Title Page

Short running head: Patient-Reported Frailty in Lupus

Full title of manuscript: Evaluation of a Patient-Reported Frailty Tool in Women with Systemic Lupus Erythematosus

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Abstract:

Objective:

Frailty is associated with mortality in systemic lupus erythematosus (SLE), but how best to measure frailty is unclear. We aimed to compare two frailty metrics, the self-reported FRAIL scale (FS) and the Fried phenotype (FP), in SLE to evaluate differences between frail and non-frail women and whether frailty is associated with self-reported disability.

Methods:

Adult women <70 years old with validated SLE and mild/moderate disease enrolled in this cross-sectional study between August 2018 and October 2019. Correlation and agreement between the FS and the FP were determined. Differences in sociodemographic and disease characteristics, patient-reported outcome measures (PROMs), and biomarkers between frail and non-frail participants were evaluated, as well as association of frailty with Valued Life Activities disability.

Results:

Of 67 participants, 27% and 18% were frail according to the FS and the FP, respectively. Correlation ($r=0.51$; $p<0.0001$) and agreement ($k=0.4627$; $p=0.0004$) between the FS and the FP were significant. Frail women had greater disease damage, high-sensitivity C-reactive protein, and interleukin 6 and worse PROMs according to both frailty definitions. Both frailty measures were associated with self-reported disability after adjustment for age, comorbidity, and disease activity and damage; this relationship was attenuated for the FP.

Conclusion:

Frailty prevalence was high in this cohort of women with SLE using both frailty definitions, suggesting that frailty may be accelerated in women with SLE, particularly when based

exclusively on self-report. Frailty remained associated with self-reported disability in adjusted analyses. The FS may be an informative point-of-care tool to identify frail women with SLE.

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Introduction:

Frailty is a syndrome reflecting decreased homeostatic reserve and has been shown to be an independent risk factor for increased morbidity and mortality (1). Frailty is commonly defined according to the Fried phenotype (FP), encompassing five domains: unintended weight loss, weakness, fatigue, slowness, and low activity (2). Frailty is present when at least three criteria are met.

Frailty has been studied in rheumatoid arthritis (3-12), and some data are available in systemic lupus erythematosus (SLE) (13-16). Frailty has been associated with increased mortality in SLE, using the FP and a SLE-specific cumulative deficits definition of frailty, the Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI) (13-16). This association remained after adjusting for potential confounding factors such as age and physician-reported SLE-associated damage (13). Frailty measured by the FP has been associated with self-reported disability, after adjusting for age and self-reported SLE disease activity and damage (16). These observations suggest that frailty is an independent risk factor for important health outcomes in SLE. However, it may be challenging to obtain the FP in clinical practice, as it requires measurement of grip strength and walking speed and completion of surveys on physical activity and depression. The FRAIL Scale (FS) is a simple five-item self-report questionnaire (17). To our knowledge, no self-reported frailty tool has been compared with the FP in SLE.

The aims of this study were to evaluate the correlation of the FS with the FP in women with SLE and to compare differences between frail and non-frail women, as measured with each frailty instrument. We hypothesized that the FS in addition to the FP would be associated with

patient-reported disability in women with SLE. We also explored whether either definition of frailty was associated with serum biomarkers that reflect increased systemic inflammation.

Materials and Methods:

Participants and Study Visit:

Women between the ages of 18 and 70 meeting American College of Rheumatology (ACR) 1997 SLE criteria who were seen at Hospital for Special Surgery (HSS) at least twice in the 12-month period preceding enrollment and could complete surveys in English were eligible (18). Enrollment occurred between August 2018 and October 2019. Women with severe SLE activity defined by the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) at the visit prior to enrollment were excluded (18); criteria for severe disease activity included new or worse central nervous system SLE, vasculitis, nephritis, myositis, anemia or thrombocytopenia, or use of prednisone or prednisone equivalent more than 0.5 milligram/kilogram (kg)/day or start of a new medication for SLE apart from hydroxychloroquine. This decision was made to facilitate direct comparisons with a recent study of frailty in women with SLE with similar enrollment criteria and to avoid potential confounding of frailty by disease severity in this relatively small study (16). Women on dialysis, who were pregnant, who had active malignancy (apart from non-melanomatous skin cancer), who had overlapping autoimmune inflammatory disease (apart from Sjogren's syndrome or antiphospholipid syndrome), or with recent surgery or injury were excluded. The decision to exclude active malignancy, despite presence of malignancy among the comorbid conditions included in the FS, was made to avoid potential confounding of FP by malignancy, given known association of frailty with malignancy (19).

