

RHEUMATOLOGY

# **Clinical science**

# Comparison of two frailty definitions in women with systemic lupus erythematosus

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#### Abstract

**Objectives:** Frailty is a risk factor for adverse health in SLE. The Fried phenotype (FP) and the SLICC Frailty Index (SLICC-FI) are common frailty metrics reflecting distinct approaches to frailty assessment. We aimed to (1) compare frailty prevalence according to both metrics in women with SLE and describe differences between frail and non-frail participants using each method and (2) evaluate for cross-sectional associations between each metric and self-reported disability.

**Methods:** Women aged 18–70 years with SLE were enrolled. FP and SLICC-FI were measured, and agreement calculated using a kappa statistic. Physician-reported disease activity and damage, Patient Reported Outcome Measurement Information System (PROMIS) computerized adaptive tests, and Valued Life Activities (VLA) self-reported disability were assessed. Differences between frail and non-frail participants were evaluated cross-sectionally, and the association of frailty with disability was determined for both metrics.

**Results:** Of 67 participants, 17.9% (FP) and 26.9% (SLICC-FI) were frail according to each metric (kappa = 0.41, *P* < 0.01). Compared with non-frail women, frail women had greater disease damage, worse PROMIS scores, and greater disability (all *P* < 0.01 for FP and SLICC-FI). After age adjustment, frailty remained associated with a greater odds of disability [FP: odds ratio (OR) 4.7, 95% Cl 1.2, 18.8; SLICC-FI: OR 4.6, 95% Cl 1.3, 15.8].

**Conclusion:** Frailty is present in 17.9–26.9% of women with SLE. These metrics identified a similar, but non-identical group of women as frail. Further studies are needed to explore which metric is most informative in this population.

Keywords: frailty, SLE, patient-reported outcome measures, disability

#### Rheumatology key messages

- Frailty prevalence ranged from 17.9% to 26.9% among women with systemic lupus erythematosus using two metrics.
- Frail participants' characteristics differed by frailty metric, suggesting that metrics measure different constructs.
- Frailty was independently associated with disability using either metric, even after adjusting for age.

## Introduction

Frailty is increasingly recognized among patients with SLE. Frailty is known to be associated with self-reported disability [1–3], organ damage [4–8], hospitalization [9], and mortality [3, 10] in adults with SLE, including young and mid-aged adults. Frail adults with SLE report worse health-related quality of life than non-frail adults with SLE [1, 2, 11].

Different definitions have been used to measure frailty in SLE, most commonly the Fried frailty phenotype [12] and the

SLICC Frailty Index (SLICC-FI) [13]. The Fried frailty phenotype, a disease-agnostic phenotypic definition in which frailty is conceptualized as a syndrome of decreased physiologic reserve, incorporates five objective and subjective components: weight loss, weakness, fatigue, slow gait, and low physical activity [2, 3, 14]; frailty is defined by having at least three of the components. The Fried frailty phenotype was developed for use in older adults in the general population and validated in both the Cardiovascular Health Study [12] and the

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Women's Health and Aging Studies [14]. This phenotypic definition of frailty has been applied broadly in the geriatric literature and in the context of multiple chronic conditions, including pulmonary [15] and cardiovascular disease [16, 17]. Among adults with SLE who are >18 years of age, Fried frailty prevalence has been found to be 16–20% and has been associated cross-sectionally and prospectively with lower health-related quality of life and increased levels of selfreported disability and mortality [1–3].

The SLICC-FI is a SLE-specific definition that is calculated based on the proportion of health deficits present out of a total of 48 items [13]; according to this definition, frailty is present when the SLICC-FI score exceeds 0.21. The SLICC-FI was derived from the multinational SLICC inception cohort based on an accumulation-of-deficits approach that has been used widely in the context of the geriatric and chronic disease populations [13, 18]. SLICC-FI frailty prevalence has been found to range from 6% to 81% [4-11], and SLICC-FI frailty has been associated with organ damage accrual [4–8], future hospitalization [9], and subsequent mortality [10]. SLICC-FI is negatively correlated with health-related quality of life [11]. As the Fried frailty phenotype and the SLICC-FI are derived differently, it is not known whether they perform similarly when applied to the same cohort of patients with SLE. Choice of frailty metric may have important implications for frailty assessment in clinical and research settings for patients with SLE, and to our knowledge, these two common frailty metrics have never been compared directly.

