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ORIGINAL ARTICLE

Association between frailty and oral function in rheumatoid arthritis patients: A multi-center, observational study

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ABSTRACT

Objectives: This study aims to investigate the association between frailty and oral function in rheumatoid arthritis (RA) patients and to identify practical markers for early frailty detection and potential intervention strategies.

Patients and methods: A multi-center observational cohort study (T-FLAG) included a total of 661 RA patients (186 males, 475 females; mean age: 68.5±13.5 years; range, 18 to 100 years) between June 2023 and August 2023. Frailty was assessed using the Kihon Checklist (KCL) (frailty: score ≥8). Oral function scores were based on Question 13 ("difficulty eating hard foods"), Question 14 ("choking"), and Question 15 ("dry mouth") of the KCL. Receiver operating characteristic (ROC) curves were generated to assess the association between frailty and oral function scores. Multivariate logistic regression was used to analyze factors associated with oral function.

Results: Among the 661 participants, 39.5% were frail. Frailty rates tended to increase with increasing oral function scores. The optimal cut-off score for oral function corresponding to frailty was 2 points, with a specificity of 89.2% and a sensitivity of 54.8%. Multivariate analysis identified age and Health Assessment Questionnaire-Disability Index (HAQ-DI) as significant factors associated with oral function decline (i.e., a total score of ≥2 for Questions 13-15 of the KCL).

Conclusion: Frailty is strongly associated with oral function decline in RA patients. This finding highlights the importance of monitoring the oral function of RA patients, since it not only reflects physical function, but also serves as a potential marker of frailty. Targeted interventions to improve oral function may play a vital role in reducing frailty risk and enhancing the overall well-being of RA patients.

Keywords: Frailty; laughter; oral function; rheumatoid arthritis, the Kihon checklist.

Frailty is a condition characterized by the transitional phase between good health and disability, involving age-related declines in physical, cognitive, social, and oral abilities.[1] Frailty can lead to serious health issues, even with minor stressors, resulting in long-term dependency on medical care and the need for caregiving.[2] In an increasingly aging society, this increases healthcare costs and places a burden on the caregiving system.[3] Therefore, early detection and management of frailty are critical and would contribute to reducing medical expenses, improving the quality of life for older adults, and alleviating the burden on caregiving resources. During the novel coronavirus disease 2019 (COVID-19) pandemic, the effect of frailty was significant, with frail patients having a significantly higher risk of in-hospital mortality, underscoring the importance of frailty assessment in clinical decision-making.[4] The restrictions on going out during the pandemic led to reduced physical activity, which further accelerated the decline in physical function among frail individuals and exacerbated their vulnerability to adverse health outcomes.[5] Furthermore, limitations on social interactions and opportunities to use one's voice likely contributed to declines in cognitive, social, and oral abilities, deepening the overall impact on the well-being of frail individuals.

Lifestyle changes have persisted even after the COVID-19 pandemic, affecting daily habits as well as social connections. These changes are particularly concerning for individuals with chronic conditions such as rheumatoid arthritis (RA), where disease-specific factors may further exacerbate vulnerabilities to frailty and associated health issues. These patients are more susceptible to frailty due to the chronic inflammation and joint damage associated with the disease.[6] The percentage of RA patients who experience frailty is believed to be higher compared to the general population.[6,7] With significant advancements in RA treatment through the use of methotrexate (MTX), biologics, and Janus kinase inhibitors, the survival of RA patients has improved.[8] However, as life expectancy increases, there is a greater need to be vigilant about frailty, as the extended lifespan can lead to a higher risk of functional decline in these patients.

Rheumatoid arthritis patients are particularly susceptible to dry mouth due to both systemic effects and disease-related factors.[9] Beyond systemic manifestations, RA is associated with oral function decline, including hyposalivation and periodontal disease which are recognized as non-articular manifestations of the condition.[10] Several studies have indicated that RA patients have a significantly higher risk of severe periodontal disease compared to the general population,[10] highlighting the potential for oral function decline to adversely affect overall health and quality of life. In light of these concerns, in the present study, we aimed to explore the association between frailty and oral function in RA patients.

