Title

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Prediction of hospitalizations 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) predicts mortality and damage accrual in SLE, but its association with hospitalizations has not been described. We estimated the association of baseline SLICC-FI values with future hospitalizations in the SLICC inception cohort.

Methods: Baseline SLICC-FI scores were calculated. The number and duration of inpatient hospitalizations during follow-up were recorded. Negative binomial regression was used to estimate the association between baseline SLICC-FI values and the rate of hospitalizations per patient-year of follow-up. Linear regression was used to estimate the association of baseline SLICC-FI scores with the proportion of follow-up time spent in hospital. Multivariable models were adjusted for relevant baseline characteristics.

Results: The 1549 SLE patients eligible for this analysis were mostly female (88.7%) with mean (SD) age 35.7 (13.3) years and median (IQR) disease duration 1.2 (0.9-1.5) years at baseline. Mean (SD) baseline SLICC-FI was 0.17 (0.08). During mean (SD) follow-up of 7.2 (3.7) years, 614 patients (39.6%) experienced 1570 hospitalizations. Higher baseline SLICC-FI values (per 0.05 increment) were associated with more frequent hospitalizations during follow-up (Incidence Rate Ratio 1.21; 95%CI 1.13-1.30), adjusting for baseline age, sex, corticosteroid use, immunosuppressive use, ethnicity/location, SLE disease activity index 2000 (SLEDAI-2K), SLICC/ACR damage index (SDI), and disease duration. Among patients with ≥1 hospitalization, higher baseline SLICC-FI values predicted a greater proportion of follow-up time spent hospitalized (Relative Rate 1.09; 95%CI 1.02-1.16).

Conclusion: The SLICC-FI predicts future hospitalizations among incident SLE patients, further supporting the SLICC-FI as a valid health measure in SLE.

Keywords

Systemic lupus erythematosus; Frailty; Hospitalization

Patients with systemic lupus erythematosus (SLE) experience higher rates of hospitalization compared to the general population. Most commonly, these hospitalizations are related to active SLE(1-5), treatment complications(1-6), or comorbidities(7). Hospitalizations are a major source of direct and indirect costs in SLE(6,8-13), and correlate with increased mortality(4). While hospitalization rates, length of admission, in-hospital mortality rates, and reasons for hospitalization have been well-documented in prior SLE studies(1-3,5,6,14), our understanding of the patient characteristics associated with hospitalizations in SLE remains incomplete(1,4,5,15,16). In particular, our ability to predict which SLE patients are at highest risk for hospitalization is limited.

In geriatric medicine(17), and increasingly in other disciplines(18-21), differences in susceptibility to adverse health outcomes, such as hospitalizations, can be quantified using

the construct of frailty, defined as a state of increased vulnerability with diminished ability to respond to stressors(22). One approach to operationalizing frailty is the frailty index (FI)(23), which conceptualizes frailty as a loss of physiologic reserve arising from the accumulation of health deficits across multiple systems(24,25). Individuals with few deficits are relatively fit, while those with more health problems are increasingly frail and thus more vulnerable to adverse outcomes(26,27). The validity of the FI approach is well-established in non-lupus populations(23,28-31). Recently, we utilized data from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort to construct the first FI specifically for use in SLE(32). We demonstrated a strong association between higher baseline SLICC-FI values and increased risk of subsequent organ damage accrual(33) and mortality(34) among SLE patients.

Given the mortality risk, economic costs, and decreased quality of life associated with hospitalizations in SLE, it would be advantageous to be able to predict which SLE patients are at highest risk for hospitalization. Our primary objective was to estimate the association between baseline SLICC-FI values and the rate of hospitalizations during follow-up in the SLICC inception cohort. A secondary objective was to estimate the association of baseline SLICC-FI scores with the proportion of follow-up time spent hospitalized.

PATIENTS & METHODS

Data source.

This was a secondary analysis of longitudinal data collected in the SLICC inception cohort. The SLICC network comprises 52 investigators at 43 academic centers 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. Patients were enrolled within 15 months of SLE diagnosis, based on the revised ACR classification criteria for SLE(36). Data were collected on 1826 SLE patients per a standardized protocol, submitted to the coordinating centers 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 centers and all participants provided written informed consent.

