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Locomotive syndrome in rheumatoid arthritis patients during the COVID-19 pandemic

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ABSTRACT

This study aimed to longitudinally evaluate the development of locomotive syndrome (LS) in rheumatoid arthritis (RA) patients during the COVID-19 pandemic using the 25-question Geriatric Locomotive Function Scale (GLFS-25). Subjects were 286 RA patients (female, 70.6%; mean age, 64.2 years) who had GLFS-25 and Clinical Disease Activity Index (CDAI) data available for a 1-year period during the COVID-19 pandemic and who did not have LS at baseline. Associations between subject characteristics and development of LS were determined using logistic regression analysis. Among the 286 patients, 38 (13.3%, LS group) developed LS at 1 year after baseline. In the LS group, scores of the GLFS-25 categories "GLFS-5" and "Social activities" were significantly increased at 1 year relative to baseline. GLFS-5 is a quick 5-item version of the GLFS-25, including questions regarding the difficulty of going up and down stairs, walking briskly, distance able to walk without rest, difficulty carrying objects weighing 2 kg, and ability to carry out load-bearing tasks and housework. A significant correlation was also observed between changes in "Social activities" and that of "GLFS-5." Multivariable logistic regression analysis revealed that the development of LS was significantly associated with BMI (OR: 1.11 [95% confidence interval (CI): 1.00–1.22]) and CDAI (OR: 1.08 [95%CI: 1.00–1.16]) at baseline. Adequate exercise and tight control of RA disease activity are important for preventing the development of LS in view of restrictions on going out imposed during the COVID-19 pandemic. GLFS-5 is useful for evaluating the physical function of RA patients.

Keywords: COVID-19, locomotive syndrome, rheumatoid arthritis, 25-question Geriatric Locomotive Function Scale (GLFS-25), Clinical Disease Activity Index (CDAI)

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Abbreviations:
BMI: body mass index
CDAI: Clinical Disease Activity Index
COVID-19: coronavirus disease 2019
LS: locomotive syndrome
RA: rheumatoid arthritis
GLFS-25: 25-question Geriatric Locomotive Function Scale

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has spread globally with devastating impact.[1-3] COVID-19 can cause shortness of breath, fever, and fatal pneumonia in the most progressive and worst cases. Rheumatoid arthritis (RA) patients, who are often on immunosuppressants, need to pay close attention to COVID-19.[4-6] The Japanese government has taken various measures to prevent the spread of COVID-19, including declaring a state of emergency and a requirement to refrain from going out.[7] Consequently, physical activity in the general population has decreased since the appearance of the disease.[8] An extended period of inactivity can lead to the deterioration of physical function and development of locomotive syndrome (LS).

LS is a concept proposed by the Japanese Orthopedic Association in 2007 as a national health policy target and refers to a condition of reduced mobility due to disorders of the musculoskeletal system (bones, joints, and muscles). It is a high-risk condition that requires caregiving and can lead to a bedridden state.[9,10] Since LS impacts frailty, quality of life and healthy life expectancy,[11-13] its prevention is highly important. RA, which can lead to the degeneration of cartilage, destruction of bones and joint structure, and rapid joint damage, especially in the lower limbs, can reduce mobility from a young age. Moreover, since aging of the RA population is progressing, RA is one of the causative diseases of LS.[14-16] In fact, the proportion of RA patients with LS is estimated to be higher than that of the general Japanese population at each age.[17-19]

It is thus clear that RA patients are susceptible and vulnerable to LS, and this might be exacerbated by refraining from going out. Therefore, it is important for rheumatologists to evaluate the physical function of RA patients from the perspective of LS. To this end, the present study aimed to examine the development of LS in RA patients during the COVID-19 pandemic.

MATERIALS AND METHODS

Subjects

A total of 581 RA patients consecutively visited Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Japan Community Health care Organization Kani Tono Hospital, and Yokkaichi Municipal Hospital between June and August 2020 (Tsurumai - Frailty and Locomotive syndrome of rheumatoid Arthritis for Globalization, T-FLAG Study, which began in 2020 for the purpose of analyzing frailty and locomotive syndrome of RA patients in clinical practice; enrollment started on June 1, 2020). Among these patients, data on clinical characteristics, including scores for the 25-question Geriatric Locomotive Function Scale (GLFS-25)[20] and Clinical Disease Activity Index (CDAI)[21] were available for 538, all of whom fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria.[22] Non-LS and LS are defined as GLFS-25 <16 points and ≥16 points, respectively.[10] Among the 538 patients, 325 belonged to the non-LS group, and GLFS-25 and CDAI data were available