PATIENTS AND METHODS

This multi-center, observational cohort study (T-FLAG) was conducted at Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Japan Community Health Care Organization Kani Tono Hospital, and Yokkaichi Municipal Hospital, Department of Orthopedic Surgery between June 2023 and August 2023. A total of 696 RA patients consecutively visited three affiliated hospitals. Clinical data, including Kihon Checklist (KCL) scores[11] and Clinical Disease Activity Index (CDAI),[12] were available for 661 of these patients. All patients met the 2010 classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[13] We did not establish formal exclusion criteria for this study; however, patients with missing data for either KCL score or CDAI were excluded to ensure reliability of the dataset. Finally, a total of 661 patients with complete data (186 males, 475 females; mean age: 68.5±13.5 years; range, 18 to 100 years) were included in the study. A written informed consent was obtained from each patient. The study was approved by the Ethics Committees of Nagoya University School of Medicine (2017-0271), the Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital (2020-451), the Japan Community Health Care Organization Kani Tono Hospital (20110901), and Yokkaichi Municipal Hospital (2017-29), (date: 01.06.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Documented characteristics included age, duration of disease, sex, body mass index (BMI), marital status, smoking status, alcohol intake, Steinbrocker classification stage (evaluated at the most progressed joint),[14] drug therapy (glucocorticoids [GCs], MTX, other conventional synthetic disease-modifying antirheumatic drugs [csDMARDs] including salazosulfapyridine, tacrolimus, bucillamine, and iguratimod, all of which are approved and commonly used for the treatment of RA in Japan,[15] and biological DMARDs [bDMARDs]/targeted synthetic DMARDs [tsDMARDs]), diabetes mellitus (DM), osteoporosis, Charlson Comorbidity Index (CCI),[16] rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), swollen and tender 28-joint count, subject's global assessment of disease activity Visual Analog Scale (VAS), physician's global assessment of disease activity VAS, CDAI, Health Assessment Questionnaire-Disability Index (HAQ-DI),[17] grip strength on the dominant side (i.e., side with the higher value), laughter frequency (almost every day/1 to 5 days per week/1 to 3 days per month/never or almost never),[18] and the KCL. The CDAI was classified 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).[12] The daily frequency of laughter was measured using a standard single-item question: "How often do you laugh out loud?"[18] "Almost every day" and "1-5 days per week" were defined as "frequent laughter," and "1-3 days per month" and "never or almost never" were defined as "infrequent laughter".[19]

Definition of frailty and oral function decline

Frailty categories were determined using KCL scores, with ≥8 points indicating frailty, 4-7 points indicating pre-frailty, and 0-3 points indicating robustness. The KCL is a widely utilized tool developed by Ministry of Health, Labour and Welfare of Japan to identify older adults at risk of needing care or support.[11] The KCL consists of a total of 25 Yes/No questions, covering seven distinct domains. The domain "Activities of daily living" includes Question Nos. 1-5; "Physical strength" includes Question Nos. 6-10; "Nutrition" includes Question Nos. 11 and 12; "Oral function" includes Question Nos. 13-15; "Isolation" includes Question Nos. 16 and 17; "Cognitive function" includes Question Nos. 18-20; and "Depressive mood" includes Question Nos. 21-25. Studies have shown that the KCL is significantly correlated with Fried's Cardiovascular Health Study criteria, confirming its validity as a screening instrument to assess frailty.[1,11]

Oral function was assessed based on Questions 13 ("difficulty eating hard foods"), 14 ("choking on tea or soup"), and 15 ("dry mouth") of the KCL. These questions were chosen, as they address critical aspects of oral health that are closely associated with nutrition, swallowing ability, and salivary function. Declines in these functions are commonly observed in older adults, particularly those with RA, and have been shown to significantly impact physical health, nutritional status, and overall quality of life.[20] A score of ≥2 was defined as oral function decline.[11,21] The simplicity and practicality of these items make them highly suitable for use in both clinical and research settings, facilitating consistent and efficient data collection.

Missing data

The breakdown of missing data (final numbers and percentages in parentheses) is as follows: three for BMI (658/661, 99.5%), six for married (655/661, 99.1%), 242 for smoking (419/661, 63.4%), 247 for alcohol intake (414/661, 62.6%), five for RF (656/661, 99.2%), two for CRP (659/661, 99.7%), seven for MMP3 (654/661, 98.9%), and nine for grip strength (652/661, 98.6%).

