to the model containing the baseline SDI alone was associated with significant improvement in model fit (Model 2 vs. Model 3: likelihood ratio test statistic 40.49 [$p<0.001$]) and relative predictive quality (Model 2 AIC=3602.1 vs. Model 3 AIC=3563.6).

Sensitivity analyses: The association between higher baseline SLICC-FI values and higher rates of damage accrual remained statistically significant when the above analyses were repeated after removing all SDI-related items from the SLICC-FI **(Table 4)**. We also repeated the above analyses in the subgroup of patients without preexisting organ damage (SDI=0) at baseline. Among these 1179 patients, those classified as frail at baseline (SLICC-FI >0.21) accrued organ damage at a rate that was 89% higher compared to non-frail individuals (IRR 1.89, 95% CI 1.51-2.36). In multivariable analysis, each 0.05 increase in baseline SLICC-FI was associated with a 21% increase in the rate of change in the SDI during follow-up (IRR 1.21, 95% CI 1.14-1.30), after adjusting for baseline age, sex, steroid use, antimalarial use, immunosuppressive use, ethnicity/location, post-secondary education, and SLEDAI-2K**.**

The main analyses were then repeated in subgroups stratified by follow-up time **(Table 5)**. The relationship between baseline SLICC-FI scores and subsequent damage accrual was maintained in all subgroups, with the exception of the small subset of patients (n=188) followed for ≤2.5 years after their baseline assessment. This may have been related to small sample size, as well as low event rate, as most of these patients (n=142; 75.5%) did not experience any damage accrual during follow-up.

DISCUSSION

In a well-characterized, international cohort of recently diagnosed SLE patients, we have demonstrated an association between higher baseline SLICC-FI values and higher rates of increase in the SDI during follow-up, independent of other demographic and clinical characteristics known to predict damage accrual in SLE. This finding adds to our previous work that demonstrated the SLICC-FI predicts mortality in SLE(15) and further supports the SLICC-FI as a valid and robust measure for predicting clinically meaningful outcomes among SLE patients.

The association between the SLICC-FI and organ damage accrual in SLE agrees with prior work investigating frailty in non-lupus populations. For example, in addition to mortality, frailty indices can predict other important health outcomes, including falls, fractures, health service utilization, hospitalizations, institutionalization, and multimorbidity(11-13,36,37). The ability of baseline SLICC-FI values to predict future damage accrual is also consistent with the theoretical basis of the deficit accumulation approach to frailty. As frailty represents a loss of physiologic reserve with resultant inability to withstand future insults(8), it is expected that SLE patients with

higher baseline SLICC-FI values will be more likely to sustain organ damage when faced with new health threats.

Given the importance of preexisting damage, measured using the SDI, for predicting subsequent damage accumulation in SLE(19,21,22), some may question whether the ability of the SLICC-FI to predict damage accrual is heavily reliant upon baseline SDI scores. However, our sensitivity analysis demonstrated persistence of the relationship between baseline SLICC-FI values and the rate of damage accrual during follow-up, despite removal of all SDI-related items from the index. This suggests that it is not only organ damage, but the global effect of deficit accumulation, that is driving the association between baseline SLICC-FI values and the rate of subsequent damage accrual. This highlights a key strength of the deficit accumulation approach to frailty – it is the cumulative impact of all health deficits, and not the specific nature of the individual deficits, that is important(9,38).

We found that the baseline SLICC-FI and the baseline SDI were both significant predictors of the rate of damage accrual during follow-up. Thus, these two instruments are likely measuring separate constructs that each provide valuable prognostic information. As many SLE patients will remain free of organ damage captured by the SDI for several years after diagnosis(20), the added prognostic value of the SLICC-FI when compared with the SDI may be most evident early in the disease course. For example, even in our subgroup analysis of patients without organ damage at baseline (SDI=0), the baseline SLICC-FI remained a significant predictor of damage accrual over time.