The aim of this study was to measure agreement between the Fried frailty phenotype and the SLICC-FI when applied to a cross-sectional sample of women with SLE. We also evaluated whether patient-reported outcomes, including selfreported disability, differed between frail and non-frail women according to each frailty definition.

#### Methods

#### Participants

Women with SLE seen at the Hospital for Special Surgery (HSS) between August 2018 and October 2019 were invited to enrol. Participants were identified by an ICD-10 code (M32), and a medical record review was performed to check that all patients met the 1997 ACR SLE classification criteria [19]. Patients had to be between 18 and 70 years of age, have been seen at least twice in a 12-month period, and be able to complete surveys in English. Women with severe SLE disease activity (including new or worsening CNS SLE, vasculitis, nephritis, myositis, anaemia, or thrombocytopenia by physician report; use of prednisone or prednisone equivalent of >0.5mg/kg/day; or start of a new medication for SLE apart from HCQ) were excluded to avoid potential confounding of frailty by disease severity or acute disease flare [20]. Dialysis, pregnancy, active malignancy (apart from non-melanomatous skin cancer), overlap autoimmune inflammatory disease (apart from SS or APS), and impairment due to recent surgery or injury were additional exclusion criteria.

A hand grip strength test and a 4-metre walk test were performed, questionnaires administered, and laboratory markers obtained during a single study visit [20, 21] by trained study personnel. The study was approved by the HSS Institutional Review Board (#2017–1061), and written informed consent was received from all participants.

#### Frailty

Frailty was measured according to the Fried frailty phenotype [2, 3, 14] and the SLICC-FI [10, 13] (Fig. 1). According to the Fried frailty phenotype, participants were defined as frail if  $\geq$ 3 of the following criteria were present, consistent with prior studies of frailty in SLE [2, 3, 14]: (1) unintended weight loss (a BMI of <18.5 kg/m<sup>2</sup> or self-reported unintended weight loss of  $\geq$ 4.5 kg over the past year); (2) weakness [of hand grip, normalized for BMI (Jamar dynamometer, Bolingbrook, IL, USA)]; (3) fatigue (affirmative response to 'Everything I did was an effort' or 'I could not get "going" on the Center for Epidemiologic Studies Depression (CES-D) scale) [22]; (4) slow gait (measured as time to walk 4 m, normalized for height); and (5) low activity [<600 metabolic equivalent of task-min/week according to the International Physical Activity Questionnaire (IPAQ)] [23].

The SLICC-FI was determined based on data from the study visit [10, 13]. In addition to physician-reported data, relevant components were derived using self-reported instruments used to assess participant frailty: vigorous and moderate activities from the IPAQ [23]; walking 100 metres and self-rated fatigue using the FRAIL scale, a 5-item patientreported frailty questionnaire [24]; and lifting/carrying groceries, climbing stairs, bathing or dressing, and self-rated pain from the LupusQOL, a SLE-specific patient-reported outcome measure (PROM) [25]. Data for 45 of 48 health deficits included in the original SLICC-FI were available; data on selfrated health, self-reported deterioration in health, and bending, kneeling, or stooping were not collected. The performance of frailty indices constructed using a similar approach has been found to be robust to changes in composition [26]. The SLICC-FI score was calculated for each participant for whom at least 37 of 45 variables were available, representing <20% missing variables for a given participant, consistent with prior application of the SLICC-FI [13]. Frailty was defined by a SLICC-FI score of >0.21 [10].

#### Socio-demographic and clinical characteristics

Date of birth and Charlson Comorbidity Index [27] were determined from medical record review. Race, ethnicity, education level, cigarette smoking (never/past/current), CS use (current dose), immunomodulatory and immunosuppressive medication use (within the past year), SLE duration, and presence of FM were self-reported.

