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Relationship between rheumatoid arthritis and locomotive syndrome: validation of the 25-question Geriatric Locomotive Function Scale in patients with rheumatoid arthritis

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ABSTRACT

This study aimed to understand the clinical state of locomotive syndrome (LS) in patients with rheumatoid arthritis (RA) and to validate the use of the 25-question Geriatric Locomotive Function Scale (GLFS-25) in patients with RA and compare it side-by-side with the Health Assessment Questionnaire-Disability Index (HAQ-DI). Subjects were 159 patients with RA (female, 112 (70.4%); mean age, 66.2 ± 12.0 years) who consecutively visited Yokkaichi Municipal Hospital between June and August 2017. Mean disease duration was 11.4 ± 9.3 years, mean HAQ-DI score was 0.5 ± 0.7 points, and mean GLFS-25 score was 17.8 ± 19.1 points. The correlation between GLFS-25 and HAQ-DI was analyzed using Spearman's rank correlation coefficient. The cut-off point of GLFS-25 corresponding to HAQ-DI≤0.5, which represents functional remission in patients with RA, was calculated by ROC analysis. GLFS-25 and HAQ-DI were positively and strongly correlated (correlation coefficient=0.798). The cut-off point of GLFS-25 corresponding to HAQ-DI≤0.5 was 20 points (sensitivity, 81%; specificity, 90%). Thus, the cut-off point of GLFS-25 corresponding to functional remission is higher than that for developing LS (i.e., 16 points). Moreover, the proportion of patients with LS among those with HAQ-DI ≤0.5 was 17.9%. In conclusion, our findings suggest that some patients with RA in remission may have LS, as well as the need to consider appropriate interventions for such patients.

Keywords: locomotive syndrome, rheumatoid arthritis, Health Assessment Questionnaire, 25-question Geriatric Locomotive Function Scale, GLFS-25

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease. RA can lead to the degeneration of cartilage and destruction of bones and joint structure, and results in physical disability. With the introduction of methotrexate and biologics, RA treatment has ad-

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vanced significantly, and clinical remission and functional remission are achieved in many cases.[1]

Locomotive syndrome (LS) is a concept that was proposed by the Japanese Orthopedic Association in 2007 and relates to a condition of reduced mobility due to the dysfunction of bones, joints, and muscles.[2,3] Osteoarthritis, fragility fracture accompanying osteoporosis, and degenerative spondylosis are representative diseases of LS. LS can be considered a general disease, given that 47 million people in Japan suffer from osteoarthritis and osteoporosis.[4-8] RA is one of the causative diseases of LS, since rapid joint damage, especially in the lower limbs, can reduce mobility from a young age.

Japan has a rapidly aging population, and a substantial elderly population. The population of aging patients with RA is also increasing,[9] suggesting that the susceptibility of this population to LS is also likely to increase. Thus, strategies to prevent LS are all the more important. Yet, only a few studies have assessed the relationship between RA and LS.[10]

The present study aimed to understand the clinical state of LS in patients with RA and to clarify the relationship between physical function and LS in these patients by comparing two assessment tools: the 25-question Geriatric Locomotive Function Scale (GLFS-25) and the Health Assessment Questionnaire-Disability Index (HAQ-DI).

MATERIALS AND METHODS

Subjects

Subjects of this study were 159 patients with RA who consecutively visited Yokkaichi Municipal Hospital between June and August 2017. All patients fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria.[11] Documented subject characteristics included age, disease duration, sex, Steinbrocker classification stage and functional class, drug therapy (prednisone, methotrexate, biologics), rheumatoid factor, C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), swollen and tender joint count, subject's assessment of pain visual analog scale (VAS), subject's global assessment of disease activity VAS, physician's global assessment of disease activity VAS, Disease Activity Score 28-CRP (DAS28-CRP), HAQ-DI, and GLFS-25. DAS28-CRP was categorized as follows: remission (DAS28-CRP<2.3); LDA, low disease activity (2.3≤DAS28-CRP<2.7); MDA, moderate disease activity (2.7≤DAS28-CRP≤4.1); and HDA, high disease activity (4.1<DAS28-CRP).[12,13]

HAQ-DI is widely used as an index of functional remission in patients with RA. HAQ-DI is a patient-based questionnaire consisting of eight categories (Dressing and grooming, Arising, Eating, Walking, Hygiene, Reaching, Gripping, and Other activities) and 20 questions in total,[14,15] and is used to assess the degree of disability.[16] Response coding scores are as follows: "without any difficulty" =0, "with some difficulty" =1, "with much difficulty" =2, and "unable to do" =3. HAQ-DI is calculated as the average of the highest score of questions in each category. Calculated scores range from 0 to 3 points.[14,15] HAQ-DI≤0.5 reflects minimal disease activity[17] and, according to some studies, functional remission.[18-20] Therefore, HAQ-DI≤0.5 was defined as functional remission in the present study.