for 286 during the period of June-August 2021. Reasons for patient drop-out from the follow-up study were unclear, but there were no significant differences in patient baseline characteristics except for C-reactive protein (CRP) and the proportion of methotrexate (MTX) use between the 286 patients in this study and the remaining 39 patients (data not shown). Documented subject characteristics included age, duration of disease, sex, body mass index (BMI), marital status, and school education (number of years in school), Steinbrocker classification stage (evaluated at the most progressed joint),[23] drug therapy (glucocorticoid (GC), MTX, other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including salazosulfapyridine, tacrolimus, bucillamine, and iguratimod, and biological DMARDs (bDMARDs)/targeted synthetic DMARDs (tsDMARDs)), rheumatoid factor (RF), CRP, swollen and tender 28-joint count (SJC and TJC), subject's global assessment of disease activity visual analog scale (VAS), physician's global assessment of disease activity VAS, CDAI,[21] Health Assessment Questionnaire-Disability Index (HAQ-DI),[24] Kihon Checklist (KCL),[25,26] and GLFS-25. CDAI is the simple sum of SJC, TJC, subject's global assessment of disease activity VAS (0–10 scale), and physician's global assessment of disease activity VAS (0–10 scale).[21] Since the analysis included RA patients being treated with interleukin-6 receptor inhibitors and Janus kinase inhibitors, we used CDAI to evaluate disease activity rather than composite measures using CRP. CDAI was categorized as follows: remission (CDAI ≤2.8); low disease activity (LDA; 2.8< CDAI ≤10); moderate disease activity (MDA; 10< CDAI ≤22); and high disease activity (HDA; CDAI >22).[21]

This retrospective study was approved by the Ethics Committees of Nagoya University School of Medicine (2017-0271), Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital (2020-451), Japan Community Health care Organization Kani Tono Hospital (20110901), and Yokkaichi Municipal Hospital (2017-29). As this study involved retrospective research, rather than obtaining consent from each patient, we disclosed information pertaining to the study at the cooperating facilities according to the procedure stipulated by the Ethics Committees.

25-question Geriatric Locomotive Function Scale (GLFS-25)

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 "Body pain" during the last month (Nos. 1, 2, 3, and 4) and 21 questions regarding "Movement-related difficulty" (Nos. 5, 6, and 7), "Usual care" (Nos. 8, 9, 10, 11, and 14), "GLFS-5" (Nos. 12, 13, 15, 17, and 20), "Social activities" (Nos. 18, 21, 22, and 23), and "Cognitive" (Nos. 24 and 25) during the last month.[20] GLFS-5 was set as the key domain and consists of questions regarding the difficulty of going up and down stairs, walking briskly, distance able to walk without rest, difficulty carrying objects weighing 2 kg, and ability to carry out load-bearing tasks and housework.[20] The scale is based on a 5-point system, with 0 points assigned for no impairment to 4 points for severe impairment. Total scores range from 0 (no symptom) to 100 (most severe) points. LS grade is defined as follows: GLFS-25 <7 points corresponds to Stage 0; 7–15 points corresponds to Stage 1; 16–23 points corresponds to Stage 2,[10] and ≥24 points corresponds to Stage 3.[27] "Stage 1" marks the beginning of the decline in mobility function, "Stage 2" reflects progression of the decline, and "Stage 3" reflects progression to the extent that it interferes with social participation. Seichi et al reported on the reliability and validity of GLFS-25 and set a cut-off of 16 points for identifying LS (ie, Stage 2).[20]

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) and were analyzed using the Mann-Whitney U test. Ordinal variables and categorical variables are expressed as percentages and were analyzed using Fisher's exact test. Differences between two surveys

were examined by Wilcoxon's signed rank test. Multivariable logistic regression analyses were performed to confirm the independent impact of variables on the development of LS. Among the assessed variables (age, duration of disease, sex, BMI, marital status, school education, Steinbrocker stage, GC use, MTX use, other csDMARD use, bDMARD/tsDMARD use, RF positive, CDAI, KCL, and GLFS-25, all at baseline), those with a p value <0.10 in the univariable analyses were included in the multivariable model. Linear regression analyses were performed to explore factors contributing to changes in the GLFS-25 at 1 year after baseline. Receiver operating characteristic (ROC) curves were generated to assess associations between LS at 1 year after baseline and BMI, CDAI, and GLFS-25 at baseline. 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. Finally, correlations between changes in GLFS-25 categories were analyzed using Spearman's rank correlation coefficients.