Patient assessments.

Patients were evaluated at enrolment and annually for the following variables: demographic features (age, sex, race/ethnicity, and education); physical measurements (blood pressure, height and weight); medications (corticosteroids, antimalarials, and immunosuppressives); ACR classification criteria for SLE(36); medical comorbidities; neuropsychiatric events(37,38); SLE disease activity [SLE Disease Activity Index 2000 (SLEDAI-2K)(39)]; cumulative organ damage [SDI(40)]; and health-related quality of life [Medical Outcomes Study Short-Form 36 (SF-36)(41)]. Pertinent laboratory investigations were performed locally at each visit(42).

SLICC-FI construction.

Construction of the SLICC-FI is described in detail elsewhere(32). Briefly, we established a baseline dataset of 1683 patients, consisting of each patient's first SLICC visit at which both the SDI and SF-36 were completed. Variables were selected from the baseline dataset for inclusion 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 patients, and (v) non-missing for ≥95% of patients(23). There was no requirement for the relationships of each individual variable with either age or mortality to reach statistical significance.

Of 222 candidate variables, 48 items met the criteria for inclusion in the SLICC-FI. The 48 health deficits spanned multiple organ systems and included items related to organ damage, disease activity, comorbidities, and functional status. Each health deficit was assigned a scoring system from 0 (deficit completely absent) to 1 (deficit fully present) using definitions from the SLE literature(36,37,39-41). Detailed information is located in the supplementary file.

Baseline SLICC-FI scores were calculated for each patient as the sum of their individual health deficit scores divided by the total number of deficits considered. For example, an individual with 12 of 48 health deficits would have a SLICC-FI score of 12/48=0.25.

Measurement of hospitalizations.

Inpatient hospital admissions were recorded systematically at each follow-up visit. Hospitalizations were initially identified by patient self-report and then confirmed by medical record review. All hospitalizations were recorded, regardless of attribution. The dates of hospital admission and discharge were obtained from the medical record and the length of stay (LOS) was recorded. Patients with no follow-up assessments after their baseline visit were excluded from the analysis.

Using LOS data for each hospitalization, we calculated the total number of follow-up days spent hospitalized for each patient. We were unable to fit regression models to evaluate the relationship of baseline SLICC-FI values with the total number of days spent hospitalized or the average LOS, due to the significant overdispersion and non-normality of these variables. Instead, we calculated the proportion of follow-up time spent hospitalized for each patient with ≥1 hospitalization during follow-up, by dividing the total number of days spent hospitalized by total follow-up time.

Statistical analysis.

Descriptive statistics were calculated for baseline demographic and clinical characteristics, baseline SLICC-FI values, and the number of hospitalizations during follow-up. We compared the rate of hospitalizations per patient-year of follow-up between patients classified as frail at baseline (SLICC-FI>0.21) versus those who were not frail (SLICC-FI≤0.21). This FI cut-off value has been validated in non-SLE populations where FI scores

>0.21 are strongly associated with phenotypic frailty and <5% of individuals with FI scores above this threshold are phenotypically non-frail(28,43,44).

We initially fit Poisson models for the number of hospitalizations during follow-up, which assume that the variance of count data is equal to its mean. However, the observed variability in the number of hospitalizations during follow-up was greater than expected. While the majority of patients were never hospitalized during follow-up, a few patients had very frequent hospital admissions. To accommodate for this overdispersion in the count data, negative binomial regression was used. To account for differential follow-up time, we evaluated the association of baseline SLICC-FI scores with the rate of hospitalizations during follow-up, including follow-up time (in patient-years) as an offset in all models.

To evaluate the association of baseline SLICC-FI scores with the proportion of follow-up time spent in hospital, we log-transformed the outcome variable to achieve normality. We used linear regression to assess the relationship between baseline SLICC-FI values and the proportion of follow-up time spent in hospital (log-transformed), adjusting for total follow-up time (log-transformed). All models met the assumptions of linearity, homoscedasticity and normality of errors required for linear regression.