GLFS-25 is a screening tool developed for the early detection of LS. The scale consists of 25 questions in total, including four questions regarding pain during the last month and 21 questions about daily life (movement-related difficulty, usual care, social activities, cognition) during the last month.[21] The scale is based on a five-point system, with 0 points for no impairment to 4 points for severe impairment. Total scores range from 0 (no symptom) to 100 (most severe) points.[21] LS grade is defined as follows: GLFS-25<7 points corresponds to Stage 0; 7–15 points corresponds to Stage 1; and ≥16 points corresponds to Stage 2.[3] "Stage 1" marks the beginning

of the decline in mobility function and "Stage 2" reflects progression of the decline.[3] Seichi et al reported on the reliability and validity of GLFS-25, and set a cut-off of 16 points for identifying LS, i.e., Stage 2. This cut-off point was derived from an analysis of the relationship between GLFS-25 and locomotion dysfunction in elderly people.[21]

This study was approved by the Ethics Committee of Nagoya University School of Medicine (2017-0271) and Yokkaichi Municipal Hospital (2017-29). This study involved retrospective research. Therefore, rather than obtaining consent from each participant, we disclosed information pertaining to the study at the cooperating facilities according to the procedure stipulated by the Ethics Committee.

Statistical Analysis

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[22] and SPSS version 24 software (IBM Corp.). $P<0.05$ was considered statistically significant.

Continuous variables were expressed as mean and standard deviation (SD). Ordinal variables and categorical variables were expressed as percentages and analyzed using Fisher's exact test. The proportion of patients in each LS stage by age group was calculated and analyzed using the Cochran-Armitage trend test. Correlations between patient characteristics and HAQ-DI and GLFS-25, and between each HAQ-DI category and GLFS-25, were analyzed using Spearman's rank correlation coefficient. Univariate analysis of variance was used and estimated marginal means were calculated with patient characteristics as covariates, and mean scores of GLFS-25 for each age group or for each HAQ-DI score (i.e., 0, 1, 2, or 3) were analyzed using multiple comparisons with Bonferroni's correction. Receiver operating characteristic (ROC) curves were generated to assess associations between GLFS-25 and the achievement of HAQ-DI≤0.5. The best cut-off point was identified as the maximum point of the Youden index, which was calculated using the following formula: Youden index = sensitivity + specificity − 1.

RESULTS

Subject characteristics are summarized in Table 1. There were 159 subjects, of whom 112 (70.4%) were female. The mean age was 66.2 years, and the mean disease duration was 11.4 years. There were 72 subjects (45.3%) who achieved remission of disease activity and 19 subjects (12.0%) with high disease activity.

A scatter plot of GLFS-25 versus HAQ-DI is shown in Fig. 1. Associations between subject characteristics and HAQ-DI and GLFS-25 are shown in Table 2. Among the assessed characteristics, the highest correlation coefficient was observed between HAQ-DI and GLFS-25 (0.798). Correlation coefficients of VAS (in particular, subject global VAS) and DAS28-CRP were higher than those of most of the other assessed characteristics for both HAQ-DI and GLFS-25. Correlation coefficients of VAS and DAS28-CRP for GLFS-25 tended to be higher than those for HAQ-DI. The correlation coefficient of CRP tended to be low for both GLFS-25 and HAQ-DI.