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).[28] P<0.05 was considered statistically significant.

RESULTS

Of the 286 subjects (202 females, 70.6%), 38 (13.3%) had developed LS at 1 year after baseline. Demographics and clinical characteristics at baseline are summarized in Table 1. Mean age at baseline (standard deviation (SD)) was 63.6 (16.0) / 64.3 (12.7) years (LS group / non-LS group), disease duration was 8.6 (9.1) / 10.8 (9.0) years, BMI was 23.7 (3.9) / 21.8 (3.6) kg/m^2, CDAI was 5.7 (5.1) / 3.3 (4.9), and GLFS-25 was 9.6 (3.4) / 6.3 (4.4) points. BMI, CDAI, and GLFS-25 were significantly higher in the LS group than in the non-LS group at baseline.

Figure 1a shows changes in GLFS-25 for the LS and non-LS groups over the 1-year study period. For GLFS-25 in both the LS and non-LS groups, scores were significantly increased at 1 year relative to baseline. Figures 1b and 1c show changes of each GLFS-25 category in the non-LS and LS groups, respectively. While only the "Social activities" category showed a significant increase in the non-LS group, all categories, in particular, "Social activities", "Body pain", "Cognitive", and "GLFS-5" categories, showed a significant increase in the LS group at 1 year relative to baseline. The category "Social activities" in the LS group showed the largest increase at 1 year relative to baseline.

Table 2 shows changes in the median score for each question of the GLFS-25 for the non-LS group during the 1-year study period. Median scores for question Nos. 22 and 23 (two questions from "Social activities") were increased at 1 year relative to baseline. Table 3 shows changes in the median score for each question of the GLFS-25 for the LS group during the 1-year study period. Question Nos. 1, 2, 3, and 4 (all questions from "Body pain"); 13 and 15 (two questions from "GLFS-5"); 23 (one question from "Social activities"); and 25 (one question from "Cognitive") already had a median above 0 points (no symptom) at baseline. Significant differences were observed between baseline and 1 year later for all questions except for question Nos. 2, 7, 8, and 9. Median scores for question Nos. 12, 13, 15, 17, and 20 (all questions from "GLFS-5"); 21, 22, and 23 (three questions from "Social activities", which increased by over 1 point); and 24 (one question from "Cognitive") were increased at 1 year relative to baseline.

Table 1 Demographics and clinical characteristics of subjects at baseline

Variables		Total (n=286)	LS group (n=38)	non-LS group (n=248)	p value
Age (years)	Mean (SD)	64.2 (13.1)	63.6 (16.0)	64.3 (12.7)	0.995
Duration of disease (years)	Mean (SD)	10.5 (9.0)	8.6 (9.1)	10.8 (9.0)	0.028
Sex, female (%)		70.6	73.7	70.2	0.800
BMI (kg/m^2)	Mean (SD)	22.0 (3.7)	23.7 (3.9)	21.8 (3.3)	0.009
Married (%)		67.5	55.3	69.4	0.123
School education ≥13 years (%)		31.5	34.2	31.0	0.839
Steinbrocker stage (3/4) (%)		33.9	21.6	35.8	0.131
Glucocorticoid use (%)		23.4	28.9	22.6	0.511
Methotrexate use (%)		69.2	60.5	70.6	0.289
Other csDMARD use (%)		42.7	47.4	41.9	0.650
bDMARD/tsDMARD use (%)		35.3	42.1	34.3	0.448
Rheumatoid factor positive (%)		67.7	71.1	67.2	0.777
CRP (mg/dl)	Mean (SD)	0.22 (0.39)	0.19 (0.26)	0.22 (0.41)	0.924
Swollen 28-joint count	Mean (SD)	0.5 (1.7)	0.7 (1.9)	0.5 (1.6)	0.410
Tender 28-joint count	Mean (SD)	1.0 (1.9)	1.3 (2.2)	0.9 (1.9)	0.211
Subject's global assessment of disease activity VAS (mm)	Mean (SD)	11.6 (15.7)	19.3 (18.6)	10.4 (14.9)	<0.001
Physician's global assessment of disease activity VAS (mm)	Mean (SD)	9.5 (13.5)	18.1 (16.6)	8.2 (12.5)	<0.001
CDAI	Mean (SD)	3.6 (5.0)	5.7 (5.1)	3.3 (4.9)	0.001
HAQ-DI	Mean (SD)	0.11 (0.21)	0.18 (0.24)	0.10 (0.21)	0.004
KCL	Mean (SD)	4.5 (3.0)	5.7 (3.6)	4.3 (2.8)	0.017
GLFS-25	Mean (SD)	6.8 (4.4)	9.6 (3.4)	6.3 (4.4)	<0.001