Similar model-building procedures were used to evaluate the association of baseline SLICC-FI scores with 1) the rate of hospitalizations during follow-up using negative binomial regression; and 2) the proportion of follow-up time spent in hospital (log-transformed) using linear regression. First, a univariable model was constructed with the baseline SLICC-FI (per 0.05 increase) as the independent variable. To identify potential confounders of the relationship between the baseline SLICC-FI and subsequent hospitalizations, we considered demographic and clinical variables previously shown to be associated with hospitalizations in SLE(42,45). Univariable models for the hospitalization outcomes were constructed with each potential confounder as the independent variable. Multivariable models were then constructed, which included the baseline SLICC-FI and any potentially confounding variables with p-values <0.1 in univariable analysis.

For each outcome, we used a likelihood ratio (LR) test to compare the goodness-of-fit of the multivariable model with versus without the inclusion of the baseline SLICC-FI as a predictor variable. We compared the relative performance of these alternative models using Akaike information criterion (AIC), with smaller AIC values indicating better predictive quality. All models were assessed for multicollinearity between independent variables. Data analysis was conducted using STATA-IC Version 14 (StataCorp, TX, USA).

Sensitivity analyses.

The SLICC-FI contains 15 health deficits that are also captured by the SDI (see the supplementary file for details). To determine the relationship between baseline SLICC-FI scores and future hospitalizations independent of baseline organ damage, we repeated the above analyses after removing the overlapping damage items and calculating modified SLICC-FI scores using the remaining 33 deficits. As a large proportion of SLE patients have SDI scores of zero early in disease(42,45), we also investigated whether the SLICC-FI could

predict future hospitalizations among patients without baseline organ damage by repeating the above analyses in the subgroup of patients with SDI=0 at baseline.

For some hospitalizations, LOS was <24 hours. As these events may have represented elective interventions rather than acute medical issues, we repeated the above analyses, excluding all <24-hour hospitalizations. To address the potential impact of differential follow-up, we selected different follow-up time cut-points, based on the 10th percentile (2.5 years), 25th percentile (5 years), 50th percentile (7.5 years), 75th percentile (10 years), and 90th percentile (12.5 years) for follow-up time in the overall dataset. We repeated the primary analysis separately for patients with follow-up time above versus below each cut-point.

RESULTS

Baseline characteristics.

Baseline characteristics of the 1549 eligible patients (92.0% of the baseline dataset; 84.8% of the SLICC cohort) are shown in Table 1. Median (IQR) SLE disease duration at baseline was 1.2 (0.9-1.5) years. Baseline SLICC-FI values ranged from 0.004 to 0.510, with a mean (SD) of 0.17 (0.08). There were 422 patients (27.2%) classified as frail at baseline (SLICC-FI >0.21).

Excluded patients.

143 SLICC patients were excluded from the baseline dataset for SLICC-FI construction due to missing data(32). Specific reasons for exclusion are detailed elsewhere(32). These excluded patients were similar to the patients included in the baseline dataset with respect to their enrolment characteristics(32).

An additional 134 patients (8.0% of the baseline dataset) were excluded from this analysis. One patient was excluded due to insufficient baseline data to calculate a baseline SLICC-FI score. The remaining 133 patients were excluded due to lack of follow-up data on hospitalizations. Eight of these patients died prior to their next follow-up visit, while 125 patients were lost to clinic follow-up. The mortality rate during follow-up was not significantly different between excluded and included patients [8/134 (6.0%) versus 58/1549 (3.7%); p-value=0.196].

There were no significant baseline differences between excluded and included patients with respect to age, sex, educational attainment, SLEDAI-2K scores, therapeutic exposures, or specific SLE manifestations (data not shown). There were differences between excluded and included 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 slightly longer among excluded patients (median 15.6 months versus 14.0 months among included patients; p-value=0.003), resulting in slightly higher baseline SDI scores among excluded patients (mean 0.54 versus 0.40 among included patients; p-value=0.05). Baseline SLICC-FI scores were similar between excluded and included patients (p-value=0.603).

Hospitalizations during follow-up.

