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The dual presence of frailty and locomotive syndrome is associated with a greater decrease in the EQ-5D-5L index

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ABSTRACT

Japan's aging society is facing an increase in the prevalence of frailty and locomotive syndrome (LS) among older adults. To evaluate the association of these age-related declines on health-related quality of life (QOL) in Japan, we investigated this relationship among Japanese middle-aged and older adults who underwent general checkups and examined whether LS or frailty has a stronger association with the Japanese version of EuroQol's five-level EQ-5D (EQ-5D-5L) index. Participants were 231 middle-aged and older Japanese adults receiving routine health checkups. The study utilized the 25-item Geriatric Locomotive Function Scale, the Japanese version of the Cardiovascular Health Study, and the Japanese version of the EQ-5D-5L. Univariate and multivariate analyses were performed to examine how frailty and LS are related to the EQ-5D-5L index. Patients with both frailty ($p = 0.003$) and LS ($p < 0.001$) had a significantly lower EQ-5D-5L index. After adjusting for age, gender, and body mass index, LS was significantly associated with a decrease in the EQ-5D-5L index ($p < 0.001$), whereas frailty had no significant association with the EQ-5D-5L index ($p = 0.052$). Further analysis showed no significant decrease in the EQ-5D-5L index among those with frailty but no LS, and a significant decrease among those with frailty and LS. The results suggest that frailty and LS are associated with a decrease in the EQ-5D-5L index, but LS has a more pronounced effect. In evaluating frailty's effects on health-related QOL, we determined the importance of separately assessing frailty both with and without LS, even within the same frailty group.

Keywords: EQ-5D-5L, frailty, locomotive syndrome, quality of life, Yakumo Study

INTRODUCTION

Japan's rapidly aging society has been facing a host of problems, particularly by placing additional burden on the medical establishment. As social demand for an economic evaluation of medical technology increases, there is a need for quantitative methods to evaluate how various health conditions affect the quality of life (QOL). One example of health conditions is mobility

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issues, which are becoming ever more prevalent as Japan's population continues to age. In 2007, the Japanese Orthopaedic Association proposed the diagnosis of locomotive syndrome (LS) to identify individuals with musculoskeletal disorders who are at a high risk of requiring long-term care. Several previous reports on LS[1-3] have focused on different aspects of the condition; for example, increase in extracellular water ratio in body composition components, decrease in phase angle measured by bioelectrical impedance analysis, and decrease in health-related QOL measured using the Short Form-36.

Frailty has also become a concern among the aging population in Japan. The international community has agreed that frailty is best defined as a fragile state in which individuals are susceptible to minor stresses due to decline in their homeostasis maintenance mechanism.[4,5] Frailty is not only a physical problem represented by muscle weakness but is also a mental/psychological problem that includes cognitive dysfunction and depression, as well as social problems and economic distress.[5] Fried et al[6] developed one of the most well-known frailty evaluation tools: the Cardiovascular Health Study (CHS). In recent years, scholars have established an effective Japanese version of the criteria (J-CHS) that accounts for Japan's unique social context.[7]

LS and frailty are well understood in Japan, but it remains unclear the extent to which these conditions are associated with health-related QOL, and existing studies report conflicting findings. In particular, one study reported that frailty is associated with deterioration of QOL,[8] and one reported that frailty and QOL are not related.[9] To this end, we suggest using the five-dimension EuroQol index (EQ-5D), a questionnaire that evaluates individuals' QOL and provides a QOL index, allowing researchers to calculate the Quality-Adjusted Life Years, a tool that can be used in the economic evaluation of medical technology.[10] The previous tool, called the EQ-5D-3L, consisted of only three dimensions and was limited by its low sensitivity and ceiling effect. Thus, the EQ-5D-5L increased the number of levels for each dimension from three to five. However, since the scoring algorithm of the EQ-5D-5L is created independently by each country, the QOL index calculated for the same health condition varies among countries.