Statistical analysis

Statistical analysis was performed using the 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 software (R Foundation Statistical Computing, Vienna, Austria).[22] Continuous variables were expressed in mean and standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. The Kruskal-Wallis test or Mann-Whitney U test were used to analyze continuous variables. Categorical variables were analyzed using the Fisher exact test. Proportions of patients with each oral function score (total score from Questions 13 to 15 in the KCL) by age group, CDAI category, and frailty status were calculated and analyzed using the Cochran-Armitage trend test. Correlations between KCL categories were analyzed using the Spearman rank correlation coefficient. Receiver operating characteristic (ROC) curves were generated to assess the association between frailty and oral function scores. The most optimal 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. Multivariate logistic regression analyses were performed to confirm the independent impact of variables on oral function decline. To further address potential confounding factors, propensity score matching was performed to balance variables, as informed by the results of multivariate logistic regression analyses. A p value of <0.05 was considered statistically significant.

RESULTS

Table 1 presents the characteristics of participants according to their oral function score (i.e., total score from Questions

Table 1. Demographics and clinical characteristics of patients according to scores from questions 13 to 15 of the Kihon Checklist

	Oral function scores (total score from questions 13 to 15 of the KCL)										
	0 points (n=271)		1 point (n=204)		2 points (n=137)		3 points (n=49)		Total (n=661)		
Variables	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	*p*
Age (year)		64.4±14.5		68.5±12.7		73.8±11.0		76.2±9.3		68.5±13.5	<0.001
Duration of disease (year)		11.2±9.3		13.0±9.9		14.8±10.8		13.4±10.3		12.7±10.0	0.002
Sex											0.757
Female	73.1		69.0		73.0		73.5		71.8		
BMI (kg/m^2)		22.2±3.7		22.1±3.9		22.2±3.9		21.7±3.2		22.2±3.8	0.914
Married	65.9		69.5		55.9		57.1		64.3		0.047
Smoking (yes)	18.7		17.1		11.0		26.7		17.0		0.181
Alcohol intake											0.144
Regular	17.4		13.9		12.9		10.0		14.7		
Occasional	19.9		22.1		10.9		10.0		17.6		
No	62.7		63.9		76.2		80.0		67.6		
Steinbrocker stage											0.009
1	45.3		38.9		24.1		28.6		37.6		
2	24.2		21.7		27.7		26.5		24.3		
3	12.1		15.3		19.0		20.4		15.1		
4	18.5		24.1		29.2		24.5		22.9		
Glucocorticoid use	20.3		35.8		29.2		36.7		28.1		0.001
Methotrexate use	64.9		62.7		50.4		57.1		60.7		0.032
Other csDMARD use	44.6		45.1		44.5		38.8		44.3		0.879
bDMARD use	30.6		34.8		33.6		34.7		32.8		0.785
tsDMARD use	7.4		9.8		12.4		12.2		9.5		0.361
Diabetes mellitus	6.6		8.3		12.4		20.4		9.4		0.011
Osteoporosis	18.5		22.5		31.4		32.7		23.5		0.012
Charlson comorbidity index		1.4±0.7		1.5±0.8		1.7±1.0		1.7±0.9		1.5±0.8	0.001
Rheumatoid factor positive	65.2		66.5		67.2		61.2		65.7		0.884
CRP (mg/dL)		0.3±0.6		0.4±0.9		0.3±0.5		0.4±0.6		0.4±0.7	0.598
MMP-3 (ng/mL)		98.2±104.2		117.6±140.6		101.3±78.2		112.9±83.3		105.9±111.1	0.072
Swollen joint count		0.6±1.7		1.0±2.9		1.0±2.9		1.0±1.8		0.8±2.4	0.104
Tender joint count		1.2±2.6		1.6±3.2		2.2±3.7		1.9±4.1		1.6±3.2	0.008
Subject's assessment of pain VAS (mm)		15.5±22.3		20.7±23.8		27.2±26.8		31.2±31.5		20.7±25.0	<0.001
Subject's global assessment of disease activity VAS (mm)		15.1±21.4		21.4±23.8		28.7±28.3		33.0±31.9		21.2±25.3	<0.001