Table 1 Demographics and clinical characteristics of subjects

Variables		Total (n=159)
Age (years)	Mean (SD)	66.2 (12.0)
Duration of disease (years)	Mean (SD)	11.4 (9.3)
Sex, female (%)		70.4
Steinbrocker stage (1/2/3/4) (%)		44.9/19.6/15.8/19.6
Steinbrocker class (1/2/3/4) (%)		48.1/38.0/13.3/0.6
Prednisone use (%)		52.2
Prednisone dose (mg/day)	Mean (SD)	4.9 (3.8)
Methotrexate use (%)		61.6
Methotrexate dose (mg/week)	Mean (SD)	8.6 (3.4)
Biologic use (%)		15.7
Rheumatoid factor (IU/ml)	Mean (SD)	136.2 (448.4)
CRP (mg/dl)	Mean (SD)	0.74 (1.66)
MMP-3 (ng/ml)	Mean (SD)	141.8 (192.8)
Swollen joint count	Mean (SD)	1.2 (2.3)
Tender joint count	Mean (SD)	2.9 (5.1)
Subject's assessment of pain VAS (mm)	Mean (SD)	27.5 (26.9)
Subject's global assessment of disease activity VAS (mm)	Mean (SD)	27.2 (26.0)
Physician's global assessment of disease activity VAS (mm)	Mean (SD)	22.2 (22.3)
DAS28-CRP	Mean (SD)	2.61 (1.19)
HAQ-DI	Mean (SD)	0.48 (0.72)
25-question Geriatric Locomotive Function Scale	Mean (SD)	17.8 (19.1)

CRP, C-reactive protein; MMP-3, matrix metalloproteinase-3; VAS, visual analog scale; DAS28-CRP, 28-joint count Disease Activity Score using C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; SD, standard deviation.

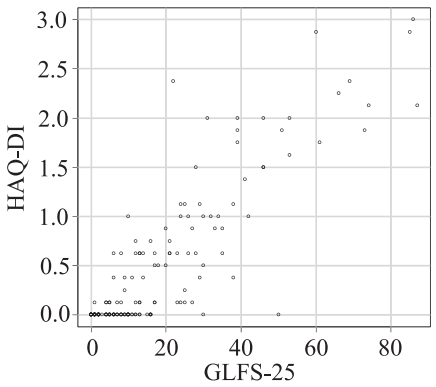

Fig. 1 Scatter plot of the 25-question Geriatric Locomotive Function Scale (GLFS-25) (x axis) versus HAQ-DI (y axis)

Each point corresponds to data from a single patient.

Table 2 Association between subject characteristics and HAQ-DI and the 25-question Geriatric Locomotive Function Scale

Variables	HAQ-DI		The 25-question Geriatric Locomotive Function Scale	
	r	p-value	r	p-value
Age (years)	0.219	0.006	0.230	0.004
Duration of disease (years)	0.148	0.064	0.190	0.016
Steinbrocker stage (1/2/3/4)	0.182	0.022	0.241	0.002
Steinbrocker class (1/2/3/4)	0.419	<0.001	0.434	<0.001
Rheumatoid factor (IU/ml)	0.080	0.318	0.082	0.303
CRP (mg/dl)	0.199	0.012	0.279	<0.001
MMP-3 (ng/ml)	0.284	<0.001	0.373	<0.001
Swollen joint count	0.209	0.008	0.250	0.001
Tender joint count	0.274	<0.001	0.374	<0.001
Subject's assessment of pain VAS (mm)	0.571	<0.001	0.660	<0.001
Subject's global assessment of disease activity VAS (mm)	0.592	<0.001	0.687	<0.001
Physician's global assessment of disease activity VAS (mm)	0.561	<0.001	0.670	<0.001
DAS28-CRP	0.493	<0.001	0.585	<0.001
HAQ-DI	-	-	0.798	<0.001
The 25-question Geriatric Locomotive Function Scale	0.798	<0.001	-	-

CRP, C-reactive protein; MMP-3, Matrix metalloproteinase-3; VAS, visual analog scale; DAS28-CRP, The 28 joint count Disease Activity Score using C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index. Data represent Spearman's rank correlation coefficient (r). P<0.05 was considered statistically significant.

Fig. 2a shows the proportion of subjects in each LS stage by age group. The proportion of those in Stage 2 significantly increased from subjects aged ≤59 years to those aged ≥80 years (27.0% and 62.5%, respectively; p<0.001, Cochran Armitage trend test). Moreover, even after adjusting for sex and DAS28-CRP,[10] GLFS-25 scores tended to be higher with increasing age (Fig. 2b). The estimated marginal mean of GLFS-25 scores even for the younger age group exceeded 7 points (i.e., >Stage 1 of LS).