Importantly, this study focused on predictors of damage accrual based on information available to clinicians early in the course of incident SLE. As a result, our analysis does not account for the complex variations in disease activity, therapeutic exposures, and frailty that subsequently occur over the course of follow-up. While the current analysis provides relevant information for clinical decision-making early in disease, the impact of changes in frailty over time on the risk of adverse outcomes remains to be determined. Future work will investigate how the trajectories of SLICC-FI scores over multiple time points are related to the risk of future adverse health outcomes in incident SLE. It would also be valuable to determine whether SLICC-FI values are more strongly associated with the development of certain types of organ damage. While damage accrual in this sample was not sufficient to facilitate an analysis of the association between baseline SLICC-FI values and individual damage items, this is an objective for future studies.

Our study has some limitations. First, observation time differed between patients, which could introduce bias if the association between the SLICC-FI and damage accrual were to vary depending on follow-up time. However, our sensitivity analysis stratified by length of follow-up demonstrated a consistent association between baseline SLICC-FI values and the rate of damage accrual across strata, suggesting that this was not a major concern. Second, our analysis assumed a constant rate of damage accrual throughout the follow-up period and thus could not account for potential accelerations or decelerations in the average rate of change in SDI scores over time. However, consistent with the results of previous studies conducted in a variety of different healthcare systems(19,21,39,40), we found a steady, linear rate of increase in mean SDI scores during follow-up, suggesting that our assumption about the constant rate of damage accrual among SLE patients is valid. Third, 277 patients (15.2% of the SLICC cohort) were excluded

due to missing baseline or follow-up data. This raises the possibility of selection bias due to exclusion of more severe SLE cases with early mortality. However, the demographic and clinical characteristics of the patients included in our analysis were comparable to those of excluded patients, and were similar to those reported in previous studies of the SLICC cohort(19,30), suggesting that our dataset remained representative of the overall cohort. Last, it should be acknowledged that the SLICC-FI has been constructed and evaluated in a cohort of relatively young, incident SLE patients. It remains unclear whether these findings can be generalized to older patients with longstanding SLE. Therefore, external validation of the SLICC-FI in prevalent SLE cohorts is required.

In conclusion, the SLICC-FI predicts damage accrual among patients with SLE, which is clinically relevant given the association of organ damage with increased mortality risk(19-24), lower quality of life(19,27), and increased healthcare costs(25). The SLICC-FI holds potential value as a prognostic tool for identifying SLE patients who are at increased risk for the development of significant organ damage. As frailty is potentially reversible(1), the SLICC-FI may also be useful as an outcome measure in future intervention studies.

Table 1. Baseline demographic and clinical characteristics of SLE patients in the SLICC inception cohort eligible for the analysis of organ damage accrual (n=1549).

Variables		Missing values, n(%)
Age at baseline (years)		
Mean (S.D.)	35.7 (13.3)	
Sex		
Female, n (%)	1374 (88.7)	
Male, n (%)	175 (11.3)	
Race/Ethnicity		
Caucasian, n (%)	767 (49.5)	
Black, n (%)	249 (16.1)	
Asian, n (%)	245 (15.8)	
Hispanic, n (%)	236 (15.2)	
Other, n (%)	52 (3.4)	
Region		
United States, n (%)	393 (25.4)	
Canada, n (%)	377 (24.3)	
Mexico, n (%)	192 (12.4)	
Europe, n (%)	433 (28.0)	
Asia, n (%)	154 (9.9)	
Education		
Post-secondary education, n (%)	782 (51.2)	21 (1.4)
SLE disease duration (years)		
Median (I.Q.R.)	1.2 (0.9-1.5)	
SLEDAI-2K		
Median (I.Q.R.)	2 (0-6)	5 (0.3)
SLICC/ACR Damage Index (SDI)		
Baseline SDI = 0, n (%)	1179 (76.1)	
Medication use		
Corticosteroids, n (%)	1089 (70.3)	
Antimalarials, n (%)	1048 (67.7)	2 (0.1)
Immunosuppressives, n (%)	631 (40.8)	2 (0.1)
Comorbidities		
Taking antihypertensives n (%)	460 (29.8)	5 (0.3)
Diabetes mellitus, n (%)	33 (2.2)	34 (2.2)
Current smoker, n (%)	224 (14.5)	

Body mass index, mean (S.D.)	25.7 (6.0)	63 (4.1)
Antiphospholipid antibody positivity		
Lupus anticoagulant, n (%)	209 (22.8)	631 (40.7)
Anti-cardiolipin, n (%)	119 (13.1)	638 (41.2)
Anti-β-2-glycoprotein I, n (%)	135 (14.8)	638 (41.2)

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

Table 2. Univariable negative binomial regression models for the association of baseline demographic and clinical variables with the change in SDI score during follow-up among SLE patients in the SLICC inception cohort (n=1549).