Table 1. Continued

	Oral function scores (total score from questions 13 to 15 of the KCL)										
	0 points (n=271)		1 point (n=204)		2 points (n=137)		3 points (n=49)		Total (n=661)		
Variables	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	*p*
Physician's global assessment of disease activity VAS (mm)		13.9±18.6		18.5±20.5		22.9±21.8		24.9±24.8		18.0±20.7	<0.001
CDAI		4.7±6.3		6.5±8.1		8.3±8.2		8.7±9.3		6.3±7.7	<0.001
HAQ-DI		0.27±0.52		0.49±0.66		0.78±0.77		1.09±0.92		0.51±0.70	<0.001
Grip strength (kg)		21.7±9.9		20.0±10.0		16.2±8.1		16.6±8.6		19.6±9.7	<0.001
Laughter frequency											<0.001
Almost every day	56.1		51.5		43.1		16.3		49.0		
1-5 days per week	32.1		34.8		38.7		40.8		35.0		
1-3 days per month	6.3		8.8		10.9		26.5		9.5		
Never or almost never	5.5		4.9		7.3		16.3		6.5		
KCL		4.0±3.6		7.0±4.0		10.6±4.6		13.8±4.3		7.0±5.1	<0.001
Question 13: Difficulty in eating hard foods (yes)	0		22.5			61.3		100		27.1	<0.001
Question 14: Choking on tea or soup (yes)	0		29.9			62.8		100		29.7	<0.001
Question 15: Dry mouth (yes)	0		47.5			75.9		100		37.9	<0.001
Frailty	14.8		38.2			70.8		93.9		39.5	<0.001

KCL: The Kihon Checklist; SD: Standard deviation; BMI: Body mass index; csDMARD: Conventional synthetic disease-modifying antirheumatic drugs; bDMARD: Biological DMARD; tsDMARD: Targeted synthetic DMARD; CRP: C-reactive protein; MMP-3: Matrix metalloproteinase-3; VAS: Visual Analog Scale; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; Frailty, KCL ≥8 points; Other (DMARDs) including salazosulfapyridine, tacrolimus, bucillamine, and iguratimod; P<0.05 was considered statistically significant. P-values are from comparisons among the four groups using the Kruskal-Wallis test and Fisher exact test.

13 to 15 of the KCL). A total of 661 participants were included, of which 261 (39.5%) were classified as frail. The distribution of oral function scores was as follows: 0 points for 271 patients, 1 point for 204 patients, 2 points for 137 patients, and 3 points for 49 patients. Age, HAQ-DI, the KCL, and frailty rates tended to increase with higher scores. Among oral function questions (Questions 13-15), "Dry mouth" (Question 15) had the highest proportion in the group with an oral function score of 1 point, affecting 47.5% of the patients. In the group with a score of 2 points, "Dry mouth" was observed in 75.9% of the patients, while the proportions of "Difficulty in eating hard foods" (Question 13) and "Choking" (Question 14) were similar to each other at 61.3% and 62.8%, respectively.

Figures 1a-c show proportions of patients with each oral function score by age group, CDAI category, and frailty status, respectively. The proportion of patients with oral function decline (oral function score ≥2 points) was significantly lower in patients aged <60 years compared to those aged ≥80 years (13.9% and 50.3%, respectively; p<0.001), in those in remission compared to those with HDA (20.6% and 46.4%, respectively; p<0.001), and in those who were robust in frailty status compared to those who were frail (1.6% and 54.8%, respectively; p<0.001), as assessed by the Cochran-Armitage trend test.

Table 2 presents correlation coefficients (r) between KCL categories. The strongest associations with oral function were observed for physical strength (r=0.437, p<0.001) and depressive mood (r=0.425). For total KCL score, the strongest correlations, in descending order, were with physical strength (r=0.797), depressive mood (r=0.764), and activities of daily living (r=0.662), with oral function (r=0.616) ranking fourth.

In the ROC curve analysis for frailty, the AUC was 0.790 (95% confidence interval [CI]: 0.756-0.824) for the oral function score (Figure 2). The optimal cut-off score for the oral function score corresponding to frailty was 2 points, with a specificity of 89.2% and a sensitivity of 54.8%, corresponding to the definition of oral function decline (i.e., total score of ≥2 for Questions 13 to 15 of the KCL).

Using the above cut-off score, multivariate logistic regression was conducted to identify factors associated with oral function decline. As shown in Table 3, oral function decline was significantly associated with age (odds ratio