LS: locomotive syndrome
BMI: body mass index
DMARD: disease-modifying antirheumatic drugs
csDMARD: conventional synthetic DMARD
bDMARD: biological DMARD
tsDMARD: targeted synthetic DMARD
CRP: C-reactive protein
VAS: visual analog scale
CDAI: Clinical Disease Activity Index
HAQ-DI: Health Assessment Questionnaire-Disability Index
KCL: The Kihon Checklist
SD: standard deviation
GLFS-25: 25-question Geriatric Locomotive Function Scale
Locomotive syndrome was defined as ≥16 points on the GLFS-25. Other csDMARDs include salazosulfapyridine, tacrolimus, bucillamine, and iguratimod.
P<0.05 was considered statistically significant.

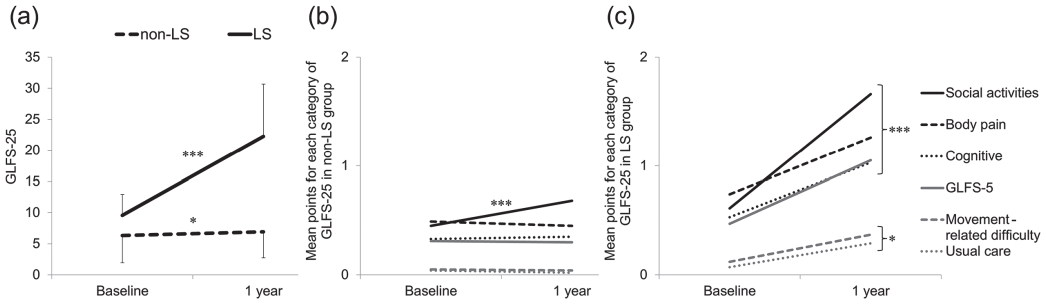

Fig. 1 Mean changes in GLFS-25 over the 1-year study period

Fig. 1a: Mean changes in GLFS-25.

Fig. 1b: Mean changes in each GLFS-25 category in the non-LS group.

Fig. 1c: Mean changes in each GLFS-25 category in the LS group.

(*) P<0.05, (***) P<0.001 (Baseline vs 1 year).

Error bars represent standard deviations. "Body pain" includes question Nos. 1, 2, 3, and 4. "Movement-related difficulty" includes question Nos. 5, 6, and 7. "Usual care" includes question Nos. 8, 9, 10, 11, and 14. "GLFS-5" includes question Nos. 12, 13, 15, 17, and 20. "Social activities" includes question Nos. 18, 21, 22, and 23.

GLFS-25: 25-question Geriatric Locomotive Function Scale

LS: locomotive syndrome

GLFS-5: 5-question Geriatric Locomotive Function Scale

Table 2 Changes in median points of GLFS-25 in non-LS group

GLFS-25 items	Baseline (2020)	1 year (2021)	p value
1. Neck or upper limb pain	1.0 [0.0, 1.0]	1.0 [0.0, 1.0]	0.048
2. Back, lower back, or buttocks pain	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.931
3. Lower limb pain	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.229
4. Painful to move body in daily life	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	0.614
5. Difficult to get up from a bed or lie down	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.655
6. Difficult to stand up from a chair	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.063
7. Difficult to walk inside the house	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	1.000
8. Difficult to put on and take off shirt	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.178
9. Difficult to put on and take off trousers and pants	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.031
10. Difficult to use the toilet	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.773
11. Difficult to wash body in bath	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.393
12. Difficult to go up and down stairs	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.409
13. Difficult to walk briskly	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.644
14. Difficult to keep oneself neat	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.080
15. Difficult to keep walking without rest	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.963
16. Difficult to go out to visit neighbors	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.530
17. Difficult to carry objects weighing 2 kg	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.059
18. Difficult to go out using public transportation	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.301
19. Difficult to carry out simple tasks and housework	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.565
20. Difficult to carry out load-bearing tasks and housework	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.046
21. Difficult to perform sports activities	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.450