Patients with SLE were identified based on at least one ICD-10 code (M32) for SLE. SLE diagnosis was confirmed by medical record review. Consent was obtained by an Institutional Review Board (IRB)-approved study team member. Grip strength, 4-meter walk test, and blood draws were performed during a single study visit. SLE disease activity and damage were

measured by the treating rheumatologist during the most recent standard of care visit (20, 21). Questionnaires were administered via RedCap, a secure web-based survey tool (22), at the time of the study visit. Participants were permitted to complete questionnaires on their own device during or following the study visit.

Approval to conduct this study was obtained from the HSS IRB (#2017-1061).

Frailty:

Frailty according to Fried's definition was operationalized as follows, largely consistent with a recent study of frailty in women with SLE (2, 16) (Table S1): 1) Unintended weight loss: body mass index (BMI) <18.5 kg/meters^2 (kg/m^2) or self-reported unintended weight loss of ≥10 pounds over the past year; 2) weakness: 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 (23); 4) slowness: time to walk 4 m (normalized for height); and 5) low activity: <600 MET-minutes/week according to the International Physical Activity Questionnaire (IPAQ) (24). Participants are considered frail if they meet three or more criteria.

The self-report FS, an alternate method of measuring frailty proposed on the basis of systemic review of the literature and expert opinion (25) and validated in middle aged adults (17), was administered during the same study visit (17) (Table S1). This 5-item questionnaire gives participants one point for each question answered in the affirmative. Participants are asked about fatigue, resistance (difficulty climbing steps), ambulation, illnesses (comorbidity), and loss of weight. Participants who score at least three points are defined as frail.

Sociodemographic and Clinical Characteristics:

Date of birth and Charlson comorbidity index (26) were extracted from the medical record. Race/ethnicity, education level, cigarette smoking (never/past/current), corticosteroid use (current dose), immunosuppressive medication use (within the past year), and SLE duration

were self-reported during the study visit. Participants were asked if they had been diagnosed with fibromyalgia, as secondary fibromyalgia is common in SLE (27).

Disease Activity and Damage:

SLE disease activity and damage were scored using the SELENA-SLEDAI (20) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (SDI) (21). The SELENA-SLEDAI ranges from 0-105, with higher scores indicating worse disease activity. The SDI ranges from 0-46, with higher scores indicating worse damage. Both disease activity and damage were reported as continuous variables.

Patient Reported Outcomes:

The following Patient Reported Outcomes Measurement Information System (PROMIS) computerized adaptive tests (CATs) were assessed: physical function (v2.0), mobility (v2.0), pain behavior (v1.0), pain interference (v1.1), fatigue (v1.0), anxiety (v1.0), and depression (v1.0) (28). These generic instruments have been validated in women with SLE (29). PROMIS CAT domains are scored using T-scores, where high values represent more of the domain being measured. A score of 50 represents the population mean and a difference of 5 (a half standard deviation) is generally accepted as being clinically meaningful.

The LupusQOL is a validated SLE-specific patient-reported outcome measure (PROM) that includes 34 questions across 8 domains (30). Scores range from 0-100, with higher scores indicating better health-related quality of life. Disability was assessed using the Valued Life Activities instrument, which includes 21 items each rated on a 0-3-point scale and has been validated in SLE (31). Scores range from 0-3, with higher scores indicating greater disability. Depression was additionally assessed using the CES-D scale, which includes 20 items each rated on a 0-3-point scale (23). Scores range from 0-60, with higher scores indicating greater depressive symptoms. PROMs were reported as continuous variables.

