CONSTRUCTING AND VALIDATING A FRAILTY INDEX AS A NOVEL HEALTH MEASURE IN SYSTEMIC LUPUS ERYTHEMATOSUS

by

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For my father.

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ABSTRACT

For patients with systemic lupus erythematosus (SLE), clinical outcomes are highly variable and challenging to predict. Such differences in susceptibility to adverse health outcomes can be quantified using a frailty index (FI). We used data from an international cohort of recently-diagnosed SLE patients to construct and validate the first FI for patients with SLE, to be known as the SLICC-FI. We assessed whether the SLICC-FI was predictive of future adverse health outcomes including hospitalizations, organ damage and mortality, after adjustment for the SLICC/ACR Damage Index (SDI), a known prognostic factor in SLE. Higher baseline SLICC-FI scores were associated with more hospitalizations, increased organ damage accrual, and increased mortality risk during follow-up. For all three outcomes, the SLICC-FI improved prediction when compared to the SDI alone. The SLICC-FI holds potential value in quantifying vulnerability among patients with SLE and provides additional prognostic information when compared to existing SLE measures.

LIST OF ABBREVIATIONS USED

SLE	Systemic lupus erythematosus
FI	Frailty index
SLICC	Systemic Lupus International Collaborating Clinics
SLICC-FI	Systemic Lupus International Collaborating Clinics Frailty Index
HRQoL	Health-related Quality of Life
SLAM	Systemic Lupus Activity Measure
BILAG-2004	Updated Version of the British Isles Lupus Assessment Group
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
ACR	American College of Rheumatology
SDI	SLICC/ACR Damage Index
MOS SF-36	Medical Outcomes Study Short Form 36
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
BMI	Body mass index
95% CI	95% confidence interval
SD	Standard deviation
IQR	Interquartile range
r	Pearson correlation coefficient
r_s	Spearman rank correlation coefficient
R^2	Coefficient of determination
HR	Hazard ratio
IRR	Incidence rate ratio

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CHAPTER 1: INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease of unknown etiology that can involve any organ system in the human body. Although arthritis and skin disease are frequent manifestations, involvement of organs such as the lungs, kidneys, and nervous system account for the majority of the morbidity and mortality attributable to SLE[1]. Overall survival in SLE patients has improved substantially in recent years[2-4], but mortality remains higher than expected in the affected age group[2-6], and irreversible organ damage as a consequence of both the disease and its treatment is well recognized. The clinical course of SLE is variable and unpredictable, ranging from a relatively benign illness to gradually progressive organ damage, fulminant organ failure, and even death. Given this variability in health trajectories, it would be extremely advantageous to be able to identify those SLE patients, ideally early in their disease, who are at increased risk for later adverse outcomes. Recognition of these high-risk individuals would allow for closer disease monitoring and more aggressive therapeutic interventions that could alter the disease course and improve long-term outcomes. However, SLE-specific instruments allowing us to prognosticate effectively are currently limited.

In geriatric medicine[7], and increasingly in other disciplines[8-10], differences in susceptibility to adverse outcomes are quantified using the construct of frailty. One method used to operationalize frailty in several prior studies in non-SLE populations is the construction of a frailty index (FI)[11]. This approach views frailty as a loss of physiologic reserve that arises from the accumulation of health deficits across multiple

systems[12]. Individuals with few deficits are relatively fit, while those with an increasing number of health deficits are considered increasingly frail, and therefore at greater risk for adverse outcomes[13]. Indeed, prior work utilizing the FI in non-SLE populations has demonstrated a clear association between higher FI scores and increased risk of future adverse health outcomes, including hospitalizations, morbidity, and mortality[11,14-17]. Given the multisystem nature of SLE, the evaluation of frailty through deficit accumulation using an FI approach may advance our understanding of the unexplained heterogeneity in health trajectories observed among patients with SLE.

The Systemic Lupus International Collaborating Clinics (SLICC) is an international research network of 52 SLE investigators from 43 academic medical centres in 16 countries. From 1999-2011, recently-diagnosed SLE patients from 31 SLICC sites were enrolled into the SLICC inception cohort, which is a multi-centre, international, prospective cohort of SLE patients evaluated from the time of diagnosis with extensive annual assessments. At 1826 patients, it is the largest inception cohort of SLE patients ever assembled.

This thesis used longitudinal data from the SLICC inception cohort to construct and validate the first frailty index for use in patients with SLE, to be known as the SLICC-FI. As part of our validation procedure, we estimated the association of SLICC-FI scores with the risk of future adverse health outcomes, including hospitalizations, organ damage accrual, and mortality. In keeping with the findings of prior FI studies conducted in non-SLE populations[11,14-17], it was expected that higher SLICC-FI values would be associated

with increased risk of future adverse outcomes. Following construction and validation, the predictive validity of the SLICC-FI for future health outcomes was compared to the predictive validity of existing measures of disease status in SLE, to determine whether the SLICC-FI could provide additional prognostic information when compared to currently used SLE instruments.

This thesis document provides a review of the literature in Chapter 2. Chapters 3, 4, 5, and 6 present the results from four separate studies, in the form of research manuscripts suitable for publication in scientific journals. Chapter 3 describes the construction of the SLICC-FI, while Chapter 4 outlines the validation of the SLICC-FI, including an assessment of its predictive validity for mortality. Chapter 5 examines the relationship between the SLICC-FI and future organ damage accrual, while Chapter 6 investigates the association between the SLICC-FI and future hospitalizations. Finally, Chapter 7 offers a conclusion of the full master's thesis project.

CHAPTER 2: LITERATURE REVIEW

2.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune inflammatory disease with complex pathogenesis. It can cause dysfunction and damage to any organ system in the human body, potentially leading to significant disability and even death. SLE typically presents between the ages of 15 to 45 years, and occurs more frequently in women than in men, at a 6-9:1 ratio[18,19]. The reported worldwide incidence and prevalence of SLE vary considerably, with estimates of overall incidence ranging from 0.3-31.5 cases per 100,000 per year[19-21], and overall prevalence estimates ranging from 3.2-517.5 cases per 100,000 individuals[19,20,22]. This substantial variation is likely related, in part, to methodological differences in case identification and data collection. Recent studies using more rigorous case ascertainment strategies have yielded more consistent estimates, with reported incidence rates of 1.0-9.9 cases per 100,000 per year[23-27] and reported overall prevalence of 20.6-97.5 cases per 100,000[23-28]. Ethnic/racial differences account for much of the remaining disparity in incidence and prevalence rates, as SLE is known to occur more commonly in certain populations, including individuals of African, Asian, Hispanic and Aboriginal ancestry[26,29-32].

SLE is a heterogeneous disease with a tremendously diverse range of possible disease manifestations. While arthritis and inflammatory skin disease occur most frequently, involvement of vital organs including the lungs, kidneys, and nervous system account for the majority of the morbidity and mortality attributable to SLE[1]. As it commonly affects women of childbearing age, SLE can also lead to a number of maternal and fetal

complications during pregnancy[33]. As well, compared to non-SLE populations, patients with SLE are known to be at increased risk of developing malignancies[34], cardiovascular disease[4,35], cerebrovascular disease[3,36] and end-stage renal disease[37] as a consequence of both the disease and its treatments.

Increased all-cause mortality among patients with SLE compared to the general population is well-recognized[38]. The most common causes of death among SLE patients include cardiovascular disease, infection, and active SLE itself[3,4,6,36,38,39]. Mortality in SLE has been described as following a bimodal distribution, with deaths occurring early in the disease course related to complications of active disease and severe infections due to immunosuppression, while causes of late death include end-stage renal disease and cardiovascular disease[38]. While studies have demonstrated significant improvements in SLE mortality over the last several decades[2-4], this is more likely related to increased recognition and reporting of mild cases and earlier diagnosis, as opposed to significant innovations in the treatment of SLE. Recent findings suggest that mortality among patients with SLE is still two to five times higher than age- and sex-matched controls[2-6]. In particular, certain subgroups of SLE patients are disproportionately affected by increased mortality risk, including men, certain ethnic/racial groups, and patients with lower socioeconomic status[38,40-42].

In addition to causing significant organ damage and mortality, the social and economic costs of SLE are substantial. Direct healthcare costs for SLE patients have been estimated at $33,223 US dollars per patient per year, with costs as high as $71,334 per patient per

year for patients with lupus nephritis[19]. As SLE commonly affects individuals during the most productive years of their life, it is also associated with major indirect costs related to high rates of work disability[43-47]. Beyond the financial burden, SLE is known to have a negative impact on all aspects of health-related quality of life (HRQoL)[48]. Patients with SLE report significantly lower HRQoL than both the general population, as well as patients with other chronic diseases[29,43,48]. Therefore, while less tangible than the economic costs, the psychosocial burden of SLE is also important and should not be overlooked.

2.2 Outcomes assessment and prognostic measures in SLE

The natural history of SLE is highly variable and challenging to predict[19]. For some patients, it is a relatively benign illness characterized by mild musculoskeletal or dermatologic manifestations and minimal impact on daily activities. Others will experience recurrent disease flares, gradually progressive organ damage, and significant disability over time. Finally, for some patients, the presentation of SLE can be catastrophic and rapidly fatal. Thus, a comprehensive, objective assessment of disease status in SLE is required in order to accurately stratify patients based on their risk of future adverse outcomes. Currently, it is recommended that studies in SLE evaluate patients across three core dimensions – inflammatory disease activity, organ damage, and health-related quality of life[49]. Multiple measurement tools have been developed and validated to assess each of these three domains.

2.2.1 Measures of disease activity

The measurement of disease activity in SLE is essential for both clinical decision-making and research purposes. Several disease-specific activity measures for SLE have been developed, validated, and used in observational studies and clinical trials. These include the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[50], the Systemic Lupus Activity Measure (SLAM)[51], and the British Isles Lupus Assessment Group (BILAG)[52] index. Studies have demonstrated that SLEDAI, SLAM, and BILAG scores correlate well with one another[53].

The two most commonly used disease activity measures in SLE studies include the SLEDAI and the BILAG Index. The SLEDAI-2K, an updated version of the original SLEDAI tool, is a global activity score based on the presence or absence of clinical features or laboratory abnormalities within 10 days of the evaluation. It is based on 24 variables, weighted across 9 organ systems, which are combined in an additive fashion to produce a total score[50]. While the SLEDAI-2K score is easy to administer, it has been criticized for its inability to capture the range of activity within organ systems[49,54].

In contrast to the SLEDAI-2K, the BILAG measures SLE disease activity over the past four weeks and provides individual organ-specific activity scores, in addition to a global activity measure[49,54]. It also allows for assessment of changes in disease state over time, such as improvement, stability, or worsening of disease manifestations[54]. The major advantage of the BILAG is its sensitivity to changes in disease activity. Compared to the SLEDAI-2K, the BILAG-2004 has been shown to better detect active disease requiring

escalation of disease-modifying therapy[52]. The major disadvantage of the BILAG is its complexity. With over 100 variables, it requires extensive formal training to use correctly and can be time-consuming to administer[49,54].

A shared characteristic of all existing disease activity measures in SLE is that only manifestations directly attributable to SLE are considered, and therefore the same abnormalities not attributable to SLE, such as treatment complications or other comorbidities, are not captured. Thus, activity measures only provide a portion of the information required for accurate prognostication in SLE. This may explain why studies examining the relationship between disease activity and clinical outcomes, such as mortality, have failed to consistently demonstrate clear associations[53].

2.2.2 Measures of organ damage

The SLICC/American College of Rheumatology (ACR) Damage Index (SDI) was developed to reflect multisystem, cumulative organ damage in SLE patients over the course of their disease[55]. It is the only validated measure of damage and is frequently used in observational studies and clinical trials in SLE. The SDI measures irreversible damage across twelve organ systems, regardless of attribution. In order to be included in the SDI, damage items must be present for at least six months and must have occurred after the diagnosis of SLE. The SDI has been extensively validated and has been demonstrated to be sensitive to changes in organ damage over time, regardless of baseline SDI scores[55]. Furthermore, the SDI has been shown to predict adverse outcomes in SLE,

including hospitalizations[56,57], future damage accrual[58,59], and mortality[58,60-62], making it one of the most useful tools currently available for prognostication in SLE.

A major advantage of the SDI is its ability to capture not only damage directly attributable to SLE, but also damage related to adverse treatment effects and sequelae from longstanding SLE, such as atherosclerotic disease[54]. However, the SDI does not capture organ damage accrued prior to SLE diagnosis and fails to consider the patient's perspective of their health status - both of which may provide additional prognostic information. Finally, once recorded in the SDI, damage items are permanent such that SDI scores cannot decrease over time, thereby limiting the capacity of the SDI to measure improvement in risk status over time.

2.2.3 Measures of health-related quality of life

Health-related quality of life (HRQoL) encompasses the physical, psychological, and social aspects of health and the impact of disease, which are heavily influenced by life experiences and expectations that are specific to each patient[63]. HRQoL is distinct from disease activity or organ damage, and is a critical outcome in studies of SLE[48,49]. Both generic and disease-specific patient-reported outcome measures have been used to measure HRQoL in SLE populations[49,64,65]. The most widely-used generic instrument is the Medical Outcomes Study (MOS) Short Form-36 (SF-36). The SF-36 includes thirty-six questions across eight domains designed to capture the patient-reported impact of disease on both physical and mental health. It has been extensively validated in SLE[48,49,65]. Recently, several disease-specific questionnaires have also been developed to

measure HRQoL in SLE, with the goal of improving content validity for SLE compared with generic measures[64]. However, whether these SLE-specific measures offer significant advantages over generic instruments, such as the SF-36, remains unclear and these disease-specific measures require further validation in more diverse SLE populations[49]. While measures of HRQoL provide crucial insight into patients' perspectives of disease impact, the correlation of HRQoL with future adverse clinical outcomes in SLE remains inadequately studied. Thus, the value of HRQoL for prognostication in SLE is poorly understood.

2.2.4 Limitations of current prognostic measures in SLE

Studies evaluating the associations between disease activity, organ damage, and HRQoL have demonstrated that these relationships are extremely complex and variable over time. In particular, measures of disease activity and organ damage seem to correlate poorly with HRQoL, suggesting that these instruments may be poor indicators of overall health status in SLE[48]. Furthermore, it remains unclear how best to aggregate information from across these three SLE disease dimensions to produce an overall estimate of prognosis. More holistic outcome measures are needed that incorporate aspects of each of these dimensions into a single instrument, capturing the impact of SLE disease activity, adverse treatment effects, and comorbidities from both the physician and patient perspectives. Such tools would likely provide a more accurate assessment of overall health status and could improve prognostication in SLE. To this end, the concept of frailty may be well-suited to aid in our understanding of the heterogeneous health outcomes observed among patients with SLE.

2.3 Frailty as a measure of vulnerability

Individuals of the same chronological age may vary considerably in terms of their health status and life expectancy. The propensity for certain individuals to experience increased vulnerability to adverse health outcomes is known as frailty[12]. While frailty has become a topic of interest across a wide range of medical disciplines[8,9,80-83], the concept initially emerged in the geriatric medicine literature through the study of community-dwelling older adults[7]. There is considerable ongoing debate regarding how best to define and operationalize frailty[13], and various types of instruments for the measurement of frailty have been developed[66-68]. The two most common approaches to conceptualizing frailty are the phenotypic approach and deficit accumulation approach[13], both of which will be discussed in greater detail.

2.3.1 The phenotypic approach to frailty

The phenotypic approach views frailty as a biological syndrome characterized by a cluster of physiologic signs and symptoms commonly observed in vulnerable older adults[13]. The original frailty phenotype, published in 2001 by Fried and colleagues[69], determined the presence or absence of frailty based on five clinical criteria: weight loss, exhaustion, physical inactivity, slow walking speed, and reduced grip strength. Individuals meeting three or more of these criteria are classified as frail, those with one or two criteria are said to be "prefrail", and those meeting none of the criteria are considered nonfrail or robust[69]. Predictive validity analyses have demonstrated that individuals meeting the phenotypic criteria for frailty are at significantly higher risk for falls, hospitalization, institutionalization, and death when compared to nonfrail individuals[13].

Since its initial publication, the frailty phenotype has become a popular clinical and research tool for identifying frailty in older adults. However, measurement strategies for the phenotypic criteria have varied widely across studies, with a recent systematic review identifying 262 modifications to the initial criteria in the literature[67]. These modifications have led to significant variability in estimates of the prevalence of frailty, as well as differences in the predictive ability of the phenotype, limiting the comparability of studies using this frailty definition[67]. While the advantages of this approach include its physiological basis and its ease of use in older adults, the generalizability of this conceptual approach to frailty in other populations, including clinical cohorts, has been questioned.

Recently, the frailty phenotype was investigated in a prevalent cohort of 152 women with SLE[70]. In this study, 20.4% of SLE patients were classified as frail and 50.7% as prefrail[70]. This is a very high prevalence of frailty when compared to individuals of similar age in the general population. The presence of frailty at baseline was associated with increased risk of functional decline, cognitive impairment, and mortality during a mean follow-up time of 7.2 years, suggesting that this operationalization of frailty may be relevant in SLE[70]. However, the authors also noted that certain components of the frailty phenotype, as defined in geriatric medicine, had limited utility in SLE, including slow walking speed and exhaustion[70]. Therefore, the authors suggested that lupus-specific measures of frailty may better quantify vulnerability in this population[70].

2.3.2 The deficit accumulation approach to frailty

The deficit accumulation approach conceptualizes frailty as a multidimensional risk state that can be measured by the quantity rather than the specific nature of health problems[12,13]. In this model, frailty reflects a stochastic dynamic process in a system with high redundancy of multiple interdependent items. This approach views frailty as an accumulation of deficits that impair the ability of the system to recover from their impact and withstand future insults[12,13]. In other words, this approach suggests that frailty is a loss of physiologic reserve that arises from the accumulation of health deficits over time. As health deficits accumulate, they impair the ability of the individual to respond to and recover from future health challenges. By this approach, it is the number of health deficits, rather than the nature of individual deficits, that is crucial. Individuals with few deficits are relatively fit, while those with an increasing number of health deficits are considered increasingly frail, and therefore at greater risk for adverse health outcomes. Because individuals may accrue deficits at different rates, the deficit accumulation approach may aid in our understanding of the differential vulnerability to adverse outcomes observed in individuals of the same chronological age.

2.4 The Frailty Index (FI)

2.4.1 Frailty operationalized using the frailty index

The deficit approach to frailty can be operationalized through the use of a frailty index (FI)[13]. An FI can be developed from any existing health dataset using a standard procedure outlined by Searle and colleagues[11]. In brief, a frailty index is constructed using a set of health deficits, where a single health deficit can be any symptom, sign,

functional impairment, or laboratory abnormality meeting the criteria of being acquired, associated with adverse outcomes, and associated with increasing age[11]. If deficits are either too infrequent (prevalence < 1%) or too common (prevalence > 80%) in the dataset, they are unlikely to provide meaningful information when included in an FI, and thus should be excluded[11]. If a single item is missing values for >5% of the sample, it should not be included as a health deficit in an FI[11].

As a whole, the health deficits included in an FI must cover several organ systems. Furthermore, it is important to remember that the concept of frailty is not merely a measure of cumulative damage, but also a measure of an individual's potential for recovery or repair. Therefore, in addition to disease manifestations and comorbidities, it is crucial for a frailty index to also include other variables that can impact repair potential, including measures of function and mobility. Once identified, each health deficit is assigned a scoring system from 0 to 1, with a score of 0 representing no deficit, a score of 1 representing the deficit fully expressed, and intermediate scores indicating that the deficit is partially expressed[11]. Finally, a patient's scores for individual deficits are combined to produce an FI score, which is a proportion, between 0 and 1, calculated from the sum of individual health deficit scores divided by the total number of deficits that were considered[11]. As individuals may become frail via multiple different pathways, a large number of variables is typically required in order to capture all aspects of frailty. Prior studies suggest that at least 30-40 health deficits should be included in an FI in order to achieve stable and precise estimates of frailty[71].

2.4.2 The properties of the frailty index

Previous work utilizing the FI in community-dwelling older adults has yielded remarkably consistent data across a wide range of studies conducted in different settings. For example, each study has demonstrated a clear association between higher FI scores and increased risk of adverse outcomes, including mortality, institutionalization, and worsening health status[11,15,72-75]. In general, FI scores in these population samples of older adults tend to approximate a gamma distribution[11,15]. The rate of deficit accumulation with increasing age has also remained stable across several different cohorts, with individuals accumulating deficits at an average rate of 3% per year after the age of 70[11,15,72,75]. Women consistently accumulate more deficits than men of similar age[71]. In addition, there appears to be a biological limit to the number of health deficits an individual can accumulate, beyond which any further deficit accumulation is incompatible with life. Frailty index measures have consistently yielded a sub-maximal limit of approximately 0.70, or 70% of the total deficits considered[11,15,72]. The reproducibility of these findings is of particular interest given that the FI measures described were constructed from separate datasets using different types and numbers of health deficits, based on the availability of data. This suggests that the concept of frailty in relation to deficit accumulation is robust and generalizable.

2.4.3 Applications of the frailty index to other populations

Although the majority of prior studies using the FI have focused on older adults, it has been demonstrated that frailty exists across the adult lifespan and is not solely an issue of the aged, but of the aging process itself. A 2011 study by Rockwood and colleagues

analyzed longitudinal data from the National Population Health Survey, which included 14,713 Canadian adults between 15-102 years of age at baseline[14]. Using an FI constructed from 42 self-report variables, the prevalence of frailty increased exponentially with age, even in the youngest age group[14]. Higher FI scores were associated with increased mortality and increased use of health care services across all age groups[14]. Interestingly, although the absolute mortality risk associated with frailty increased with increasing age, the relative risk of mortality in relation to frailty was highest in younger age groups[14], suggesting that the concept of frailty is highly relevant and important for the prediction of adverse outcomes in younger adults.

Researchers are now exploring the capabilities of the FI to quantify vulnerability to adverse outcomes in other populations. Recently, the FI has been applied to several disease-specific clinical cohorts, including patients with chronic kidney disease[76] and human immunodeficiency virus[77]. Thus far, it appears that many of the properties of the FI described in geriatric cohorts are also valid in these disease-specific patient populations. For example, in clinical samples, FI scores have demonstrated similar submaximal limits of no more than 0.7[16,17]. Most importantly, higher FI values continue to predict future adverse health outcomes, including mortality[16,17,76]. However, there are also a few notable differences. For example, in some clinical samples, FI scores have been found to be normally distributed[16]. Finally, the relationship between chronological age and FI scores tends to be less pronounced in clinical samples when compared to population-based samples[17]. This may reflect the potential for individuals with chronic illnesses to exhibit significant frailty at young ages.