22. Restricted from meeting friends	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]	<0.001
23. Restricted from joining social activities	0.0 [0.0, 1.0]	1.0 [0.0, 3.0]	<0.001
24. Anxious about falls in house	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.044
25. Anxious about being unable to walk in the future	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.525

LS: locomotive syndrome
GLFS-25: 25-question Geriatric Locomotive Function Scale
Data are presented as median [interquartile range]. Locomotive syndrome was defined as ≥16 points on the GLFS-25. P<0.05 was considered statistically significant.

Table 3 Changes in median points of GLFS-25 in LS group

GLFS-25 items	Baseline (2020)	1 year (2021)	p value
1. Neck or upper limb pain	1.0 [0.3, 1.0]	1.0 [1.0, 2.0]	<0.001
2. Back, lower back, or buttocks pain	1.0 [0.0, 1.0]	1.0 [0.0, 1.0]	0.059
3. Lower limb pain	1.0 [0.0, 1.0]	1.0 [1.0, 2.0]	0.008
4. Painful to move body in daily life	1.0 [0.0, 1.0]	1.0 [1.0, 1.8]	0.004
5. Difficult to get up from a bed or lie down	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.021
6. Difficult to stand up from a chair	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.012
7. Difficult to walk inside the house	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.110
8. Difficult to put on and take off shirt	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.065
9. Difficult to put on and take off trousers and pants	0.0 [0.0, 0.0]	0.0 [0.0, 0.8]	0.127
10. Difficult to use the toilet	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.025
11. Difficult to wash body in bath	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.029
12. Difficult to go up and down stairs	0.0 [0.0, 1.0]	1.0 [1.0, 1.0]	<0.001
13. Difficult to walk briskly	0.5 [0.0, 1.0]	1.0 [1.0, 2.0]	<0.001
14. Difficult to keep oneself neat	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.015
15. Difficult to keep walking without rest	0.5 [0.0, 1.0]	1.0 [1.0, 2.0]	<0.001
16. Difficult to go out to visit neighbors	0.0 [0.0, 0.0]	0.0 [0.0, 0.8]	0.003
17. Difficult to carry objects weighing 2 kg	0.0 [0.0, 0.0]	1.0 [0.0, 1.0]	0.001
18. Difficult to go out using public transportation	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.002
19. Difficult to carry out simple tasks and housework	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.006
20. Difficult to carry out load-bearing tasks and housework	0.0 [0.0, 1.0]	1.0 [0.3, 1.0]	<0.001
21. Difficult to perform sports activities	0.0 [0.0, 1.0]	1.5 [1.0, 2.8]	<0.001
22. Restricted from meeting friends	0.0 [0.0, 1.0]	2.0 [1.0, 3.0]	<0.001
23. Restricted from joining social activities	1.0 [0.0, 1.0]	3.0 [1.0, 4.0]	<0.001
24. Anxious about falls in house	0.0 [0.0, 0.8]	1.0 [0.0, 1.0]	0.009
25. Anxious about being unable to walk in the future	1.0 [0.0, 1.0]	1.0 [1.0, 1.0]	<0.001

LS: locomotive syndrome
GLFS-25: 25-question Geriatric Locomotive Function Scale
Data are presented as median [interquartile range]. Locomotive syndrome was defined as ≥16 points on the GLFS-25. P<0.05 was considered statistically significant.

Table 4 shows odds ratios (ORs) for LS at 1 year based on univariable and multivariable logistic regression analyses. The development of LS at 1 year was significantly associated with BMI (OR: 1.11 [95%CI: 1.00–1.22]), CDAI (OR: 1.08 [95%CI: 1.00–1.16]), and GLFS-25 (OR: 1.15 [95%CI: 1.03–1.27]) in multivariable logistic regression analyses. When linear regression was performed using the same variables as in Table 4, the change in the GLFS-25 at 1 year after baseline was only associated with GLFS-25 at baseline (regression coefficient: –0.36, 95%CI: –0.56 – –0.16). Significant associations between BMI, CDAI, and GLFS-25 at baseline and the development of LS were detected based on ROC curve analysis. The area under the ROC curve (AUC) was 0.633 (95%CI: 0.541–0.725) for BMI, and the best cut-off was 22.9 kg/m^2 (sensitivity, 50.0%; specificity, 69.5%). The AUC was 0.670 (95%CI: 0.577–0.762) for CDAI, and the best cut-off was 1.2 (sensitivity, 81.6%; specificity, 48.0%). The AUC was 0.718 (95%CI: 0.641–0.795)