Inflammatory and Metabolic Biomarkers:

Erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), insulin-like growth factor 1 (IGF-1), and soluble tumor necrosis receptor factor 1 (sTNFR1) were measured at a central laboratory. IL-6 and sTNFR1 were used to calculate a previously validated inflammatory index, which has been associated with increased mortality in community-dwelling elderly (32); higher scores have been associated with higher mortality. IGF-1 (33) has been proposed as an additional biomarker for frailty.

Analysis:

A cross-sectional analysis of baseline measurements of the prospective cohort was performed on all observed data. Participants who completed both the FP and the FS were included in this analysis. Frequencies or medians with interquartile ranges (IQR) were determined for demographic characteristics and compared between frail and non-frail subjects using Fisher's exact or Wilcoxon rank sum tests. PROMs and laboratory biomarkers were compared between frail and non-frail participants using Wilcoxon rank sum tests. Logistic regression was used to assess whether frailty was associated with disability defined as the highest quartile of Valued Life Activities disability, including after adjustment for multiple potential confounding factors, which were selected a priori informed by prior data (16). Correlation between the FS and the FP was determined using Spearman's correlation and agreement using a kappa statistic. Sensitivity and specificity of the FS as compared to the FP also were determined.

Results:

Sample Characteristics:

Of 417 potential participants with validated SLE, 172 were eligible at the time of enrollment, with the remainder ineligible due to transient factors such as severe disease activity (n=111) or fixed factors such as overlap conditions (n=134). 72 women with SLE were

enrolled during the predefined study period of August 2018 to October 2019. Median age was 44.5 years [IQR 31.0, 58.0], and the median duration of SLE was 13.0 years [IQR 7.0, 23.0]. Participants were 31.0% white, 33.8% African American, 7.0% Asian, and 28.6% Hispanic or Latino. Median SELENA-SLEDAI score was 3.5 [IQR 0, 4.0], and median SDI score was 0 [IQR 0, 2.0]; median duration between study visits and assessment of disease activity and damage was 15 days [IQR 0, 36.5]. There were no statistically significant differences in sociodemographic features or disease characteristics between those who did (N=67) and did not (N=5) complete the FS, potentially due to survey fatigue.

Frailty Classifications:

Of 67 participants who completed both the FS and the FP, significantly more women were classified as frail according to the FS than the FP (26.9% versus 17.9%; $p<0.01$) (Table 1). 9 participants were classified as frail according to both the FS and the FP. There was a statistically significant correlation between the FS and the FP ($r=0.51$; $p<0.0001$), as well as statistically significant agreement ($k=0.4627$; $p=0.0004$). Using the FP as the standard for identifying frailty, the FS had a sensitivity of 0.75 and specificity of 0.84.

Using the FS, fatigue (52.2%), ambulation (35.8%), and resistance (34.3%) were the most commonly self-reported components of frailty (Table 1). Using the FP to define frailty, fatigue (46.3%) and weakness (41.8%) were the most common components. Significantly more participants self-reported fatigue ($p=0.03$) and ambulation difficulty ($p<0.01$) based on the FS, compared to the fatigue and slow gait criteria of the FP.

Frail women according to both definitions had significantly greater SLE disease damage than non-frail women (Table 2). When classified by the FS, frail women were significantly older ($p=0.04$) with less educational attainment ($p<0.01$). Compared with non-frail women, frail women classified by the FP had significantly greater comorbidity burden ($p=0.01$). There was no

difference in SLE disease activity, current prednisone dose, or immunosuppressive medication use between frail and non-frail women using either frailty definition.

Patient-Reported Outcomes:

Generic Instruments:

Frail women, whether classified using the FS or the FP, reported clinically meaningful and statistically worse PROMIS mobility, physical function, pain interference, and fatigue as compared to non-frail participants (Table 3); pain behavior was statistically worse, but of borderline clinical significance according to the FP. Clinically meaningful and statistically worse PROMIS depression (p=0.02) was observed in frail women according to the FS. Statistically significantly greater depressive symptoms based on the CES-D scale, as well as increased prevalence of disability, were found in frail women according to both definitions.