Over a mean (SD) follow-up of 7.2 (3.7) years and a total of 11,189 patient-years, 1570 hospitalizations occurred. There were 935 patients (60.4%) without hospitalizations during follow-up. Of the 614 patients with ≥1 hospitalization, 280 (45.6%) had a single hospital admission, while 334 patients had multiple hospitalizations. Overall, the mean (SD) rate of hospitalizations was 0.15 (0.32) per patient-year of follow-up. The mean (SD) LOS was 7.4 (12.4) days with a median (IQR) of 4.5 (3.0-8.3) days. Among patients classified as frail at baseline (SLICC-FI >0.21), the number of hospitalizations per patient-year of follow-up was 90% higher than the rate among non-frail patients [Incidence Rate Ratio (IRR) 1.90, 95%CI 1.54-2.33].

Baseline SLICC-FI scores and the rate of hospitalizations during follow-up.

In unadjusted analysis, each 0.05 increase in baseline SLICC-FI was associated with a 24% increase in the rate of hospitalizations during follow-up (IRR 1.24, 95%CI 1.18-1.32) (Table 3). Evaluating potential confounders of the relationship between baseline SLICC-FI scores and subsequent hospitalizations, we found that younger age, male sex, corticosteroid use, immunosuppressive use, shorter SLE disease duration, and higher baseline SLEDAI-2K and SDI scores were associated with increased rates of hospitalizations per patient-year of follow-up (Table 2). There were also differences in hospitalization rates based on race/ethnicity and geographic region (Table 2) but these were not independent of one another. Therefore, for multivariable analysis, a combined ethnicity/region variable was created.

Each 0.05 increase in the baseline SLICC-FI remained associated with a 21% increase in the number of hospitalizations per patient-year of follow-up (IRR 1.21, 95%CI 1.13-1.30), after adjusting for baseline age, sex, corticosteroid use, immunosuppressive use, ethnicity/location, SLEDAI-2K score, SDI score, and disease duration (Table 3). The addition of the baseline SLICC-FI was associated with significant improvement in the goodness-of-fit [LR test statistic 35.56 ($p<0.001$)] and relative predictive quality (Change in AIC=−33.6) of the multivariable model for future hospitalizations.

Baseline SLICC-FI scores and the proportion of follow-up time spent hospitalized.

Among the 614 patients with ≥1 hospitalization during follow-up, the proportion of follow-up time spent hospitalized ranged from 0.02% to 18.6% with a median (IQR) of 0.33% (0.14%-0.80%). Each 0.05 increase in the baseline SLICC-FI was associated with a 9% increase in the proportion of follow-up time spent hospitalized [Relative Rate (RR) 1.09, 95%CI 1.02-1.16], after adjusting for baseline age, sex, ethnicity/location, corticosteroid use, immunosuppressive use, SLEDAI-2K score, SDI score, and follow-up time in years (log-transformed) (Table 4). Both goodness-of-fit [LR test statistic 6.19 ($p=0.013$)] and relative predictive quality (Change in AIC=−4.2) were improved with the addition of the baseline SLICC-FI to the multivariable model.

Sensitivity analyses.

The relationship between higher baseline SLICC-FI values and increased rate of hospitalizations during follow-up remained significant after removing damage-related items and calculating modified SLICC-FI scores using the remaining 33 health deficits (Table 3)

Similarly, among individuals with ≥1 hospitalization during follow-up, baseline values for the modified SLICC-FI remained significantly associated with the proportion of follow-up time spent hospitalized (Table 4).

Among the 1179 patients with baseline SDI=0, 450 (38.2%) had ≥1 hospitalization during a mean (SD) follow-up interval of 7.3 (3.6) years. In this subgroup, higher baseline SLICC-FI scores remained associated with a significant increase in the rate of subsequent hospitalizations (Table 3). Among patients without baseline damage but with ≥1 hospitalization during follow-up, higher baseline SLICC-FI values predicted a greater proportion of follow-up time spent hospitalized (Table 4).

In the sensitivity analysis stratified by follow-up time (Table 5), a consistent relationship between higher baseline SLICC-FI scores and increased rate of hospitalizations per patient-year of follow-up was maintained in all subgroups. Finally, 107 hospital admissions were <24 hours in duration. Our results were unchanged when these hospitalizations were excluded from the analysis (Table 3; Table 4).