#### Disease activity and damage

Physician-reported SLE disease activity and organ damage were determined based on the SELENA-SLEDAI [20] and the SLICC/ACR Damage Index for SLE (SDI) [21], respectively, and reported as continuous variables.

#### Patient-reported outcomes

In addition to the PROMs used as components of the frailty metrics, we also administered Patient-Reported Outcome Measurement Information System (PROMIS) computerized adaptive tests (CATs) previously validated in SLE [28], including physical function (v2.0), mobility (v2.0), pain behaviour (v1.0), pain interference (v1.1), fatigue (v1.0), anxiety (v1.0), and depression (v1.0). For each PROMIS CAT, a score of 50 reflects the population mean, and 5 is considered the minimal clinically important difference. Higher scores reflect more of the domain being measured. Valued Life Activities

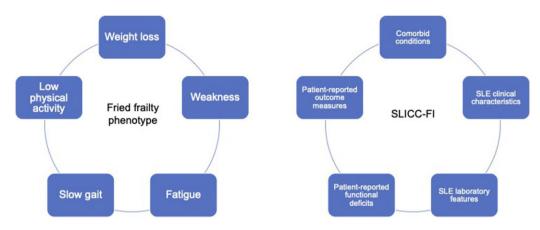


Figure 1. Comparison between the Fried frailty phenotype [12] and the SLICC Frailty Index (SLICC-FI) [13]

(VLA) self-reported disability incorporates 21 domains, with scores ranging from 0–3; higher scores are consistent with greater disability [29]. PROMIS CATs and VLA disability were reported as continuous variables.

#### Analysis

We performed a cross-sectional analysis. Socio-demographic characteristics, frailty components, and PROMs were compared between frail and non-frail participants using Chisquared, Fisher's exact, or Wilcoxon rank sum tests as appropriate. Agreement between the Fried frailty phenotype and the SLICC-FI was calculated using a kappa statistic. The association of frailty with self-reported disability, as defined by the highest quartile on the VLA scale, was determined using logistic regression, adjusting for age.

#### **Results**

#### Sample characteristics

We have previously reported the characteristics of our sample [2]. During the predefined study period of August 2018 to October 2019, 172 of 417 women with validated SLE were eligible for participation in the study, and 72 of them enrolled. The median age was 44.5 years [interquartile range (IQR) 31.0, 58.0]. The median SELENA-SLEDAI and SDI scores were 3.5 (IQR 0, 4.0) and 0 (IQR 0, 2.0), respectively. Participants self-identified as 7.0% Asian, 33.8% Black or African American, 28.6% Hispanic or Latino, and 31.0% White. Sufficient data for calculating the SLICC-FI were available for 67 participants. The 5 participants for whom the SLICC-FI could not be determined did not differ significantly in terms of socio-demographic features or disease characteristics from those for whom the SLICC-FI could be determined. Additional details regarding the sample have been published previously [2].

#### Frailty classifications

Among the 67 participants included in this analysis, frailty prevalence according to the SLICC-FI exceeded that found using the Fried frailty phenotype criteria (26.9% vs 17.9%). The median SLICC-FI score was 0.24 (IQR 0.22, 0.26) among those with frailty. There was moderate agreement between the frailty metrics (k = 0.41; P < 0.01). Fatigue (46.3%) and weakness (41.8%) were the most common domains endorsed by frail participants according to the Fried

frailty phenotype, whereas presence of immunologic disorders (41.8%) was the most common health deficit among frail participants as defined by the SLICC-FI criteria (Supplementary Table S1, available at *Rheumatology* online).