Independent variable	Incidence Rate Ratio (95% CI)	p value
Baseline age (years)	1.015 (1.010 – 1.020)	<0.0001
Male Sex	1.66 (1.33 – 2.07)	<0.0001
Race/ethnicity: Caucasian	Referent	
Hispanic	1.37 (1.09 – 1.73)	0.007
Black	1.82 (1.46 – 2.26)	<0.001
Asian	0.72 (0.56 – 0.92)	0.008
Other	1.55 (1.04– 2.31)	0.030
Geographic location: USA	Referent	
Canada	0.53 (0.42 – 0.66)	<0.001
Mexico	0.77 (0.59 – 1.02)	0.064
Europe	0.52 (0.42 – 0.64)	<0.001
Asia	0.38 (0.28 – 0.52)	<0.001
Post-secondary education[a]: No	Referent	
Yes	0.80 (0.68 – 0.95)	0.009
Cigarette smoking: No	Referent	
Yes	1.09 (0.87 – 1.36)	0.449
Corticosteroid use at baseline: No	Referent	
Yes	1.49 (1.24 – 1.78)	<0.0001
Immunosuppressive use at baseline: No	Referent	
Yes	1.44 (1.22 – 1.70)	<0.0001
Antimalarial use at baseline: No	Referent	
Yes	0.79 (0.67 – 0.94)	0.007
SLEDAI-2K[b] at baseline (per 1.0)	1.05 (1.03 – 1.07)	<0.0001
SLE disease duration at baseline (years)	1.00 (0.99 – 1.01)	0.528
Lupus-anticoagulant at baseline [c]: No	Referent	
Yes	1.19 (0.94 – 1.50)	0.152
Anti-cardiolipin at baseline [c]: No	Referent	
Yes	1.23 (0.92 – 1.65)	0.164
Anti-beta-2-glycoprotein I at baseline [c]: No	Referent	
Yes	1.06 (0.76 – 1.50)	0.727

[a] A "missing" indicator was included for the 1.4% of patients for whom this data was lacking.

[b] SLEDAI-2K = SLE disease activity index 2000

[c] Analysis included 911 patients with complete antiphospholipid antibody data

Table 3. Multivariable negative binomial regression models for the association of baseline SLICC-FI and SDI scores with the change in SDI score during follow-up among SLE patients in the SLICC inception cohort.

	Univariable model (n = 1549)		**Multivariable model [a] (n = 1539)**	
	Incidence Rate Ratio (95% CI)	**p value**	**Incidence Rate Ratio (95% CI)**	**p value**
Model 1: SLICC-FI				
SLICC-FI (per 0.05)	1.26 (1.20 - 1.33)	<0.001	1.20 (1.14 - 1.27)	<0.001
Model 2: SDI				
SDI (per 1.0)	1.31 (1.20 – 1.43)	<0.001	1.17 (1.07 – 1.28)	<0.001
Model 3: SLICC-FI & SDI				
SLICC-FI (per 0.05)	1.23 (1.17 – 1.30)	<0.001	1.19 (1.13 – 1.25)	<0.001
SDI (per 1.0)	1.19 (1.09 – 1.31)	<0.001	1.10 (1.01 – 1.21)	0.038
Overall model comparisons	**LR test statistic**	**p value**	**LR test statistic**	**p value**
Model 1 vs. Model 3	15.35	<0.001	5.18	0.023
Model 2 vs. Model 3	67.64	<0.001	40.49	<0.001
Akaike information criteria (AIC)				
Model 1: SLICC-FI	3735.12		3566.78	
Model 2: SDI	3787.41		3602.09	
Model 3: SLICC-FI & SDI	3721.78		3563.60	

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, antimalarial use, immunosuppressive use, ethnicity/location, post-secondary education, and SLEDAI-2K.