In a 2014 study, Canadian registry data was used to construct and validate an FI for use in patients with scleroderma[17] – a multisystem connective tissue disease with many similarities to our disease of interest, SLE. In this study, an FI was constructed for 1372 scleroderma patients using 44 health deficits identified from the registry database. FI scores were more strongly associated with mortality risk than either chronological age or existing scleroderma outcome measures, including the Rodnan Skin Score and the Physician Assessment of Damage, suggesting that the FI may be a useful prognostic tool in scleroderma[17].

These results support the assertion that the construction of FI measures in disease-specific cohorts, including multisystem rheumatic diseases, is both feasible and valid. To our knowledge, the deficit accumulation approach to frailty has yet to be studied in SLE. In such a clinically heterogeneous and multisystem disease, the evaluation of frailty through deficit accumulation using a frailty index may improve our understanding of the variable health trajectories observed in SLE.

2.5 Systemic Lupus International Collaborating Clinics (SLICC)

The Systemic Lupus International Collaborating Clinics (SLICC) is a research network of 52 investigators from 43 academic medical centres in 16 countries. SLICC's lengthy publication record includes studies of atherosclerosis, metabolic syndrome, neuropsychiatric disease, nephritis, organ damage and malignancies in SLE. SLICC members have also been involved in the development and validation of widely-used instruments to measure global disease activity (Systemic Lupus Erythematosus Disease

Activity Index 2000 (SLEDAI-2K))[50], cumulative organ damage (SLICC/American College of Rheumatology (ACR) Damage Index (SDI)), and health-related quality of life (Medical Outcomes Study Short Form-36 (SF-36)) in SLE.

2.5.1 SLICC inception cohort

In 1999, SLICC commenced enrollment of recently diagnosed SLE patients into a prospective inception cohort to study clinical outcomes and pathogenic mechanisms over the course of the disease. Enrollment was completed in December 2011 at 1826 patients - the largest inception cohort of SLE patients ever assembled. Patients were evaluated upon enrollment and annually thereafter using standardized clinical and laboratory assessments, including a medical history and physical examination, review of the patient's medical record, and completion of standardized instruments for the quantification of disease activity (SLEDAI-2K[50], BILAG-2004[52]), cumulative organ damage (SDI[78]), and health-related quality of life (SF-36[79]).

As of November 2016, a total of 13,388 assessments have been performed in the SLICC inception cohort with mean patient follow-up of approximately seven years. Data capture has been excellent and the number of patients lost to follow-up due to geographic relocation or withdrawal has been small. In brief, the SLICC inception cohort is a large, international, multi-centre cohort following patients prospectively from the time of SLE diagnosis with extensive annual assessments. In a secondary analysis of data from the SLICC inception cohort, we have constructed and validated the first FI measure for patients with SLE, to be known as the SLICC-FI.

CHAPTER 3: MANUSCRIPT 1

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

Authors: Alexandra Legge, Susan Kirkland, Pantelis Andreou, Kenneth Rockwood, John G. Hanly in collaboration with the Systemic Lupus International Collaborating Clinics (SLICC)

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3.1 Abstract

Objective: To construct a frailty index (FI) as a novel health measure in 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 organ damage (SLICC/ACR Damage Index [SDI]) and health-related quality of life (Short-Form 36 [SF-36]) were both assessed. Following a standard procedure, variables from the SLICC database were evaluated as potential health deficits. These 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 1682 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 to measure health status in 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.

3.2 Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with diverse manifestations, ranging from mild cutaneous and musculoskeletal involvement, to debilitating neuropsychiatric events, end-stage renal disease, and catastrophic thromboses[1]. The clinical course of SLE is variable and unpredictable. In the current era, individuals may live with SLE for several decades[2], gradually accumulating organ damage[55]. However, the mortality risk associated with SLE remains high[6,38], and for some the disease is rapidly fatal. Given this variability in health trajectories, it would be advantageous to identify, ideally early in their disease, those SLE patients who are at increased risk for later adverse outcomes. However, instruments that accurately predict long-term outcomes in SLE are currently limited[60].

In geriatric medicine[7], and increasingly in other disciplines[8,9,80-83], differences in susceptibility to adverse outcomes are quantified using the construct of frailty, which is defined as a state of increased vulnerability due to degradation of homeostatic mechanisms, resulting in diminished ability to respond to physiologic stressors[84]. Although often linked to advanced age, frailty can be observed across the life course[14], including among individuals with acquired vulnerability states, such as patients with human immunodeficiency virus[77] and childhood cancer survivors[10].

One approach to operationalizing frailty is the construction of a frailty index (FI)[11], which conceptualizes frailty as a loss of physiologic reserve arising from the accumulation of health deficits in multiple systems[12]. Individuals who possess few deficits are considered

relatively fit, while those with an increasing number of health problems are considered increasingly frail and thus more vulnerable to adverse outcomes[13]. Prior studies have consistently shown an association between higher FI values and increased risk of negative health outcomes, including hospitalizations, morbidity, and mortality[14,16,17,85]. While the FI has been utilized in many different clinical contexts[16,17,76], this approach has yet to be applied in SLE.

In SLE, the accumulation of health deficits across many organ systems may occur as a direct consequence of the disease, its treatment, other comorbidities, or ageing. Evaluating frailty through deficit accumulation may improve our understanding of the heterogeneous health outcomes observed in SLE. The aim of the present study was to construct a frailty index as a novel health measure in SLE, using data from an international inception cohort.

3.3 Methods

Data source: This was a secondary analysis of longitudinal data collected in 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 recently-diagnosed SLE patients was recruited from 31 SLICC sites in Europe, Asia, and North America. Patients were enrolled within 15 months of the diagnosis of SLE, based on ≥4 revised American College of Rheumatology (ACR) classification criteria for SLE[86]. In total, 1826 SLE patients were enrolled. 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 all participating centres and all participants provided written informed consent.

Clinical assessments: Demographic features included age, sex, race/ethnicity, geographic location, and years of post-secondary education. Medication use at each visit, including corticosteroids, antimalarials, and immunosuppressives, was noted. Medical comorbidities present prior to SLE diagnosis were recorded at the enrolment visit and updated at follow-up visits. The ACR classification criteria for SLE[86] met at the enrolment visit and the occurrence of criteria between follow-up visits was documented. Neuropsychiatric events[87] were recorded at each visit[88], as was SLE disease activity, assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K)[50]. Cumulative organ damage was measured using the SLICC/ACR Damage Index (SDI)[89], and health-related quality of life using the Medical Outcomes Study Short-Form 36 (SF-36)[79]. Blood pressure (in mmHg), height (in metres), and weight (in kilograms) were also recorded.

Laboratory data: Laboratory investigations necessary for the assessment of SLE disease activity and organ damage were performed locally at each visit. Serologic markers of disease activity included antibodies to double-stranded DNA, as well as C3 and C4 complement levels. Other laboratory investigations included 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 for item selection and coding **(Table 1)**[11]. Briefly, potential health deficits must first be identified. A health deficit is any symptom, physical sign, disease process, functional impairment, or laboratory abnormality meeting the criteria of being acquired, associated with an adverse health outcome, and associated with chronological age[11,71]. If deficits are either too infrequent or too common, they are unlikely to provide meaningful information in an FI, and should be respectively combined or excluded[11,71]. Finally, if a single item is missing values for more than 5% of individuals, it should be excluded[11,71].

The totality of health deficits included in an FI must represent several organ systems. Of note, frailty is not only a measure of cumulative damage, but also a measure of an individual's potential for recovery or repair. Therefore, it is crucial for any FI to include different types of deficits that can impact repair potential, including measures of function, mobility, and health attitude[11,71]. Finally, an FI requires a minimum of 30-40 health deficits to produce stable and precise estimates of frailty[15,16,68,71].

Once selected, each health deficit is assigned a scoring system from 0 to 1, with 0 representing no deficit and 1 representing the deficit fully expressed[11]. An individual's health deficit scores are then combined to produce an FI score, which is a proportion between 0 and 1, calculated as the sum of deficit scores for an individual divided by the total number of deficits that were considered[11,71].

Establishing a baseline dataset for SLICC-FI construction: In order to evaluate variables from the SLICC inception cohort database according to the health deficit criteria outlined in **Table 3.1**, a baseline dataset was required from which the initial SLICC-FI would be constructed. There were two important considerations that precluded the use of the SLICC enrolment visit as the baseline visit for our analysis. First, to be recorded in the SDI, organ damage must occur after the diagnosis of SLE and must be present for at least 6 months[89]. As a consequence, SDI scores could not be calculated for any SLICC enrolment visits that occurred at a disease duration of less than 6 months, resulting in missing SDI scores for 1057 patients (57.9% of the cohort) at their enrolment visit. This was problematic, given that the planned validation procedure for the SLICC-FI required the direct comparison of SLICC-FI and SDI scores from the same visit.

The second consideration related to the high rates of missing SF-36 data among SLICC enrolment visits (n=252; 13.8% of the cohort). The SF-36 is the only instrument in the SLICC inception cohort database that provides information regarding function and mobility, thus making it essential for constructing a true FI using this dataset. Given the importance of both the SDI and the SF-36 for the successful construction and validation of the SLICC-FI, the baseline visit for these analyses was defined as the first study visit for each patient at which both an SDI and an SF-36 had been completed. Therefore, patients were excluded from the analyses 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 for inclusion in the SLICC-FI were evaluated using the criteria in **Table 3.1**. Health deficits 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. We also evaluated the relationship between patient age and the prevalence of each variable in the baseline dataset using descriptive statistics. While the deficits included in an FI should generally increase in prevalence with increasing age, it is now understood that this relationship may not exist for all health deficits, in part due to survivor effects[11]. Variables were not excluded from the SLICC-FI if there was attenuation of this relationship at advanced ages.

The association between the presence of a health deficit and increased risk of future adverse health outcomes in SLE was also determined through literature review. Variables not clearly associated with adverse outcomes were excluded. For this criterion, if literature specific to SLE could not be identified, 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 in the dataset.

Coding of individual health deficits for the SLICC-FI: Binary variables were assigned either a score of 0 (absence of the deficit) or a score of 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 FI and SLE literature.

SLICC-FI calculation: Individual health deficit scores were combined to produce a SLICC-FI score for each patient using the methods described above. For example, with 48 health deficits included 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 the included health deficits[68].

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. In prior studies in non-SLE populations, individuals with FI values ≤0.03 are almost never identified as being clinically frail[72,90] while individuals

with FI values >0.21 have a less than 5% chance of being classified as phenotypically "robust"[69]. Using these cut-points derived in the general population[14,72,90], we classified patients as robust (SLICC-FI ≤0.03), relatively less fit (0.03 < SLICC-FI ≤ 0.10), least fit (0.10 < SLICC-FI ≤ 0.21), or frail (SLICC-FI >0.21) and reported the prevalence of frailty with 95% confidence intervals.

To evaluate for any bias introduced by including patients with varying SLE disease durations, the above analyses were repeated in the subgroup of patients whose baseline assessments occurred 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[11,91]. 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).

3.4 Results

Patient characteristics: There were 1683 patients (92.2% of the cohort) who had study visits at which both the SDI and SF-36 were recorded. The first such visit for each patient was included in our baseline dataset and, for the majority of patients, this occurred early in their disease course (1390/1683 patients [82.6%] within two years of SLE diagnosis). The demographic and clinical characteristics of patients in the baseline dataset are shown in **Table 3.2**.

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

SLICC-FI construction – selection of health deficits: Of the 222 candidate variables identified as potential health deficits for inclusion in the SLICC-FI **(Figure 3.1)**, 18 were excluded for failing to meet the first three health deficit criteria (i.e. being acquired, age-related, and associated with adverse outcomes) and 46 were excluded as duplicates. The remaining 158 SLICC variables were used to construct health deficits suitable for inclusion in an FI. There were 36 SLICC variables that were directly converted into 36 health deficits. In other cases, several variables representing varying aspects of the same illness 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 SLICC variables. Thus, information from the remaining 122 SLICC 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", "Congestive Heart Failure", and "Active Nephritis", as defined in the SLICC inception cohort database. There were also ordinal health deficits, including those derived from the SF-36. For example, for the health deficit "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, data from the published literature was used to define clinically significant cut-points. For example, the cut-points used for the "Body Mass Index" variables 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")[92]. These BMI cut-points have been utilized in other frailty indices[11].

The SLICC-FI: The 48 health deficits in the SLICC-FI are outlined in **Figure 3.2**. More detailed information regarding the SLICC-FI health deficits and their scoring systems can be found in **Appendix A**. There were 14 deficits related to organ damage, occurring either before or after the diagnosis of SLE. Examples included congestive heart failure, cerebrovascular disease, and chronic kidney disease. Another 14 deficits reflected active inflammation, such as serositis, inflammatory arthritis, and nephritis, while 6 items reflected comorbid conditions, including hypothyroidism, diabetes, and obesity. Finally,

the SLICC-FI included a number of deficits that capture repair potential, including 14 variables related to function, mobility, health attitude, and mental health.

SLICC-FI values: Using health deficit information from the baseline dataset, SLICC-FI scores were calculated for 1682 patients. In one patient, a SLICC-FI score could not be calculated due to missing data for 12 (25%) of the 48 health deficits. The distribution of SLICC-FI scores is shown in **Figure 3.3**. SLICC-FI values ranged from 0 to 0.51, with a median (I.Q.R.) of 0.16 (0.11–0.22) and a slightly higher mean (S.D.) of 0.17 (0.08).

Using cut points validated in the general population, 27.1% (95% CI 25.0%-29.2%) of SLE patients were classified as frail, based on SLICC-FI values > 0.21 (**Table 3.3**). The prevalence of frailty increased with increasing age, from 19.3% (95% CI 16.4%-22.6%) among patients less than 30 years of age, to 28.1% (95% CI 24.6%-31.8%) for patients aged 30-45 years, and 38.5% (95% CI 33.7%-43.5%) among patients aged 45 years or older. Very few patients (n=28; 1.7%) were classified as robust (SLICC-FI ≤0.03). These individuals were combined with patients who were considered relatively less fit (0.03 < SLICC-FI ≤ 0.10) into a single category ("Relatively Fit").

Compared to the relatively fittest patients, those who were classified as frail were older, less well-educated, and more likely to be current smokers (**Table 3.3**). 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 3.3**).

Sensitivity analysis: Our results were similar when only patients with baseline assessments within the first two years after 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.

3.5 Discussion

In this secondary analysis of data from the SLICC inception cohort, we have demonstrated the feasibility of constructing the first FI to measure overall health status in SLE. We have described each step of the process in detail, to provide a precise account of the criteria used to evaluate variables as potential health deficits, how these criteria were applied to select deficits for inclusion in the SLICC-FI, and how these deficits were operationalized to allow the calculation of SLICC-FI values for SLE patients. We identified a considerable prevalence of frailty among SLE patients, the majority of whom were early in their disease.

The process outlined for constructing the SLICC-FI has many strengths. First, variables were selected using standard criteria[11]. The health deficits and their cut points were derived from existing instruments that are well-validated in SLE. With 48 items, the

number of variables included in the SLICC-FI is sufficient to provide stable and reliable estimates of frailty[15,16,68,71]. Last, the deficits contained in the SLICC-FI cover multiple organ systems and capture information related to function and mobility[11].

That many small effects can aggregate to produce larger ones is well-recognized in other disciplines, such as computer science. Applying this principle in medicine allows for the cumulative impact of multiple small deficits, which individually might not be statistically or clinically significant, but once combined, contribute valuable information regarding overall health status[93]. Some may be concerned about redundancy within the SLICC-FI, and desire a more parsimonious list of fewer items. However, as long as one deficit is not identical to another already included in the index, each item will still contribute new information, regardless of the correlation between them. One strength of the deficit accumulation approach to quantifying vulnerability is its ability to embrace the complexity that is inherent in human systems, by placing less emphasis on the influence of specific items, and instead focusing on the overall impact of multiple health problems[13]. Indeed, similar to the results of prior work in other populations[11,72], our sensitivity analysis demonstrated that SLICC-FI scores were not driven by a small number of specific variables, but were a reflection of the global effect of deficit accumulation.

The relationships that exist between deficits within the SLICC-FI are not a weakness – rather they are critical to the performance of any FI as an accurate measure of vulnerability[11]. For example, the equal weighting of transient ischemic attacks (TIAs) and

debilitating strokes in the "Cerebrovascular Disease" health deficit may be considered to lack face validity, as these events clearly differ in their impact on overall health. However, compared to a person who has experienced a TIA, an individual with a disabling stroke is more likely to have additional deficits related to their functional performance and mobility, and therefore the greater health impact of their cerebrovascular event will be reflected in their SLICC-FI score. Thus, the inclusion of deficits related to function and mobility in the SLICC-FI ensures that the overall health impact of different medical problems is accurately captured in the assessment of vulnerability.

An alternative conceptual approach to the measurement of frailty is the frailty phenotype[69]. In the phenotypic approach, frailty is assessed using five specific criteria: weight loss, exhaustion, physical inactivity, slow walking speed, and reduced grip strength[13,69]. Individuals meeting three or more criteria are classified as frail, those with one or two criteria are pre-frail, and those meeting no criteria are considered robust[13,69]. Prior studies of non-lupus populations have found that individuals meeting the phenotypic criteria for frailty are at higher risk for adverse health outcomes[13,69]. Recently, the frailty phenotype was evaluated in a prevalent cohort of 152 women with SLE[70]. In this study, 20% of the sample was classified as frail and 50% as prefrail[70]. The presence of frailty was associated with increased risk of functional decline and mortality[70], suggesting that this operationalization of frailty is relevant in SLE. However, the authors also found that certain components of the frailty phenotype, as defined in geriatric

medicine, may have limitations in SLE[70], suggesting that lupus-specific measures of frailty may better-quantify vulnerability in this population.

There are several challenges associated with applying the frailty phenotype to patients with SLE that may be overcome using the deficit accumulation approach described in our study. First, the frailty phenotype requires the collection of physical performance data[13,69,70] that is not routinely collected in SLE, limiting its feasibility. In contrast, the variables used to construct the SLICC-FI are derived from existing, validated instruments that are commonly used in SLE cohorts. Other limitations of the frailty phenotype include its lack of granularity, as individuals fall into one of three risk categories[13,69]. 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[11,15-17]. 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[67]. In contrast, the properties of the FI remain remarkably consistent regardless of the number or type of variables included[11,15-17,85].

When the SLICC-FI was used to characterize frailty among SLE patients in our dataset, 27.1% were classified as frail. This is a much higher prevalence of frailty than would be expected for individuals in the general population with similar age distribution[14,94,95] 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[14]. Interestingly, the proportion of SLE patients in our study who were

classified as frail using the SLICC-FI was similar to the prevalence of frailty estimated for SLE patients in the Katz et al. study[70] using the frailty phenotype. SLICC-FI values (mean FI 0.17) were substantially lower than FI scores reported in other clinical cohorts, including among patients with HIV (mean FI 0.31)[16] and systemic sclerosis (mean FI 0.33)[17]. This could be partially explained by the higher mean age of patients in these other cohorts, as deficits accumulate with increasing age[71]. 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[11,14,15].

The increased prevalence of frailty that we have observed in SLE may be biologically plausible. 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[96]. Furthermore, certain inflammatory cytokines, such as interleukin-6, have been implicated in the pathogenesis of both frailty and SLE[96,97]. 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 visit for this study within two years of SLE diagnosis, allowing SLICC-FI values to be calculated at a similar time point early in disease for the majority

of patients. Second, our sample size is small compared with some other FI studies[11,14,15], but is still sufficient for FI construction[17]. Furthermore, the SLICC cohort is the largest inception cohort of SLE patients ever assembled, making it a reasonable choice for the initial construction of an FI in SLE. Finally, we used FI cut-points derived from general population samples to estimate the prevalence of frailty in our dataset[14,72,90]. 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.

In conclusion, evaluating frailty through deficit accumulation provides a novel approach to the quantification of vulnerability among SLE patients. Using data from the SLICC inception cohort, we have demonstrated the feasibility of constructing an FI as a measure of vulnerability to adverse outcomes in SLE. Using this FI, we identified a high prevalence of frailty among SLE patients, which warrants additional investigation. Following validation, the SLICC-FI could be a useful tool for identifying SLE patients who are at increased risk for adverse health outcomes.

3.6 Tables

Table 3.1 - Standard criteria for the identification of health deficits for inclusion in a frailty index
Health deficit definition
Any symptom, physical sign, disease process, functional impairment, or laboratory/radiographic abnormality
Criteria to be met by each individual health deficit
1. Must be acquired, as opposed to innate 2. Must be associated with an adverse health outcome 3. Prevalence should generally increase with increasing chronological age 4. Must be present in at least 1%, but not more than 80% of the sample 5. Must have non-missing values for at least 95% of the sample
Criteria to be met by the overall set of health deficits
1. Must cover a range of physiologic organ systems 2. Must include integrated variables indicative of repair potential, including measures of function and mobility 3. Must include at least 30-40 deficits in total

Table 3.2 - Demographic and clinical characteristics of SLICC inception cohort patients included in the dataset for SLICC-FI construction (n=1683).

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

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

Table 3.3 - Demographic characteristics of SLE patients from the SLICC inception cohort included in the dataset for SLICC-FI construction, stratified by health status[1] (n=1682).