#### Participant characteristics by frailty classification

Compared with non-frail women, frail women according to either measure had significantly greater SLE disease damage (P < 0.01) (Table 1). Using the Fried phenotype, frail women were older (P = 0.05), had a greater comorbidity burden (P < 0.01), and had a higher prevalence of cigarette smoking (P = 0.02) than non-frail women. Based on the SLICC-FI, frail women had significantly greater SLE disease activity (P < 0.01) and a non-significant trend towards longer SLE disease duration (P = 0.06), compared with non-frail women. Frail women had less educational attainment than non-frail women according to the SLICC-FI (P = 0.03). The proportion of chronic kidney disease was significantly higher among frail (vs non-frail) participants according to the Fried phenotype (P = 0.02), while the proportion of active inflammatory arthritis was significantly higher among frail (vs non-frail) participants according to the SLICC-FI (P = 0.02) (Table S1).

#### Patient-reported outcomes

Frail women according to either measure were found to have clinically meaningful and statistically significantly worse PROMIS mobility, pain interference, and fatigue scores compared with non-frail participants (P < 0.01) (Table 2). Self-reported disability was more common among frail than among non-frail women, based on either frailty measure (P < 0.01).

The odds of disability were significantly higher in frail women with SLE compared with non-frail women, using both frailty definitions [Fried frailty definition: odds ratio (OR) 6.2 (95% CI 1.6, 23.5); SLICC-FI: OR 5.0 (95% CI 1.5, 16.5)] (Table 3). These associations were attenuated, but remained statistically significant after adjustment for age [Fried frailty definition: OR 4.7 (95% CI 1.2, 18.8); SLICC-FI: OR 4.6 (95% CI 1.3, 15.8)].

### Discussion

Frailty was found in 17.9% and 26.9% of women with SLE in this cross-sectional single-centre cohort according to the Fried frailty phenotype and the SLICC-FI, respectively. Despite a median age of only 44.5 years among participants,

Table 1. Characteristics of stud	y sample by frailty classification
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Characteristic (median and inter- quartile range, unless otherwise specified)	Fried definition $(N=67)$			SLICC-FI ( $N = 67$ )		
	Non-frail (N=55)	Frail (N=12)	P-value	Non-frail (N=49)	Frail (N=18)	P-value
Age (years)	41.0 [31.0, 57.0]	57.0 [52.5, 62.0]	0.05	46.0 [29.0, 57.0]	53.5 [36.0, 64.0]	0.15
Race, N (%)			0.18			0.34
Asian	5 (9.1)	0(0)		5 (10.4)	0(0)	
Black or African American	15 (27.3)	7 (63.6)		14 (29.2)	8 (44.4)	
White	19 (34.6)	2 (18.2)		17 (35.4)	4 (22.2)	
Other or declined to state	16 (29.1)	2 (18.2)		12 (25.0)	6 (33.3)	
Ethnicity, N (%)			0.72			0.10
Hispanic or Latino	15 (27.8)	4 (36.4)		11 (23.4)	8 (44.4)	
Not Hispanic or Latino	39 (72.2)	7 (63.4)		36 (76.6)	10 (55.6)	
Educational attainment			0.26			0.03
High school or less	6 (10.9)	4 (33.3)		4 (8.2)	6 (33.3)	
Some college education	13 (23.6)	3 (25.0)		10 (20.4)	6 (33.3)	
College	22 (40.0)	3 (25.0)		21 (42.9)	4 (22.2)	
Graduate or professional school	14 (25.4)	2 (16.7)		14 (28.6)	2 (11.1)	
SLE disease duration (years)	13.0 [6.0, 23.0]	15.0 [12.5, 32.0]	0.17	13.0 [6.0, 20.0]	12.0 [10.0, 16.0]	0.06
SELENA-SLEDAI <sup>a</sup> score	4.0 [0, 4.0]	1.0 [0, 7.5]	0.58	2.0 [0, 4.0]	4.0 [4.0, 7.0]	< 0.01
SLICC/ACR Damage Index <sup>b</sup> score	0 [0, 2.0]	3.5 [2.5, 6.0]	< 0.01	0 [0, 1.0]	3.5 [2.0, 5.0]	< 0.01
Charlson Comorbidity Index	2.0 [1.0, 3.0]	3.5 [2.5, 6.0]	< 0.01	2.0 [2.0, 3.0]	3.0 [1.0, 5.0]	0.14
Current prednisone dose (milligrams)	5.0 [4.0, 9.0]	5.0 [5.0, 5.0]	0.79	5.0 [5.0, 10.0]	5.0 [3.0, 5.0]	0.12
Ever smoking, N (%)	6 (10.9)	5 (41.7)	0.02	6 (12.2)	5 (27.8)	0.15
Self-reported FM, N (%)	8 (14.6)	4 (33.3)	0.21	7 (14.3)	5 (27.8)	0.28