DISCUSSION

In an international disease inception cohort of SLE patients, we demonstrated an association between baseline SLICC-FI values and the rate of all-cause hospitalizations during follow-up. Higher levels of baseline frailty were associated with more frequent hospital admissions, independent of other baseline characteristics previously shown to predict hospitalizations in SLE. Furthermore, among patients with at least one hospitalization, higher baseline SLICC-FI scores were associated with a greater proportion of follow-up time spent hospitalized.

Our results highlight the added value of the SLICC-FI for predicting future hospitalizations when considered in addition to existing prognostic factors in SLE. These findings add to our previous work showing an association between baseline SLICC-FI values and increased risk of damage accrual(33) and mortality(34) in the SLICC inception cohort. The ability of the SLICC-FI to predict multiple adverse health outcomes among incident SLE patients suggests that it is a robust measure of vulnerability in this population.

Health problems rarely occur in isolation, especially in patients with a complex, systemic disease like SLE. Prior SLE studies have shown that the presence of multisystem involvement and the number of organ systems affected are associated with more frequent hospitalizations, increased risk of readmission, longer admissions, and increased in-hospital mortality(1,4,16). These findings are likely explained by a loss of physiologic reserve as health problems accumulate, impairing the individual's ability to respond to and recover from future health challenges. In an individual with many preexisting deficits, new health threats are more likely to result in severe illness requiring hospitalization.

The SLICC-FI extends this deficit accumulation approach to capture the cumulative impact of the totality of an individual's health issues, regardless of whether the deficits represent manifestations of SLE, complications of its treatment, or unrelated comorbidities. Acknowledging that health deficits contribute to an individual's risk of adverse outcomes irrespective of their attribution may aid the prediction of hospitalizations, which often

result from complex, inter-related health and social issues. A more holistic approach to prognostication may be particularly relevant for patients with SLE, in whom attribution of a health issue to a single, underlying cause is often difficult to ascertain.

Traditionally, the core dimensions of SLE – disease activity, organ damage, and health-related quality of life – have been evaluated separately. However, this approach fails to capture interactions between these domains and their potential impact on prognosis. Conversely, the relationships that exist between deficits from different domains within the SLICC-FI are essential to its performance as a predictive tool. For example, the scoring of the "Cerebrovascular Disease" health deficit weighs transient ischemic attacks and debilitating strokes equally, despite clear differences in their likely impact on prognosis. However, an individual with a disabling stroke will likely have additional deficits related to their functional status, resulting in a higher SLICC-FI score. Thus, incorporating deficits from different domains into a single measure ensures that the overall impact of complex health events is accurately represented in the SLICC-FI. As this inter-relatedness of health deficits from different domains contributes significantly to the prognostic value of the frailty index, examining its components separately is unlikely to provide additional insights and is not typically advised(25).

SLE patients in different geographic regions demonstrated significant variability in hospitalization rates, which was not fully explained by differences in disease characteristics. Other possible explanations include variation in healthcare funding models, accessibility of healthcare resources, and clinical practice patterns. Importantly, despite these regional differences in hospitalization rates, a consistent relationship between higher baseline SLICC-FI values and more frequent hospitalizations during follow-up was maintained across all five geographic regions, suggesting that the performance of the SLICC-FI as a prognostic tool may be robust to differences in healthcare delivery.

Organ damage, measured using the SDI, is an important predictor of adverse outcomes in SLE, including hospitalizations(15,35). Some may question whether the relationship between baseline SLICC-FI scores and future hospitalizations is reliant upon the inclusion of deficits related to organ damage. However, in our sensitivity analysis, the relationship between the modified SLICC-FI and future hospitalizations persisted, despite removal of items related to organ damage from the index. This suggests that it is not only organ damage, but the global effect of deficit accumulation, that is driving the association of baseline SLICC-FI values with future hospitalizations. As a proportion of SLE patients remain free of organ damage captured by the SDI for several years following diagnosis(42,45), the added prognostic value of the SLICC-FI may be greatest early in disease, as demonstrated in our subgroup analysis of patients without baseline organ damage, in whom baseline SLICC-FI scores remained predictive of future hospitalizations.