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

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

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

3.7 Figures

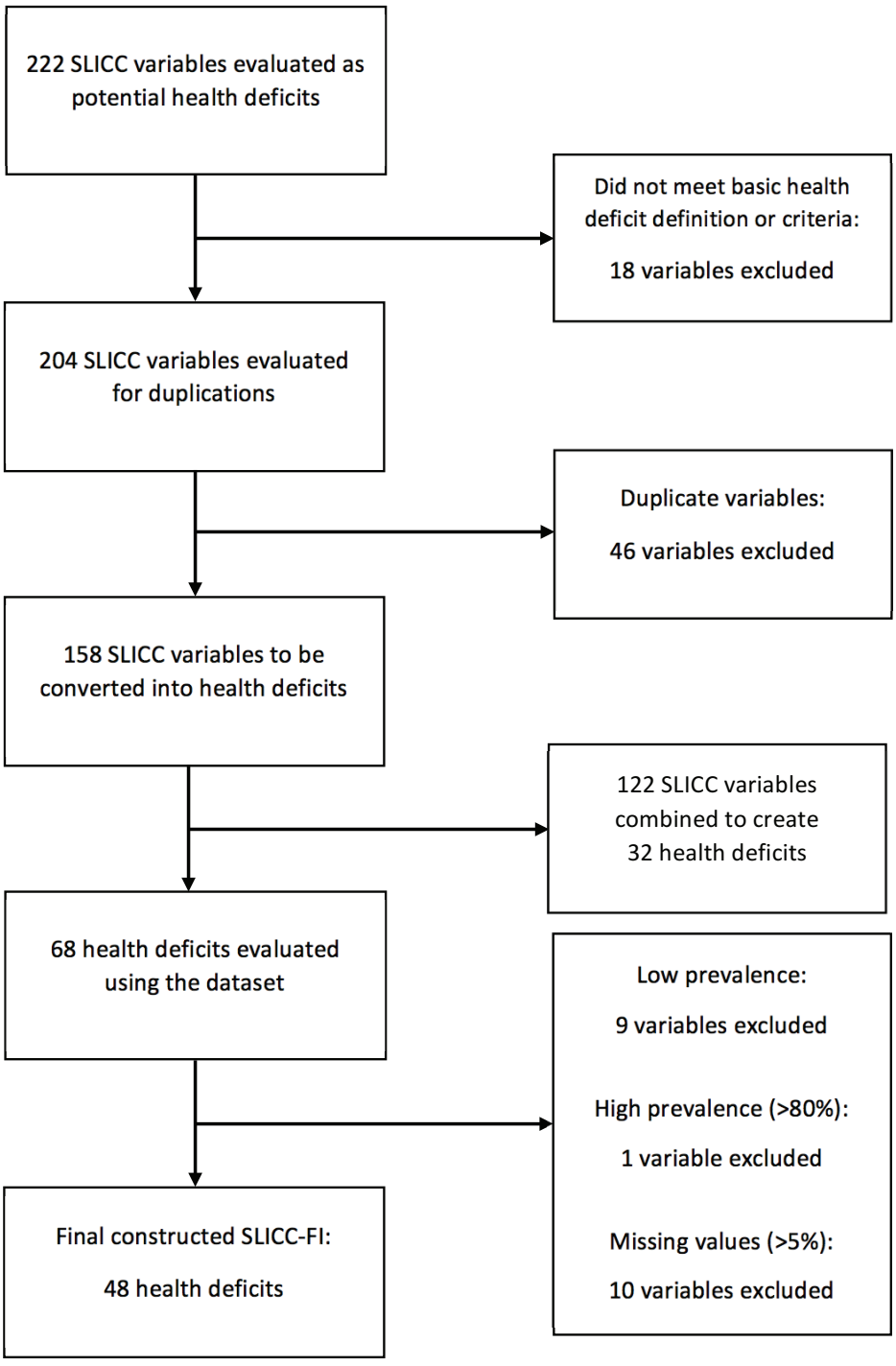

Figure 3.1 - Flow diagram of the evaluation of Systemic Lupus International Collaborating Clinics (SLICC) inception cohort database variables for inclusion as health deficits in the SLICC-Frailty Index (SLICC-FI).

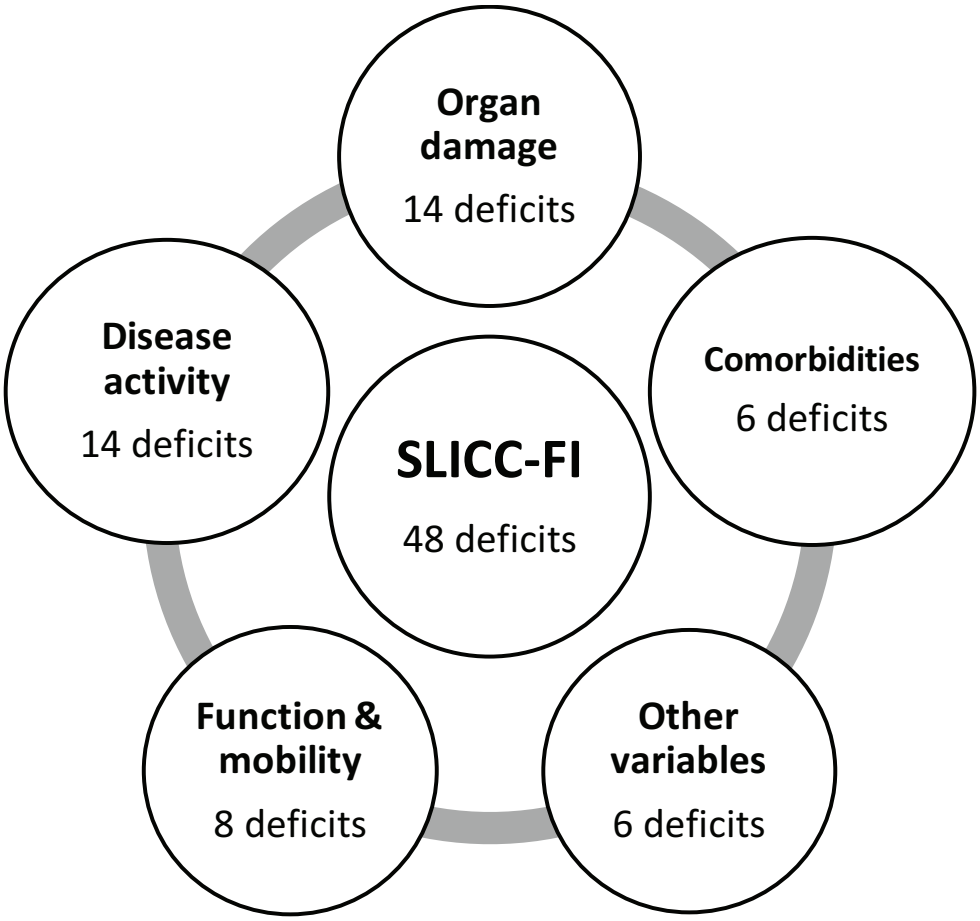

Figure 3.2 - Types of health deficits included in the Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI).

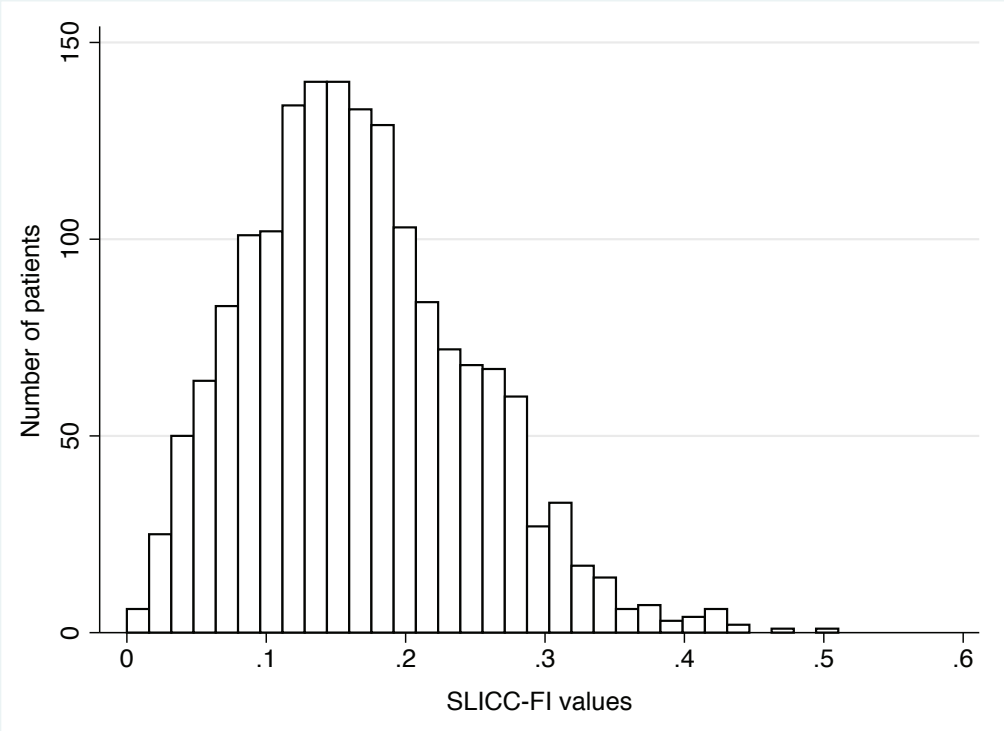

Figure 3.3 - Distribution of Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI) values among 1682 SLE patients in the baseline dataset.

CHAPTER 4: MANUSCRIPT 2

Validation of a frailty index in patients with systemic lupus erythematosus

Authors: Alexandra Legge, Susan Kirkland, Pantelis Andreou, Kenneth Rockwood, John G. Hanly in collaboration with the Systemic Lupus International Collaborating Clinics (SLICC)

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Student contribution to the manuscript: In collaboration with the co-authors, the student led the study design process. She was responsible for all data extraction, data cleaning, and data analyses. She performed the initial interpretation of the data and wrote the first draft of the manuscript.

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4.1 Abstract

Objective: To validate the Systemic Lupus International Collaborating Clinics (SLICC) frailty index (FI) as a novel health measure in SLE.

Methods: In this secondary analysis of the SLICC inception cohort, 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. Following a standard procedure, the SLICC-FI was constructed using baseline data. The SLICC-FI comprises 48 health deficits, including items related to organ damage, disease activity, comorbidities, and functional status. Content, construct, and criterion validity of the SLICC-FI were assessed. Multivariable Cox regression was used to estimate the association between baseline SLICC-FI values and mortality risk.

Results: Of 1682 SLE patients, most (89%) were female, with mean (SD) age 35.7 (13.4) years and mean (SD) disease duration 18.8 (15.7) months. At baseline, the mean (SD) SLICC-FI score was 0.17 (0.08) with a range from 0 to 0.51. Baseline SLICC-FI values exhibited the expected measurement properties and were weakly correlated with baseline SDI scores ($r=0.262$; $p<0.0001$). Higher baseline SLICC-FI values (per 0.05 increment) were associated with increased mortality risk (Hazard Ratio 1.59; 95%CI 1.35-1.87), after adjusting for age, sex, steroid use, ethnicity/region, and baseline SDI scores.

Conclusion: The SLICC-FI is a valid health measure in SLE and predicts future mortality risk. The SLICC-FI is potentially valuable for quantifying vulnerability among patients with SLE and adds to existing prognostic scores.

4.2 Introduction

The diverse manifestations of systemic lupus erythematosus (SLE) range from mild cutaneous and musculoskeletal involvement to debilitating neuropsychiatric events and end-stage renal disease[1]. The clinical course of SLE is highly variable and difficult to predict in individual patients. Currently, the evaluation of SLE patients encompasses three core dimensions[98] – disease activity, organ damage, and health-related quality of life (HRQoL) - each providing valuable prognostic information. In particular, the Systemic Lupus International Collaborating Clinics (SLICC) / ACR Damage Index (SDI)[89] consistently predicts adverse outcomes in SLE, including future organ damage accrual[58,59,61] and mortality[58-62]. Even so, studies evaluating the associations between disease activity, organ damage, and HRQoL in SLE have reported complex and variable relationships between these three disease dimensions[48,58,99]. A more comprehensive instrument is required to more accurately predict the risk of future adverse health outcomes among SLE patients.

In geriatric medicine[7], and increasingly in other disciplines[8,9,83], differences in susceptibility to adverse outcomes are quantified using the construct of frailty, which represents a state of increased vulnerability resulting in diminished ability to respond to physiologic stressors[84]. One approach to operationalizing frailty is the construction of a frailty index (FI)[11], which conceptualizes frailty as a loss of physiologic reserve due to the accumulation of health deficits in multiple systems[12]. Individuals with few deficits are considered relatively fit, while those with a greater number of health problems are considered increasingly frail and thus more vulnerable to adverse outcomes[13]. Prior work

in non-lupus populations has identified properties of the FI that remain remarkably consistent across settings[11,15-17,71], demonstrating the robustness and generalizability of this approach. For example, studies have consistently shown an association between higher FI values and increased risk of adverse outcomes, including mortality[14-17,85]. While the FI has been utilized in many different clinical contexts[16,17,76,81], this approach has not previously been applied in SLE.

We hypothesized that evaluating frailty via the deficit accumulation approach could provide important insights into the differential vulnerability to adverse outcomes in SLE. Using data from the SLICC inception cohort, we have constructed an FI for SLE patients, known as the SLICC-FI. The primary aim of this study was to evaluate the validity of the SLICC-FI, including its ability to predict mortality within the SLICC inception cohort. Secondarily, we assessed whether the SLICC-FI could provide additional prognostic information compared to existing health status measures in SLE, specifically the SDI. To this end, we compared the predictive validity of the SLICC-FI and the SDI for mortality risk.

4.3 Methods

Data source: This was a secondary analysis of prospectively collected longitudinal data in 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. Patients were enrolled within 15 months of SLE diagnosis,

based on ≥4 ACR classification criteria for SLE[86]. In total, 1826 SLE patients were enrolled. 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 thereafter. Demographic features included age, sex, race/ethnicity, geographic location, and post-secondary education. Medication use noted at each visit included corticosteroids, antimalarials, and immunosuppressives. Medical comorbidities were recorded at the enrolment visit and updated at follow-up visits. We documented ACR classification criteria for SLE[86] and neuropsychiatric events[87] present at the enrolment visit, as well as their occurrence between follow-up visits. SLE disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K)[50], cumulative organ damage was measured using the SLICC/ACR Damage Index (SDI)[89], and health-related quality of life was evaluated using the Medical Outcomes Study Short-Form 36 (SF-36)[79]. Blood pressure (in mmHg), height (in metres), and weight (in kilograms) were also recorded. Laboratory investigations necessary for the assessment of SLE disease activity and organ damage were performed locally at each visit[58].

Construction of the SLICC Frailty Index (SLICC-FI): A standard procedure for FI construction, described in detail elsewhere[11], was used to generate the SLICC-FI. Briefly,

we first established a baseline dataset, consisting of the first visit for each patient at which both the SDI and the SF-36 had been completed. Using this baseline dataset, variables were selected 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 the sample, and (v) having non-missing values for ≥95% of the sample[11]. Of 222 candidate variables, 48 items met all required criteria for inclusion in the SLICC-FI. Health deficits spanned a range of organ systems and included items related to organ damage, disease activity, comorbidities, and functional status. Each health deficit was assigned a score from 0 (complete absence of the deficit) to 1 (deficit fully present) using established cut points[50,79,86,87,89]. More detailed information regarding the SLICC-FI health deficits and their scoring systems can be found in **Appendix A**.

Calculation of SLICC-FI scores: For each patient, their SLICC-FI score at a given time point is a proportion, between 0 and 1, calculated from the sum of their health deficit scores divided by the total number of deficits considered. For example, an individual in whom 12 of 48 deficits are fully present would have a SLICC-FI score of 12/48 = 0.25. Each additional health deficit increases the SLICC-FI by 0.021. Previous studies have demonstrated changes in FI values of 0.03 or greater to be clinically important. A SLICC-FI score was calculated for each patient using baseline data. We also calculated follow-up SLICC-FI scores in a second dataset consisting of the last study visit for each patient at which both the SDI and SF-36 were recorded, excluding visits already included in the

baseline dataset.

Validation strategy for the SLICC-FI: We employed a tripartite approach, considering each of content, construct, and criterion validity[100]. Content validity was inherent in the derivation of health deficits from existing, well-validated SLE instruments[50,79,86,87,89]. The use of a standard procedure[11] for the selection and coding of health deficits further enhanced the face validity of our approach. To assess construct validity, we compared the properties of the SLICC-FI with the properties of existing FI measures in non-SLE populations. We estimated the relationship between patient age and SLICC-FI values (in clinical samples, FI values typically increase by 1% per year on a log scale[15,16]), as well as the distribution of SLICC-FI values (typically Gaussian in clinical samples[16]) and its 99th percentile value (typically less than 0.7[11,15-17]). To further assess construct validity, we estimated the correlation between baseline SLICC-FI scores and baseline values of existing health status measures in SLE, including the SLEDAI-2K and the SDI. For criterion validity, we estimated the predictive validity of baseline SLICC-FI scores for the risk of mortality during follow-up.

Statistical analysis: Descriptive statistics were calculated for demographic and clinical characteristics, as well as for SLICC-FI values at baseline and at last visit. The distributions of SLICC-FI scores at baseline and at last follow-up visit were visualized and compared with theoretical distributions using goodness-of-fit tests. The association between patient age and baseline SLICC-FI scores was estimated using correlation coefficients and simple linear regression. Spearman rank correlation coefficients were

used to estimate the association of baseline SLICC-FI scores with SDI and SLEDAI-2K scores from the same study visit. Correlation coefficients and linear regression models were also used to estimate the association of baseline SLICC-FI values with SLICC-FI scores at last follow-up. All linear regression models met the required assumptions of linearity, homoscedasticity, and normality of errors.

We generated Kaplan-Meier survival curves to describe the risk of mortality during follow-up, starting at the date of the baseline visit. The event date was the date of death, while patients who remained alive throughout follow-up were censored at the date of their last visit. To evaluate the association between baseline frailty and mortality risk, we first used an FI cut point that has been validated in non-SLE populations[14,72,90] to dichotomize patients into those considered frail at baseline (SLICC-FI > 0.21) versus those who were not frail (SLICC-FI ≤ 0.21). We then compared mortality risk between these two groups using a log-rank test.

The predictive validity of baseline SLICC-FI scores for the risk of mortality during follow-up was further evaluated using Cox proportional hazards regression. First, a univariable model was constructed with the baseline SLICC-FI (per 0.05 increase) as the independent variable of interest. Demographic and clinical variables were identified as potential confounders and univariable models for mortality risk were constructed for each of these variables. A full multivariable model for mortality risk was then constructed, which included the baseline SLICC-FI, as well as any potentially confounding variables with p-values < 0.1 in univariable analysis. Next, a backwards stepwise procedure was

used to remove potential confounders that were no longer statistically significant in multivariable analysis. Likelihood ratio tests, which compared full models containing the variable in question to nested models where the variable had been removed, were used to determine which potential confounders would be retained in the final model. The final multivariable model included the baseline SLICC-FI, any potentially confounding variables for which removal from the model resulted in a statistically significant likelihood ratio test ($p<0.05$), as well as patient age and sex, which were retained in the final model regardless of statistical significance. A similar procedure was followed to construct unadjusted and adjusted models for mortality risk with 1) baseline SDI scores as the independent variable of interest; and 2) both baseline SLICC-FI and baseline SDI scores as independent variables in the same model. We then used likelihood ratio tests to compare the goodness-of-fit of the models containing both baseline SLICC-FI and baseline SDI scores to the models containing 1) the baseline SLICC-FI alone and 2) the baseline SDI alone. For all Cox models, the proportional hazards assumption was tested using log-log plots, time-varying covariates, and Schoenfeld residuals. 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 several health deficits related to organ damage that overlap with items that are also captured by the SDI. To assess whether there is a relationship between baseline SLICC-FI scores and mortality risk independent of organ damage, we repeated the above analyses omitting any overlapping damage items from the SLICC-FI and recalculating SLICC-FI scores using the remaining deficits.

As a large proportion of SLE patients have SDI scores of zero, particularly early in disease[58], we investigated whether the SLICC-FI could predict future mortality risk in the subgroup of patients with no organ damage (SDI=0) at their baseline visit. Finally, to evaluate the influence of SLE disease duration on our results, we repeated the above analyses including only patients whose baseline visits occurred within two years of SLE diagnosis.

4.4 Results

Baseline dataset characteristics: There were 1683 patients (92.2% of the SLICC cohort) who had at least one study visit at which both the SDI and SF-36 were recorded. The first such visit for each patient was included in the baseline dataset and this occurred within two years of SLE diagnosis for 1390 [82.6%] patients. The baseline demographic and clinical characteristics of these 1683 patients are shown in **Table 4.1**.

Assessing construct validity - baseline SLICC-FI properties: SLICC-FI scores were calculated for 1682 patients in the baseline dataset. There was one patient for whom a baseline SLICC-FI score could not be calculated due to missing data for >20% of health deficits[68]. Baseline SLICC-FI scores ranged from a minimum of 0 to a maximum of 0.51, with a median (I.Q.R.) of 0.16 (0.11–0.22) and a slightly higher mean (S.D.) of 0.17 (0.08).

The distribution of baseline SLICC-FI scores closely approximated a beta distribution with shape parameters α=3.506 and β=17.487 (**Figure 4.1)**. This was confirmed using the Kolmogorov-Smirnov and Cramer-von-Mises goodness-of-fit tests. There was a positive, linear relationship between patient age and baseline SLICC-FI values (Pearson correlation coefficient (r) = 0.203; p<0.0001). However, this correlation was weak in strength and accounted for only 4% of the total variation in baseline SLICC-FI scores. The submaximal limit (99^{th} percentile value) of baseline SLICC-FI values was 0.39. There was no longer a significant relationship between age and baseline SLICC-FI scores in this 99^{th} percentile sample.

Baseline SLICC-FI scores were slightly higher among females (mean [S.D.] 0.168 [0.08]) compared to males (mean [S.D.] 0.159 [0.077]), although this difference was not statistically significant (t-test p-value=0.119). However, males were also significantly older (mean [S.D.] age 40.0 [16.4] years) than females (mean [S.D.] age 35.1 [12.8] years) at baseline (t-test p-value <0.0001). In linear regression, male sex was associated with significantly lower baseline SLICC-FI scores (β=-0.015; p=0.011), after adjusting for patient age.

Using Spearman rank correlation coefficients (r_s), we estimated the correlation of baseline SLICC-FI scores with SDI and SLEDAI-2K scores from the same visit. We found higher baseline SLICC-FI values to be associated with higher SDI (r_s = 0.262; p<0.0001) and SLEDAI-2K (r_s = 0.227; p<0.0001) scores at baseline. These associations were weak in strength, despite the presence of overlapping SDI and SLEDAI-2K

variables that were also captured as health deficits in the SLICC-FI. Interestingly, the correlations with baseline SLICC-FI scores remained statistically significant after removing overlapping items from the SLICC-FI (r_s = 0.154, p<0.0001 for the SDI; r_s = 0.110, p<0.0001 for the SLEDAI-2K).

Assessing construct validity - SLICC-FI at last follow-up visit: There were 1507 patients with last visits occurring after a mean (S.D.) follow-up time of 7.2 (3.7) years from baseline. Demographic characteristics including race/ethnicity, post-secondary education status, and sex distribution were similar to the baseline dataset (**Table 4.1**). When compared to their baseline visit, these patients had less active disease (mean [S.D.] SLEDAI-2K 2.82 [3.37] vs. 3.98 (4.28) at baseline) and more organ damage (mean [S.D.] SDI 1.19 [1.61] vs. 0.40 (0.84) at baseline) at last follow-up, although 721 patients (47.8%) still had no organ damage (SDI=0) at the time of their last visit.

Last SLICC-FI values ranged from 0.004 to 0.49, with a mean (S.D.) value of 0.15 (0.08) and a median (I.Q.R.) of 0.14 (0.09–0.21). Compared to baseline SLICC-FI scores, the properties of the SLICC-FI at last follow-up were very similar, including its distribution (**Figure 4.1**), its 99th percentile value (0.38), and its weakly positive, linear relationship with age (r=0.264; p<0.0001). Similar to the results obtained at baseline, SLICC-FI values at last follow-up were positively associated with both SDI (r_s=0.444; p<0.0001) and SLEDAI-2K (r_s=0.260; p<0.0001) scores from the same visit. Last SLICC-FI values were moderately correlated with baseline SLICC-FI scores (r=0.567; p<0.0001).