<sup>a</sup> SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI. Scores range from 0 to 105, with higher scores indicating greater disease activity.

<sup>b</sup> SLICC/ACR Damage Index: scores range from 0 to 47, with higher scores indicating greater damage. FI: Frailty Index

Table 2. Patient-reported outcome measures in study sample by frailty classification

Characteristic (median and interquartile range)	Fried definition $(N = 67)$			SLICC-FI ( $N = 67$ )		
	Non-frail (N=55)	Frail (N=12)	P-value	Non-frail (N=49)	Frail (N=18)	P-value
PROMIS <sup>a</sup> measure						
Mobility	46.4 [40.2, 49.7]	34.1 [31.9, 38.1]	< 0.01	46.4 [41.4, 49.7]	37.2 [33.0, 39.4]	< 0.01
Pain behaviour	56.6 [49.7, 59.8]	60.5 [57.6, 63.1]	< 0.01	54.2 [48.5, 58.7]	61.4 [59.7, 63.4]	< 0.01
Pain interference	54.3 [46.6, 60.1]	62.7 [58.4, 67.6]	< 0.01	53.9 [46.6, 57.7]	62.8 [58.2, 66.9]	< 0.01
Fatigue	55.6 [49.1, 62.7]	72.8 [64.0, 73.9]	< 0.01	55.4 [48.5, 62.7]	65.0 [58.7, 73.9]	< 0.01
Depression	51.3 [44.7, 57.5]	56.5 [48.1, 69.5]	0.12	51.3 [44.6, 57.5]	54.7 [48.1, 65.8]	0.13
Anxiety	54.1 [50.6, 61.5]	61.2 [48.1, 69.1]	0.33	53.6 [50.4, 61.3]	61.5 [52.9, 65.1]	0.15
Valued Life Activities <sup>b</sup> disability	0.5 [0.2, 0.9]	1.2 [1.1, 1.8]	< 0.01	0.4 [0.1, 0.9]	1.1 [0.9, 1.5]	< 0.01

<sup>a</sup> PROMIS: Patient-Reported Outcome Measurement Information System, scored using a T score metric, with 50 representing the population mean and a difference of 5 considered clinically significant. A higher score indicates more of the domain being measured.

<sup>b</sup> Valued Life Activities: scores range from 0 to 3, with higher scores indicating greater disability. FI: Frailty Index

the frailty prevalence in this cohort was higher than the 10.7% average frailty prevalence of community-dwelling older adults [30]. Why women with SLE are frail at younger ages is intriguing and not yet understood.

The Fried frailty phenotype and the SLICC-FI reflect distinct approaches to frailty measurement. The Fried frailty phenotype takes the phenotypic approach, in which frailty is envisioned as a disease-agnostic syndrome of decreased homeostatic reserve [2, 3, 14]. The SLICC-FI takes an accumulation-of-deficits approach, in which frailty is measured as a proportion of possible functional deficits and comorbid conditions [3–7, 9].