SLE-Specific Instruments

Frail women reported statistically significantly worse physical health, pain, planning, and fatigue according to the LupusQOL, regardless of which frailty definition was used (Table 3). Frail women according to the FP also endorsed less satisfactory intimate relationships (p<0.01).

Associations with Disability:

Odds of disability were significantly higher in frail women with SLE compared with non-frail women using both frailty definitions (Table 4). Using the FS definition resulted in a nearly three-fold higher odds ratio (OR) of disability compared with the FP (17.2, 95% confidence interval [CI] 4.5-66.2, p<0.01 versus 6.2, 95% CI 1.6-23.5, p<0.01). This association remained significant after adjustment for age, comorbidity burden, and disease activity (FP: p=0.03; FS: p<0.01). After adjusting further for disease damage, the association remained statistically significant when using the FS (OR 17.8, 95% CI 3.4-94.2, p<0.01), but the association was attenuated when using the FP (OR 4.2, 95% CI 0.8-21.7, p=0.09) (Table 4).

Inflammatory Biomarkers:

Frail women according to either definition had significantly greater hsCRP (FP: p<0.01; FS: p=0.02), and IL-6 (p<0.01) (Table 5). Frail women also had a higher inflammatory index score (FP: p<0.01; FS: p=0.02). Compared with non-frail women, frail women classified by the FP also had a higher ESR (p<0.01).

Discussion:

Frailty was present in 27% and 18% of this cohort of women with SLE according to the FS and the FP, respectively. These estimates exceed the prevalence of frailty of 10.7% seen in community-dwelling elderly (34). This is despite the low median SELENA-SLEDAI score of 2-4, representing minimal SLE disease activity (35). These are surprisingly high prevalence values for women with a median age of 44.5 years, suggesting that frailty may be accelerated in women with SLE. Our FP prevalence is comparable to the 20% prevalence of FP-calculated frailty reported in what is, to our knowledge, the only other cohort of women with SLE in which frailly according to the FP has been evaluated; these women had similar sociodemographic and disease characteristics, which provides face validity for our findings (16).

Although the FP is the most widely used disease-agnostic definition of frailty, it is challenging to implement at point of care due to multiple non-standard-of-care performance-based measures and PROMs. The prevalence of frailty in our cohort was higher according to the FS (27% versus 18%, p<0.01), with statistically significant correlation between the two instruments (r=0.51; p<0.0001). Educational attainment differed between frail and non-frail participants according to the FS, but not the FP while comorbidity burden differed between frail and non-frail participants according to the FP, but not the FS. These differences suggest that although similar, these two metrics measure slightly different constructs. Frailty according to the FP has been associated with higher comorbidity burden, similar to our findings (36). In contrast with our findings, frailty according to the FP has been associated with lesser educational

attainment (37). Further study is needed to understand the performance characteristics of both metrics in diverse patients with SLE.

The proportion of subjects who reported fatigue and slow gait/ambulation differed significantly between the FS and the FP. There was a higher prevalence of fatigue in the FS compared to the FP (52.2% versus 46.3%; p=0.03). Although both are self-report, the Fried definition asks about fatigue over the past week, whereas the FS asks about fatigue over the past month; therefore, the FS gives participants a longer time in which to consider themselves fatigued. The FP asks about fatigue tangentially whereas the FS asks directly if the subject felt "tired." The FS wording may be more likely to elicit a positive response. Whether this is specific to patients with SLE, or might differ by age, gender, or presence of concurrent fibromyalgia is not known. Ambulation difficulty was two times higher when self-reported in the FS compared with the objective measurement of slow gait in the FP (35.8% versus 17.9%; p<0.01). This may relate to the walking distance in each definition: The FS assesses participant comfort with walking several hundred yards while the FP requires a 4-m walk test. Although self-reported walking speed has been found to be strongly associated with observed walking speed in older adults and both measures have been associated with mortality in this population (38), it is possible that a subjective self-report of ambulation difficulty is not a good proxy for gait speed. A person's perception of ambulation difficulty may be tied more closely to real world function, and thus morbidity and mortality, than how quickly a person can walk a short distance when required by a study investigator. How best to operationalize gait speed and ambulation to optimize the predictive value for frailty studies is an important area for future research.