Looking at the change in SLICC-FI from baseline to last visit (n=1506), 67.8% of patients had a clinically meaningful change (±0.03) in the SLICC-FI during follow-up (**Figure 4.2**). There were 395 patients (26.2%) with a clinically meaningful increase in the SLICC-FI, while 626 patients (41.6%) experienced a clinically meaningful decrease in their SLICC-FI over time. Longer follow-up time was found to be weakly associated with more positive changes (i.e. worsening) in SLICC-FI scores (r=0.103; p=0.0001).

Assessing criterion validity –the baseline SLICC-FI and mortality risk: Among patients in the baseline dataset, there were 66 deaths that occurred during follow-up at a mean (S.D.) follow-up time of 5.4 (3.7) years (**Figure 4.3**). As 117 patients had no available follow-up data after their baseline visit, 1566 patients were included in the survival analysis for mortality, with mean (S.D.) follow-up time among censored individuals of 6.7 (4.0) years.

At baseline, 431/1566 patients (27.5%) were considered frail (SLICC-FI >0.21). As shown in **Figure 4.3**, baseline frailty was associated with a significant increase in the risk of mortality during follow-up (log rank test p<0.0001). Specifically, mortality risk was over four times higher among frail individuals (SLICC-FI >0.21) when compared to patients who were classified as non-frail (SLICC-FI ≤0.21) at baseline (hazard ratio (HR) 4.37; 95% CI 2.67-7.17).

In unadjusted Cox regression, an increase in baseline SLICC-FI by 0.05 was associated with a 62% increase in the risk of mortality during follow-up (HR 1.62; 95% CI 1.41-

1.85). Baseline SDI scores (per one-unit increase) demonstrated a similar association with mortality risk in unadjusted analysis (HR 1.65; 95% CI 1.38, 1.97). Looking at potential confounders, we found that older age, male sex, steroid use, immunosuppressive use, and higher disease activity (SLEDAI-2K) at baseline were associated with increased risk of mortality during follow-up **(Table 4.2)**. Antimalarial use and post-secondary education were both associated with lower mortality risk. There were also differences in mortality risk based on race/ethnicity and geographic region **(Table 4.2)**. However, the effects of race/ethnicity and geographic region were not independent of one another. Therefore, for the purposes of multivariable analysis, a combined ethnicity/region variable was created.

In multivariable analysis, baseline SLICC-FI values remained significantly associated with the risk of mortality during follow-up after accounting for potentially confounding variables **(Table 4.3–Model 1)**. In our final multivariable model, an increase in baseline SLICC-FI by 0.05 was associated with a 66% increase in the risk of mortality during follow-up (HR 1.66; 95% CI 1.42-1.94), after adjusting for age, sex, steroid use, and ethnicity/region. Similar multivariable models were constructed for the baseline SDI **(Table 4.3–Model 2)**. In the final multivariable model, baseline SDI scores remained significantly associated with mortality risk (HR 1.50; 95% CI 1.23-1.83). When baseline SLICC-FI and SDI scores were included in the same models for mortality risk during follow-up, both measures remained independently associated with the risk of death **(Table 4.3–Model 3)**. Compared to the models containing the baseline SLICC-FI or the baseline SDI alone, the models containing both baseline SLICC-FI and SDI scores

demonstrated superior model fit (**Table 4.3**). In the final multivariable model, an increase in baseline SLICC-FI by 0.05 remained associated with a 59% increase in mortality risk (HR 1.59; 95% CI 1.35-1.87), after adjusting for age, sex, steroid use, ethnicity/region, and baseline SDI scores **(Table 4.3–Model 3)**.

Sensitivity analyses: In a subgroup analysis including only those patients without organ damage (SDI = 0) at baseline (n=1187), frailty (baseline SLICC-FI >0.21) was still associated with a three-fold increase in the risk of mortality during follow-up when compared to individuals who were classified as non-frail at baseline (HR 3.09; 95% CI 1.56-6.14). In our final multivariable model for this subgroup, each increase in baseline SLICC-FI by 0.05 was associated with a statistically significant increase in mortality risk by approximately 50% (HR 1.47; 95% CI 1.18-1.83), after adjusting for age, sex, steroid use, and ethnicity/region (**Table 4.4**).

Similar results were also obtained when we repeated the survival analyses for mortality after removing any health deficits from the SLICC-FI that overlapped with damage-related items captured by the SDI (**Table 4.5**). Finally, we repeated the above survival analyses for mortality in the subgroup of patients whose baseline visits occurred early in disease – within two years of SLE diagnosis. We identified a similar relationship between baseline SLICC-FI values and mortality risk during follow-up in this subgroup (**Table 4.6**).

4.5 Discussion

In a well-characterized, international cohort of recently-diagnosed SLE patients, we have demonstrated the validity of using a frailty index as a measure of overall health status. The SLICC-FI was correlated with existing measures of disease activity and organ damage in SLE. Higher SLICC-FI values were associated with increased risk of mortality, independent of other demographic and clinical factors known to predict mortality in SLE.

In both the baseline and last follow-up datasets, the SLICC-FI exhibited measurement properties similar to those consistently demonstrated by other frailty indices in non-lupus populations[11,15-17,71]. For example, at all ages, women demonstrated higher mean SLICC-FI values than men[11,15]. We found a positive, linear association between chronological age and SLICC-FI values that was very weak in strength. As expected, we found that the relationship between age and SLICC-FI values attenuated to zero at the highest levels of frailty, as severely frail individuals die rather than accumulate further deficits[101]. Finally, although the mean SLICC-FI value (0.17) was high compared to estimates for similarly-aged individuals in the general population[14,94,95], the upper limit of SLICC-FI scores was not higher than expected (maximum value 0.51), suggesting that the SLICC-FI was not overestimating the prevalence of frailty among SLE patients.

After a mean follow-up interval of 7.2 years, mean SLICC-FI values, as well as the overall distribution of SLICC-FI scores, remained largely unchanged when compared to baseline. This is not common in FI studies with such a long follow-up period and may

reflect the impact of treatment – as seen by the large number of SLE patients in whom SLICC-FI scores improved during follow-up. This finding may provide insight into the relationship between frailty and chronological age in disease-specific cohorts. In the general population, a very strong correlation is typically observed between age and mean FI values for individuals of a given age[14,15]. This correlation tends to be less pronounced in clinical samples[17], reflecting the potential for younger individuals with chronic diseases to be very frail. In a post-hoc analysis, we found a weak association between age and mean SLICC-FI values at baseline ($R^2 = 0.35$), while a considerably stronger association was observed at the last follow-up visit ($R^2 = 0.53$). It is possible that, following appropriate treatment, there is partial restoration of the relationship between age and SLICC-FI values, such that it more closely resembles the expected relationship in the general population[14,15]. Future work will aim to explore these novel observations further and to investigate whether similar relationships exist in other disease-specific cohorts.

We can also view the lack of change in mean SLICC-FI scores during follow-up as resulting from a tradeoff between deficits related to SLE disease activity and those related to organ damage. Early in disease, frailty may primarily arise due to active SLE, with minimal organ damage. As appropriate disease-modifying therapies are initiated, disease activity recedes and damage starts to accumulate related to the disease, its treatment, and other comorbidities[55,59,102]. With longer follow-up, we expect that mean SLICC-FI scores will increase, as deficits continue to accumulate with increasing age[94]

and increasing disease duration. This hypothesis is supported by the finding that longer follow-up time was weakly associated with worsening SLICC-FI scores over time.

While the overall distribution of SLICC-FI values remained largely unchanged between baseline and last follow-up, there was important variation in individual SLICC-FI scores, with approximately 2/3 of patients having clinically meaningful changes in their SLICC-FI values between the two time points. The potential for SLICC-FI scores to decrease supports the view that frailty itself can be reversible and treatable[7]. To this end, the SLICC-FI warrants investigation as both a clinical prognostic tool and as an endpoint in intervention studies.

Similar to the findings of FI studies in non-lupus populations[16,17,85], we identified a significant association between baseline SLICC-FI scores and the risk of mortality during follow-up. Given that prior work has emphasized the importance of the SDI for predicting mortality in SLE[58,60,62], some may question whether the ability of the SLICC-FI to predict mortality risk is heavily reliant upon the inclusion of deficits related to organ damage. However, our sensitivity analysis demonstrated persistence of the relationship between baseline SLICC-FI values and mortality risk, despite removal of all damage-related deficits from the index. This finding highlights a key strength of the deficit accumulation approach to frailty – it is the cumulative impact of multiple small effects, and not the specific nature of a small number of individual deficits, that is important[13,93]. As long as a sufficient number of variables are included in an FI (generally more than

30), its predictive ability for adverse outcomes remains robust, even when a subset of the included deficits are removed[11,15,68,71,91].

Baseline SLICC-FI and baseline SDI were both independent predictors of mortality risk during follow-up. Despite some overlap in the variables captured, these two instruments are likely measuring separate constructs that each provide valuable prognostic information. The SDI can be viewed as a measure of SLE disease severity in one of three core dimensions[98] – organ damage. Meanwhile, the SLICC-FI takes a more holistic approach, incorporating both patient and healthcare provider perspectives of the impact of the disease, its treatment, and other deficits, including comorbidities, on the health of SLE patients as they age. Prior FI studies in other disease-specific cohorts have yielded similar findings – that is, both the FI and existing measures of disease severity maintain independent associations with the risk of future adverse health outcomes[16,17]. As many SLE patients may not develop any organ damage captured by the SDI until several years after diagnosis[58,60,62], the added prognostic value of the SLICC-FI may be highest early in the disease course. This was demonstrated in our subgroup analysis of SLE patients without baseline organ damage (SDI=0), where each 0.05 increase in the baseline SLICC-FI was still associated with a 50% increase in mortality risk.

Our study has some limitations. First, a relatively low number of deaths occurred during follow-up, which limited statistical power in our analysis for mortality. Although this low number of endpoints would have increased our type II error rate, it would not have changed the direction of our finding that baseline SLICC-FI values were a significant

predictor of mortality risk. The low mortality rate in the SLICC inception cohort reflects improved survival among SLE patients compared to previous eras[2]. As such, future work will seek to evaluate the ability of the SLICC-FI to predict other clinically meaningful outcomes. Second, we have only evaluated the change in SLICC-FI values between two time points. Future work will focus on better understanding the trajectories of SLICC-FI values over multiple time points. Third, we were unable to calculate SLICC-FI values for 144 patients (7.9%) due to missing data. However, the characteristics of the patients included in our analysis were very similar to those reported in previous studies using data from the SLICC cohort[58,103], suggesting that our dataset was fairly representative of the overall cohort. Missing data also precluded using SLICC enrolment visits as baseline visits for many patients. Despite this, over 80% of patients had their baseline visit within two years of SLE diagnosis and our results were unchanged in a subgroup analysis including only these individuals. Last, it should be acknowledged that we have constructed and validated 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. External validation of the SLICC-FI in prevalent SLE cohorts is required.

In conclusion, evaluating frailty through deficit accumulation provides a holistic approach to assessing health status among SLE patients, incorporating aspects of disease activity, organ damage, and health-related quality of life into a single measure. We have demonstrated the SLICC-FI to be a valid measure of health status in SLE with the ability to vary over time and to predict mortality. Although the practical utility of frailty

assessment in the routine clinical care of SLE patients has yet to be explored, the SLICC-FI holds potential as a clinical and research tool for the identification of vulnerable SLE patients and may also be a valuable outcome measure for future intervention studies.

4.6 Tables

Table 4.1 - Demographic and clinical characteristics of SLE patients in the SLICC inception cohort at the time of their baseline visit and last follow-up visit.

Variables	Baseline visit (n = 1683)	Last follow-up visit (n=1507)
Patient age at baseline (years)		
Mean (S.D.)	35.7 (13.4)	42.8 (13.6)
Sex		
Female, n (%)	1493 (88.7)	1337 (88.7)
Male, n (%)	190 (11.3)	170 (11.3)
Race/Ethnicity		
Caucasian, n (%)	834 (49.6)	742 (49.2)
Black, n (%)	280 (16.6)	246 (16.3)
Asian, n (%)	260 (15.5)	245 (16.3)
Hispanic, n (%)	248 (14.7)	222 (14.7)
Other, n (%)	61 (3.6)	52 (3.5)
Region		
United States, n (%)	467 (27.7)	377 (25.0)
Canada, n (%)	395 (23.5)	376 (25.0)
Mexico, n (%)	197 (11.7)	181 (12.0)
Europe, n (%)	461 (27.4)	419 (27.8)
Asia, n (%)	163 (9.7)	154 (10.2)
Education		
Post-secondary education, n (%)	847 (50.3)	767 (50.9)
Missing, n (%)	22 (1.3)	20 (1.3)
SLE disease duration (years)		
Median (I.Q.R.)	1.2 (0.9-1.5)	8.5 (5.6 – 11.3)
SLEDAI-2K		
Median (I.Q.R.)	2 (0-6)	2 (0-4)
SLICC/ACR Damage Index (SDI)		
Baseline SDI = 0, n (%)	1270 (75.5)	721 (47.8)
Medication use		
Corticosteroids, n (%)	1179 (70.1)	
Antimalarials, n (%)	1149 (68.3)	
Immunosuppressives, n (%)	681 (40.5)	

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

Table 4.2 - Univariable Cox regression models for the association of baseline demographic and clinical variables with the risk of mortality during follow-up among SLE patients in the SLICC inception cohort (n=1566).

Independent variable	Log-rank test p value[a]	Hazard ratio (95% CI)	p value
Baseline age (years)[b]		1.055 (1.040 – 1.072)	<0.0001
Sex: Female	0.061	Referent	
Male		1.80 (0.96 – 3.37)	0.065
Race/ethnicity: Caucasian	0.025	Referent	
Hispanic		1.54 (0.86 – 2.77)	0.146
Black		1.11 (0.56 – 2.19)	0.765
Asian		0.25 (0.08 – 0.82)	0.023
Other		0.41 (0.06 – 3.03)	0.386
Geographic location: USA	0.052	Referent	
Canada		1.07 (0.52 – 2.21)	0.860
Mexico		1.71 (0.81 – 3.64)	0.162
Europe		0.86 (0.41 – 1.81)	0.692
Asia		0.26 (0.06 – 1.18)	0.080
Post-secondary education[c]: No	0.009	Referent	
Yes		0.46 (0.27 – 0.77)	0.003
Corticosteroid use: No	0.002	Referent	
Yes		3.12 (1.49 – 6.55)	0.003
Immunosuppressive use: No	0.002	Referent	
Yes		2.19 (1.33 – 3.59)	0.002
Antimalarial use: No	0.007	Referent	
Yes		0.52 (0.32 – 0.84)	0.008
SLEDAI-2K (per 1.0)		1.05 (1.00 – 1.09)	0.039
SLE disease duration (years)		1.00 (0.98 – 1.02)	0.649

[a] For categorical variables only

[b] Time-varying covariate (proportional hazards assumption not met)

[c] A "missing" indicator was included for the 1.3% of patients for whom this data was lacking.

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

Table 4.3 - Multivariable Cox regression models for the association of baseline SLICC-FI and SDI scores with the risk of mortality during follow-up among SLE patients in the SLICC inception cohort.

	Full multivariable model [a] (n = 1556)		Final multivariable model [b] (n = 1565)	
	Hazard Ratio (95% CI)	**p value**	**Hazard Ratio (95% CI)**	**p value**
Model 1: SLICC-FI				
SLICC-FI (per 0.05)	1.62 (1.36 - 1.92)	<0.001	1.66 (1.42 – 1.94)	<0.001
Model 2: SDI				
SDI (per 1.0)	1.45 (1.18 – 1.78)	<0.001	1.50 (1.23 – 1.83)	<0.001
Model 3: SLICC-FI & SDI				
SLICC-FI (per 0.05)	1.55 (1.30 – 1.84)	<0.001	1.59 (1.35 – 1.87)	<0.001
SDI (per 1.0)	1.27 (1.03 – 1.57)	0.025	1.27 (1.03 – 1.57)	0.023
Overall model comparisons	**LR test statistic**	**p value**	**LR test statistic**	**p value**
Model 1 vs. Model 3	4.34	0.037	4.71	0.030
Model 2 vs. Model 3	27.79	<0.001	30.07	<0.001

[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] Models adjusted for the following baseline characteristics: age, sex, steroid use, and ethnicity/location.

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

Table 4.4 - Cox regression models for the association between baseline SLICC-FI scores and the risk of mortality during follow-up among SLE patients without organ damage (SDI = 0) at the time of their baseline visit.

	Hazard Ratio (95% CI)	p value
Unadjusted model (n=1187)		
SLICC-FI (per 0.05)	1.48 (1.20 - 1.84)	<0.001
Full multivariable model (n = 1183) [a]		
SLICC-FI (per 0.05)	1.46 (1.14 – 1.85)	0.002
Final multivariable model (n = 1186) [b]		
SLICC-FI (per 0.05)	1.47 (1.18 – 1.83)	0.001

[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] Models adjusted for the following baseline characteristics: age, sex, steroid use, and ethnicity/location.

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

Table 4.5 - Cox regression models for the association of baseline SLICC-FI and SDI scores with the risk of mortality during follow-up among SLE patients in the SLICC inception cohort, excluding damage-related health deficits from the SLICC-FI.

	Univariable model (n=1566)	**Full multivariable model [a] (n = 1556)**	**Final multivariable model [b] (n = 1565)**
	Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI[c] (per 0.05)	1.36 (1.23 – 1.50)	1.36 (1.20 – 1.54)	1.39 (1.24 – 1.56)
Model 2: SDI			
SDI (per 1.0)	1.65 (1.38 – 1.97)	1.45 (1.18 – 1.78)	1.50 (1.23 – 1.83)
Model 3: SLICC-FI & SDI			
SLICC-FI[c] (per 0.05)	1.29 (1.17 – 1.43)	1.34 (1.19 – 1.52)	1.37 (1.22 – 1.53)
SDI (per 1.0)	1.46 (1.22 – 1.76)	1.40 (1.14 – 1.71)	1.41 (1.16 – 1.72)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	13.37 (p=0.0003)	8.86 (p=0.003)	9.72 (p=0.002)
Model 2 vs. Model 3	22.96 (p<0.0001)	25.29 (p<0.0001)	27.53 (p<0.0001)

[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] Models adjusted for the following baseline characteristics: age, sex, steroid use, and ethnicity/location.

[c] 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 4.6 - Cox regression models for the association of baseline SLICC-FI and SDI scores with the risk of mortality during follow-up among SLE patients whose baseline assessments occurred within 2 years of SLE diagnosis [a].

	Univariable model (n=1315)	Full multivariable model [b] (n = 1306)	Final multivariable model [c] (n = 1314)
	Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI (per 0.05)	1.75 (1.50 – 2.05)	1.69 (1.40 – 2.02)	1.72 (1.44 – 2.04)
Model 2: SDI			
SDI (per 1.0)	1.72 (1.40 – 2.09)	1.50 (1.19 – 1.88)	1.54 (1.23 – 1.93)
Model 3: SLICC-FI & SDI			
SLICC-FI (per 0.05)	1.62 (1.37 – 1.92)	1.62 (1.33 – 1.96)	1.64 (1.37 – 1.97)
SDI (per 1.0)	1.31 (1.05 – 1.64)	1.28 (1.01 – 1.63)	1.27 (1.01 – 1.61)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	5.18 (p=0.023)	4.01 (p=0.045)	3.72 (p=0.054)
Model 2 vs. Model 3	30.66 (p<0.0001)	25.83 (p<0.0001)	28.74 (p<0.0001)

[a] Survival analysis includes 1315 patients with 54 deaths occurring during follow-up (75 patients lost to follow-up after the baseline visit with no follow-up time to contribute to survival analysis)

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

[c] Models adjusted for the following baseline characteristics: age, sex, steroid use, and ethnicity/location.

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

4.7 Figures

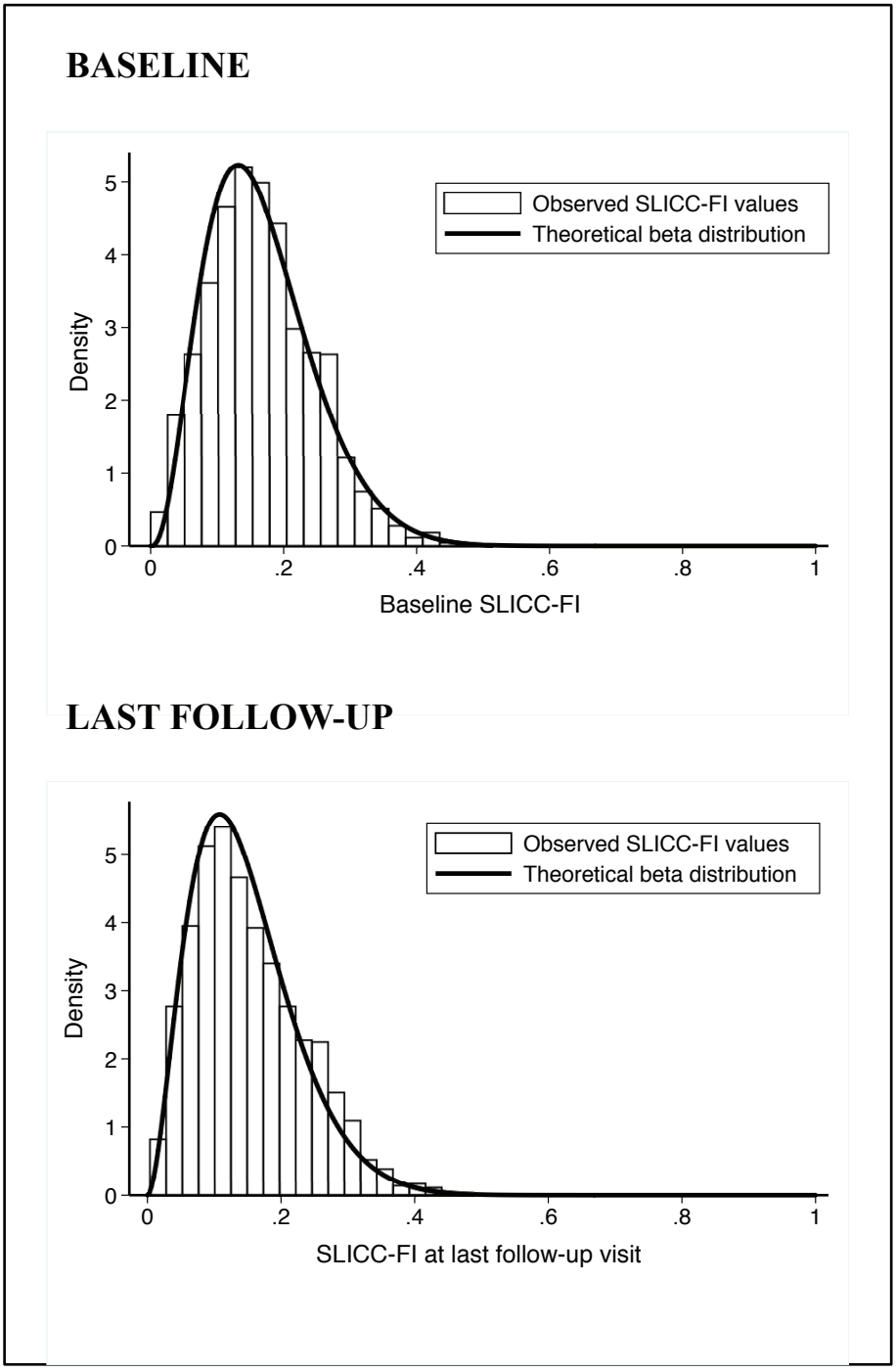

Figure 4.1 - Observed distribution of SLICC-FI values at baseline (n=1682) and at last follow-up visit (n=1507) among SLE patients in the SLICC inception cohort.