Table 4 Baseline factors for development of LS at 1 year by logistic regression analysis

Variables	Univariable OR			Multivariable OR		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
Age (years)	0.99	(0.97–1.02)	0.758		—	
Duration of disease (years)	0.97	(0.92–1.01)	0.172		—	
Sex, female	1.19	(0.55–2.58)	0.657		—	
BMI (kg/m^2)	1.15	(1.05–1.26)	0.003	1.11	(1.00–1.22)	0.043
Married	0.55	(0.27–1.09)	0.087	0.64	(0.29–1.39)	0.260
School education ≥ 13 years	1.15	(0.56–2.38)	0.696		—	
Steinbrocker stage (3/4)	0.50	(0.22–1.13)	0.095	0.44	(0.18–1.06)	0.068
Glucocorticoid use	1.40	(0.65–2.99)	0.390		—	
Methotrexate use	0.64	(0.32–1.30)	0.214		—	
Other csDMARD use	1.25	(0.63–2.47)	0.529		—	
bDMARD or tsDMARD use	1.39	(0.70–2.80)	0.348		—	
Rheumatoid factor positive	1.20	(0.57–2.54)	0.639		—	
CDAI	1.08	(1.02–1.14)	0.011	1.08	(1.00–1.16)	0.046
KCL	1.16	(1.04–1.29)	0.007	1.10	(0.97–1.25)	0.137
GLFS-25	1.20	(1.10–1.31)	<0.001	1.15	(1.03–1.27)	0.009

LS: locomotive syndrome
OR: odds ratio
CI: confidence interval
BMI: body mass index
DMARD: disease-modifying antirheumatic drugs
csDMARD: conventional synthetic DMARD
bDMARD: biological DMARD
tsDMARD: targeted synthetic DMARD
CDAI: Clinical Disease Activity Index
KCL: The Kihon Checklist
GLFS-25: 25-question Geriatric Locomotive Function Scale
Locomotive syndrome was defined as ≥16 points on the GLFS-25. Other csDMARDs include salazosulfapyridine, tacrolimus, bucillamine, and iguratimod. P<0.05 was considered statistically significant.

for GLFS-25, and the best cut-off was 9 points (sensitivity, 73.7%; specificity, 69.4%). Table 5 shows the ORs of baseline GLFS-25 categories and their changes for the development of LS at 1 year by logistic regression analyses. The development of LS at 1 year was significantly associated with the baseline "Body pain" category (OR: 1.29 [95%CI: 1.05–1.58]) and all changes in GLFS-25 categories except for the change in the "Usual care" category, with the change in the "GLFS-5" category having the highest OR (2.57 [95%CI: 1.75–3.77]).

Table 6 shows correlation coefficients (r) between changes in GLFS-25 categories in the LS group. The highest correlation coefficient was observed between the change in the "Social activities" category and that of the "GLFS-5" category (r=0.442).

Table 5 GLFS-25 categories for development of LS at 1 year by logistic regression analysis

Variables	Multivariable OR		
	OR	(95% CI)	p-value
Baseline			
Social activities	1.13	(0.96–1.33)	0.148
Body pain	1.29	(1.05–1.58)	0.016
Cognitive	1.37	(0.94–1.99)	0.105
GLFS-5	1.17	(0.95–1.44)	0.153
Movement-related difficulty	1.38	(0.72–2.62)	0.330
Usual care	1.10	(0.64–1.88)	0.740
Change			
ΔSocial activities	1.41	(1.16–1.73)	<0.001
ΔBody pain	1.68	(1.25–2.27)	<0.001
ΔCognitive	1.99	(1.15–3.45)	0.014
ΔGLFS-5	2.57	(1.75–3.77)	<0.001
ΔMovement-related difficulty	2.45	(1.15–5.21)	0.020
ΔUsual care	1.31	(0.72–2.39)	0.379

LS: locomotive syndrome
OR: odds ratio
CI: confidence interval
GLFS-25: 25-question Geriatric Locomotive Function Scale
Locomotive syndrome was defined as ≥16 points on the GLFS-25. Body pain includes question Nos. 1, 2, 3, and 4. Movement-related difficulty includes question Nos. 5, 6, and 7. Usual care includes question Nos. 8, 9, 10, 11, and 14. GLFS-5 includes question Nos. 12, 13, 15, 17, and 20. Social activities includes question Nos. 18, 21, 22, and 23. Cognitive includes question Nos. 24 and 25. Δ indicates change in score between baseline and 1 year later. OR for 1-score increase. P<0.05 was considered statistically significant.