Both definitions of frailty were associated with poor health-related quality of life using global and disease-specific instruments. While poor physical function and fatigue are components of frailty, and thus would be expected to be reported more frequently by frail women with SLE, pain was also significantly more common in frail women as compared to non-frail women. This is consistent with prior observations in women with SLE, suggesting that pain

is increased in frail versus non-frail women (16). Persistent pain is a risk factor for frailty in the general population (39). Further study of the longitudinal relationship of pain with frailty in SLE is needed to better understand causal relationships. Although self-reported fibromyalgia was about three times more common in frail versus non-frail women, the difference was not statistically significant. Fibromyalgia was present in only one third of frail women, calling into question the potential critique that frailty is simply a proxy for fibromyalgia.

In unadjusted models, frailty, according to both the FS and the FP, was associated with significantly increased odds of patient-reported disability, confirming the association previously observed in a different cohort of women with SLE, in which frailty was defined according to the FP (16). This association was attenuated for the FP, but not the FS definition of frailty, after adjustment for multiple confounders, though confidence intervals were wide. The stronger association between Valued Life Activities disability and the FS as compared to the FP may reflect the collinearity between two exclusively self-reported instruments. Whether the FS is also more strongly associated with objectively measured adverse health outcomes in SLE, or is a better predictor of downstream morbidity and mortality, requires further study.

We found higher hsCRP and IL-6 in frail as compared to non-frail women with SLE, using either frailty definition. Higher ESR was observed among frail women with SLE as defined by the FP. Frail women using both definitions had higher inflammatory index scores, which have been associated with increased mortality in community-dwelling elderly, though not validated in SLE (32). While inflammatory biomarkers often reflect SLE disease activity, in this study disease activity did not differ between frail and non-frail women and would be unlikely to explain differences in inflammatory markers between frail and non-frail women. Larger studies are needed to explore this relationship.

There has been limited prior study of frailty in SLE (13-16). In a longitudinal cohort of 152 women with SLE, frailty, defined according to the FP, was present in 20% of patients with SLE despite low self-reported disease activity and damage (16). Frailty was associated with

greater self-reported functional decline and higher mortality in patients with SLE, after adjustment for age, disease duration, and self-reported disease damage over an up to 8.8-year period. In a cohort of 1683 patients with SLE, using the SLICC-FI, a SLE-related frailty index, higher frailty scores at baseline were independently associated with increased risk of mortality (13). These studies did not explore associations of frailty with inflammatory or metabolic biomarkers, and only evaluated a limited number of patient-reported outcomes.

Our study has some limitations. Our sample size was limited, and our results, generated through multiple statistical comparisons, should be viewed as hypothesis-generating. Our results cannot be generalized to men or patients with high SLE disease activity; frailty may be underrepresented in our study compared to the general SLE population due to multiple exclusion criteria. To ensure homogeneity of our sample, we excluded those whose SLE diagnosis could not be validated according to ACR criteria (18); hence our subjects are unlikely representative of all patients treated as SLE in clinical practice. It was beyond the scope of this study to enroll non-English speakers. Our study likely was underpowered to evaluate confounding or effect modification by age, SLE disease characteristics, and steroid and immunosuppressive medication use, and there may be residual confounding by measured and unmeasured factors. We excluded participants who did not complete the FS, potentially introducing selection bias, though those who did and did not complete the FS did not differ significantly in terms of sociodemographic characteristics. Although we classified participants as frail according to two previously validated phenotypic definitions of frailty in widespread use, there are multiple additional frailty constructs, notably including the SLICC-FI (13, 40), and it is possible that some participants might have been misclassified in the absence of a single definitive frailty definition. Since our study is cross-sectional, a causal pathway between frailty and disability could not be established.