Prior work suggests that a considerable proportion of hospitalizations among SLE patients are potentially preventable(47). Patients at high-risk for hospitalization based on their SLICC-FI score could be identified for closer outpatient monitoring or more aggressive outpatient therapies to potentially avoid hospital admission. To guide the development of such interventions, it would be important to determine whether SLICC-FI values are

more strongly associated with hospitalization for certain indications, such as infections, SLE flares, or thromboembolic events. Unfortunately, data regarding the most responsible diagnosis for each hospitalization were not available for this analysis.

There are many factors that could contribute to the association between baseline SLICC-FI scores and the proportion of follow-up time spent hospitalized. One hypothesis is that a new health event will lead to more severe illness and slower recovery in a frail individual, resulting in a more prolonged hospitalization. Data regarding illness severity was not available for the SLICC inception cohort, limiting our ability to explore this further. Another potential determinant of hospital LOS is social vulnerability. Studies show that many components of social vulnerability, such as low socioeconomic status, housing instability, and social isolation, behave similarly to health deficits by accumulating slowly over time and strongly associating with adverse health outcomes(48). While social factors are often adjusted for separately(48), these variables have also been successfully included as health deficits in an FI(49). Unfortunately, we could not assess the influence of social vulnerability on the relationship between baseline SLICC-FI scores and future hospitalizations due to a lack of available data in the SLICC inception cohort.

This study focused on the prediction of future hospitalizations based on information available to clinicians early in the course of incident SLE. While the current analysis provides relevant information for clinical decision-making early in disease, the impact of changes in SLICC-FI scores over time remains unclear. Recent studies in non-SLE populations suggest that rapidly increasing frailty is associated with worse health outcomes when compared to arriving at the same level of frailty more slowly(50). Therefore, future work should aim to understand the trajectories of SLICC-FI scores over time and how different trajectories relate to the risk of adverse outcomes in SLE. This longitudinal analysis would also provide valuable insights to inform recommendations regarding the optimal frequency of SLICC-FI measurement in clinical practice.

Our study has important limitations. First, observation time differed between patients, which could introduce bias if the association between the SLICC-FI and future hospitalizations varies depending on follow-up time. However, our sensitivity analysis demonstrated a consistent association between baseline SLICC-FI values and future hospitalizations across follow-up time strata, suggesting that this was not a major concern. Second, 277 patients (15.2% of the cohort) were excluded due to missing data. However, we did not identify any major demographic or clinical differences between exclude and included patients that would have biased our results, suggesting that our dataset remains representative. Last, the SLICC-FI has been constructed and evaluated in a cohort of relatively young, recently-diagnosed SLE patients managed in specialized clinics at academic centers. It remains unclear whether these findings can be generalized to other SLE populations, such as older patients with longstanding SLE. External validation of the SLICC-FI in other cohorts is required to confirm our results.

In conclusion, the SLICC-FI predicted future hospitalizations in a cohort of relatively young patients with recently diagnosed SLE. While additional validation studies are needed, the SLICC-FI holds potential value as a method for identifying the most vulnerable SLE

patients who may benefit from closer outpatient monitoring to prevent costly hospital admissions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovations

- The Systemic Lupus International Collaborating Clinics (SLICC) frailty index (FI) predicts the rate of all-cause hospitalizations during follow-up among SLE patients in the SLICC inception cohort, independent of other patient characteristics known to be associated with hospitalizations in SLE.
- The SLICC-FI has now been shown to predict multiple adverse health outcomes among SLE patients, including hospitalizations, organ damage accrual, and mortality, suggesting that it is a robust measure of vulnerability in this population.
- Following external validation, the SLICC-FI may be a useful prognostic tool for identifying high-risk SLE patients who may benefit from closer outpatient monitoring or more aggressive outpatient interventions to prevent hospital admissions.

Table 1.

Baseline demographic and clinical characteristics for all SLE patients (n=1549) and for the subgroup who were hospitalized at least once during follow-up (n=614).