Table 6 Association between changes in GLFS-25 categories in LS group

Variables	ΔSocial activities		ΔBody pain		ΔCognitive		ΔGLFS-5		ΔMRD	
	r	p	r	p	r	p	r	p	r	p
ΔBody pain	–0.083	0.620	—	—	—	—	—	—	—	—
ΔCognitive	0.130	0.438	0.042	0.802	—	—	—	—	—	—
ΔGLFS-5	0.442	0.006	0.096	0.565	0.236	0.154	—	—	—	—
ΔMRD	–0.112	0.502	0.248	0.134	0.197	0.235	0.056	0.739	—	—
ΔUsual care	0.062	0.713	0.396	0.014	0.186	0.262	0.379	0.019	0.376	0.020

LS: locomotive syndrome
r: correlation coefficient
p: p-value
GLFS-25: 25-question Geriatric Locomotive Function Scale
MRD : Movement-related difficulty
Locomotive syndrome was defined as ≥16 points on the GLFS-25. Body pain includes question Nos. 1, 2, 3, and 4. MRD includes question Nos. 5, 6, and 7. Usual care includes question Nos. 8, 9, 10, 11, and 14. GLFS-5 includes question Nos. 12, 13, 15, 17, and 20. Social activities includes question Nos. 18, 21, 22, and 23. Cognitive includes question Nos. 24 and 25. Δ indicates change in score between baseline and 1 year later. $P<0.05$ was considered statistically significant.

DISCUSSION

The present study, to our knowledge, is the first to longitudinally investigate the development of LS in RA patients during the COVID-19 pandemic by using the GLFS-25. We previously reported that 15 of 58 RA patients (25.9%) developed LS, as defined by GLFS-25, in a 5-year longitudinal cohort study prior to the COVID-19 pandemic.[16] In the present study, 38 of 286 RA patients (13.3%) developed LS within a one-year period during the COVID-19 pandemic, suggesting that LS of RA patients progressed compared to the natural course of the disease. The development of LS was significantly associated with CDAI and BMI at baseline (Table 4). With respect to GLFS-25 categories, while scores in the "Social activities" category of the non-LS group were increased at 1 year relative to baseline (Table 2), the LS group had higher scores in the "Body pain" and "Social activities" categories relative to other categories at baseline (Table 3), and had even higher scores in the "Social activities" and "GLFS-5" categories at 1 year (Fig. 1c and Table 3). Furthermore, the baseline "Body pain" category and the change in the "GLFS-5" category were significantly associated with the development of LS at 1 year (Table 5), and the change in the "Social activities" category was significantly associated with that of the "GLFS-5" category (Table 6). In other words, RA patients with LS, who felt body pain and refrained from going out at baseline, further refrained from going out and experienced a deterioration in physical function related to activities of daily living (eg, going up and down stairs, walking briskly, and carrying out load-bearing tasks and housework). Among the questions of the GLFS-25, GLFS-5 is set as a key domain, and is considered to be more affected in the early stages of LS.[20] Naturally, scores of the "Social activities" category increased as a result of refraining from going out during the COVID-19 pandemic.[7,29,30] This could have resulted in a higher GLFS-25 score without a concomitant deterioration of physical function. However, we found that, in addition to the "Social activities" category, scores of the "GLFS-5" category also increased in the LS group. This highlights the importance of asking RA patients questions from

the GLFS-5 to easily evaluate whether their physical function has deteriorated or not.