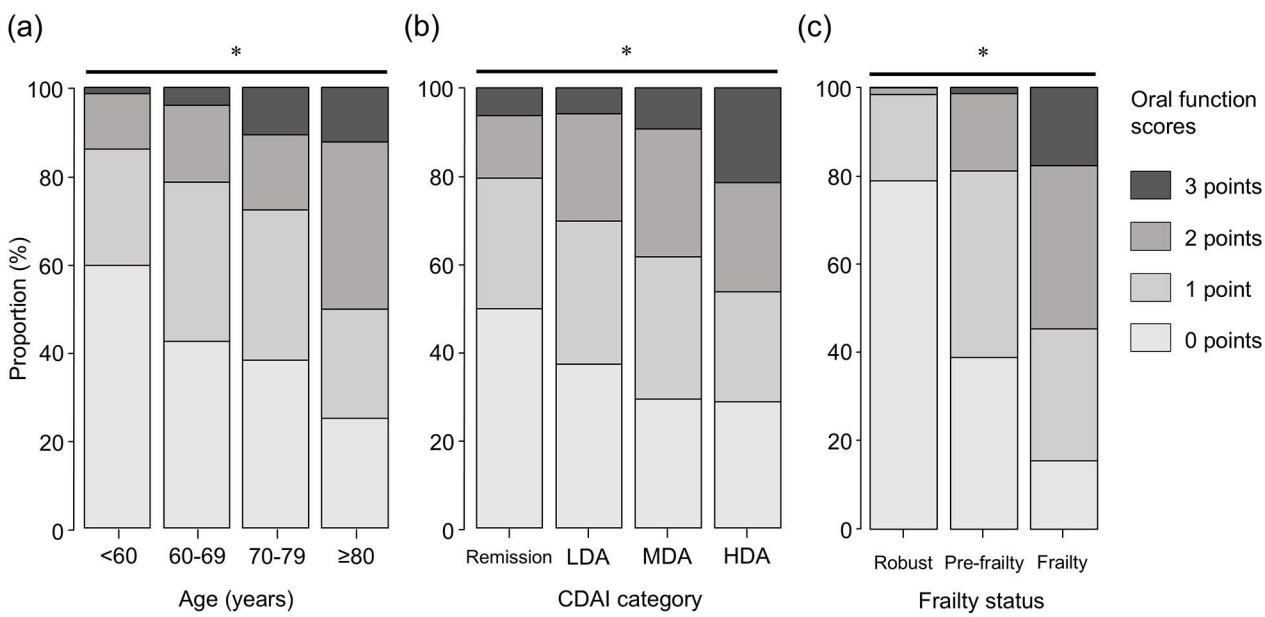

Figure 1. Proportions of patients with each score of oral function (total score from Questions 13 to 15 in the KCL) by **(a)** age group, **(b)** CDAI category, and **(c)** frailty status. * p<0.001 by Cochran-Armitage trend test.

KCL: The Kihon Checklist; CDAI: Clinical Disease Activity Index.

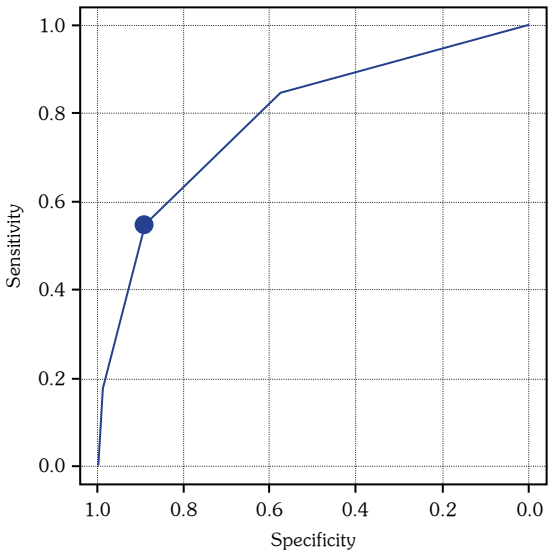

Figure 2. ROC curves for frailty and oral function score (total score from Questions 13 to 15 in the KCL). The area under curve was 0.790 (95% CI: 0.756-0.824) and the cut-off value was 2 points (specificity 89.2%; sensitivity 54.8%).

ROC: Receiver operating characteristic; KCL: The Kihon Checklist; CI: Confidence interval.

[OR]=1.06 [95% CI: 1.04-1.08]) and HAQ-DI (OR=1.06 [95% CI: 1.03-1.10] per 0.1-point increase) in both Model 1 (including DM and osteoporosis as factors) and Model 2 (including CCI as a composite factor). For "infrequent laughter," Models 1 and 2 showed an OR of 1.67 [95% CI: 1.00-2.76] and 1.68 [95% CI: 1.02-2.79], respectively, both indicating a significant association. To further confirm these findings, propensity score matching was performed to adjust for potential confounding factors, including disease duration, sex, BMI, CDAI, GC use, MTX use, and CCI (Table 4). The logistic regression model incorporating propensity score as a covariate demonstrated consistent results, with significant associations between oral function decline and age (OR=1.04 [95% CI: 1.02-1.06]) and HAQ-DI (OR=1.07 [95% CI: 1.03-1.10]), and a marginal association between oral function decline and infrequent laughter (OR=1.52 [95% CI: 0.85-2.73]).