Variables	All patients (n=1549)	Hospitalized patients (n=614)
Age at baseline (years)		
Mean (S.D.)	35.7 (13.3)	34.0 (13.4)
Sex		
Female, n (%)	1374 (88.7)	539 (87.8)
Race/Ethnicity		
Caucasian, n (%)	767 (49.5)	264 (43.0)
Black, n (%)	249 (16.1)	97 (15.8)
Asian, n (%)	245 (15.8)	139 (22.6)
Hispanic, n (%)	236 (15.2)	88 (14.3)
Other, n (%)	52 (3.4)	26 (4.2)
Region		
United States, n (%)	393 (25.4)	121 (19.7)
Canada, n (%)	377 (24.3)	148 (24.1)
Mexico, n (%)	192 (12.4)	73 (11.9)
Europe, n (%)	433 (28.0)	161 (26.2)
Asia, n (%)	154 (9.9)	111 (18.1)
Education		
Post-secondary education, n (%)	782 (50.5)	285 (46.4)
Missing, n (%)	21 (1.4)	10 (1.6)
SLE disease duration (years)		
Median (I.Q.R.)	1.2 (0.9-1.5)	1.2 (0.9-1.5)
SLEDAI-2K		
Median (I.Q.R.)	2 (0-6)	4 (2-6)
Missing, n (%)	5 (0.3)	2 (0.3)
SLICC/ACR Damage Index (SDI)		
Baseline SDI = 0, n (%)	1179 (76.1)	450 (73.3)
Medication use		
Corticosteroids, n (%)	1089 (70.3)	470 (76.5)
Antimalarials, n (%)	1048 (67.7)	412 (67.1)
Immunosuppressives, n (%)	631 (40.8)	278 (45.3)
SLICC Frailty Index (SLICC-FI)		
Mean (S.D.)	0.167 (0.079)	0.178 (0.082)

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 number of hospitalizations per patient-year of follow-up among SLE patients in the baseline dataset (n=1549).

Independent variable	Incidence Rate Ratio (95% CI)	p value
Baseline age (years)	0.99 (0.98 – 1.00)	0.001
Sex: Female	Referent	
Male	1.36 (1.00 – 1.85)	0.048
Race/ethnicity: Caucasian	Referent	
Hispanic	0.87 (0.63 – 1.18)	0.370
Black	1.58 (1.17 – 2.13)	0.003
Asian	2.03 (1.62 – 2.55)	<0.001
Other	1.83 (1.14– 2.94)	0.012
Geographic location: USA	Referent	
Canada	0.82 (0.60 – 1.12)	0.203
Mexico	0.60 (0.42 – 0.84)	0.003
Europe	0.87 (0.64 – 1.18)	0.355
Asia	2.17 (1.62 – 2.91)	<0.001
Post-secondary education [a]: No	Referent	
Yes	0.85 (0.70 – 1.04)	0.120
Corticosteroid use: No	Referent	
Yes	1.91 (1.53 – 2.38)	<0.0001
Immunosuppressive use: No	Referent	
Yes	1.49 (1.23 – 1.81)	0.0001
Antimalarial use: No	Referent	
Yes	0.91 (0.73 – 1.13)	0.377
SLEDAI-2K (per 1.0)	1.06 (1.04 – 1.08)	<0.001
SDI (per 1.0)	1.25 (1.13 – 1.38)	<0.001
SLE disease duration (years)	0.99 (0.98 – 1.00)	0.008

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

Notes: SLEDAI-2K = SLE disease activity index 2000; SDI = SLICC/ACR Damage Index.

Table 3.

Univariable and multivariable negative binomial regression models for the association of baseline SLICC-FI scores with the number of hospitalizations per patient-year of follow-up among SLE patients.

	Univariable models		Multivariable models [a]	
	n	**Incidence Rate Ratio (95% CI) [b]**	**n**	**Incidence Rate Ratio (95% CI) [b]**
Main analysis	1549		1541	
SLICC-FI (per 0.05)		1.24 (1.18 – 1.32)		1.21 (1.13 – 1.30)
Modified SLICC-FI [c]	1549		1541	
SLICC-FI (per 0.05)		1.16 (1.11 – 1.21)		1.14 (1.08 – 1.19)
>24-hour hospitalizations [d]	1549		1541	
SLICC-FI (per 0.05)		1.24 (1.17 – 1.31)		1.22 (1.13 – 1.31)
Baseline SDI=0 subgroup [e]	1179		1173	
SLICC-FI (per 0.05)		1.26 (1.17 – 1.35)		1.26 (1.16 – 1.38)

[a] Model adjusted for the following baseline characteristics: age, sex, ethnicity/location, SLE Disease Activity Index 2000 (SLEDAI-2K), SLICC/ACR Damage Index (SDI), immunosuppressive use, steroid use, and SLE disease duration.