In 2015, the Japanese version of the EQ-5D-5L became available.[11] Since this tool has just become available, more research is needed to verify its efficacy in the Japanese context. As of yet, there have been no studies examining the association of frailty or LS with the EQ-5D-5L index in the Japanese context. With this in mind, our study investigated this relationship among Japanese middle-aged and older adults receiving general checkups and examined the extent to which LS and frailty are associated with the EQ-5D-5L index.

MATERIALS AND METHODS

Participants

Study participants were volunteers receiving health checkups in Yakumo, Japan in 2018. Since 1982, the local government has been covering an annual checkup consisting of voluntary orthopedic and physical examinations, internal medical examinations, psychological tests, and a health-related QOL survey.[12-17]

The inclusion criteria were participants who completed the Japanese version of the EQ-5D-5L and underwent evaluations for frailty and LS. We excluded participants with a history of spine and limb joint surgery, severe knee injury, severe osteoarthritis, a history of hip or spine fractures, neurological disorders, severe mental illness, diabetes, and/or kidney or heart disease. Of the 546 individuals who participated in the 2018 annual check-up, 483 participants completed the Japanese version of the EQ-5D-5L and GLFS-25 survey for LS evaluation. Of these, 237 participants were evaluated for frailty, and six were excluded based on the above-mentioned criteria. Thus, data

from 231 (101 men and 130 women) who met the inclusion criteria were analyzed.

The study protocol was approved by our university's Ethics Committee of Human Research and Institutional Review Board. All participants provided written informed consent before participation, and the study procedures were carried out in accordance with the tenets of the Declaration of Helsinki 1976 (as revised in Brazil 2013).

EQ-5D-5L

The EQ-5D-5L[18] is a self-administered questionnaire and descriptive system comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to rate each dimension on a five-point scale: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. The responses for the five dimensions are then combined into a five-digit number indicating the respondent's health, from 11111 (no problems at all) to 55555 (extreme problems on all five dimensions). This results in a total of 3,125 possible health states, which may then be converted into a single health index by applying a formula that attaches values (also called weights) to each response.

To obtain the EQ-5D-5L index in this study, we used the Japanese version of the EQ-5D-5L[19] value, which is estimated using the EuroQol Group's crosswalk methodology.[20]

Frailty evaluation

We evaluated frailty using the J-CHS criteria[7,21,22] adapted from the original CHS criteria: unintentional weight loss, fatigue, inactivity, poor grip strength, and slow walking speed. Unintentional weight loss was defined as a decrease in body weight of more than 2 kg over the past six months with no apparent cause. Fatigue was defined as self-reported exhaustion and was assessed using the following question: "In the past two weeks, have you felt tired for no reason?" Activity level was evaluated using the following questions: "Do you engage in moderate levels of physical exercise or sports in an effort to maintain health?" and "Do you engage in low levels of physical exercise in an effort to maintain health?" Participants who answered "no" to both questions were considered inactive. Poor grip strength was defined as a grip strength of < 26 kg in men and < 18 kg in women, based on the Asian Working Group for Sarcopenia criteria.[23] Grip strength measurements were made twice, with the left and right upper limbs hanging at the side of the body. Grip strength measurement was obtained for each hand, and the average was used for the analysis. Slow walking speed was defined as a gait speed of < 1.0 m/s.[24] The walking speed measurement was performed on a 10-meter section with a 3-meter reserve road at its beginning and end. The start and end timings were recorded when the toe of the leading foot was on the line or had crossed the line. In this study, participants with impairments in three or more of the five criteria were classified as frail.