Table 3 shows correlation coefficients between each HAQ category and GLFS-25. All categories were positively and significantly correlated with GLFS-25. When comparing mean GLFS-25 scores by HAQ-DI score, and calculating estimated marginal means adjusted by age and sex, GLFS-25 scores tended to be higher as HAQ-DI scores increased in all HAQ categories. Fig. 3 shows GLFS-25 scores for the three HAQ categories with the highest correlation coefficients: 4. Walking; 6. Reaching; and 8. Other activities. Here too, the estimated marginal mean of GLFS-25 scores even for HAQ-DI score 0 exceeded 7 points.

Using ROC analysis, we detected significant associations between GLFS-25 and the achievement of HAQ-DI≤0.5 (Fig. 4a). The area under the ROC curve was 0.924 (95%CI: 0.884–0.964)

for GLFS-25, and the best cut-off was 20 points (sensitivity, 81.1%; specificity, 89.6%). Fig. 4b shows the proportion of subjects in each LS stage by HAQ-DI. Proportions of subjects in Stage 1 and Stage 2 among those with HAQ-DI ≤0.5 were 31.1% and 17.9% respectively.

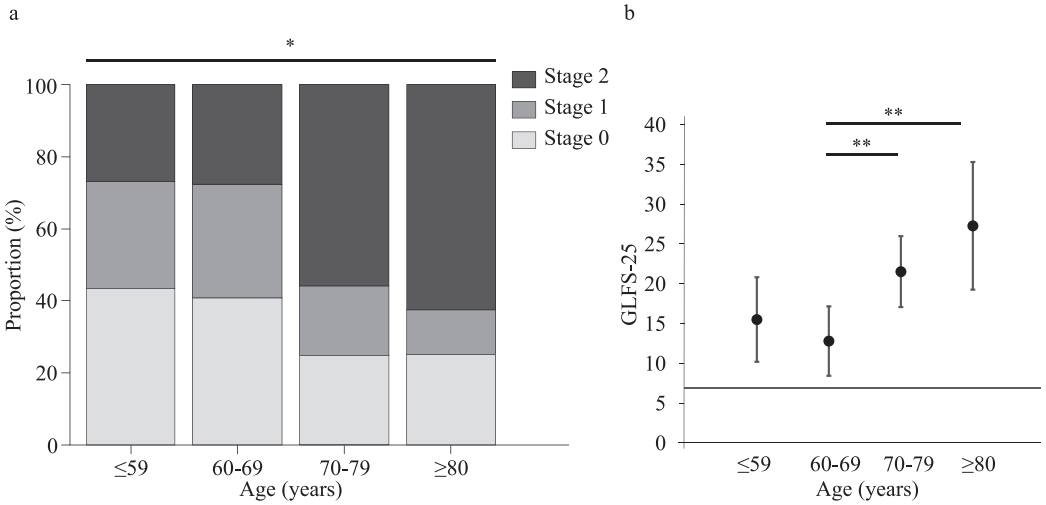

Fig. 2 Locomotive syndrome (LS) stage and estimated marginal means of the 25-question Geriatric Locomotive Function Scale (GLFS-25) by age group

Fig. 2a: GLFS-25 <7 points, Stage 0; 7-15 points, Stage 1; ≥16 points, Stage 2. (*) P<0.001 by Cochran Armitage trend test.

Fig. 2b: Univariate analysis of variance adjusted by sex and DAS28-CRP, and multiple comparisons with Bonferroni's correction. (**) P<0.05. Error bars represent 95% confidence intervals. The bar indicates 7 points. Number of patients by age: ≤59 years, n=37; 60–69 years, n=54; 70–79 years, n=52; ≥80 years, n=16.

Table 3 Relationship between each HAQ category and the 25-question Geriatric Locomotive Function Scale

	Total (n=159)
	r
1. Dressing and grooming	0.673
2. Arising	0.698
3. Eating	0.666
4. Walking	0.708
5. Hygiene	0.657
6. Reaching	0.717
7. Gripping	0.633
8. Other activities	0.751

Response coding scores are: "without any difficulty" =0, "with some difficulty" =1, "with much difficulty" =2, "unable to do" =3. Data represent Spearman's rank correlation coefficient (r). P<0.05 was considered statistically significant. All p-values are p<0.001.