DISCUSSION

To the best of our knowledge, the present study is the first to investigate the association

Table 2. Association between KCL categories

Variables	Oral function (questions 13-15)		Activities of daily living (questions 1-5)		Physical strength (questions 6-10)		Nutrition (questions 11-12)		Isolation (questions 16-17)		Cognitive function (questions 18-20)		Depressive mood (questions 21-25)	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Activities of daily living	0.238	<0.001	-	-	-	-	-	-	-	-	-	-	-	-
Physical strength	0.437	<0.001	0.417	<0.001	-	-	-	-	-	-	-	-	-	-
Nutrition	0.070	0.073	0.101	0.009	0.119	0.002	-	-	-	-	-	-	-	-
Isolation	0.272	<0.001	0.382	<0.001	0.444	<0.001	0.114	0.003	-	-	-	-	-	-
Cognitive function	0.259	<0.001	0.258	<0.001	0.294	<0.001	0.021	0.587	0.270	<0.001	-	-	-	-
Depressive mood	0.425	<0.001	0.376	<0.001	0.470	<0.001	0.101	0.009	0.446	<0.001	0.363	<0.001	-	-
Total KCL score	0.616	<0.001	0.662	<0.001	0.797	<0.001	0.231	<0.001	0.600	<0.001	0.514	<0.001	0.764	<0.001

KCL: The Kihon Checklist; r: Correlation coefficient; P<0.05 was considered statistically significant.

Table 3. Odds ratios for oral function decline by multivariate logistic regression analyses

	Model 1			Model 2		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)	1.06	1.04-1.08	<0.001*	1.06	1.04-1.08	<0.001*
Duration of disease (year)	0.99	0.96-1.01	0.234	0.98	0.96-1.01	0.206
Sex Female	1.06	0.62-1.82	0.820	1.07	0.63-1.81	0.795
BMI (kg/m^2)	1.01	0.96-1.07	0.721	1.01	0.96-1.07	0.635
Married	0.74	0.50-1.11	0.143	0.77	0.51-1.15	0.195
Steinbrocker stage (3/4)	1.19	0.73-1.95	0.477	1.21	0.74-1.96	0.450
Glucocorticoid use	0.78	0.50-1.20	0.256	0.78	0.51-1.20	0.262
Methotrexate use	0.90	0.58-1.38	0.618	0.95	0.61-1.49	0.824
Other csDMARD use	0.77	0.51-1.17	0.223	0.77	0.51-1.17	0.223
bDMARD use	1.03	0.66-1.62	0.889	1.05	0.67-1.65	0.835
tsDMARD use	1.05	0.54-2.06	0.881	1.05	0.53-2.05	0.895
Diabetes mellitus	1.36	0.73-2.53	0.329	-	-	-
Osteoporosis	0.95	0.59-1.53	0.834	-	-	-
Charlson comorbidity index	-	-	-	1.19	0.95-1.48	0.140
Rheumatoid factor positive	0.83	0.55-1.25	0.366	0.82	0.54-1.23	0.328
CDAI	1.03	1.00-1.06	0.054	1.03	0.99-1.06	0.070
Grip strength (kg)	0.99	0.96-1.02	0.477	0.99	0.96-1.02	0.492
HAQ-DI	1.06	1.03-1.10	<0.001*	1.06	1.03-1.10	<0.001*
Infrequent laughter (1-3 days per month/never or almost never)	1.67	1.00-2.76	0.048*	1.68	1.02-2.79	0.043*

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; csDMARD: Conventional synthetic disease-modifying antirheumatic drugs; bDMARD: Biological DMARD; tsDMARD: Targeted synthetic DMARD; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index. Oral function decline, oral function score (from questions 13 to 15 in the Kihon Checklist) ≥2 points; Odds ratio for 0.1 point increase in HAQ-DI. * $p<0.05$ was considered statistically significant.

between frailty and oral function in RA patients. Our study showed a tendency for frailty to increase with declining oral function and that the proportion of patients with oral function decline significantly increased with frailty. A cut-off score of ≥2 for oral function was identified as having high specificity (89.2%) according to the ROC curve analysis, indicating that patients with this score are more likely to be frail, offering a straightforward and accessible tool to facilitate early detection of frailty in clinical settings. Oral function decline was significantly associated with HAQ-DI, a measure of physical function, as demonstrated in both the multivariate logistic regression analysis and the propensity score-adjusted model. This consistent result highlights the robust relationship between oral function decline and physical function. The findings of the present study collectively suggest the importance of monitoring oral function, since it not only reflects physical function, but also serves as a practical marker for identifying frailty in RA patients. Incorporating oral function assessments into routine RA management can help healthcare providers identify patients at higher risk of frailty and implement targeted interventions to mitigate this risk, potentially improving long-term patient outcomes.