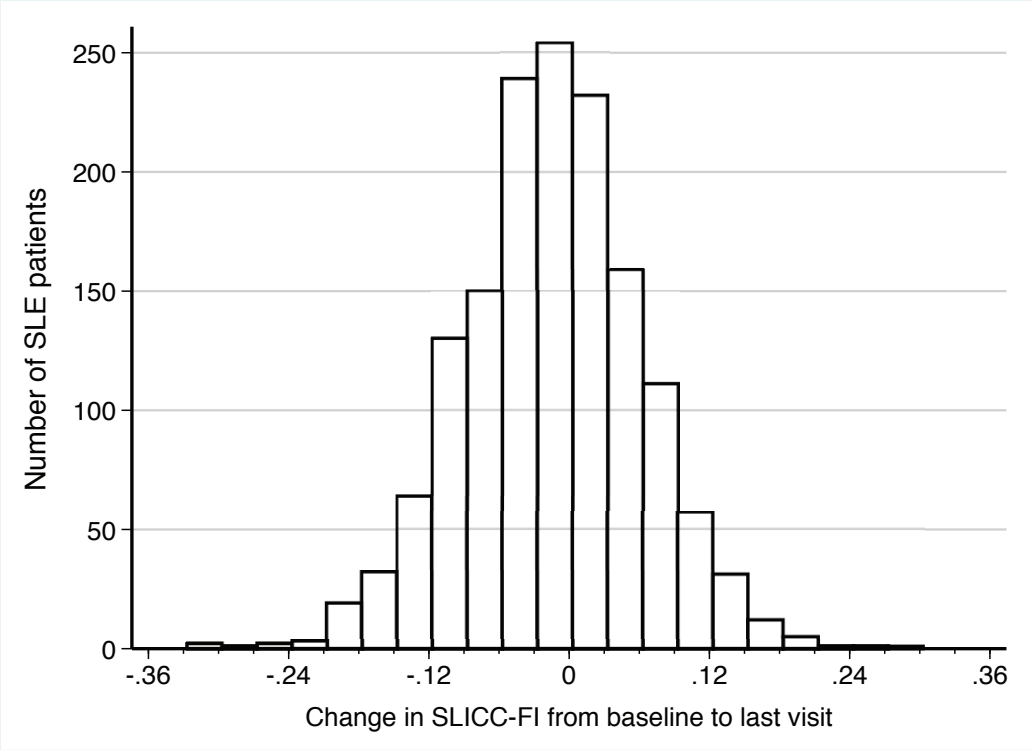

Figure 4.2 - Distribution of the change in SLICC-FI values from the baseline visit to the last follow-up visit among SLE patients in the SLICC inception cohort (n=1506).

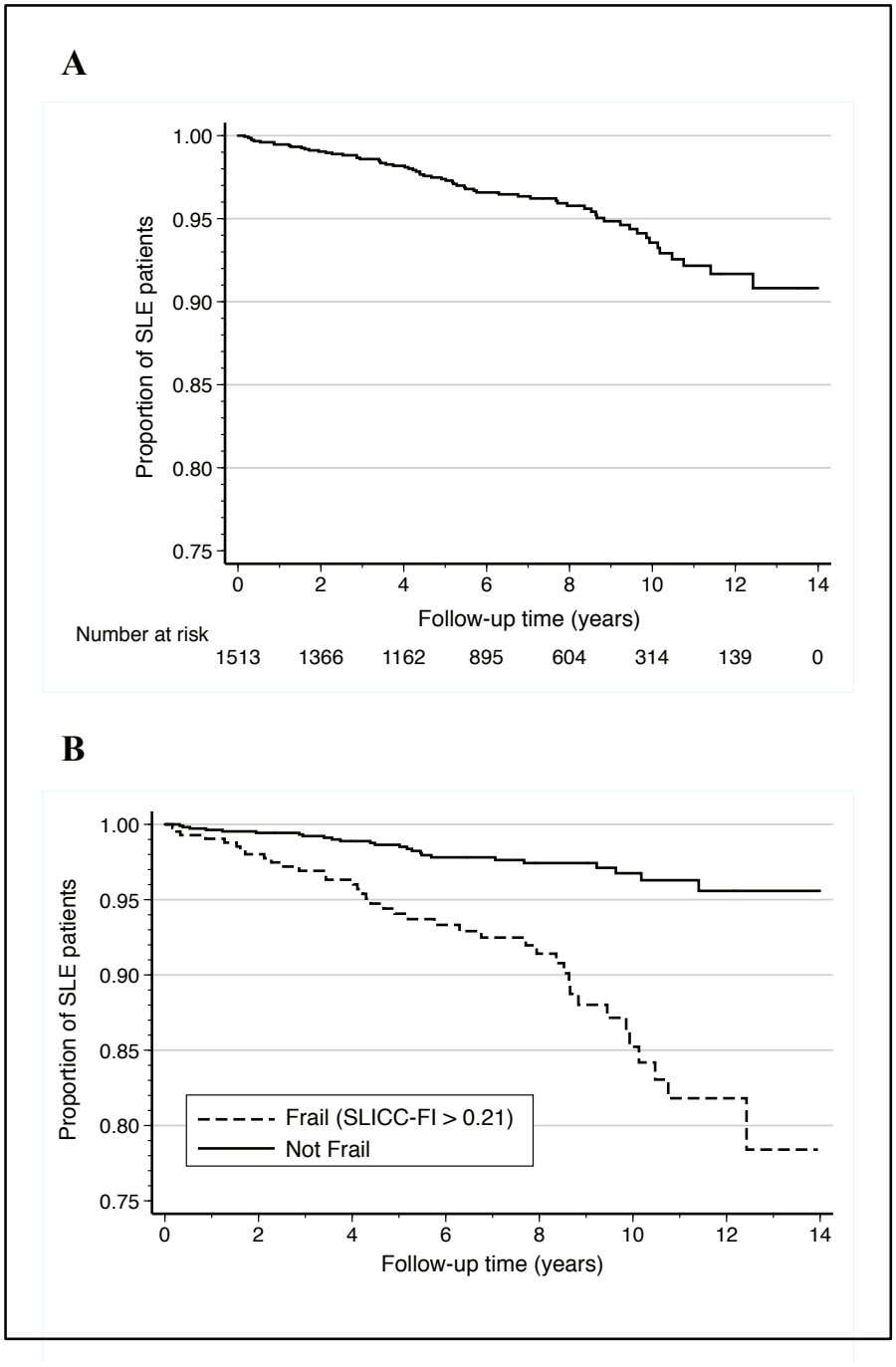

Figure 4.3 - Kaplan-Meier survival curves for the risk of mortality during follow-up among SLE patients in the SLICC inception cohort, overall (A) and stratified by baseline frailty status (B).

CHAPTER 5: MANUSCRIPT 3

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

Authors: Alexandra Legge, Susan Kirkland, Pantelis Andreou, Kenneth Rockwood, John G. Hanly in collaboration with the Systemic Lupus International Collaborating Clinics (SLICC)

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Student contribution to the manuscript: In collaboration with the co-authors, the student led the study design process. She was responsible for all data extraction, data cleaning, and data analyses. She performed the initial interpretation of the data and wrote the first draft of the manuscript.

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5.1 Abstract

Objective: Using the Systemic Lupus International Collaborating Clinics (SLICC) frailty index (FI), we examined the association of baseline SLICC-FI values with the rate of organ damage accrual in the SLICC inception cohort.

Methods: In this secondary analysis, the baseline visit was defined as the first visit at which both organ damage (SLICC/ACR Damage Index [SDI]) and health-related quality of life (Short-Form 36 [SF-36]) were assessed. SLICC-FI scores were calculated using baseline data. For each patient, we calculated the change in SDI scores between the baseline visit and the final study visit. Multivariable negative binomial regression was used to estimate the association between baseline SLICC-FI values and the rate of change in SDI scores during follow-up.

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) with a range from 0 to 0.51. Over a mean (SD) follow-up time of 7.2 (3.7) years, 653 patients (42.2%) experienced an increase in SDI. Higher baseline SLICC-FI values (per 0.05 increment) were associated with higher rates of change in SDI scores during follow-up (Incidence Rate Ratio [IRR] 1.20; 95% CI 1.14-1.26), after adjusting for age, sex, steroid use, ethnicity/region, and baseline SDI and SLEDAI-2K scores.

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

5.2 Introduction

The manifestations of systemic lupus erythematosus (SLE) are diverse, ranging from mild cutaneous and musculoskeletal involvement, to debilitating neuropsychiatric events and end-stage renal disease[1]. Similarly, the clinical course of SLE is highly variable and challenging to predict in individual patients. In geriatric medicine[7], and increasingly in other disciplines[8-10,77], these differences in susceptibility to adverse outcomes are quantified using the construct of frailty, defined as increased vulnerability due to the degradation of homeostatic mechanisms, resulting in diminished ability to respond to physiologic stressors[84]. Evaluating frailty among patients with SLE may advance our understanding of the heterogeneity in health trajectories observed in this disease.

One approach to operationalizing frailty is the construction of a frailty index (FI)[11], which conceptualizes frailty as a loss of physiologic reserve arising from the accumulation of health deficits across multiple systems[12]. Individuals with few deficits are considered relatively fit, while those with an increasing number of health problems are considered increasingly frail and thus more vulnerable to adverse outcomes, including mortality[13]. The validity of the FI approach is well-established in non-lupus populations[11,14-17]. Recently, we utilized data from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort to construct and validate the first FI specifically for use in SLE. We also demonstrated higher SLICC-FI values to be strongly associated with increased mortality risk among SLE patients. In light of improved survival of SLE patients in the current era[2], it is important to determine whether the SLICC-FI also predicts other clinically meaningful outcomes in SLE.

Organ damage is one of three core disease dimensions described in SLE[98]. It is primarily evaluated using the SLICC/American College of Rheumatology (ACR) Damage Index (SDI)[89]. The SDI measures irreversible organ damage occurring after the diagnosis of SLE, regardless of attribution[78,89]. Once recorded in the SDI, damage items are permanent such that SDI scores cannot decrease over time. The SDI has been shown to predict mortality in SLE[55,58-62], and higher SDI scores are associated with lower health-related quality of life[58,99], as well as increased direct and indirect healthcare costs[46]. While mean SDI scores tend to gradually increase over time, organ damage accumulates at different rates in individual patients[55]. As such, it would be advantageous to be able to predict, ideally early in disease, which SLE patients are likely to experience the highest rates of damage accrual.

In non-lupus populations, the FI has been shown to predict a range of clinical outcomes in addition to mortality, including falls, fractures, hospitalizations, institutionalization, and multimorbidity[14,16,17,74,91]. As higher levels of frailty indicate decreased reserve to withstand further health threats, we hypothesize that the SLICC-FI will assist in identifying which SLE patients are most vulnerable to accumulating organ damage over time. Therefore, the primary objective of this study was to estimate the association between baseline SLICC-FI values and the rate of organ damage accrual during follow-up in the SLICC inception cohort. As preexisting organ damage has been consistently shown to predict future damage accrual in SLE[55,58], a secondary aim was to compare the

predictive validity of baseline SLICC-FI and baseline SDI scores for the rate of damage accrual during follow-up.

5.3 Methods

Data source: This was a secondary analysis of longitudinal data collected in 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. Patients were enrolled within 15 months of SLE diagnosis, based on ≥4 revised ACR classification criteria for SLE[86]. In total, 1826 SLE patients were enrolled. 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 the time of enrolment and annually thereafter with standardized assessments. Demographic features included age, sex, race/ethnicity, geographic location, and years of post-secondary education. Medication at each visit included corticosteroids, antimalarials, and immunosuppressives. Medical comorbidities were recorded at the enrolment visit and updated at follow-up visits. Individual ACR classification criteria for SLE[86] fulfilled at the enrolment visit, and the occurrence of criteria between follow-up visits, was documented. Neuropsychiatric

events[87] were recorded at each visit[88]. SLE disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K)[50], cumulative organ damage using the SLICC/ACR Damage Index (SDI)[89], and health-related quality of life using the Medical Outcomes Study Short-Form 36 (SF-36)[79]. Blood pressure (in mmHg), height (in metres), and weight (in kilograms) were also recorded. Laboratory investigations necessary for the assessment of SLE disease activity and organ damage were performed locally at each SLICC site[58].

Construction of the SLICC Frailty Index (SLICC-FI): A standard procedure for FI construction, described in detail elsewhere[11], was used to generate the SLICC-FI. Briefly, we first established a baseline dataset of 1683 patients, consisting of the first study visit at which both the SDI and the SF-36 had been completed. Variables were selected 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 the sample, and (v) having non-missing values for ≥95% of the sample[11]. Of 222 candidate variables, 48 items met all required criteria for inclusion as health deficits in the SLICC-FI. These deficits spanned multiple organ systems and included items related to organ damage, disease activity, comorbidities, and functional status. Each selected health deficit was assigned a scoring system from 0 (complete absence of the deficit) to 1 (deficit fully present) using established cut points from the SLE literature[50,79,86,87,89]. More detailed information regarding the SLICC-FI health deficits and their scoring systems can be found in

Appendix A.

Calculation of baseline SLICC-FI scores: For an individual patient, their SLICC-FI score at a given time point is a proportion, between 0 and 1, calculated from the sum of their individual health deficit scores divided by the total number of deficits considered. For example, with 48 items qualifying as health deficits for the SLICC-FI, an individual in whom 12 of these deficits are fully present would have a SLICC-FI score of 12/48=0.25. In this case, each additional health deficit results in an increase in the SLICC-FI by 0.021. Using health deficit information from the baseline dataset, a baseline SLICC-FI score was calculated for each patient.

Measurement of organ damage accrual during follow-up: For each patient in the baseline dataset, we identified their last follow-up visit at which the SDI was completed. Patients with no follow-up assessments after their baseline visit were excluded. 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. In general, each one-point increase in the SDI corresponds to the accrual of one additional damage item. Thus, we considered the change in SDI values as count data – representing the number of damage items accumulated during follow-up. As follow-up time could vary for each patient based on the dates of their baseline and last follow-up visits, we calculated the rate of change in SDI scores per patient-year of follow-up in order to account for differing observation times.

Statistical analysis: Descriptive statistics were calculated for baseline demographic and clinical characteristics, as well as for baseline SLICC-FI values. The distribution was visualized and descriptive statistic calculated for the change in SDI values during follow-up. Spearman rank correlation coefficients were used as an initial assessment of the relationship between baseline SLICC-FI and SDI scores and the change in SDI values during follow-up. We also compared the change in SDI scores during follow-up between patients classified as frail at baseline (SLICC-FI > 0.21) versus those who were not (baseline SLICC-FI ≤ 0.21)[14,72,90], as well as between those with organ damage (SDI > 0) at baseline versus those without baseline organ damage (SDI = 0).

For regression analyses, we initially fit Poisson models for the change in SDI scores during follow-up. We used likelihood ratio tests to evaluate for overdispersion in the Poisson models, and fit negative binomial models in cases where significant overdispersion was identified. In order to account for differential follow-up time between patients, we considered the rate of change in the SDI as our outcome variable of interest by including follow-up time (in patient-years) as an offset in our models. All models were evaluated for goodness-of-fit and assessed for multicollinearity between independent variables.

First, a univariable model was constructed with the baseline SLICC-FI (per 0.05 increase) as the independent variable of interest. To identify potential confounders of the relationship between the baseline SLICC-FI and organ damage accrual, we considered demographic and clinical variables previously shown to be associated with damage

accrual in SLE[55,58]. We included only those potential confounding variables for which data were available at the time of the baseline assessment. Univariable models for the rate of change in SDI during follow-up were constructed for each of the potential confounders identified. We did not include any potential confounders that overlapped with items included in the SLICC-FI, such as specific disease manifestations (e.g. lupus nephritis, neuropsychiatric disease), comorbidities (e.g. hypertension, obesity), or autoantibodies (e.g. anti-dsDNA antibodies).

A fully adjusted multivariable model for the rate of damage accrual was then constructed, which included the baseline SLICC-FI, as well as any potentially confounding variables with p-values < 0.1 in univariable analysis. Next, we used a backwards stepwise elimination procedure to remove potential confounders that were no longer statistically significant in multivariable analysis. Likelihood ratio tests, which compared full models containing the variable in question to nested models where the variable had been removed, were used to determine which potential confounders would be retained in the final model. The final adjusted model included the baseline SLICC-FI, any potentially confounding variables for which removal from the model resulted in a statistically significant likelihood ratio test (p<0.05), as well as patient age and sex, which were retained in the final model regardless of statistical significance. A similar procedure was followed to construct unadjusted and adjusted models for the rate of damage accrual during follow-up with 1) baseline SDI scores (per one-unit increase) as the independent variable of interest; and 2) both baseline SLICC-FI and baseline SDI scores as independent variables in the same model. We then used likelihood ratio tests to compare

the goodness-of-fit of the models containing both baseline SLICC-FI and baseline SDI scores to the models containing 1) the baseline SLICC-FI alone and 2) the baseline SDI alone. Data analysis was conducted using STATA-IC Version 14 (StataCorp, TX, USA).

Sensitivity analyses: The SLICC-FI contains several health deficits related to organ damage which overlap with items that are also captured by the SDI. In order to assess whether there is a relationship between baseline SLICC-FI scores and organ damage accrual independent of baseline organ damage, we repeated the above analyses after removing any overlapping damage items from the SLICC-FI and then recalculating SLICC-FI scores using the remaining 33 health deficits. Next, as a large proportion of SLE patients have SDI scores of zero early in disease[55,58], we investigated whether the SLICC-FI could differentiate between these individuals in terms of their predicted rate of organ damage accrual during follow-up. To accomplish this, we reassessed the predictive validity of baseline SLICC-FI scores for the rate of change in the SDI during follow-up in a subgroup analysis including only those patients without organ damage (SDI = 0) at the time of their baseline visit.

Follow-up time from the baseline assessment to the last follow-up visit varied between patients. It is possible that our results could be biased by this differential follow-up interval, if the relationship between baseline SLICC-FI values and the rate of organ damage accrual varies depending on the duration of follow-up. To evaluate for this potential source of bias, we first selected different follow-up time cut-points, based approximately 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 then repeated the above analyses separately for patients with follow-up time above versus below each cut-point.

Finally, our baseline visit definition for this analysis allowed baseline visits to occur at varying time points in the SLE disease course. To evaluate the influence of SLE disease duration at baseline on our results, we repeated the above analyses in the subgroup of patients whose baseline visits occurred within two years of SLE diagnosis.

5.4 Results

Baseline patient characteristics: There were 1549 patients (92.0% of the baseline dataset; 84.8% of the overall SLICC cohort) who had at least one follow-up visit subsequent to their baseline visit, such that two data points were available to model the change in SDI scores over time in relation to baseline SLICC-FI values. Baseline demographic and clinical characteristics of these patients are shown in **Table 5.1**. Median (I.Q.R.) SLE disease duration at baseline was 1.2 (0.9-1.5) years, with the majority of patients (n=1300 [83.9%]) having their baseline visit within two years of SLE diagnosis. There were 1179 patients (76.1%) without organ damage (SDI=0) at the time of their baseline assessment. Baseline SLICC-FI values ranged from a minimum of 0.004 to a maximum of 0.510, with a median (I.Q.R.) of 0.16 (0.11–0.22) and a slightly higher mean (S.D.) of 0.17 (0.08). There were 422 patients (27.2%) who were classified as frail at baseline (SLICC-FI > 0.21).

Organ damage accrual during follow-up: Over a mean (S.D.) follow-up time of 7.2 (3.7) years and a total of 11,189 patient-years of follow-up, there were 896 patients (57.8%) with no change in their SDI score during follow-up. There were 332 patients (21.4%) who experienced a one-point increase in SDI over time, with 178 patients (11.5%) experiencing a two-point SDI increase during follow-up (**Figure 5.1**).

Baseline SLICC-FI and organ damage accrual: Among patients who were classified as frail at baseline, the rate of change in the SDI per patient-year of follow-up was twice the rate of organ damage accrual among patients who were classified as non-frail at baseline (Incidence Rate Ratio (IRR) 1.98, 95% CI 1.68-2.34). In comparison, among patients with preexisting organ damage at baseline, the rate of change in the SDI during follow-up was 70% higher than the rate for patients without preexisting organ damage (IRR 1.70, 95% CI 1.43-2.01). Using Spearman correlation coefficients (r_s), both the baseline SLICC-FI ($r_s = 0.222$; $p<0.0001$) and baseline SDI ($r_s = 0.166$; $p<0.0001$) demonstrated weak, positive associations with the rate of change in SDI scores per patient-year of follow-up.

Unadjusted models for the rate of organ damage accrual during follow-up: All Poisson regression models demonstrated evidence of significant overdispersion. Therefore, the results of negative binomial regression are presented here. In unadjusted analysis, each 0.05 increase in the baseline SLICC-FI was associated with a 26% increase in the rate of change in the SDI during follow-up (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 organ damage accrual during follow-up (IRR 1.31, 95% CI 1.20-1.43) in unadjusted analysis. When the baseline SLICC-FI (IRR 1.23, 95% CI 1.17-1.30) and the baseline SDI (IRR 1.19, 95% CI 1.09-1.31) were included in the same model, both measures maintained independent associations with the rate of subsequent damage accrual.

Identifying other demographic and clinical factors associated with damage accrual: Looking at potential confounders of the relationship between baseline SLICC-FI scores and the rate of organ damage accrual, we found that older age, male sex, steroid use, immunosuppressive use, and higher disease activity (SLEDAI-2K) at baseline were associated with a higher rate of change in the SDI during follow-up **(Table 5.2)**. Antimalarial use and post-secondary education at baseline were both associated with lower rates of organ damage accrual **(Table 5.2)**. There were also differences in the rate of change in the SDI based on race/ethnicity and geographic region **(Table 5.2)**. However, the effects of race/ethnicity and geographic region were not independent of one another. Therefore, for the purposes of multivariable analysis, a combined ethnicity/region variable was created.