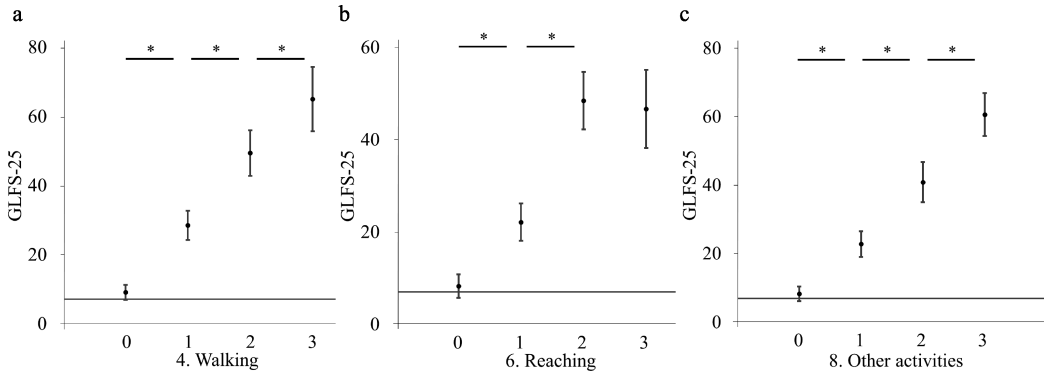

Fig. 3 Estimated marginal means of the 25-question Geriatric Locomotive Function Scale (GLFS-25) by HAQ score, using univariate analysis of variance adjusted by age and sex, and multiple comparisons with Bonferroni's correction

Fig. 3a: "Walking": HAQ-DI score 0, n=112; 1, n=29; 2, n=12; 3, n=6.
Fig. 3b: "Reaching": HAQ-DI score 0, n=96; 1, n=38; 2, n=16; 3, n=9.
Fig. 3c: "Other activities": HAQ-DI score 0, n=102; 1, n=32; 2, n=13; 3, n=12.
Error bars represent 95% confidence intervals. The bar indicates 7 points. (*) P<0.05.

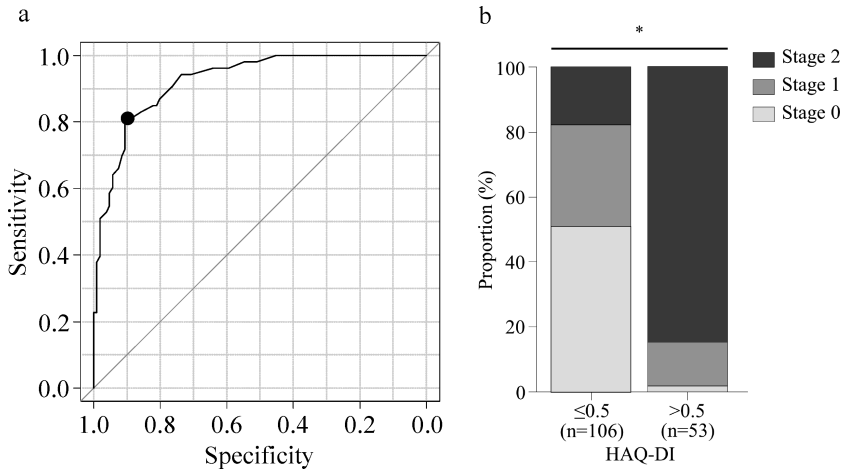

Fig. 4 ROC curves for the 25-question Geriatric Locomotive Function Scale and achievement of HAQ-DI≤0.5, and Locomotive syndrome (LS) stage by HAQ-DI

Fig. 4a: Black dots indicate cut-off points. Area under the ROC curve: 0.924 (95%CI: 0.884–0.964); 81.1% sensitivity and 89.6% specificity for a cut-off of 20 points.
Fig. 4b: GLFS-25 <7 points, Stage 0; 7–15 points, Stage 1; ≥16 points, Stage 2. (*) P<0.001 using Fisher's exact test.

DISCUSSION

In this study, we validated the use of GLFS-25 in patients with RA by comparing it with HAQ-DI. Specifically, we found that GLFS-25 was positively and significantly correlated with HAQ-DI. The cut-off point of GLFS-25 corresponding to functional (HAQ) remission (i.e., 20 points) was higher than that for developing LS (i.e., Stage 2 of LS, 16 points).[21]

The proportion of people with LS reportedly increase with age (i.e., 4.6% in 40s, 7.8% in 50s, 12.0% in 60s and 24.5% in 70s).[6] In the present study, which targeted patients with RA, the proportion of subjects in Stage 2 (i.e., which reflects LS[21]) also increased in proportion to age (Fig. 2a). Moreover, the proportion of those with LS was higher than that of the Japanese general population described above[6] for each age group. This suggests that when considering the possibility of LS in patients with RA, the susceptibility to LS as well as age should be accounted for.