The relationship between oral function and physical function remains unclear in terms of which influences the other. Oral frailty, defined as a decline in three or more of six oral measures (remaining teeth, chewing, tongue pressure, oral motor skills, eating difficulty, and swallowing),

Table 4. Demographics and clinical characteristics of patients by oral function decline status after propensity score matching

	Oral function scores (total score from questions 13 to 15 of the KCL)				
	No oral function decline 0-1 points (n=172)		Oral function decline 2-3 points (n=172)		
Variables	%	Mean±SD	%	Mean±SD	*p*
Age (year)		68.3±14.1		74.0±10.7	<0.001
Duration of disease (year)		13.8±10.3		13.9±10.3	0.859
Sex Female	71.5		73.3		0.810
BMI (kg/m^2)		22.3±4.1		22.1±3.6	0.889
Glucocorticoid use	29.7		29.7		1.000
Methotrexate use	54.7		55.2		1.000
Charlson comorbidity index		1.7±0.9		1.6±0.8	0.401
CDAI		7.2±7.4		8.0±8.5	0.559
HAQ-DI		0.53±0.69		0.84±0.81	<0.001
Laughter frequency Almost every day 1-5 days per week 1-3 days per month Never or almost never	 50.6 34.9 7.6 7.0		 35.5 39.0 15.1 10.5		<0.001
KCL		6.1±4.5		11.3±4.7	<0.001
Question 13: Difficulty in eating hard foods (yes)	13.4		70.9		<0.001
Question 14: Choking on tea or soup (yes)	14.5		73.8		<0.001
Question 15: Dry mouth (yes)	21.5		82		<0.001
Frailty	33.7		76.7		<0.001

KCL: The Kihon Checklist; SD: Standard deviation; BMI: Body mass index; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index. Oral function decline, oral function score (from questions 13 to 15 in the Kihon Checklist) ≥2 points. Propensity score matching analysis was conducted to adjust for disease duration, sex, BMI, CDAI, glucocorticoid use, methotrexate use, and Charlson comorbidity index.

has been reported to be significantly associated with both physical frailty and mortality.[23] In older adults, a decline in oral function reportedly leads to reduced protein intake.[24] Typically, a decline in oral function would affect nutritional intake and the ability to eat properly, which can then lead to reduced muscle strength and a subsequent decline in overall physical function. However, impaired physical function can also affect oral function. The HAQ-DI, a physical function index, is a significant indicator of sarcopenia in RA patients.[25] Sarcopenia, characterized by a progressive loss of muscle mass and function, affects not only the body's skeletal muscles but also masticatory and swallowing muscles, thereby impairing oral function.[20] It is likely that oral function and physical function are mutually related, making it difficult to clearly determine which influences the other. In any case, as both oral function and physical function inevitably decline with age,[20] it is crucial for older adults to maintain these functions through comprehensive monitoring and care.

Among KCL categories, "physical strength" (Questions 6-10) and "depressive mood" (Questions 21-25) were most strongly associated with "oral function" (Questions 13-15). "Physical strength" is assessed through questions regarding the ability to walk, climb stairs, and stand up from a chair, which are closely related to items assessed with the HAQ-DI. The assessment of "depressive mood" is based on factors such as the lack of fulfillment, reduced enjoyment, task difficulty, uselessness, and

fatigue. These factors were particularly relevant during the COVID-19 pandemic, when there were restrictions on going out and engaging in social interactions. RA patients are more likely to experience depressive symptoms than the general population.[26] Moreover, participants living alone during the COVID-19 pandemic experienced more negative emotions than those living with relatives or spouses.[27] Negative emotions, such as depressive mood, further reduce social interactions, leading to fewer opportunities to use one's voice. This may have also contributed to a decline in oral function.