Our frailty prevalence figures are generally consistent with prevalence data from the limited number of other studies of women with SLE [3, 6, 7, 13]. However, our SLICC-FI frailty prevalence was lower than the 36% frailty prevalence found in a single-centre prospective cohort of women with prevalent SLE with similar disease duration (mean 11.9 years), but who had greater organ damage (mean SDI score of 1.6) [5]. Our SLICC-FI frailty prevalence was also lower than the 81% frailty prevalence observed in a multicentre prospective cohort of adults with prevalent SLE with shorter disease duration (mean 1.5 years), but greater organ damage (mean SDI score of 0.6) and moderate-to-high disease activity (mean Systemic Lupus Activity Measure score of 8.7) [8, 31]. This might have been due to our more stringent exclusion criteria. Further, our SLICC-FI frailty prevalence exceeded the 6% frailty prevalence identified in a cross-sectional sample of

**Table 3.** Cross-sectional association of frailty with disability in study sample

Model	Fried definition ( $N = 66$ )		SLICC-FI	C-FI (N=66)	
	Odds ratio	95% CI	Odds ratio	95% CI	
Unadjusted <sup>a</sup>	6.2	1.6, 23.5	5.0	1.5, 16.5	
Adjusted for age	4.7	1.2, 18.8	4.6	1.3, 15.8	

 $^{\rm a}~$  Odds of Valued Life Activities score in the top quartile in frail vs non-frail women.

adults with prevalent SLE with similar organ damage (mean SDI score of 0.5), but shorter disease duration (median 9 years) [32]. Regardless, the discrepancy in frailty prevalence between the Fried frailty phenotype and the SLICC-FI in our SLE cohort suggests fundamental differences in phenotypic and accumulation-of-deficits frailty constructs. This is particularly notable considering we excluded participants with severe disease or active flares, which we anticipated might decrease the prevalence of frail women according the SLICC-FI. More comparative studies of frailty definitions are needed in longitudinal SLE cohorts to understand the clinical relevance of different frailty metrics.

Frail women with SLE differed from non-frail women with SLE in several meaningful ways. Frail women according to either measure had greater disease damage than non-frail women (P < 0.01). Frail women according to the Fried frailty phenotype were older (P = 0.05), had greater comorbidity burden (P < 0.01), and had higher prevalence of cigarette smoking (P = 0.02) than non-frail women, while frail women based on the SLICC-FI had greater disease activity (P < 0.01) and a trend towards longer SLE duration (P = 0.06). Consistent with our findings, others have found that organ damage is higher in frail vs non-frail women with SLE, according to the Fried frailty phenotype [3], and higher SLICC-FI scores were weakly associated with greater organ damage in the multinational prospective cohort of incident SLE in which the SLICC-FI was developed [10]. Baseline frailty according to the SLICC-FI also has been associated with longitudinal organ damage accrual [4–8]. Whether the relationship between frailty and SLE organ damage is bidirectional is not yet well understood.

Both frailty metrics were associated with poor healthrelated quality of life based on PROMIS CATs, providing face validity for the measures. As the Fried frailty phenotype incorporates measures of mobility and fatigue, it is not surprising that participants who were frail according to this particular measure reported on average more fatigue and less mobility than non-frail women according to the same phenotype. In addition, although fatigue and mobility are only minor domains in the SLICC-FI, women who were frail according to the SLICC-FI also had decreased self-reported mobility and increased fatigue relative to non-frail women. Frail women, as defined by both metrics, reported worse pain than non-frail women, even though pain is a component of the SLICC-FI, but not the Fried frailty phenotype. These findings are consistent with prior observations of adults with SLE and suggest that both metrics reflect fatigue, mobility, and pain in women with SLE [3, 32].

Frailty based on either the Fried frailty phenotype or the SLICC-FI was associated with statistically significantly elevated odds of self-reported disability, even after adjustment for age. This association has been demonstrated in another SLE cohort, in which frailty was defined by the Fried frailty phenotype; baseline frailty also was found to predict increase in self-reported disability longitudinally in that cohort [3]. To our knowledge, the association of SLICC-FI frailty with self-reported disability (as defined by the HAQ [33] and the Disabilities of the Arm, Hand, and Shoulder Questionnaire [34]) has been observed in only one other SLE cohort [32]. Whether the SLICC-FI or the disease-agnostic Fried frailty phenotype is a better predictor of self-reported disability longitudinally in patients with SLE is an intriguing question that requires further study.