Multivariable models for the rate of organ damage accrual during follow-up: The relationship between the baseline SLICC-FI and the rate of change in the SDI during follow-up remained largely unchanged following multivariable adjustment for potentially confounding baseline demographic and clinical factors **(Table 5.3 – Model 1)**. In the final multivariable model, each 0.05 increase in the baseline SLICC-FI was associated

with a 21% increase in the rate of organ damage accrual during follow-up (IRR 1.21, 95% CI 1.16-1.27), after adjusting for baseline age, sex, steroid use, ethnicity/location, and SLEDAI-2K at baseline. Baseline SDI scores also remained significantly associated with the rate of further damage accrual during follow-up after multivariable adjustment **(Table 5.3 – Model 2)**. In multivariable models including both the baseline SLICC-FI and the baseline SDI as independent variables of interest, both measures maintained independent, statistically significant associations with the rate of change in the SDI per patient-year of follow-up **(Table 5.3 – Model 3)**. Compared to the models containing either the baseline SLICC-FI or the baseline SDI alone, the models containing both baseline SLICC-FI and SDI scores demonstrated superior model fit for the rate of organ damage accrual during follow-up (**Table 5.3**).

Sensitivity analyses: The relationship between higher baseline SLICC-FI values and increased rate of damage accrual during follow-up remained highly statistically significant when the above analyses were repeated after removing all damage-related health deficits from the SLICC-FI and recalculating baseline SLICC-FI scores using the remaining 33 health deficits **(Table 5.4)**. This suggests that the association between the baseline SLICC-FI and subsequent damage accrual is not solely dependent upon the inclusion of items related to organ damage within the SLICC-FI. We also repeated the above regression analyses in the subgroup of patients without preexisting organ damage (SDI = 0) at baseline. Among these 1179 patients, those who were classified as frail at baseline (SLICC-FI > 0.21) accrued organ damage during follow-up at a rate that was 89% higher compared to patients who were considered non-frail at baseline (IRR 1.89,

95% CI 1.51-2.36). In multivariable analysis, each 0.05 increase in baseline SLICC-FI was associated with a 23% increase in the rate of change in the SDI during follow-up (IRR 1.23, 95% CI 1.15-1.31), after adjusting for baseline age, sex, steroid use, ethnicity/location, and SLEDAI-2K **(Table 5.5**).

The main regression analyses were then repeated in subgroups stratified by follow-up time **(Table 5.6)**. The relationship between higher baseline SLICC-FI scores and increased organ damage accrual during follow-up was maintained in all subgroups, with the exception of the small subset of patients (n=188) who were followed for ≤ 2.5 years after their baseline assessment. The lack of a statistically significant association between the baseline SLICC-FI and the rate of change in SDI scores in this subgroup was likely related to small sample size, as well as a low event rate, as the majority of these patients (n=142; 75.5%) did not experience any damage accrual during follow-up. Finally, similar results to the main analysis were obtained when the above regression analyses were repeated in the subgroup of 1300 patients whose baseline visits occurred within two years of SLE diagnosis **(Table 5.7)**.

5.5 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 change in the SDI during follow-up, independent of other demographic and clinical characteristics known to predict organ damage accrual in SLE. This finding adds to our previous work that demonstrated the SLICC-FI to be predictive of mortality in SLE and

further supports the SLICC-FI as a valid and robust measure that is capable of predicting clinically meaningful outcomes among SLE patients.

The association between the SLICC-FI and future organ damage accrual is in agreement with prior work applying the FI to non-lupus populations. For example, in addition to mortality, frailty indices have been shown to predict a range of other important health outcomes, including falls, fractures, health service utilization, hospitalizations, institutionalization, and multimorbidity[14,16,17,74,91]. 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[12], 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.

Our findings are also consistent with prior work investigating predictors of organ damage accrual in SLE. Specifically, the observed associations of older age, male sex, steroid exposure, higher baseline SLEDAI-2K scores, and higher baseline SDI scores with increased rates of damage accrual during follow-up have previously been demonstrated in other SLE cohorts[55,58]. Given the importance of preexisting damage, measured using the SDI, for predicting the subsequent rate of accumulation of organ damage in SLE[58,59,61], some may question whether the ability of the SLICC-FI to predict damage accrual is heavily reliant upon the inclusion of health deficits that capture baseline organ damage. However, our sensitivity analysis demonstrated persistence of the relationship between

baseline SLICC-FI values and the rate of change in SDI scores during follow-up, despite removal of all damage-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[13,93].

We found that the baseline SLICC-FI and the baseline SDI were both independent predictors of the rate of damage accrual during follow-up. This suggests that, despite some overlap in the variables captured by these two instruments, they are likely measuring separate constructs that each provide valuable prognostic information for SLE patients. As a proportion of SLE patients will remain free of organ damage captured by the SDI for several years after diagnosis[55], the added prognostic value of the SLICC-FI when compared with the SDI may be greatest early in the disease course. This is reflected in the results of our subgroup analysis including only patients without organ damage at baseline (SDI=0), as the baseline SLICC-FI remained a significant predictor of the rate of organ damage accrual during follow-up in a subgroup of patients who were identical to one another with respect to their baseline SDI scores.

It is important to recognize that this study focused on predictors of organ damage accrual in SLE based on information available to clinicians at the time of a baseline assessment. As a result, our analysis does not account for variations in disease activity, therapeutic

exposures, and frailty that may subsequently occur over the course of follow-up. While we believe that the current analysis provides relevant information for clinical decision-making early in disease, it would also be valuable to examine how changes in frailty over time might influence the risk of adverse outcomes. 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 SLE. It would also be important 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 organ damage accrual were to vary over time. However, our sensitivity analysis stratified by follow-up time demonstrated a consistent association between baseline SLICC-FI values and the rate of organ 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 rate of change in SDI scores over time. However, consistent with the results of previous studies[58,59,102], 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 was valid. Third, 277 patients (15.2% of the cohort) were excluded due to missing baseline or follow-up data. However, the characteristics of the patients included in our analysis were

very similar to those reported in previous studies of the SLICC cohort[58,88], suggesting that our dataset remained fairly representative of the overall cohort. Missing data also precluded using SLICC enrolment visits as baseline visits for some patients. Despite this, approximately 84% of patients had their baseline assessment within two years of SLE diagnosis and our results were unchanged in a subgroup analysis including only these individuals with baseline visits occurring early in disease. Last, it should be acknowledged that the SLICC-FI has been constructed and validated 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. External validation of the SLICC-FI in prevalent SLE cohorts is required.

In conclusion, the SLICC-FI predicts future organ damage accrual among patients with SLE, which is clinically relevant given the association of organ damage with increased mortality risk[55,58-62], lower quality of life[58,99], and increased healthcare costs[46]. The SLICC-FI holds potential value as a prognostic tool for identifying SLE patients who are at highest risk for the development of significant organ damage. As frailty is potentially reversible[7], the SLICC-FI may also be useful as an outcome measure in interventions studies.

5.6 Tables

Table 5.1 - Baseline demographic and clinical characteristics of SLE patients eligible for the organ damage accrual analysis (n=1549).

Variables	Descriptive statistics	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 (50.5)	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)

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

Table 5.2 - Univariable negative binomial regression models for the association of baseline demographic and clinical variables with the change in SDI scores 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
Sex: Female	Referent	
Male	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
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

[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

Table 5.3 - Multivariable 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 in the SLICC inception cohort.

	Full multivariable model [a] (n = 1539)		Final multivariable model [b] (n = 1543)	
	Incidence Rate Ratio (95% CI)	**p value**	**Incidence Rate Ratio (95% CI)**	**p value**
Model 1: SLICC-FI				
SLICC-FI (per 0.05)	1.20 (1.14 - 1.27)	<0.001	1.21 (1.16 – 1.27)	<0.001
Model 2: SDI				
SDI (per 1.0)	1.17 (1.07 – 1.28)	0.001	1.18 (1.08 – 1.29)	<0.001
Model 3: SLICC-FI & SDI				
SLICC-FI (per 0.05)	1.19 (1.13 – 1.25)	<0.001	1.20 (1.14 – 1.26)	<0.001
SDI (per 1.0)	1.10 (1.01 – 1.21)	0.038	1.11 (1.01 – 1.21)	0.028
Overall model comparisons	**LR test statistic**	**p value**	**LR test statistic**	**p value**
Model 1 vs. Model 3	5.18	0.023	5.77	0.016
Model 2 vs. Model 3	40.49	<0.001	45.80	<0.001

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

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

Table 5.4 – 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)	Full multivariable model [a] (n = 1539)	Final multivariable model [b] (n = 1543)
	Incidence Rate Ratio (95% CI)	**Incidence Rate Ratio (95% CI)**	**Incidence Rate Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI[c] (per 0.05)	1.17 (1.12 – 1.21)	1.13 (1.09 – 1.17)	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)	1.18 (1.08 – 1.29)
Model 3: SLICC-FI & SDI			
SLICC-FI[c] (per 0.05)	1.15 (1.11 – 1.20)	1.12 (1.08 – 1.16)	1.13 (1.09 – 1.17)
SDI (per 1.0)	1.26 (1.15 – 1.37)	1.15 (1.05 – 1.25)	1.16 (1.06 – 1.26)
Overall model comparisons	**LR test statistic (p value)**	**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)	11.98 (p=0.001)
Model 2 vs. Model 3	61.25 (p<0.0001)	35.72 (p<0.0001)	40.64 (p<0.0001)

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

[c] 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 5.5 - Negative binomial regression models for the association between baseline SLICC-FI scores and the change in SDI scores during follow-up among SLE patients without organ damage (SDI = 0) at the time of their baseline visit.

	Incidence Rate Ratio (95% CI)	p value
Unadjusted model (n=1179)		
SLICC-FI (per 0.05)	1.28 (1.20 - 1.37)	<0.001
Full multivariable model (n = 1172) [a]		
SLICC-FI (per 0.05)	1.21 (1.14 – 1.30)	<0.001
Final multivariable model (n = 1175) [b]		
SLICC-FI (per 0.05)	1.23 (1.15 – 1.31)	<0.001

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

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

Table 5.6 – 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 Incidence Rate Ratio[c] (95% CI)	Full multivariable model [a] Incidence Rate Ratio[c] (95% CI)	Final multivariable model [b] Incidence Rate Ratio[c] (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)	0.94 (0.79 – 1.12)
> 2.5 years follow-up (n=1361)	1.27 (1.21 – 1.34)	1.22 (1.16 – 1.29)	1.23 (1.17 – 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)	1.16 (1.05 – 1.27)
> 5.0 years follow-up (n=1063)	1.26 (1.19 – 1.33)	1.22 (1.15 – 1.29)	1.23 (1.16 – 1.30)
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)	1.14 (1.07 – 1.22)
> 7.5 years follow-up (n=724)	1.30 (1.22 – 1.37)	1.25 (1.17 – 1.34)	1.27 (1.19 – 1.35)
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)	1.19 (1.13 – 1.27)
> 10.0 years follow-up (n=365)	1.27 (1.17 – 1.38)	1.22 (1.12 – 1.34)	1.24 (1.14 – 1.35)
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)	1.20 (1.14 – 1.26)
> 12.5 years follow-up (n=154)	1.42 (1.25 – 1.62)	1.35 (1.16 – 1.56)	1.36 (1.18 – 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] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location, and SLEDAI-2K.

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

Table 5.7 - 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 whose baseline assessments occurred within 2 years of SLE diagnosis (n=1300).

	Univariable model (n=1300)	Full multivariable model [a] (n = 1291)	Final multivariable model [b] (n = 1295)
	Incidence Rate Ratio (95% CI)	**Incidence Rate Ratio (95% CI)**	**Incidence Rate Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI (per 0.05)	1.31 (1.24 – 1.38)	1.22 (1.16 – 1.29)	1.23 (1.17 – 1.30)
Model 2: SDI			
SDI (per 1.0)	1.30 (1.18 – 1.44)	1.17 (1.05 – 1.31)	1.18 (1.06 – 1.32)
Model 3: SLICC-FI & SDI			
SLICC-FI (per 0.05)	1.29 (1.21 – 1.36)	1.21 (1.15 – 1.28)	1.22 (1.16 – 1.29)
SDI (per 1.0)	1.14 (1.03 – 1.27)	1.09 (0.98 – 1.21)	1.09 (0.98 – 1.22)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	6.52 (p=0.012)	2.96 (p=0.085)	3.30 (p=0.069)
Model 2 vs. Model 3	78.29 (p<0.0001)	41.89 (p<0.0001)	46.87 (p<0.0001)

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

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

5.7 Figures

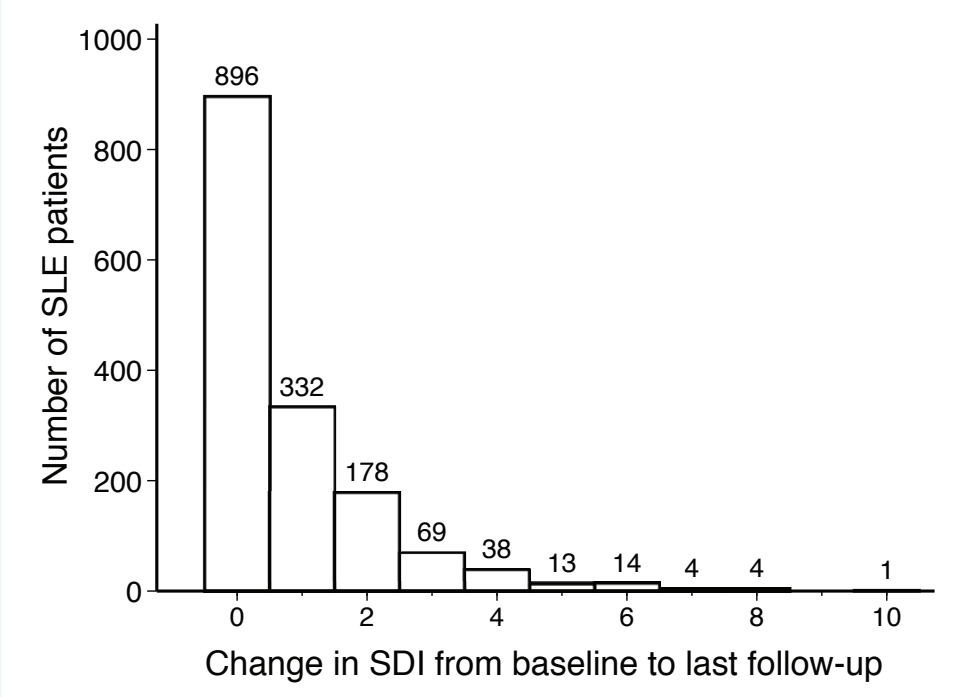

Figure 5.1 - Distribution of the change in SDI score between the baseline assessment and the last follow-up visit among SLE patients in the SLICC inception cohort (n=1549).

CHAPTER 6: MANUSCRIPT 4

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

Authors: Alexandra Legge, Susan Kirkland, Pantelis Andreou, Kenneth Rockwood, John G. Hanly in collaboration with the Systemic Lupus International Collaborating Clinics (SLICC)

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6.1 Abstract

Objective: Using the Systemic Lupus International Collaborating Clinics (SLICC) frailty index (FI), we examined the association of baseline SLICC-FI values with the rate of hospitalizations during follow-up in the SLICC inception cohort.

Methods: In this secondary analysis, the baseline visit was defined as the first visit at which both organ damage (SLICC/ACR Damage Index [SDI]) and health-related quality of life (Short-Form 36 [SF-36]) were assessed. SLICC-FI scores were calculated using baseline data. For each patient, we counted the number of inpatient hospital stays that occurred during follow-up. Multivariable negative binomial regression was used to estimate the association between baseline SLICC-FI values and the number of hospitalizations per patient-year of follow-up.

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) with a range from 0 to 0.51. Over a mean (SD) follow-up time of 7.2 (3.7) years, 614 patients (39.6%) experienced a total of 1570 hospitalizations. Higher baseline SLICC-FI values (per 0.05 increment) were associated with more frequent hospitalizations during follow-up (Incidence Rate Ratio [IRR] 1.22; 95% CI 1.14-1.30), after adjusting for age, sex, steroid use, ethnicity/region, and baseline SDI and SLEDAI-2K scores.

Conclusion: The SLICC-FI predicts future hospitalizations among SLE patients, which further supports the SLICC-FI as a valid and robust health measure in SLE.

6.2 Introduction

Patients with systemic lupus erythematosus (SLE) experience higher rates of hospitalization compared to the general population[104]. Most commonly, these hospitalizations are related to active SLE[105-109], complications of treatment (e.g. infections, adverse drug reactions)[105-110], or comorbidities (e.g. atherosclerotic disease). Inpatient hospitalizations are a major source of both direct and indirect costs[104,110-113], contributing substantially to the economic burden associated with SLE. Furthermore, in-hospital mortality rates for SLE patients are significant[57,105-107,114] and overall mortality risk is particularly high for SLE patients with frequent hospitalizations[108]. While overall rates of hospital admission, length of hospital stay, in-hospital mortality rates, and reasons for hospitalization have been well documented in prior SLE studies[105-107,109,110,114], our understanding of the patient characteristics that are associated with increased risk of hospitalizations in SLE remains incomplete[57,105,108,109,115]. Hospitalization rates vary widely among SLE patients - some patients may never require hospitalization, while others experience multiple hospitalizations per year[108]. Currently, our ability to predict which SLE patients are at highest risk for hospitalizations is limited.

In geriatric medicine[7], and increasingly in other disciplines[8-10,77], differences in susceptibility to adverse health outcomes, such as hospitalizations, can be quantified using the construct of frailty, which is defined as a state of increased vulnerability due to the degradation of homeostatic mechanisms, resulting in diminished ability to respond to physiologic stressors[84]. One approach to operationalizing frailty is the construction of a frailty index (FI)[11], which conceptualizes frailty as a loss of physiologic reserve arising

from the accumulation of health deficits across multiple systems[12]. Individuals with few deficits are considered relatively fit, while those with an increasing number of health problems are considered increasingly frail and thus more vulnerable to adverse outcomes[13]. The validity of the FI approach is well-established in non-lupus populations[11,14-17]. Recently, we utilized data from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort to construct and validate the first FI specifically for use in SLE. We also demonstrated higher SLICC-FI values to be strongly associated with increased risk of future adverse health outcomes among SLE patients, including organ damage accrual and mortality.

Given the mortality risk and economic costs associated with hospitalizations in SLE, it would be advantageous to be able to predict which SLE patients are at highest risk for requiring hospital admissions. We hypothesized that the concept of frailty, operationalized using the SLICC-FI, may aid in our understanding of the variability in hospitalization rates that is observed among patients with SLE. Therefore, the primary objective of the present study was to estimate the association between baseline SLICC-FI values and the number of hospitalizations during follow-up among SLE patients in the SLICC inception cohort. As prior studies have identified the SLICC/ACR Damage Index (SDI) as a predictor of hospitalizations in SLE[56,57], a secondary objective was to compare the associations of baseline SLICC-FI scores and baseline SDI scores with the number of hospitalizations during follow-up.

6.3 Methods

Data source: This was a secondary analysis of longitudinal data collected in 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. Patients were enrolled within 15 months of SLE diagnosis, which was based on the presence of four or more ACR classification criteria for SLE[86]. In total, 1826 SLE patients were enrolled. 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 the time of enrolment and annually thereafter with standardized assessments. Demographic features included age, sex, race/ethnicity, geographic location, and years of post-secondary education. Medication use noted at each visit included corticosteroids, antimalarials, and immunosuppressives. Medical comorbidities were recorded at the enrolment visit and updated at follow-up visits. Individual ACR classification criteria for SLE[86] fulfilled at the enrolment visit, and the occurrence of criteria between follow-up visits, were documented. Neuropsychiatric events[87] were recorded at each visit[88]. SLE disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K)[50], cumulative organ damage measured using the SLICC/ACR Damage Index (SDI)[89], and

health-related quality of life evaluated using the Medical Outcomes Study Short-Form 36 (SF-36)[79]. Blood pressure (in mmHg), height (in metres), and weight (in kilograms) were also recorded. Laboratory investigations necessary for the assessment of SLE disease activity and organ damage were performed locally at each visit as described previously[58].

Construction of the SLICC Frailty Index (SLICC-FI): A standard procedure for FI construction, described in detail elsewhere[11], was used to generate the SLICC-FI. Briefly, we first established a baseline dataset of 1683 patients, consisting of the first study visit for each patient at which both the SDI and the SF-36 had been completed. Variables were selected from this 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 the sample, and (v) having non-missing values for ≥95% of the sample[11]. Of 222 candidate variables, 48 items met all required criteria for inclusion as health deficits in the SLICC-FI. These deficits spanned multiple organ systems and included items related to organ damage, disease activity, comorbidities, and functional status. Once selected, each health deficit was assigned a scoring system from 0 (complete absence of the deficit) to 1 (deficit fully present) using established cut points from the SLE literature[50,79,86,87,89]. More detailed information regarding the SLICC-FI health deficits and their scoring systems can be found in **Appendix A**.

Calculation of baseline SLICC-FI scores: For an individual patient, their SLICC-FI

score at a given time point is a proportion, between 0 and 1, calculated from the sum of their individual health deficit scores divided by the total number of deficits considered. For example, with 48 items qualifying as health deficits for the SLICC-FI, an individual in whom 12 of these deficits are fully present would have a SLICC-FI score of 12/48=0.25. In this case, each additional health deficit results in an increase in the SLICC-FI by 0.021. Using health deficit information from the baseline dataset, a baseline SLICC-FI score was calculated for each patient.

Measurement of the number of hospitalizations during follow-up: At each follow-up visit, the number of inpatients hospital stays occurring since the last SLICC assessment was recorded, in addition to the admission and discharge dates for each hospitalization. Hospitalizations were recorded regardless of whether they were attributable to SLE. For each patient in the baseline dataset, we identified all of their subsequent follow-up visits and associated hospitalization data. Patients with no follow-up assessments after their baseline visit were excluded from this analysis. For each patient, we counted the number of hospitalizations that occurred from the date of their baseline assessment to the date of their last follow-up visit. As follow-up time could vary for each patient based on the dates of their baseline and last follow-up visits, we calculated the rate of hospitalizations per patient-year of follow-up in order to account for differing observation times.

Statistical analysis: Descriptive statistics were calculated for the baseline demographic and clinical characteristics of included patients, as well as for baseline SLICC-FI values. Distributions were visualized and descriptive statistics calculated for the number of

hospitalizations during follow-up, as well as for the rate of hospitalizations per patient-year of follow-up. Spearman rank correlation coefficients were used as an initial assessment of the relationship of baseline SLICC-FI and SDI scores with the number of hospitalizations during follow-up. We also compared the number of hospitalizations during follow-up between patients who were classified as frail at baseline (SLICC-FI > 0.21) versus those who were not (baseline SLICC-FI ≤ 0.21)[14,72,90], as well as between those with organ damage (SDI > 0) at baseline versus those without (baseline SDI = 0).