Locomotive syndrome (LS) evaluation

We asked respondents to complete a Japanese version of the 25-item Geriatric Locomotive Function Scale (GLFS-25) ("Locomo 25"), which is a self-administered questionnaire. Each item is rated on a five-point scale, with responses ranging from no impairment (0 points) to severe impairment (4 points).[25] The sum of all item scores ranges from 0 to 100, and higher scores indicate more severe LS. The validity and reliability of this measurement are satisfactory, and a cutoff score of ≥ 16 indicates LS.[25]

Statistical Analysis

All continuous variables were expressed as means and standard deviations (SDs), while categorical variables were expressed as percentages. We performed the Mann–Whitney *U* test

and Fisher's exact test to compare the two groups. In multiple comparisons of three or more groups, we performed a Kruskal–Wallis analysis. To examine the associations of the EQ-5D-5L index with certain variables, a multiple regression analysis was performed, with EQ-5D-5L index as the dependent variable, and frailty, LS, age, gender, and BMI as independent variables. A p-value of < 0.05 was considered significant in all analyses. We conducted all statistical analyses using SPSS Statistics 25.1 for Mac (IBM Corp., Armonk, NY, USA).

RESULTS

Table 1 shows the demographic data, GLFS-25 and EQ-5D-5L scores, and prevalence of frailty and LS, both for the entire sample and separated by gender. Men had a significantly higher average age and body mass index (BMI) than women, but there were no noticeable gender differences in GLFS-25 or EQ-5D-5L index. The prevalence of LS also did not differ by gender, although frailty was significantly more common among women (3.1% of men and 12.3% of women).

Table 1 Participants' demographic, GLFS-25, and EQ-5D-5L data

Variables	Total	Male	Female	p-value
Number of participants	231	101	130	
Age (years)	65.2 (9.9)	67.2 (9.3)	63.8 (10.1)	**0.021***
BMI (kg/m^2)	23.7 (3.5)	24.5 (3.2)	23.2 (3.6)	**0.001****
GLFS-25	7.2 (8.0)	7.0 (8.9)	7.4 (7.2)	0.23
EQ-5D-5L index	0.889 (0.111)	0.877 (0.130)	0.898 (0.094)	0.23
EQ-5D-5L dimensions				
Mobility	1.19 (0.55)	1.26 (0.61)	1.14 (0.49)	0.11
Self-care	1.04 (0.25)	1.07 (0.35)	1.02 (0.12)	0.15
Usual activities	1.12 (0.44)	1.16 (0.51)	1.08 (0.37)	0.22
Pain/discomfort	1.78 (0.74)	1.82 (0.79)	1.75 (0.71)	0.49
Anxiety/depression	1.27 (0.67)	1.32 (0.76)	1.24 (0.60)	0.38
Prevalence of frailty (%)	8.5	3.1	13.0	**0.024***
Prevalence of LS (%)	13.2	10.9	12.3	0.84

*< 0.05, **< 0.01, Mann–Whitney *U*-test, Fisher's exact test.
Parameter values are shown as the mean (standard deviation) or numbers.
Bold indicates a statistically significant difference.
BMI: body mass index
EQ-5D-5L: 5-dimension EuroQol
GLFS-25: 25-item geriatric locomotive function scale
LS: locomotive syndrome

Table 2 provides a comparison of the demographic data and EQ-5D-5L index according to frailty and LS status. As shown in Table 2, women were significantly more likely to suffer from frailty ($p = 0.024$), and frailty had a lower EQ-5D-5L index ($p = 0.003$). Age and BMI, meanwhile, did not differ according to frailty status. LS was also correlated with a significantly

lower EQ-5D-5L index ($p < 0.001$), but there was no significant difference based on age, gender, or BMI.

Table 2 Demographic data and EQ-5D-5L index by frailty and LS status

Variables	Frailty			LS		
	non-frailty (N = 213)	frailty (N = 18)	p-value	non-LS (N = 204)	LS (N = 27)	p-value
Age (years)	65.2 (9.8)	65.6 (10.7)	0.72	64.8 (9.6)	68.3 (11.3)	0.53
Sex (male/female)	98/115	3/15	**0.024***	90/114	11/16	0.84
BMI (kg/m^2)	23.8 (3.4)	22.8 (4.0)	0.22	23.7 (3.5)	24.2 (2.8)	0.32
EQ-5D-5L index	0.895 (0.11)	0.813 (0.14)	**0.003****	0.907 (0.08)	0.754 (0.20)	**<0.001*****