A significant association was also found between oral function decline and infrequent laughter. The muscles used for laughing are reportedly the same as those involved in oral function, such as swallowing and chewing muscles.[28] In addition, laughter temporarily increases salivary immunoglobulin A (IgA) levels, suggesting that laughter may enhance certain aspects of immune function.[29] Laughter is also known to have positive effects on health[30] and has been shown to reduce stress hormones.[31] In a six-year follow-up cohort study, shared social interactions, through laughter, were associated more strongly with a reduced risk of functional disability than laughing alone (e.g., laughing while watching television).[32] Conversely, a lack of laughter has been associated with future functional decline and mortality.[33] These findings highlight the importance of maintaining oral function by creating social interactions through laughter to support both emotional well-being and physical health.

Frailty in RA patients is influenced by systemic inflammation, which may also affect oral function decline through molecular pathways. Chronic inflammation in RA has been associated with structural changes in salivary glands, such as fibrosis, which can impair salivary gland function, reduce mucin production, and lead to hyposalivation.[34] These changes may compromise the protective functions of saliva, increasing the susceptibility to infections and disrupting oral immune components including salivary IgA.[35] Salivary IgA plays a crucial role in mucosal immunity by preventing microbial adhesion and neutralizing pathogens, and alterations in its levels are associated with an increased risk of oral and systemic infections.[35] Salivary immune components have also been linked to autoimmune conditions such as primary Sjögren's syndrome, in which interleukin (IL)-6, to illustrate, correlates with disease activity and mucosal immune responses.[36] However, specific involvement of these components in RA-related oral dysfunction remains to be fully elucidated. In addition to its direct effects on oral health, systemic inflammation in RA, driven by tumor necrosis factor-alpha (TNF-α) and other inflammatory cytokines with catabolic effects on skeletal muscle, contributes to muscle loss (sarcopenia)[37] which negatively impacts mastication and swallowing muscles. This cross-system interaction exacerbates difficulties in chewing and swallowing, further contributing to oral dysfunction. Moreover, oral dysfunction may perpetuate systemic inflammation through poor nutrition and increased susceptibility to infections, creating a vicious cycle that worsens health outcomes and promotes frailty. Future studies should explore the role of inflammatory biomarkers, such as IL-6 and TNF-α, to clarify the complex relationships between systemic inflammation, oral health, and frailty in RA patients. Understanding these molecular pathways will aid in the development of targeted therapeutic strategies to address both systemic and oral inflammation, ultimately reducing frailty and improving patient outcomes.

Building on these findings, targeted interventions could help mitigate oral function decline and its impact on frailty in RA patients. Regular oral function assessments could be seamlessly integrated into standard RA management workflows, providing valuable insights into both physical and frailty-related risks. Such integration would enable personalized care plans, including physical and oral rehabilitation programs, to address the multifaceted challenges faced by RA patients. Programs such as COPE-TeL, a comprehensive oral and physical exercise program including textured lunch gatherings, have demonstrated significant benefits in improving oral health and overall physical well-being among older adults with oral function decline.[38] Similarly, progressive lingual resistance exercises have been shown to enhance tongue strength and swallowing function, addressing key aspects

of oral function decline.[39] Implementing such interventions in RA management could improve both physical and emotional well-being, reduce the risk of frailty, and enhance the quality of life for these patients.

Nonetheless, the present study has several limitations. First, there was no evaluation of oral function specifically related to oral frailty, such as swallowing function tests (e.g., water swallowing test, repetitive saliva swallowing test). Second, as this is a cross-sectional study, causal relationships between associated factors remain unclear. Third, while the study was conducted during the COVID-19 pandemic, i.e., a period influenced by lifestyle changes, data on participants' infection status or its direct effects were not collected.

In conclusion, an oral function score of ≥2 points, based on Questions 13-15 of the KCL (i.e., difficulty eating hard foods, choking, and dry mouth), strongly indicates a higher likelihood of frailty in RA patients. Thus, this score may serve as a simple and accessible marker of frailty, enabling early detection in clinical practice. Moreover, oral function decline was closely associated with physical function, as measured by HAQ-DI, highlighting the interconnectedness of oral and physical health. These results underscore the importance of routine monitoring of oral function, which could be seamlessly integrated into clinical workflows to facilitate early identification of frailty and guide targeted interventions. Promoting oral health and physical resilience through comprehensive strategies, including interventions to foster laughter, to illustrate, may help mitigate the risk of frailty in RA patients. Further longitudinal studies are warranted to explore the relationship between physical and oral function in relation to frailty and to clarify causal relationships between these factors.

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