This study has several strengths. Our study cohort was diverse in terms of race, ethnicity, and educational attainment. All participants were validated according to ACR criteria

for SLE. Our study is the first, to our knowledge, in which the FS, a self-reported frailty instrument that could be feasibly integrated into clinical and research settings, was evaluated in a cohort of women with SLE.

Frailty was present in up to a quarter of our cohort and may represent a distinct subset of physiologically vulnerable women with SLE at risk of worse outcomes, independent of disease severity, organ damage, or comorbidity. Targeting behavioral or pharmacologic interventions for frailty is a rich area for future study and may be an especially attractive complementary therapeutic approach for SLE patients.

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Table 1. Prevalence of frailty categories and individual components by frailty definition

FRAIL scale (N=67)		**Fried phenotype (N=67)**		**p-value**
Component	N (%)	*Component*	N (%)	
Weight loss	14 (20.9)	Weight loss	10 (14.9)	0.20
Fatigue	35 (52.2)	Fatigue	31 (46.3)	0.03
Ambulation	24 (35.8)	Slow gait	12 (17.9)	<0.01
Resistance	23 (34.3)	Weakness	28 (41.8)	0.12
N.A.*		Inactivity	16 (23.9)	N.A.*
Illnesses	3 (4.5)	N.A.*		N.A.*
Classification	N (%)	*Classification*	N (%)	N.A.*
Frail	18 (26.9)	Frail	12 (17.9)	<0.01

*N.A.: Not applicable

Table 2. Characteristics of women by frailty classification

Characteristic (Median and interquartile range unless otherwise specified)	**FRAIL scale (N=67)**			**Fried phenotype (N=67)**		
	Non-frail (N=49)	Frail (N=18)	p-value	Non-frail (N=55)	Frail (N=12)	p-value
Age (years)	42.0 [29.0, 56.0]	55.0 [37.0, 64.0]	0.04	41.0 [31.0, 57.0]	57.0 [52.5, 62.0]	0.05
Race, N (%) Asian Black or African American White Other Declined to state	 5 (10.4) 15 (31.3) 15 (31.3) 11 (22.9) 2 (4.2)	 0 (0) 7 (38.9) 6 (33.3) 5 (27.8) 0 (0)	0.70	 5 (9.1) 15 (27.3) 19 (34.6) 14 (25.5) 2 (3.6)	 0 (0) 7 (63.6) 2 (18.2) 2 (18.2) 0 (0)	0.27
Ethnicity, N (%) Hispanic Non-Hispanic	 11 (23.4) 36 (76.6)	 8 (44.4) 10 (55.6)	0.10	 15 (27.8) 39 (72.2)	 4 (36.4) 7 (63.6)	0.71
Education, N (%) High school or less Some college College Graduate/professional school	 2 (4.1) 12 (24.5) 22 (44.9) 13 (26.5)	 8 (44.4) 4 (22.2) 3 (16.7) 3 (16.7)	<0.01	 6 (10.9) 13 (23.6) 22 (40.0) 14 (25.5)	 4 (33.3) 3 (25.0) 3 (25.0) 2 (16.7)	0.25
SELENA-SLEDAI* score	2.0 [0.0, 4.0]	4.0 [2.0, 7.0]	0.11	1.0 [0.0, 7.5]	4.0 [0.0, 4.0]	0.59
SLICC/ACR Damage Index** score	0.0 [0.0, 1.0]	2.0 [1.0, 4.0]	<0.01	0.0 [0.0, 2.0]	3.0 [1.0, 5.0]	<0.01
Charlson comorbidity index	3.0 [2.0, 6.0]	3.0 [1.0, 5.0]	0.35	2.0 [1.0, 3.0]	3.5 [2.5, 6.0]	0.01
Current prednisone dose (milligrams)	5.0 [4.0, 8.0	5.0 [4.5, 6.5]	0.88	5.0 [4.0, 9.0]	5.0 [5.0, 5.0]	0.81
Immunosuppressive medication use, N (%)	32 (65.3)	15 (83.3)	0.23	36 (65.5)	11 (91.7)	0.09
Body mass index (kilograms/meters^2)	24.1 [22.1, 29.7]	28.3 [23.2, 31.2]	0.09	24.1 [22.1, 30.8]	27.0 [25.7, 33.9]	0.08
Current smoking, N (%)	2 (4.1)	2 (11.1)	0.29	2 (3.6)	2 (16.7)	0.14
Self-reported fibromyalgia, N (%)	6 (12.2)	6 (33.3)	0.07	8 (14.6)	4 (33.3)	0.21

*SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index. Scores range from 0-105, with higher scores indicating greater disease activity.
**SLICC/ACR Damage Index: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. Scores range from 0-46, with higher scores indicating greater damage.
†Immunosuppressive medications: azathioprine, belimumab, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, mycophenolic acid, rituximab, tacrolimus, tocilizumab
Missing values: Race (1); ethnicity (2); prednisone (26)

Table 3. Patient-reported outcome measures by frailty classification

Patient-reported outcome measure (Median and interquartile range)	FRAIL scale (N=67)			Fried phenotype (N=67)		
	Non-frail (N=49)	Frail (N=18)	p-value	Non-frail (N=55)	Frail (N=12)	p-value
PROMIS domains*						
Mobility	46.6 [42.0, 49.7]	35.2 [33.0, 37.7]	<0.01	46.4 [40.2, 49.7]	34.1 [31.9, 38.1]	<0.01
Physical function	44.8 [40.9, 50.1]	32.7 [28.8, 37.5]	<0.01	43.9 [39.8, 48.5]	32.7 [26.7, 35.5]	<0.01
Pain behavior	55.4 [48.5, 59.0]	62.1 [58.5, 63.6]	<0.01	56.6 [49.7, 59.8]	60.5 [57.6, 63.1]	<0.01
Pain interference	54.3 [46.6, 57.3]	65.7 [58.5, 68.2]	<0.01	54.3 [46.6, 60.1]	62.7 [58.4, 67.6]	<0.01
Fatigue	55.4 [48.5, 62.4]	65.9 [62.4, 73.9]	<0.01	55.6 [49.1, 62.7]	72.8 [64.0, 73.9]	<0.01
Depression	51.2 [44.6, 55.0]	56.8 [49.9, 67.6]	0.02	51.3 [44.7, 57.5]	56.5 [48.1, 69.5]	0.12
Anxiety	53.7 [49.9, 61.3]	60.2 [52.9, 65.1]	0.17	54.1 [50.6, 61.5]	61.2 [48.1, 69.1]	0.33
LupusQOL domains**						
Physical health	75.0 [56.3, 84.4]	39.1 [25.0, 56.3]	<0.01	71.9 [53.1, 84.4]	32.8[17.2, 51.6]	<0.01
Pain	83.3 [50.0, 91.7]	45.8 [25.0, 50.0]	<0.01	75.0 [50.0, 91.7]	45.8 [25.0, 50.0]	<0.01
Planning	75.0 [66.7, 91.7]	50.0 [16.7, 83.3]	<0.01	75.0 [66.7, 91.7]	45.8 [16.7, 75.0]	<0.01
Intimate relationships	75.0 [50.0, 100.0]	12.5 [0, 75.0]	0.05	75.0 [50.0,100.0]	0.0 [0.0, 37.5]	<0.01
Burden to others	75.0 [50.0, 83.3]	62.5 [50.0, 83.3]	0.27	75.0 [58.3, 83.3]	62.5 [29.2, 83.3]	0.48
Emotional health	83.3 [58.3, 91.7]	56.3 [50.0, 83.3]	0.06	83.3 [58.3, 91.7]	52.1 [37.5, 91.7]	0.20
Body image	90.0 [50.0, 91.7]	61.3 [50.0, 83.3]	0.19	80.0 [50.0, 91.7]	59.2 [43.8, 79.2]	0.12
Fatigue	56.3 [37.5, 75.0]	43.8 [18.8, 56.3]	0.02	56.3 [37.5, 75.0]	40.6 [15.6, 56.3]	0.04
Valued Life Activities†	0.5 [0.1, 0.8]	1.2 [1.0, 1.7]	<0.01	0.5 [0.2, 0.9]	1.2 [1.1, 1.8]	<0.01
Center for Epidemiologic Studies Depression Scale‡	17.0 [15.0, 22.0]	22.5 [19.0, 28.0]	<0.01	17.0 [15.0, 22.0]	25.0 [20.5, 33.5]	<0.01