Frailty is an emerging risk factor for multiple adverse health outcomes among individuals with SLE. Frailty according to both the Fried frailty phenotype and the SLICC-FI has been significantly associated with mortality, including after adjustment for multiple covariates [3, 10]. Frailty as defined by the SLICC-FI also has been found to predict hospitalization [9]. As the Fried frailty phenotype and the SLICC-FI do not reflect identical constructs, it is likely that they have differential utility in risk-stratifying different populations. Since the SLICC-FI includes points for domains reflecting active disease, use of this index likely will result in higher prevalence of frailty in adults with more active SLE; this may be why frailty prevalence in our study is higher according to the SLICC-FI than the Fried frailty phenotype. How much SLE disease activity at a single point in time should contribute to the calculation of frailty is an interesting question, which perhaps can be answered by evaluating the longitudinal impact of frailty, using different definitions, on health-related quality of life or other relevant outcomes, such as organ damage, over time.

Our results must be interpreted in light of several limitations. Our sample was limited in size and did not include men or patients with high SLE disease activity, impacting generalizability. We included only participants with validated SLE and imposed multiple exclusion criteria; thus, participants in this study may differ from the broader population treated for SLE in clinical practice. Only 45 of 48 health deficits were available for inclusion in the SLICC-FI, and several patientreported domains were drawn from available survey data, which were analogous, but not identical, to self-reported data used to construct and validate the SLICC-FI. However, previous work has demonstrated the SLICC-FI to be robust to minor adaptations in the included health deficits [5, 6, 13]. We were unable to control for covariates beyond age in logistic regression models relating frailty to self-reported disability, owing to the small sample size and collinearity between the SLICC-FI and the measures of disease activity and organ damage.

Despite these limitations, our study has notable strengths. We enrolled participants who were diverse in terms of race, ethnicity, and educational attainment. We are the first, to our knowledge, to compare the Fried frailty phenotype and the SLICC-FI in a cohort of women with SLE. Finally, we collected validated PROMs that have not been assessed previously in relation to the SLICC-FI.

Frailty, regardless of the metric used, was associated with worse health outcomes in our sample of women with SLE, independent of age. Choice of which metric to use may depend on the available data points or resources. Measurement of phenotypic frailty alongside assessment of an accumulation of deficits frailty index may serve as complementary approaches to identify patients with SLE who are at risk of decreased health-related quality of life and other health-related outcomes. Further study of the Fried frailty phenotype and the SLICC-FI in larger prospective SLE cohorts will help elaborate the utility of frailty in SLE.

#### Supplementary material

Supplementary material is available at Rheumatology online.

#### **Data availability**

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author after Institutional Review Board approval and completion of a data use agreement.

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#### References

- 1. Lieber SB, Nahid M, Rajan M *et al.* Association of baseline frailty with patient-reported outcomes in systemic lupus erythematosus at 1 year. J Frailty Aging 2023;12:247–51.
- Lieber SB, Nahid M, Paget S *et al.* Evaluation of a patient-reported frailty tool in women with systemic lupus erythematosus. J Rheumatol 2022;49:60–7.
- 3. Katz PP, Andrews J, Yazdany J *et al.* Is frailty a relevant concept in SLE? Lupus Sci Med 2017;4:e000186.
- Legge A, Kirkland S, Rockwood K *et al.* Prediction of damage accrual in systemic lupus erythematosus using the Systemic Lupus International Collaborating Clinics Frailty Index. Arthritis Rheumatol 2020;72:658–66.
- Lima K, Legge A, Hanly JG *et al.* Association of the systemic lupus international collaborating clinics frailty index and damage accrual in longstanding systemic lupus erythematosus. Arthritis Care Res 2023;75:578–84.
- Legge A, Malone A, Hanly JG. External validation of the SLICC Frailty Index (SLICC-FI) as a predictor of adverse health outcomes in systemic lupus erythematosus. Rheumatology (Oxford) 2022; 61:1919–27.