*<0.05, **<0.01, ***<0.001, Mann-Whitney U-test, Fisher's exact test.
Parameter values are shown as the mean (standard deviation)
Bold indicates a statistically significant difference.
BMI: body mass index
EQ-5D-5L: 5-dimension EuroQol
LS: locomotive syndrome

Table 3 shows the associations of frailty and LS with EQ-5D-5L index after statistically correcting for age, gender, and BMI. The results of the multiple regression analysis showed that LS was significantly associated with the EQ-5D-5L index ($p < 0.001$), while frailty was not ($p = 0.052$).

Table 3 Summary of multiple regression analysis

	EQ-5D-5L index		
Independent variables	β	95% CI	p-value
LS	–0.443	–0.194 – –0.113	**<0.001*****
Frailty	–0.117		0.052
Sex (male)	0.104		0.080
Age (years)	–0.023		0.70
BMI (kg/m^2)	–0.013		0.83

***<0.001, Multiple regression analysis.
The dependent variable was the EQ-5D-5L index. Covariates were age, sex, BMI, frailty, and LS.
Bold indicates a statistically significant difference.
EQ-5D-5L: 5-dimension EuroQol
β: standardized partial regression coefficient
LS: locomotive syndrome
BMI: body mass index
CI: confidence interval

For further analysis, we then compared demographic data and the EQ-5D-5L index among the following four groups: those with neither frailty nor LS, those with LS and non-frailty, those with frailty and non-LS, and those with both frailty and LS (Table 4). We found that gender ($p = 0.015$) and EQ-5D-5L index ($p < 0.001$) had significant differences in the multiple comparisons. We further compared the EQ-5D-5L index between the four groups (Fig. 1) and found that frailty and non-LS was not associated with a significant decrease in the EQ-5D-5L index, but that the dual presence of frailty and LS was associated with a significant decrease.

Table 4 Examining EQ-5D-5L and demographic data among four patient groups

Variables	non-frailty and non-LS ($N = 192$)	LS only ($N = 21$)	Frailty only ($N = 12$)	Frailty and LS ($N = 6$)	p-value
Age (years)	64.8 (9.6)	69.2 (10.8)	65.9 (9.9)	64.8 (13.3)	0.186
Sex (male/female)	90/102	8/13	1/11	3/3	**0.015***
BMI (kg/m^2)	23.8 (3.5)	24.0 (2.4)	21.8 (3.6)	24.9 (4.1)	0.174
EQ-5D-5L index	0.910 (0.08)	0.762 (0.20)	0.857 (0.09)	0.723 (0.18)	**<0.001****

*<0.05, ***<0.001, Kruskal-Wallis test, Fisher's exact test.
Bold indicates a statistically significant difference.
BMI: body mass index
EQ-5D-5L: 5-dimension EuroQol
LS: locomotive syndrome