Notes: SLICC = Systemic Lupus International Collaborating Clinics; FI = Frailty Index; SDI = SLICC / ACR Damage Index; LR = Likelihood Ratio

Table 4. Negative binomial regression models for the association of baseline SLICC-FI and SDI scores with the change in SDI scores during follow-up among SLE patients, excluding damage-related health deficits from the SLICC-FI.

	Univariable model (n=1549)	**Multivariable model [a] (n = 1539)**
	Incidence Rate Ratio (95% CI)	**Incidence Rate Ratio (95% CI)**
Model 1: SLICC-FI		
SLICC-FI [b] (per 0.05)	1.17 (1.12 – 1.21)	1.13 (1.09 – 1.17)
Model 2: SDI		
SDI (per 1.0)	1.31 (1.20 – 1.43)	1.17 (1.07 – 1.28)
Model 3: SLICC-FI & SDI		
SLICC-FI [b] (per 0.05)	1.15 (1.11 – 1.20)	1.12 (1.08 – 1.16)
SDI (per 1.0)	1.26 (1.15 – 1.37)	1.15 (1.05 – 1.25)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	26.46 (p<0.0001)	10.74 (p=0.001)
Model 2 vs. Model 3	61.25 (p<0.0001)	35.72 (p<0.0001)
Akaike Information Criteria (AIC)		
Model 1: SLICC-FI	3752.61	3577.12
Model 2: SDI	3787.41	3602.09
Model 3: SLICC-FI & SDI	3728.16	3568.37

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, antimalarial use, immunosuppressive use, ethnicity/location, post-secondary education, and SLEDAI-2K.

[b] Baseline SLICC-FI calculated using the 33 health deficits not related to organ damage.

Notes: SLICC = Systemic Lupus International Collaborating Clinics; FI = Frailty Index; SDI = SLICC / ACR Damage Index; LR = Likelihood Ratio

Table 5. Negative binomial regression models for the association between baseline SLICC-FI values and the change in the SDI during follow-up among SLE patients, stratified by follow-up time.

	Univariable model	**Full multivariable model [a]**
	Incidence Rate Ratio [b] (95% CI)	**Incidence Rate Ratio [b] (95% CI)**
Cut point: 2.5 years follow-up		
≤ 2.5 years follow-up (n=188)	1.09 (0.91 – 1.30)	0.93 (0.77 – 1.11)
> 2.5 years follow-up (n=1361)	1.27 (1.21 – 1.34)	1.22 (1.16 – 1.29)
Cut point: 5.0 years follow-up		
≤ 5.0 years follow-up (n=486)	1.23 (1.11 – 1.36)	1.15 (1.04 – 1.27)
> 5.0 years follow-up (n=1063)	1.26 (1.19 – 1.33)	1.22 (1.15 – 1.29)
Cut point: 7.5 years follow-up		
≤ 7.5 years follow-up (n=825)	1.22 (1.14 – 1.32)	1.14 (1.06 – 1.22)
> 7.5 years follow-up (n=724)	1.30 (1.22 – 1.37)	1.25 (1.17 – 1.34)
Cut point: 10.0 years follow-up		
≤ 10.0 years follow-up (n=1184)	1.26 (1.19 – 1.33)	1.18 (1.12 – 1.26)
> 10.0 years follow-up (n=365)	1.27 (1.17 – 1.38)	1.22 (1.12 – 1.34)
Cut point: 12.5 years follow-up		
≤ 12.5 years follow-up (n=1395)	1.25 (1.18 – 1.32)	1.19 (1.13 – 1.25)
> 12.5 years follow-up (n=154)	1.42 (1.25 – 1.62)	1.35 (1.16 – 1.56)

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, antimalarial use, immunosuppressive use, ethnicity/location, post-secondary education, and SLEDAI-2K.

[b] All incidence rate ratios are per 0.05 increase in baseline SLICC-FI score

Notes: SLICC = Systemic Lupus International Collaborating Clinics; FI = Frailty Index; SDI = SLICC / ACR Damage Index; LR = Likelihood Ratio

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