- Elera-Fitzcarrald C, Gamboa-Cárdenas RV, Reatégui-Sokolova C et al. The SLICC-FI predicts damage accrual in SLE patients. data from the Almenara lupus cohort. Lupus 2022;31:1666–70.
- Ugarte-Gil MF, Dubey J, McGwin G *et al.* Association of systemic lupus international collaborating clinics frailty index with damage in systemic lupus erythematosus patients: Results from a multiethnic, multicenter US cohort of patients with lupus. Arthritis Care Res 2023;75:585–9.
- Legge A, Kirkland S, Rockwood K *et al.* Prediction of hospitalizations in systemic lupus erythematosus using the systemic lupus international collaborating clinics frailty index. Arthritis Care Res 2022;74:638–47.
- Legge A, Kirkland S, Rockwood K *et al*. Evaluating the properties of a frailty index and its association with mortality risk among patients with systemic lupus erythematosus. Arthritis Rheumatol 2019;71:1297–307.
- Keramiotou K, Anagnostou C, Konstantonis G *et al*. SLICC-frailty index is independently associated with impaired physical function, activities of daily living and quality of life measures. Rheumatology (Oxford) 2022;61:3808–13.
- Fried LP, Tangen CM, Walston J *et al.*; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56: M146–56.
- 13. Legge A, Kirkland S, Rockwood K *et al.* Construction of a frailty index as a novel health measure in systemic lupus erythematosus. J Rheumatol 2020;47:72–81.
- Bandeen-Roche K, Xue Q-L, Ferrucci L *et al.* Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 2006;61:262–6.
- 15. Hanlon P, Guo X, McGhee E *et al.* Systematic review and metaanalysis of prevalence, trajectories, and clinical outcomes for frailty in COPD. NPJ Prim Care Respir Med 2023;33:1.
- Liperoti R, Vetrano DL, Palmer K *et al.*; ADVANTAGE JA WP4 Group. Association between frailty and ischemic heart disease: a systematic review and meta-analysis. BMC Geriatr 2021;21:357.
- Denfeld QE, Winters-Stone K, Mudd JO *et al.* The prevalence of frailty in heart failure: a systematic review and meta-analysis. Int J Cardiol 2017;236:283–9.
- Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62:722–7.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
- Petri M, Kim MY, Kalunian KC *et al.*; OC-SELENA Trial. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550–8.
- Gladman D, Ginzler E, Goldsmith C *et al.* The development and initial validation of the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
- 22. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
- Craig CL, Marshall AL, Sjöström M *et al.*; International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.
- Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601–8.
- Jolly M, Pickard AS, Wilke C *et al.* Lupus-specific health outcome measure for US patients: the LupusQoL-US version. Ann Rheum Dis 2010;69:29–33.
- Rockwood K, Mitnitski A, Song X *et al.* Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc 2006;54:975–9.
- Charlson ME, Pompei P, Ales KL *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

- Kasturi S, Szymonifka J, Burket JC *et al.* Validity and reliability of patient reported outcomes measurement information system computerized adaptive tests in systemic lupus erythematosus. J Rheumatol 2017;44:1024–31.
- 29. Katz P, Morris A, Trupin L *et al.* Disability in valued life activities among individuals with systemic lupus erythematosus. Arthritis Rheum 2008;59:465-73.
- Collard RM, Boter H, Schoevers RA *et al.* Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012;60:1487–92.
- Liang MH, Socher SA, Larson MG *et al*. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 1989;32:1107–18.
- 32. Keramiotou K, Anagnostou C, Konstantonis G *et al.* SLICC-Frailty Index is independently associated with impaired physical function, activities of daily living, and quality of life measures. Rheumatology (Oxford) 2022;61:3808–13.
- 33. Chatzitheodorou D, Kabitsis C, Papadopoulos NG et al. Assessing disability in patients with rheumatic diseases: translation, reliability and validity testing of a Greek version of the Stanford Health Assessment Questionnaire (HAQ). Rheumatol Int 2008;28: 1091–7.
- 34. Themistocleous GS, Goudelis G, Kyrou I *et al.* Translation into Greek, cross-cultural adaptation and validation of the Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH). J Hand Ther 2006;19:350–7.