[b] All reported incidence rate ratios associated with p-values < 0.001.

[c] Excludes 15 health deficits related to organ damage. Modified baseline SLICC-FI scores calculated using the remaining 33 health deficits.

[d] Excludes hospital admissions with length-of-stay < 24 hours in duration.

[e] Excludes SLE patients with preexisting organ damage (SDI > 0) at baseline. All included patients had baseline SDI scores of 0, and therefore baseline SDI was omitted from the multivariable model.

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

Table 4.

Unadjusted and adjusted linear regression models for the association of baseline SLICC-FI scores with the proportion of follow-up time spent hospitalized among SLE patients with at least one hospitalization during follow-up.

	Unadjusted models [a]		Adjusted models [b]	
	n	Relative Rate [c] (95% CI)	n	Relative Rate [c] (95% CI)
Main analysis	614		610	
SLICC-FI (per 0.05)		1.10 (1.04 – 1.17)		1.09 (1.02 – 1.16)
Modified SLICC-FI [d]	614		610	
SLICC-FI (per 0.05)		1.06 (1.01 – 1.11)		1.05 (1.00 – 1.10)
>24-hour hospitalizations [e]	579		575	
SLICC-FI (per 0.05)		1.10 (1.03 – 1.18)		1.08 (1.00 – 1.16)
Baseline SDI=0 subgroup [f]	450		447	
SLICC-FI (per 0.05)		1.10 (1.02 – 1.19)		1.13 (1.05 – 1.22)

[a] Model adjusted for follow-up time in years (log-transformed) only.

[b] Model adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLE disease activity index (SLEDAI-2K), SLICC/ACR Damage Index (SDI), and follow-up time in years (log-transformed).

[c] Log-transformed outcome; regression coefficients (β) and 95% CI back-transformed, exp (β), as relative rate and 95% CI.

[d] Excludes 15 health deficits related to organ damage. Modified baseline SLICC-FI scores calculated using the remaining 33 health deficits.

[e] Excludes hospital admissions with length-of-stay < 24 hours in duration.

[f] Excludes SLE patients with preexisting organ damage (SDI > 0) at baseline. All included patients had baseline SDI scores of 0, and therefore baseline SDI was omitted from the multivariable model.

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

Table 5.

Sensitivity analysis evaluating the impact of follow-up time on the association of baseline SLICC-FI values with the number of hospitalizations per patient-year of follow-up among SLE patients in the SLICC inception cohort.

	Univariable model	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)	1.55 (1.27 – 1.91)	1.35 (1.04 – 1.75)
> 2.5 years follow-up (n=1361)	1.22 (1.15 – 1.30)	1.21 (1.12 – 1.30)
Cut point: 5.0 years follow-up		
≤ 5.0 years follow-up (n=484)	1.31 (1.17 – 1.46)	1.19 (1.06 – 1.35)
> 5.0 years follow-up (n=1065)	1.21 (1.13 – 1.30)	1.22 (1.13 – 1.31)
Cut point: 7.5 years follow-up		
≤ 7.5 years follow-up (n=824)	1.27 (1.18 – 1.37)	1.21 (1.10 – 1.33)
> 7.5 years follow-up (n=725)	1.21 (1.11 – 1.31)	1.23 (1.12 – 1.35)
Cut point: 10.0 years follow-up		
≤ 10.0 years follow-up (n=1184)	1.24 (1.16 – 1.32)	1.20 (1.11 – 1.30)
> 10.0 years follow-up (n=365)	1.26 (1.11 – 1.43)	1.24 (1.07 – 1.43)
Cut point: 12.5 years follow-up		
≤ 12.5 years follow-up (n=1395)	1.23 (1.16 – 1.31)	1.19 (1.11 – 1.28)
> 12.5 years follow-up (n=154)	1.34 (1.14 – 1.58)	1.41 (1.15 – 1.72)

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLE disease activity index (SLEDAI-2K), SLICC/ACR Damage Index (SDI), and SLE disease duration.

[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.