The cut-off point of GLFS-25 for HAQ remission in patients with RA is higher than that for developing LS. This suggests that even patients who achieve functional remission could potentially develop LS. Moreover, the mean GLFS-25 score even in the younger age group (Fig. 2b) or for HAQ-DI score 0 (Fig. 3) exceeded 7 points (i.e., >Stage 1 of LS), which marks the beginning of the decline in mobility function. Thus, patients with RA are likely susceptible to develop LS, and thus proper interventions should be considered.

LS is related to quality of life,[23,24] and regular exercise habits during the middle-age years can prevent LS later on.[25] This highlights the importance of suppressing the disease activity of RA early on in order to allow these patients to exercise without pain from a younger age. Helpful strategies for preventing LS include one-leg stands and squats, which are recommended by the Japanese Orthopedic Association (https://locomo-joa.jp), as well as back muscle strengthening exercises.[26]

The correlation between HAQ-DI and GLFS-25 was the strongest among assessed variables (Table 2). When the contents of HAQ and GLFS-25 are considered in detail, 9 of 20 questions in HAQ (Question No. 1, 3, 4, 8, 9, 10, 12, 18, and 20) and 10 of 25 questions in GLFS-25 (Question No. 5, 6, 8, 9, 10, 11, 12, 15, 16, and 20) are very similar.[15,21] In terms of differences between GLFS-25 and HAQ, questions in the HAQ tend to focus more on upper limb movements. On the other hand, questions in GLFS-25 that have no counterparts in the HAQ relate to, e.g., body pain, social activities, and anxiety about the future. Pain is related to VAS and DAS28-CRP and results in functional disability. Thus, it is understandable that correlation coefficients of VAS and DAS28-CRP were higher, and when comparing GLFS-25 and HAQ-DI, correlation coefficients of VAS and DAS28-CRP for GLFS-25 were higher than those for HAQ-DI (Table 2). Interestingly, the correlation coefficient of CRP tended to be low for both GLFS-25 and HAQ-DI, suggesting that even if CRP is suppressed, existing pain and disability affect the evaluation of physical function using GLFS-25 and HAQ-DI.

This study has several limitations. First, this study was conducted at only one facility and had a limited study duration. Future studies that follow patients with RA longitudinally will be helpful in further elucidating relationships between RA and LS. Second, we did not obtain information regarding the history of surgery or detailed treatments. However, we did obtain information regarding MTX and PSL use and DAS28-CRP, which are important factors in the evaluation of RA. Third, tests for locomotive functions, such as the stand-up test and the two-step test, were not performed. Finally, given the small sample size and single facility design, our results may not reflect the general RA population. Studies that involve a larger population will be important to validate the cut-off point for GLFS-25 determined in this study.

The results of our study indicate two perspectives. They suggest that patients with RA are

susceptible to LS. Females are more prone to develop osteoporosis and a weakening of lower limb muscles. Thus, they may be more likely to develop LS.[3,7] Since RA is more common in females than in males, the background of patients with RA may reflect the susceptibility to LS, regardless of whether they achieve remission or not. Further studies will be needed to determine whether there is gender specificity for susceptibility to LS in patients with RA. Secondly, we suggest that, when possible, rheumatologists should use the GLFS-25 to screen for LS in patients with RA and consider proper interventions against LS at an appropriate stage. In this regard, an intervention study aimed at preventing LS by exercise in patients with RA may be informative. In addition to aiming for RA remission, LS remission should also be set as a treatment goal.

In conclusion, GLFS-25 and HAQ-DI were positively and strongly correlated in patients with RA. The cut-off point of GLFS-25 corresponding to HAQ remission (HAQ-DI≤0.5) was 20 points, which is higher than the cut-off point for developing LS (i.e., 16 points). These findings suggest that patients with RA are susceptible to LS, requiring future studies of gender effect and intervention for preventing LS in patients with RA.

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CONFLICT OF INTEREST

None to report.

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