There was some variation regarding subjects who had low GLFS-25 scores and those who did not, despite their similar circumstances of refraining from going out during the COVID-19 pandemic. This variation may have been influenced by RA patient characteristics and associated behavioral patterns. We found the mean score (SD) of CDAI at baseline in the LS group to be 5.7 (5.1), which was significantly higher than that in the non-LS group (Table 1). In addition, CDAI at baseline was a significant factor in the development of LS (Table 4). Among GLFS-25 categories at baseline, the proportion of subjects experiencing "Body pain" in the LS group was relatively high (Fig. 1c and Table 3), and the cut-off point for CDAI at baseline was 1.2, with high sensitivity. In other words, if CDAI is ≤1.2 (corresponding to CDAI remission, ie, CDAI ≤2.8), the possibility of developing LS is low.[21] This suggest that tight painless control of RA disease activity for deeper remission is important for preventing the development of LS during the COVID-19 pandemic. On the other hand, if RA patients suffered from pain or had low to higher disease activity, rheumatologists should consider proper interventions against LS at an appropriate stage in addition to RA treatment, given that RA patients are susceptible to developing LS.[16,18]

Interestingly, BMI at baseline was significantly associated with the development of LS (Table 4). It is worth noting that the higher the BMI, the worse the GLFS-25 score was and the more likely it is to develop LS. Low BMI (<18.5 kg/m^2) is one of the 25 items in the KCL, which is used to diagnose frailty,[25] and a symptom of sarcopenia.[31] Since LS is a condition caused by disorders of the musculoskeletal system, low BMI is considered a risk factor for LS. On the other hand, both high BMI, as well as low BMI, are reportedly associated with frailty.[32] High BMI is also associated with LS.[33] Notably, the findings may derive from the fact that high BMI is associated with knee osteoarthritis,[34] a causative disease of LS. Moreover, high BMI (obesity) is a risk factor for severity of COVID-19.[35] This is because obesity affects the immune system, and the secretion of cytokines and adipokines from adipose tissue leads to a pro-inflammatory state, inadequate antibody response, and a cytokine storm.[36] Refraining from going out can lead to a lack of exercise, resulting in a condition referred to as "COVID-19 obesity". Therefore, attention should be paid to patients with a BMI >22 kg/m^2, the LS cut-off point determined in the present study. "22 kg/m^2" just corresponds to ideal BMI with the lowest morbidity.[37] Certainly, while it is important to avoid going out during the COVID-19 pandemic to prevent the spread of the disease, it is just as important to increase physical activity through exercise and to maintain and improve physical function. Adequate exercise can reduce pain in RA patients.[38] Moreover, we found that scores of the "Cognitive" category were significantly increased in the LS group. Since exercise can also relieve anxiety, being physically active is all the more important during the COVID-19 pandemic.[39,40]

This study has several limitations. First, LS was defined using the GLFS-25, and tests for locomotive function, such as the stand-up test and the two-step test, were not performed. Thus, it is possible that subjects identified as having LS based on the GLFS-25 may differ from those identified using the stand-up test or two-step test. This could have led to an overestimation of LS in the present study, given the possibility that "Social activities" or "Cognitive" category scores may have increased during the COVID-19 pandemic. However, since the study was initiated during the COVID-19 pandemic and our patients did not have LS (as determined by the GLFS-25) at baseline, extracted factors other than GLFS-25 which are related to development of LS (CDAI and BMI at baseline), as well as the significant changes observed in GLFS-25 (including on a category-by-category basis), are considered to be valid. Notwithstanding, future studies which use the stand-up test and two-step test will be necessary to validate our present results. Second, we did not obtain information regarding the history of surgery, comorbidities, complications, or detailed treatments from subjects. However, we did obtain information regarding the use of

MTX, other csDMARDs, bDMARDs/tsDMARDs, and GC, as well as disease activity, which are important factors for better understanding the RA patient population. Third, the follow-up period was from between June and August 2020 (at baseline) to between June and August 2021 (at 1 year), which was not exactly 1 year. Finally, psychosocial factors such as depression, anxiety, and social support, which could impact the decision to refrain from going out, social activities, and LS, were not evaluated in detail. However, the KCL contains questions about psychosocial factors, which were not identified as factors associated with the development of LS in the multivariable logistic regression analyses, although they were significant in the univariable analyses (Tables 1 and 4).[25,26] Since the above-mentioned factors can affect physical function and RA disease activity, future studies that take these into account are warranted.

In conclusion, we investigated longitudinally the development of LS in RA patients during the COVID-19 pandemic, and identified CDAI and BMI at baseline as being associated with the development of LS. With respect to GLFS-25 categories, GLFS-5 was found to be important for evaluating the physical function of RA patients. These findings suggest that the tight painless control of RA disease activity for deeper remission, as well as exercise, are important for maintaining physical function and preventing LS during the COVID-19 pandemic.

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CONFLICT OF INTEREST

None to report.

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