*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.
**LupusQOL: Scores range from 0-100, with higher scores indicating higher health-related quality of life.
†Valued Life Activities: Scores range from 0-3, with higher scores indicating greater disability.
‡Center for Epidemiologic Studies Depression Scale: Scores range from 0-60, with high scores indicating greater depression.
Missing values: Intimate relationships (18); Valued Life Activities (1)

Table 4. Cross sectional association of frailty with self-report disability by frailty classification

Model	**FRAIL scale (N=66)**				**Fried phenotype (N=66)**			
	Non-frail (N=48)		Frail (N=18)		Non-frail (N=54)		Frail (N=12)	
	Disability (N=5)	No disability (N=43)	Disability (N=12)	No disability (N=6)	Disability (N=10)	No disability (N=44)	Disability (N=7)	No disability (N=5)
	Odds ratio	*95% confidence interval*	*p-value*		*Odds ratio*	*95% confidence interval*	*p-value*	
Unadjusted*	17.2	4.5-66.2	<0.01		6.2	1.6-23.5	<0.01	
Adjusted for age	15.1	3.8-59.6	<0.01		4.7	1.2-18.8	0.03	
Adjusted for age and CCI**	16.5	4.0-68.5	<0.01		6.6	1.4-32.2	0.02	
Adjusted for age, CCI**, and disease activity	20.8	4.1-105.8	<0.01		6.0	1.2-29.6	0.03	
Adjusted for age, CCI**, disease activity, and disease damage	17.8	3.4-94.2	<0.01		4.2	0.8-21.7	0.09	

*Odds of Valued Life Activities score in the top quartile in frail versus non-frail women.
**Charlson comorbidity index

Table 5. Inflammatory and metabolic biomarkers by frailty classification

Biomarker (Median and interquartile range)	**FRAIL scale (N=67)**			**Fried phenotype (N=67)**		
	Non-frail (N=49)	Frail (N=18)	p-value	Non-frail (N=55)	Frail (N=12)	p-value
Erythrocyte sedimentation rate (millimeters)	14.0 [8.0, 24.0]	20.0 [13.0, 32.0]	0.06	13.0 [8.0, 22.0]	28.0 [20.0, 52.0]	<0.01
High-sensitivity C-reactive protein (milligrams/liter)	1.4 [0.6, 4.1]	4.6 [2.0, 10.2]	0.02	1.6 [0.6, 4.2]	8.3 [2.1, 10.2]	<0.01
Insulin-like growth factor 1 (nanograms [ng]/mL)	137.3 [102.0, 206.6]	107.5 [78.3, 131.1]	0.06	128.2 [100.0, 206.5]	109.4 [78.1, 173.3]	0.28
Interleukin 6 (picograms(pg)/mL)	0.8 [0.4, 1.3]	1.6 [1.2, 2.2]	<0.01	0.8 [0.4, 1.3]	2.1 [1.6, 3.0]	<0.01
Soluble tumor necrosis factor receptor 1 (pg/mL)	1141.3 [983.2, 1367.1]	1275.9 [1136.2, 1524.1]	0.11	1148.5 [1012.8, 1361.9]	1390.7 [1229.4, 1992.5]	0.06
Inflammatory index score*	4.7 [4.4, 4.8]	4.9 [4.7, 5.2]	0.02	4.7 [4.4, 4.8]	5.1 [4.8, 5.4]	<0.01

*Inflammatory index score = 1/3 log(Interleukin 6) + 2/3 log(soluble tumor necrosis factor receptor 1). Higher inflammatory index score is worse.
Missing values: Erythrocyte sedimentation rate (2); high-sensitivity C-reactive protein (1); insulin-like growth factor 1 (1); interleukin 6 (10); soluble tumor necrosis factor receptor 1 (4); inflammatory index score (13)