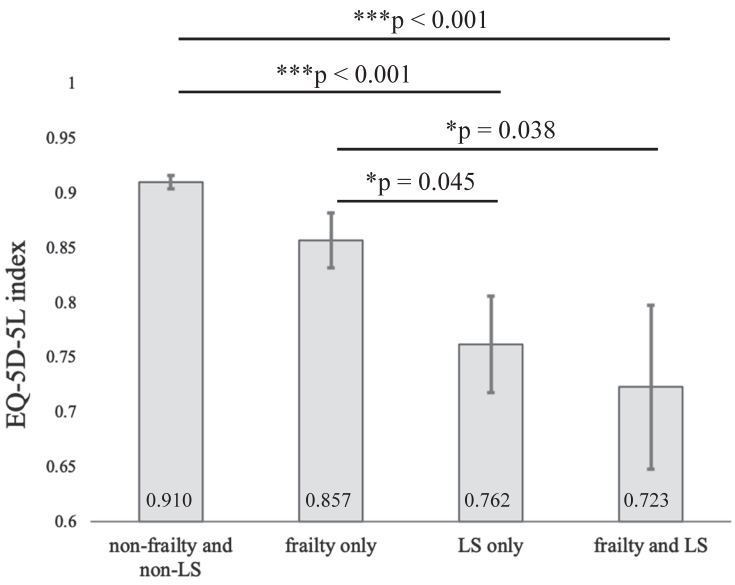

Fig. 1 The EQ-5D-5L index was compared among 4 groups
Non-frailty and non-LS, LS only, frailty only, and frailty and LS. Frailty alone was not associated with a significant decrease in the EQ-5D-5L index, but that the combination with LS was associated with a significant decrease.
*<0.05, ***<0.001, Kruskal–Walls test

DISCUSSION

This study is the first to report on how frailty and LS are associated with the EQ-5D-5L index in Japan. The instruments used to assess health-related QOL can be roughly divided into disease-specific and generic ones.[26] The former is useful and have been used to understand the effects of rheumatoid arthritis[27] and type 2 diabetes[28] on QOL. However, they do not allow a comparison of the association of frailty or LS with that of other diseases. To the best of our knowledge, no previous studies have assessed the association of frailty and LS with disease-specific, health-related QOL.

The EQ-5D, meanwhile, is one of the most widely employed generic tools due to its low respondent burden and good psychometric properties.[29,30] It can be used to not only analyze various diseases separately but also compare and examine the involvement of different diseases. This made it an ideal tool for our study, which compares the associations of frailty and LS both alone and together. Furthermore, since frailty and LS are conceptually similar, it is important to investigate how frailty and LS are associated with and subsequently affects the EQ-5D-5L index.

Our study found no gender differences in the EQ-5D-5L index, either overall or in any of the five dimensions. Furthermore, we found that patients with both frailty and LS had a significantly lower EQ-5D-5L index. After correcting for age, gender, and BMI by multivariate analysis to investigate whether frailty or LS is associated with decline in the EQ-5D-5L index, only LS was significant and frailty was not significant. In other words, the presence or absence of LS is associated with declining EQ-5D-5L index. To further examine these findings, we classified patients into four groups and found no significant decrease in the EQ-5D-5L index among those with frailty and non-LS, but found a significant decrease in the EQ-5D-5L index among those with both frailty and LS.

While LS is one of the main types of musculoskeletal disorders, frailty is a broad concept that includes not only physical function but also mental and social aspects. Furthermore, LS is a high-risk condition that requires long-term care, whereas frailty has the characteristics of flexibility and being able to return to a non-frailty state after intervention. Based on these findings, LS is suggested to have a more direct association with declining EQ-5D-5L index than frailty. The finding from separately evaluating those with both frailty and LS is important, and we also need to consider the presence or absence of LS to fully understand the association and effects of frailty on health-related QOL.

This study has several limitations. First, the number of participants was relatively small, and there were few respondents with both frailty and LS. Nevertheless, this study found a significant relationship between the Japanese version of EQ-5D-5L and frailty/LS, as well as between frailty and LS. Future large-scale studies may reveal stronger associations. Second, the study was cross-sectional and took place at a single institution; thus, a selection bias might have occurred. Longitudinal and multi-institutional studies are needed to validate our findings.

In conclusion, this study investigated the relationship between frailty, as measured using the J-CHS and including LS, and the Japanese EQ-5D-5L index. Univariate analysis demonstrated that the EQ-5D-5L index decreases are associated with patients with frailty and LS. However, as shown in the multivariate analysis, LS was a significantly associated with decline in the EQ-5D-5L index, but frailty was not. Further analysis showed no significant decrease in the EQ-5D-5L index among those with frailty but non-LS and a significant decrease among those with both frailty and LS. In the assessment of frailty's effects on health-related QOL, it was determined that it is important to separately assess frailty both with and without LS, even within the same frailty group.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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