For our regression analyses, we initially fit Poisson models for the number of hospitalizations during follow-up. We used likelihood ratio tests to evaluate for overdispersion in the Poisson models, and fit negative binomial models in cases where significant overdispersion was identified. In order to account for differential follow-up time between patients, we considered the rate of hospitalizations as our outcome variable of interest by including follow-up time (in patient-years) as an offset in our models. All models were evaluated for goodness-of-fit and assessed for multicollinearity between independent variables.

First, a univariable model was constructed with the baseline SLICC-FI (per 0.05 increase) as the independent variable of interest. To identify potential confounders of the relationship between the baseline SLICC-FI and hospitalizations, we considered demographic and clinical variables previously shown to be associated with hospitalizations in SLE[57,105,108,109,115]. We included only those potential confounding variables for which data were available at the time of the baseline assessment.

Univariable models for the rate of hospitalizations during follow-up were constructed for each of the potential confounders identified.

A fully adjusted multivariable model for the rate of hospitalizations was then constructed, which included the baseline SLICC-FI, as well as any potentially confounding variables with p-values < 0.1 in univariable analysis. Next, we used a backwards stepwise elimination procedure to remove potential confounders that were no longer statistically significant in multivariable analysis. Likelihood ratio tests, which compared full models containing the variable in question to nested models where the variable had been removed, were used to determine which potential confounders would be retained in the final model. The final adjusted model included the baseline SLICC-FI, any potentially confounding variables for which removal from the model resulted in a statistically significant likelihood ratio test (p<0.05), as well as patient age and sex, which were retained in the final model regardless of statistical significance. A similar procedure was followed to construct unadjusted and adjusted models for the rate of hospitalizations during follow-up with 1) baseline SDI scores (per one-unit increase) as the independent variable of interest; and 2) both baseline SLICC-FI and baseline SDI scores as independent variables in the same model. We then used likelihood ratio tests to compare the goodness-of-fit of the models containing both baseline SLICC-FI and baseline SDI scores to the models containing 1) the baseline SLICC-FI alone and 2) the baseline SDI alone. Data analysis was conducted using STATA-IC Version 14 (StataCorp, TX, USA).

Sensitivity analyses: The SLICC-FI contains several health deficits related to organ

damage which overlap with items that are also captured by the SDI. In order to assess whether there is a relationship between baseline SLICC-FI scores and the number of hospitalizations during follow-up independent of baseline organ damage, we repeated the above analyses after removing any overlapping damage items from the SLICC-FI and then recalculating SLICC-FI scores using the remaining 33 health deficits.

Next, as a large proportion of SLE patients have SDI scores of zero early in disease[55,58], we wanted to investigate whether the SLICC-FI could differentiate between these individuals in terms of their predicted rate of hospitalizations during follow-up. To accomplish this, we reassessed the predictive validity of baseline SLICC-FI scores for the number of hospitalizations during follow-up in a subgroup analysis including only those patients without organ damage (SDI = 0) at the time of their baseline visit.

There were some hospitalizations where the recorded length of stay was less than 24 hours. Due to concerns that these events may have represented planned interventions or procedures as opposed to acute medical issues, we repeated the above analyses, excluding all hospitalizations with length of stay less than 24 hours.

Follow-up time from the baseline assessment to the last follow-up visit varied between patients. It is possible that our results could be biased by this differential follow-up interval, if the relationship between baseline SLICC-FI values and hospitalizations were to vary depending on the length of the follow-up interval. To evaluate for this potential source of bias, we first selected different follow-up time cut-points, based approximately

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 then repeated the above analyses separately for patients with follow-up time above versus below each cut-point.

Finally, our baseline visit definition for this analysis allowed baseline visits to occur at varying time points in the SLE disease course. To evaluate the influence of SLE disease duration at baseline on our results, we repeated the above analyses including only those patients whose baseline visits occurred within two years of SLE diagnosis.

6.4 Results

Baseline patient characteristics: There were 1549 patients (92.0% of the baseline dataset; 84.8% of the overall SLICC cohort) who were eligible for this analysis. Baseline demographic and clinical characteristics of these patients are shown in **Table 6.1**. Median (I.Q.R.) SLE disease duration at baseline was 1.2 (0.9-1.5) years, with the majority of patients (n=1300 [83.9%]) having their baseline visit within two years of SLE diagnosis. There were 1179 patients (76.1%) without organ damage (SDI=0) at the time of their baseline assessment. Baseline SLICC-FI values ranged from a minimum of 0.004 to a maximum of 0.510, with a median (I.Q.R.) of 0.16 (0.11–0.22) and a slightly higher mean (S.D.) of 0.17 (0.08). There were 422 patients (27.2%) who were classified as frail as baseline (SLICC-FI > 0.21).

Number of hospitalizations during follow-up: Over a mean (S.D.) follow-up time of 7.2 (3.7) years and a total of 11,189 patient-years of follow-up, 1570 inpatient hospital stays occurred. There were 935 patients (60.4%) who did not have any hospitalizations during follow-up. Of the remaining 614 patients (39.6%) with at least one hospitalization, 280 (45.6%) had a single inpatient hospital stay, while 334 patients had multiple hospitalizations during follow-up (**Figure 6.1**). Overall, the mean (S.D.) rate of hospitalizations per patient-year of follow-up was low at 0.15 (0.32) hospitalizations per year.

Baseline SLICC-FI and hospitalizations: Among patients who were classified as frail at baseline (SLICC-FI > 0.21), the number of hospitalizations per patient-year of follow-up was 90% higher than the hospitalization rate among patients who were classified as non-frail at baseline (Incidence Rate Ratio (IRR) 1.90, 95% CI 1.54-2.33). By comparison, among patients with preexisting organ damage at baseline (n=370), the rate of hospitalizations during follow-up was 50% higher than the rate for patients without preexisting organ damage (IRR 1.48, 95% CI 1.18-1.85). Using Spearman correlation coefficients (r_s), both the baseline SLICC-FI ($r_s = 0.122$; $p<0.0001$) and the baseline SDI ($r_s = 0.070$; $p<0.0001$) demonstrated weak, positive associations with the number of hospitalizations per patient-year of follow-up.

Unadjusted models for the number of hospitalizations during follow-up: All Poisson regression models demonstrated evidence of significant overdispersion. Therefore, the results of negative binomial regression are presented here. In unadjusted analysis, each

0.05 increase in the 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). Similarly, each one-point increase in baseline SDI was associated with a 25% increase in the number of hospitalizations per patient-year of follow-up (IRR 1.25, 95% CI 1.13-1.38) in unadjusted analysis. When the baseline SLICC-FI (IRR 1.22, 95% CI 1.15-1.30) and the baseline SDI (IRR 1.14, 95% CI 1.03-1.26) were included in the same model, both measures maintained independent associations with the rate of subsequent hospitalizations.

Identifying other demographic and clinical factors associated with hospitalizations: Looking at potential confounders of the relationship between baseline SLICC-FI scores and the number of hospitalizations during follow-up, we found that younger age, male sex, steroid use, immunosuppressive use, shorter SLE disease duration, and higher disease activity (SLEDAI-2K) at baseline were associated with a higher number of hospitalizations per patient-year of follow-up **(Table 6.2)**. There were also differences in the hospitalization rate based on race/ethnicity and geographic region **(Table 6.2)**. However, the effects of race/ethnicity and geographic region were not independent of one another. Therefore, for the purposes of multivariable analysis, a combined ethnicity/region variable was created.

Multivariable adjusted models for the number of hospitalizations during follow-up: The relationship between the baseline SLICC-FI and the number of hospitalizations during follow-up remained unchanged following multivariable adjustment for potentially confounding baseline demographic and clinical factors **(Table 6.3 – Model 1)**. In the

final multivariable model, each 0.05 increase in the baseline SLICC-FI was associated with a 24% increase in the rate of hospitalizations per patient-year of follow-up (IRR 1.24, 95% CI 1.16-1.32), after adjusting for baseline age, sex, baseline steroid use, ethnicity/location, and SLEDAI-2K at baseline. Baseline SDI scores also remained significantly associated with the number of hospitalizations during follow-up after multivariable adjustment **(Table 6.3 – Model 2)**. In multivariable models including both the baseline SLICC-FI and the baseline SDI as independent variables of interest, both of these baseline measures maintained statistically significant associations with the number of hospitalizations per patient-year of follow-up **(Table 6.3 – Model 3)**. Each 0.05 increase in the baseline SLICC-FI remained associated with a 22% increase in the number of hospitalizations per patient-year of follow-up (IRR 1.22, 95% CI 1.14-1.30), after adjusting for baseline age, sex, baseline steroid use, ethnicity/location, baseline SLEDAI-2K, and baseline SDI scores **(Table 6.3 – Model 3)**. Compared to the models containing either the baseline SLICC-FI or the baseline SDI alone, the models containing both baseline SLICC-FI and SDI scores demonstrated superior model fit for the rate of hospitalizations during follow-up (**Table 6.3**).

Sensitivity analyses: The relationship between higher baseline SLICC-FI values and increased hospitalizations during follow-up remained highly statistically significant when the above analyses were repeated after removing all damage-related health deficits from the SLICC-FI and recalculating baseline SLICC-FI scores using the remaining 33 health deficits **(Table 6.4)**. This suggests that the association between the baseline SLICC-FI

and subsequent hospitalizations is not solely dependent upon the inclusion of organ damage variables within the SLICC-FI.

We also repeated the above regression analyses in the subgroup of patients without preexisting organ damage (SDI = 0) at baseline. Among these 1179 patients, 450 (38.2%) had at least one hospitalization during a mean (S.D.) follow-up interval of 7.3 (3.6) years. In this subgroup, patients who were classified as frail at baseline (SLICC-FI > 0.21) experienced 89% more hospitalizations during follow-up compared to patients who were considered non-frail at baseline (IRR 1.89, 95% CI 1.52-2.34). In multivariable analysis, each 0.05 increase in baseline SLICC-FI was associated with a 18% increase in the rate of change in the SDI during follow-up (IRR 1.18, 95% CI 1.12-1.25), after adjusting for baseline age, sex, baseline steroid use, ethnicity/location, and SLEDAI-2K at baseline **(Table 6.5**).

The main regression analyses were then repeated in subgroups stratified by follow-up time **(Table 6.6)**. A consistent relationship between higher baseline SLICC-FI scores and increased hospitalizations during follow-up was maintained in all subgroups. Similar results to the main analysis were also obtained when the above regression analyses were repeated in the subgroup of 1300 patients whose baseline visits occurred within two years of SLE diagnosis **(Table 6.7)**. Finally, there were 107 hospitalizations that were same-day hospital admissions. Our results were unchanged when the above analyses were repeated including only overnight hospital stays **(Table 6.8)**.

6.5 Discussion

In an international cohort of recently-diagnosed SLE patients, we have demonstrated an association between baseline SLICC-FI values and the number of subsequent all-cause hospitalizations during follow-up. Higher levels of baseline frailty were associated with more hospital admissions during follow-up, independent of other demographic and clinical characteristics previously shown to be associated with hospitalizations in SLE. In particular, our sensitivity analyses demonstrated persistence of the association between the baseline SLICC-FI and future hospitalizations, independent of baseline SDI values. These findings add to our previous work that has shown baseline SLICC-FI values to be associated with increased risk of organ damage accrual and mortality among SLE patients in the SLICC inception cohort. The ability of the SLICC-FI to predict multiple adverse health outcomes among SLE patients suggests that it is a valid and robust measure of vulnerability in this population.

The association of baseline SLICC-FI values with future hospitalizations is consistent with prior work that has described similar associations between FI values and hospital admissions in non-SLE populations. Through the construction of a frailty index, the deficit accumulation approach attempts to quantify the level of frailty in a given individual by counting the number of health problems they possess[12]. Interestingly, prior work in SLE has shown the presence of multisystem disease, as well as the number of organ systems affected, to be associated with several adverse hospitalization-related outcomes, including more frequent hospitalizations, increased risk of readmission, longer length of stay, and increased risk of in-hospital mortality[105,108,115]. These findings are

likely explained by a loss of physiologic reserve that occurs as multiple health problems accumulate, such that new health threats are more likely to result in severe illness requiring hospitalization. The SLICC-FI extends this approach to capture the cumulative impact of the totality of an individual's health problems, with less emphasis placed on the specific nature of their deficits.

Our results are also consistent with the findings of several prior studies in SLE that have demonstrated higher disease activity to be associated with increased risk of hospitalization among SLE patients[108,109,115]. We also found baseline use of corticosteroids and immunosuppressives to be associated with a higher number of hospitalizations during follow-up. Similar associations have been demonstrated previously[109,111]. However, it is unclear to what degree these associations are being driven by complications of these therapies versus that fact that patients receiving these therapies are likely to have more severe disease. Finally, we found that younger age and shorter disease duration at baseline were weakly associated with more frequent hospitalizations during follow-up. These findings may be explained by prior work that has demonstrated hospitalization rates among SLE patients to be highest early in the disease course, gradually declining thereafter[116]. Of note, the relationship between baseline SLICC-FI values and the number of hospitalizations during follow-up remained unchanged after accounting for all of these factors, suggesting that the SLICC-FI may provide valuable prognostic information when considered in addition to those patient characteristics previously shown to be associated with hospitalizations in SLE.

There was significant variation in the number of hospitalizations during follow-up between SLE patients in different geographic regions. Compared to patients in Canada, the United States and Europe, patients in Mexico experienced significantly fewer hospitalizations during follow-up, while patients in Asia demonstrated significantly higher rates of hospitalization when compared to other regions. This variation could not be accounted for by differences in disease severity, as these regional differences persisted in multivariable models. There are several other possible explanations for these regional differences in hospitalization rates, including variation in healthcare funding models, accessibility of healthcare resources, and clinical practice patterns. Importantly, despite these differences in the overall rates of hospitalization of SLE patients, a consistent relationship between higher baseline SLICC-FI values and more frequent hospitalizations during follow-up was maintained across all five geographic regions.

Given that prior studies have shown the SDI to be predictive of hospital admissions in SLE[56,57], we conducted a sensitivity analysis to determine whether the relationship of baseline SLICC-FI scores with future hospitalizations was reliant upon the inclusion of damage-related items in the SLICC-FI. In this analysis, the relationship between baseline SLICC-FI values and future hospitalizations persisted, despite removal of all items related to organ damage from the index. This supports the assertion that it is not organ damage, but the global effect of health deficit accumulation, that is driving the association between baseline SLICC-FI values and the number of hospitalizations during follow-up. The finding that baseline SLICC-FI and baseline SDI scores were both independent predictors of future hospitalizations suggests that, despite some overlap in

the variables captured by these two instruments, they are likely measuring separate constructs that each provide valuable prognostic information for SLE patients. As a proportion of SLE patients will remain free of organ damage captured by the SDI for several years after diagnosis[55], the added prognostic value of the SLICC-FI may be highest early in the disease course. This was reflected in the results of our subgroup analysis that included only those SLE patients without organ damage (SDI=0) at baseline, where the baseline SLICC-FI remained a significant predictor of future hospitalizations in a subgroup of patients who were identical to one another with respect to their baseline SDI scores.

The ability to predict which SLE patients are likely to experience the highest hospitalization rates has potential implications for clinical practice. Prior work suggests that a considerable proportion of hospital admissions among SLE patients are potentially preventable. A population-based observational study of hospitalizations occurring in New York state between 2000-2002 found that 12.7% of all hospitalizations among SLE patients were for avoidable conditions[117], whereby better access to high-quality outpatient care may have prevented the need for hospital admission. Patients who are high-risk to experience a hospital admission based on their SLICC-FI score could be identified for closer outpatient monitoring or more aggressive outpatient therapies to potentially avoid the need for hospital admission.

It is important to recognize that this study focused on predictors of hospitalization in SLE based on information available to clinicians at the time of a baseline assessment. As a

result, our analysis does not account for variations in disease activity, therapeutic exposures, and frailty that may subsequently occur during follow-up. While we believe that the current analysis provides relevant information for clinical decision-making early in disease, it would also be valuable to examine how changes in frailty over time might influence the risk of adverse outcomes. 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 SLE. It would also be important to determine whether SLICC-FI values are more strongly associated with hospitalizations for certain indications, such as infections, clinical SLE flares, or thromboembolic events. While we could not determine the primary reason for each hospitalization in the SLICC inception cohort, this is a suggested aim for future studies. Finally, future work may also investigate the association between the SLICC-FI and other hospitalization-related outcomes in SLE, including length of hospital stay, in-hospital mortality rates, and rates of re-admission.

Our study has some limitations. First, observation time differed between patients, which could introduce bias if the association between the SLICC-FI and future hospitalizations were to vary based on follow-up time. However, our sensitivity analysis stratified by follow-up time demonstrated a consistent association between baseline SLICC-FI values and future hospitalizations across strata, suggesting that this was not a major concern. Second, 277 patients (15.2% of the cohort) were excluded due to missing baseline or follow-up data. However, the characteristics of the patients included in our analysis were very similar to those reported in previous studies of the SLICC cohort[58,88], suggesting that our dataset remained fairly representative of the overall cohort. Missing data also

precluded the use of SLICC enrolment visits as baseline visits for many patients. Despite this, approximately 84% of patients had their baseline assessment within two years of SLE diagnosis and our results were unchanged in a subgroup analysis including only these individuals with baseline visits occurring early in disease. Last, it should be acknowledged that the SLICC-FI has been constructed and validated 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. External validation of the SLICC-FI in prevalent SLE cohorts is required.

In conclusion, the SLICC-FI predicts future hospital admissions among SLE patients, which is an important finding given the increased mortality risk and substantial economic burden associated with hospitalizations in SLE. 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.

6.6 Tables

Table 6.1 - Baseline demographic and clinical characteristics of SLE patients eligible for the hospitalization analysis (n=1549).

Variables	Descriptive statistics	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 (50.5)	21 (1.4)
SLE disease duration (years)		
Median (I.Q.R.)	1.2 (0.9-1.5)	
SLEDAI-2K		5 (0.3)
Median (I.Q.R.)	2 (0-6)	
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)

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

Table 6.2 - 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 (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[b] (per 1.0)	1.06 (1.04 – 1.08)	<0.0001
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.

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

Table 6.3 - Multivariable negative binomial regression models for the association of baseline SLICC-FI and SDI scores with the number of hospitalizations per patient-year of follow-up among SLE patients.

	Full multivariable model [a] (n = 1541)		Final multivariable model [b] (n = 1543)	
	Incidence Rate Ratio (95% CI)	**p value**	**Incidence Rate Ratio (95% CI)**	**p value**
Model 1: SLICC-FI				
SLICC-FI (per 0.05)	1.24 (1.16 - 1.33)	<0.001	1.24 (1.16 – 1.32)	<0.001
Model 2: SDI				
SDI (per 1.0)	1.27 (1.15 – 1.41)	<0.001	1.27 (1.14 – 1.40)	<0.001
Model 3: SLICC-FI & SDI				
SLICC-FI (per 0.05)	1.21 (1.13 – 1.30)	<0.001	1.22 (1.14 – 1.30)	<0.001
SDI (per 1.0)	1.18 (1.06 – 1.31)	0.002	1.18 (1.07 – 1.31)	0.001
Overall model comparisons	**LR test statistic**	**p value**	**LR test statistic**	**p value**
Model 1 vs. Model 3	9.24	0.002	10.07	0.002
Model 2 vs. Model 3	35.56	<0.001	38.64	<0.001

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLEDAI-2K, and SLE disease duration.

[b] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location, and SLEDAI-2K.

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

Table 6.4 – Negative binomial regression models for the association of baseline SLICC-FI and SDI scores with the number of hospitalizations per patient-year of follow-up among SLE patients, excluding damage-related health deficits from the SLICC-FI.

	Univariable model (n=1549)	Full multivariable model [a] (n = 1541)	Final multivariable model [b] (n = 1543)
	Incidence Rate Ratio (95% CI)	**Incidence Rate Ratio (95% CI)**	**Incidence Rate Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI[c] (per 0.05)	1.16 (1.11 – 1.21)	1.15 (1.10 – 1.20)	1.15 (1.10 – 1.20)
Model 2: SDI			
SDI (per 1.0)	1.25 (1.13 – 1.38)	1.27 (1.15 – 1.41)	1.27 (1.14 – 1.40)
Model 3: SLICC-FI & SDI			
SLICC-FI[c] (per 0.05)	1.15 (1.10 – 1.20)	1.14 (1.08 – 1.19)	1.14 (1.09 – 1.19)
SDI (per 1.0)	1.19 (1.08 – 1.32)	1.23 (1.11 – 1.37)	1.24 (1.12 – 1.37)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	11.69 (p=0.0006)	15.74 (p=0.0001)	16.81 (p<0.0001)
Model 2 vs. Model 3	42.60 (p<0.0001)	31.79 (p<0.0001)	34.77 (p<0.0001)

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLEDAI-2K, and SLE disease duration.

[b] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location, and SLEDAI-2K.

[c] 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 6.5 - Negative binomial regression models for the association between the baseline SLICC-FI and the number of hospitalizations per patient-year of follow-up among SLE patients without organ damage (SDI = 0) at the time of their baseline visit.

	Incidence Rate Ratio (95% CI)	p value
Unadjusted model (n=1179)		
SLICC-FI (per 0.05)	1.17 (1.11 - 1.23)	<0.001
Full multivariable model (n = 1173) [a]		
SLICC-FI (per 0.05)	1.17 (1.11 – 1.24)	<0.001
Final multivariable model (n = 1178) [b]		
SLICC-FI (per 0.05)	1.18 (1.12 – 1.25)	<0.001

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLEDAI-2K, and SLE disease duration.

[b] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location and SLEDAI-2K.

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

Table 6.6 – Negative binomial regression models for the association between baseline SLICC-FI values and the number of hospitalizations per patient-year of follow-up among SLE patients, stratified by follow-up time.

	Univariable model Incidence Rate Ratio[c] (95% CI)	Full multivariable model [a] Incidence Rate Ratio[c] (95% CI)	Final multivariable model [b] Incidence Rate Ratio[c] (95% CI)
Cut point: 2.5 years follow-up			
≤ 2.5 years follow-up (n=188)	1.55 (1.27 – 1.91)	1.48 (1.15 – 1.90)	1.50 (1.18 – 1.90)
> 2.5 years follow-up (n=1361)	1.22 (1.15 – 1.30)	1.23 (1.15 – 1.31)	1.22 (1.15 – 1.31)
Cut point: 5.0 years follow-up			
≤ 5.0 years follow-up (n=484)	1.31 (1.17 – 1.46)	1.25 (1.11 – 1.40)	1.26 (1.13 – 1.41)
> 5.0 years follow-up (n=1065)	1.21 (1.13 – 1.30)	1.24 (1.15 – 1.33)	1.23 (1.14 – 1.32)
Cut point: 7.5 years follow-up			
≤ 7.5 years follow-up (n=824)	1.27 (1.18 – 1.37)	1.25 (1.14 – 1.36)	1.25 (1.15 – 1.36)
> 7.5 years follow-up (n=725)	1.21 (1.11 – 1.31)	1.25 (1.14 – 1.37)	1.23 (1.13 – 1.35)
Cut point: 10.0 years follow-up			
≤ 10.0 years follow-up (n=1184)	1.24 (1.16 – 1.32)	1.24 (1.15 – 1.33)	1.23 (1.15 – 1.32)
> 10.0 years follow-up (n=365)	1.26 (1.11 – 1.43)	1.27 (1.11 – 1.45)	1.25 (1.10 – 1.43)
Cut point: 12.5 years follow-up			
≤ 12.5 years follow-up (n=1395)	1.23 (1.16 – 1.31)	1.23 (1.15 – 1.31)	1.23 (1.15 – 1.31)
> 12.5 years follow-up (n=154)	1.34 (1.14 – 1.58)	1.42 (1.18 – 1.71)	1.33 (1.12 – 1.59)

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLEDAI-2K, and SLE disease duration.

[b] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location, and SLEDAI-2K.

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

Table 6.7 - Negative binomial regression models for the association between baseline SLICC-FI and SDI scores and the number of hospitalizations per patient-year of follow-up among SLE patients whose baseline assessments occurred within two years of SLE diagnosis.

	Univariable model (n=1300)	Full multivariable model [a] (n = 1293)	Final multivariable model [b] (n = 1295)
	Incidence Rate Ratio (95% CI)	**Incidence Rate Ratio (95% CI)**	**Incidence Rate Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI (per 0.05)	1.23 (1.15 – 1.30)	1.26 (1.17 – 1.35)	1.24 (1.16 – 1.33)
Model 2: SDI			
SDI (per 1.0)	1.28 (1.14 – 1.44)	1.30 (1.15 – 1.46)	1.30 (1.15 – 1.46)
Model 3: SLICC-FI & SDI			
SLICC-FI (per 0.05)	1.20 (1.12 – 1.28)	1.23 (1.13 – 1.33)	1.21 (1.13 – 1.30)
SDI (per 1.0)	1.16 (1.03 – 1.32)	1.18 (1.05 – 1.34)	1.21 (1.07 – 1.36)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	5.74 (p=0.017)	7.34 (p=0.007)	9.48 (p=0.002)
Model 2 vs. Model 3	30.75 (p<0.0001)	31.63 (p<0.0001)	31.94 (p<0.0001)

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLE disease duration, and SLEDAI-2K.

[b] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location, and SLEDAI-2K.

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

Table 6.8 - Negative binomial regression models for the association of baseline SLICC-FI and SDI scores with the number of hospitalizations per patient-year of follow-up among SLE patients, excluding same-day hospital admissions.

	Univariable model (n=1549)	Full multivariable model [a] (n = 1541)	Final multivariable model [b] (n = 1543)
	Incidence Rate Ratio (95% CI)	**Incidence Rate Ratio (95% CI)**	**Incidence Rate Ratio (95% CI)**
Model 1: SLICC-FI			
SLICC-FI (per 0.05)	1.24 (1.17 – 1.31)	1.24 (1.16 – 1.33)	1.24 (1.16 – 1.33)
Model 2: SDI			
SDI (per 1.0)	1.25 (1.13 – 1.39)	1.27 (1.14 – 1.41)	1.27 (1.14 – 1.41)
Model 3: SLICC-FI & SDI			
SLICC-FI (per 0.05)	1.22 (1.14 – 1.29)	1.22 (1.13 – 1.31)	1.22 (1.14 – 1.31)
SDI (per 1.0)	1.14 (1.02 – 1.27)	1.17 (1.05 – 1.31)	1.18 (1.06 – 1.32)
Overall model comparisons	**LR test statistic (p value)**	**LR test statistic (p value)**	**LR test statistic (p value)**
Model 1 vs. Model 3	5.07 (p=0.024)	6.70 (p=0.010)	8.28 (p=0.004)
Model 2 vs. Model 3	27.49 (p<0.0001)	29.26 (p<0.0001)	30.31 (p<0.0001)

[a] Models adjusted for the following baseline characteristics: age, sex, steroid use, immunosuppressive use, ethnicity/location, SLEDAI-2K, and SLE disease duration.

[b] Models adjusted for the following baseline characteristics: age, sex, steroid use, ethnicity/location, and SLEDAI-2K.

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

6.7 Figures

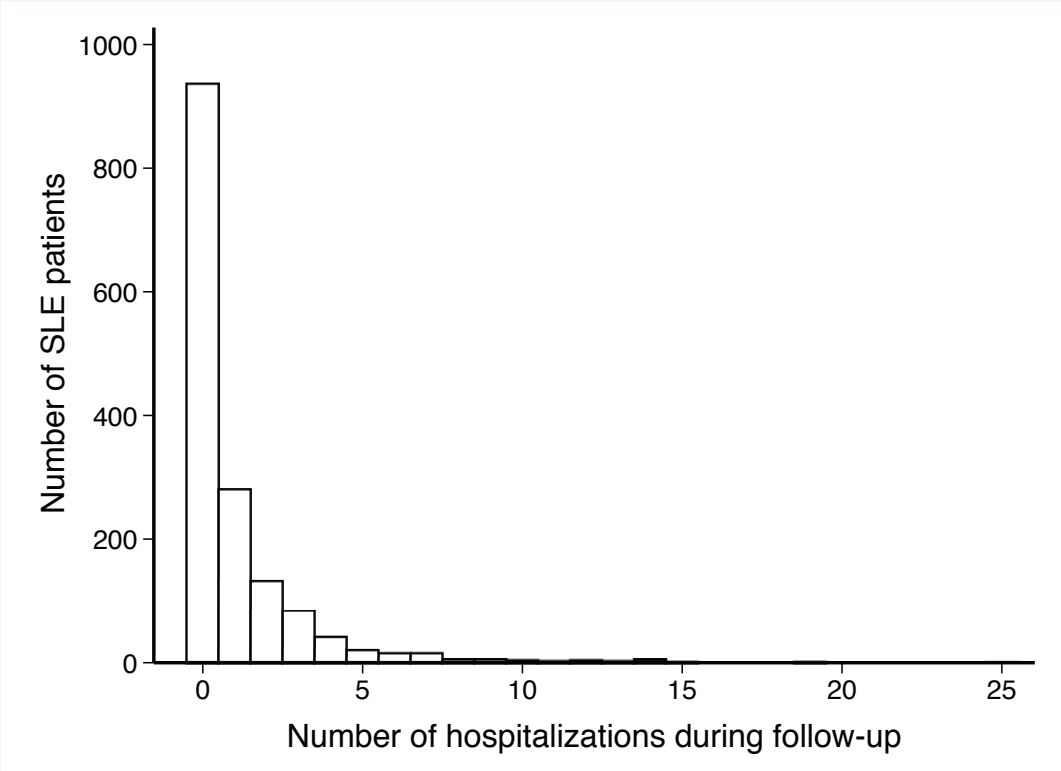

Figure 6.1 - Distribution of the number of hospitalizations between the baseline assessment and the last follow-up visit among SLE patients in the SLICC inception cohort (n=1549).

CHAPTER 7: CONCLUSION

Clinical outcomes in SLE are highly variable and challenging to predict for individual patients. In geriatric medicine, and increasingly in other disciplines, differences in susceptibility to adverse outcomes are quantified using the construct of frailty. Evaluating frailty via deficit accumulation through the construction of a frailty index provides a unique opportunity to enhance our understanding of the heterogeneity in health outcomes that is observed in SLE.

This thesis demonstrates the feasibility of constructing a frailty index to measure vulnerability among patients with SLE using longitudinal data from an international cohort of recently-diagnosed SLE patients. The SLICC-FI demonstrates the expected measurement properties for a frailty index and its values correlate with existing measures of disease status in SLE. Most importantly, SLICC-FI values measured early in disease predict future adverse health outcomes, including hospitalizations, organ damage accrual, and mortality. Furthermore, these associations between the SLICC-FI and adverse outcomes are independent of known prognostic factors in SLE, suggesting that the SLICC-FI provides additional predictive information when used in conjunction with existing SLE instruments. Overall, this thesis makes important contributions towards improving our capacity to prognosticate effectively in SLE, as well as advancing our understanding of aging and frailty more broadly.

7.1 Application of the SLICC-FI in SLE

The SLICC-FI is a valid and robust measure of vulnerability in SLE, capable of predicting multiple different adverse health outcomes using a single instrument. Traditionally, patients with SLE are evaluated across three distinct disease dimensions – inflammatory disease activity, permanent organ damage, and health-related quality of life. While each of these dimensions provides important health information, their prognostic value varies depending on the outcome of interest, and it remains unclear how best to aggregate information across dimensions to produce accurate estimates of overall prognosis. Through the construction of the SLICC-FI, the deficit accumulation approach provides a framework for measuring the cumulative impact of health deficits arising from all three SLE disease dimensions, while also considering deficits that are not routinely captured by existing SLE instruments, such as organ damage acquired prior to SLE diagnosis. Following external validation, the SLICC-FI may be a useful clinical and research tool for the identification of vulnerable SLE patients who could benefit from closer monitoring and more aggressive interventions to prevent future adverse outcomes.

Prior work in SLE has identified the SLICC/ACR Damage Index (SDI) as an important predictor of adverse outcomes, including mortality. In this thesis, the SLICC-FI and the SDI were both found to be independent predictors of future adverse outcomes, suggesting that these instruments are measuring two separate constructs that each provide valuable prognostic information for SLE patients. We've also shown the ability of the SLICC-FI to predict adverse outcomes within a subgroup of SLE patients with identical SDI scores,

further demonstrating the added prognostic value of the SLICC-FI when applied in combination with existing SLE measures.

The prevalence of frailty in this relatively young cohort of SLE patients early in their disease course is concerning. However, we have also demonstrated the potential for clinically meaningful improvement in SLICC-FI values over time. This is encouraging, as it suggests that frailty in patients with early SLE is potentially treatable with the appropriate interventions. This reversibility is also a major advantage of the SLICC-FI compared to the SDI, which only captures irreversible deficits and therefore cannot capture improvements in a patient's status over time. Given its potential reversibility, the SLICC-FI warrants further investigation as an outcome measure for future intervention studies. Future work should also focus on evaluating the properties of the SLICC-FI, including its reversibility, in older patients with longstanding SLE.

7.2 Potential utility of the SLICC-FI in the study of aging and frailty

The construction and validation of the SLICC-FI has provided a unique opportunity to study frailty in a relatively young cohort of individuals with an acquired vulnerability state. We demonstrate a high prevalence of frailty in this cohort compared to the general population and, similar to FI measures constructed in older populations, we found the SLICC-FI to be predictive of future adverse outcomes. Overall, these results support the view that frailty is a relevant concept across the entire adult lifespan and is not only an issue of the aged, but of the aging process itself.

As SLE is a systemic inflammatory condition, our work can also aid in our understanding of the role of immune dysregulation in the development of frailty. The shared inflammatory pathways that have been implicated in the pathogenesis of both SLE and frailty provide a potential mechanism by which accelerated aging may occur in SLE patients. Future work should aim to better understand the link between chronic inflammation and frailty, and this work may benefit from using SLE as a model of a chronic inflammatory disease in which frailty may develop at an accelerated rate.

Our finding that mean SLICC-FI values did not increase over a nontrivial follow-up interval is an interesting observation not seen in previous FI studies in non-SLE populations. This relates to the reversibility of SLICC-FI values discussed earlier and supports the broader view that frailty itself is a potentially treatable condition. However, this finding may also provide important insights into the relationship between frailty and chronological age in disease-specific cohorts. In the general population, there is a very strong correlation between age and mean FI values for individuals of a given age. This correlation tends to be less pronounced in clinical samples. We found a weak association between age and mean SLICC-FI values early in disease, which became much stronger after a period of follow-up. It is possible that, following treatment, there is partial restoration of the relationship between age and SLICC-FI values among SLE patients, such that it more closely resembles the expected relationship for the general population. Future work will aim to explore these novel observations further and to investigate whether similar relationships exist in other disease-specific cohorts.

In summary, this thesis has demonstrated the feasibility of constructing a frailty index using data from an international cohort of relatively young, recently-diagnosed SLE patients. We've shown the SLICC-FI to be a valid and robust measure of vulnerability that predicts the future occurrence of multiple adverse health outcomes among SLE patients. The SLICC-FI holds exciting potential both as a prognostic instrument and as an outcome measure in SLE. It could also be a useful research tool for better understanding the aging process and the development of frailty among individuals with acquired vulnerability states, including patients with chronic inflammatory diseases.

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APPENDIX A Definitions for the SLICC-FI health deficits

Definitions and scoring systems for the 48 health deficits included in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort Frailty Index (SLICC-FI).		
Health Deficit	**Definition**	**Scoring System**
Diabetes	Any diagnosis of diabetes ever, regardless of type	No = 0; Yes = 1
Malignancy	Any history of malignancy ever (excluding dysplasia)	No = 0; Yes = 1
Coronary artery disease	Any history of angina, myocardial infarction, or coronary revascularization ever	No = 0; Yes = 1
Congestive heart failure	Any history of congestive heart failure ever	No = 0; Yes = 1
Peripheral vascular disease	Any history of claudication or documented peripheral vascular disease ever	No = 0; Yes = 1
Cerebrovascular disease	Any history of transient ischemic attack (TIA) or stroke ever	No = 0; Yes = 1
Chronic kidney disease	Presence of chronic kidney disease and, if so, what stage (as per the 2002 K/DOQI guidelines)	None = 0; Stage 1 = 0.2; Stage 2 = 0.4; Stage 3 = 0.6; Stage 4 = 0.8; Stage 5 = 1.0
Deforming or erosive arthritis	Any history of deforming or erosive arthritis since the diagnosis of SLE	No = 0; Yes = 1
Venous thromboembolism	Any history of venous thromboembolism since SLE diagnosis	No = 0; Yes = 1
Pulmonary disease	Pulmonary hypertension, fibrosis, infarction, shrinking lung, or pleural fibrosis since SLE diagnosis	No = 0; Yes = 1
Gastrointestinal disease	Any of the following since SLE diagnosis: Infarction or resection of bowel, spleen, liver, or gallbladder; mesenteric insufficiency; chronic peritonitis, stricture, or UGIT surgery; pancreatic insufficiency	No = 0; Yes = 1
Osteoporosis / Avascular necrosis	Avascular necrosis and/or osteoporosis with fracture or vertebral collapse since SLE diagnosis	No = 0; Yes = 1
Ocular manifestations	Any cataract, retinal change, or optic atrophy since SLE diagnosis	No = 0; Yes = 1
SLE myocarditis/endocarditis	Any history of SLE-related myocarditis or endocarditis	No = 0; Yes = 1
Cognitive impairment	Active cognitive impairment since last assessment*	No = 0; Yes = 1
Seizures & seizure disorders	Active seizures since last assessment* and/or past history of seizures requiring anticonvulsant therapy	No = 0; Yes = 1
Altered mental status	Active psychosis or acute confusional state since last assessment*	No = 0; Yes = 1
Neuropathy	Active polyneuropathy, mononeuropathy, or cranial neuropathy since last assessment*	No = 0; Yes = 1
Other neuropsychiatric manifestations	Other active neuropsychiatric manifestations since last assessment*	No = 0; Yes = 1
Active nephritis	Active nephritis since last assessment*	No = 0; Yes = 1
Active nephrotic syndrome	Active nephrotic syndrome since last assessment*	No = 0; Yes = 1
Active serositis	Active serositis since last assessment*	No = 0; Yes = 1
Active inflammatory arthritis	Active inflammatory arthritis last since assessment*	No = 0; Yes = 1
Active inflammatory rash	Active inflammatory rash since last assessment*	No = 0; Yes = 1
Active mucosal ulcers	Active mucosal ulcers since last assessment*	No = 0; Yes = 1
Alopecia	Active, acute alopecia or chronic scarring alopecia	No = 0; Yes (acute) = 0.5; Yes (chronic) = 1
Active vasculitis	Active vasculitis attributable to SLE	No = 0; Yes = 1
Hematologic disorder	Active hematologic disorder since last assessment*	No = 0; Yes = 1
Immunologic disorder	Positive anti-dsDNA, positive anti-Sm, and/or positive antiphospholipid antibodies since last visit*	No = 0; Yes = 1
Complement levels	Active low complement (CH50, C3, or C4) attributable to SLE, with or without anti-dsDNA positivity	Normal/high = 0; Low & negative dsDNA = 0.5; Low & positive dsDNA = 1
Sjogren's syndrome	Any history of Sjogren's syndrome ever	No = 0; Yes = 1
Hypothyroidism	Any history of hypothyroidism ever	No = 0; Yes = 1

Health Deficit	Definition	Scoring System
Hypertension	Measured blood pressure > 130 mmHg systolic and/or > 85 mmHg diastolic and/or taking antihypertensives	No = 0; Yes = 1
Body mass index	Body mass index (kg/m^2) based on measured height and weight. Cut-points based on published data.	BMI 18.5 – 24.9 kg/m^2 = 0; BMI 25 – 29.9 kg/m^2 = 0.5; BMI ≥ 30 kg/m^2 = 1
Mood disorder	Active mood disorder[1] since last assessment*	No = 0; Yes = 1
Anxiety disorder	Active anxiety disorder[1] since last assessment*	No = 0; Yes = 1
Headache	Active headache disorder[1] since last assessment*	No = 0; Yes = 1
Self-rated health	"In general, how would you say your health is now?"	Excellent = 0; Very good=0.25; Good = 0.5; Fair = 0.75; Poor = 1
Self-reported deterioration in health	"Compared to one year ago, how would you rate your health in general now?"	Better or same = 0; Somewhat worse = 0.5; Much worse = 1.0
Vigorous activities	"Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Moderate activities	"Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum, bowling, or playing golf?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Lifting/carrying groceries	"Does your health now limit you in lifting or carrying groceries?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Climbing stairs	"Does your health now limit you in climbing one flight of stairs?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Bending, kneeling, or stooping	"Does your health now limit you in bending, kneeling, or stooping?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Walking 100 metres	"Does your health now limit you in walking 100 metres?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Bathing or dressing	"Does your health now limit you in bathing or dressing yourself?"	Not limited at all = 0; Somewhat limited = 0.5; Limited a lot = 1.0
Self-rated fatigue	"How much of the time during the past 4 weeks did you feel tired/fatigued?"	None = 0; A little = 0.2; Some = 0.4; Moderate = 0.6; Most = 0.8; Always = 1
Self-rated pain	"How much bodily pain have you had during the past 4 weeks?"	None = 0; Very mild = 0.2; Mild = 0.4; Moderate = 0.6; Severe = 0.8; Very severe = 1

* Or since SLE diagnosis if assessed at study enrolment visit

APPENDIX B Copyright Permission Letters

July 18, 2018

John G. Hanly
Division of Rheumatology
QEII – Nova Scotia Rehabilitation Centre
Suite 245 – 1341 Summer Street
Halifax, NS - B3H 4K4

I am preparing my Master's thesis for submission to the Faculty of Graduate Studies at Dalhousie University, Halifax, Nova Scotia, Canada. I am seeking your permission to include a manuscript version of the following papers as a chapter in the thesis:

1. Construction of a frailty index as a novel health measure in systemic lupus erythematosus
2. Validation of a frailty index in patients with systemic lupus erythematosus
3. Prediction of damage accrual in systemic lupus erythematosus using the Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI)
4. Prediction of hospitalizations in systemic lupus erythematosus using the Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI)

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Full publication details and a copy of this permission letter will be included in the thesis.

Yours sincerely,

Alexandra Legge

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Name: JOHN HANLY Title: Rheumatologist

Signature: Date: 18/July/2018

July 18, 2018

Susan Kirkland
Department of Community Health & Epidemiology
Dalhousie University
Centre for Clinical Research – 5790 University Avenue
Halifax NS – B3H 1V7

I am preparing my Master's thesis for submission to the Faculty of Graduate Studies at Dalhousie University, Halifax, Nova Scotia, Canada. I am seeking your permission to include a manuscript version of the following papers as a chapter in the thesis:

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Alexandra Legge

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Name: Susan Kirkland Title: Professor

Signature: Date: July 18, 2018

July 18, 2018

Kenneth Rockwood
Division of Geriatric Medicine
QEII – Veterans' Memorial Building
Suite 1421 – 5955 Veterans' Memorial Lane
Halifax, NS - B3H 2E1

I am preparing my Master's thesis for submission to the Faculty of Graduate Studies at Dalhousie University, Halifax, Nova Scotia, Canada. I am seeking your permission to include a manuscript version of the following papers as a chapter in the thesis:

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Yours sincerely,

Alexandra Legge

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Name: Kenneth Rockwood Title: Professor of Geriatric Medicine

Signature: Date: July 18/2018

July 18, 2018

Pantelis Andreou
Department of Community Health & Epidemiology
Dalhousie University
Centre for Clinical Research – 5790 University Avenue
Halifax NS – B3H 1V7

I am preparing my Master's thesis for submission to the Faculty of Graduate Studies at Dalhousie University, Halifax, Nova Scotia, Canada. I am seeking your permission to include a manuscript version of the following papers as a chapter in the thesis:

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Yours sincerely,

Alexandra Legge

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Name: Pantelis Andreou Title: Assistant Professor

Signature: Date: 18/07/18

Ann Clarke, MD, MSc, FRCPC
Professor, Department of Medicine
The Arthritis Society Chair in Rheumatic Diseases
Cumming School of Medicine
University of Calgary

Chair, Systemic Lupus International Collaborating Clinics (SLICC)

May 15, 2018

Dr. John Hanly
Professor of Medicine and Pathology
Dalhousie University
QEII - Nova Scotia Rehabilitation Centre
1341 Summer Street
Halifax, NS B3H 4K4

Dear Dr. Hanly,

Dr. Legge submitted a proposal outlining her research on the development of a frailty index in Systemic Lupus Erythematosus (SLE) to the Biologics Material and Data Utilization Committee of the Systemic Lupus International Collaborating Clinics (SLICC). Her proposal was approved and she was granted access to the data from the SLICC inception cohort and she has provided regular updates on her research progress to the SLICC group.

As Chair of SLICC, I grant Dr. Legge permission to use the data from the SLICC inception cohort for studies on establishing, validating, and using a frailty index in SLE. In addition to publishing in scientific journals, she is also free to include the data in her MSc thesis submission to the Department of Community Health and Epidemiology at Dalhousie University.

Sincerely,

Ann Clarke, MD, MSc, FRCPC
Professor, Division of Rheumatology
The Arthritis Society Chair in Rheumatic Diseases
Cumming School of Medicine – University of Calgary