

Prevalence of gastroesophageal reflux disease symptoms and related factors in patients with rheumatoid arthritis

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Gastroesophageal reflux disease (GERD) is common in patients with many chronic diseases, but has not been well recognized in rheumatoid arthritis (RA). We investigated the prevalence of GERD symptoms in 278 outpatients with RA and their association with such clinical factors as age, sex, height, weight, body mass index, medications drugs, and functional status evaluated by the Modified Health Assessment Questionnaire (MHAQ). GERD symptoms were evaluated by Frequency Scale for the Symptoms of GERD (FSSG). The mean FSSG score for all patients was 5.6, and 82 patients were considered to have GERD symptoms (FSSG score ≥ 8), thus the overall prevalence of GERD symptoms was 29.5%. MHAQ score and height were significantly higher and lower, respectively, and prednisolone usage was significantly more in the patients with GERD symptoms than those without. These three clinical factors were also significantly associated with GERD symptoms by univariate logistic regression. Multivariate logistic regression analysis demonstrated that MHAQ was the only clinical factor related to GERD symptoms. In conclusion, the prevalence of GERD symptoms in RA patients was high and strongly associated with decreased functional status, suggesting that physicians should pay attention to GERD symptoms in RA management, especially for patients with low functional status.

Key Words: rheumatoid arthritis, gastroesophageal reflux disease, Frequency Scale for the Symptoms of GERD, Modified Health Assessment Questionnaire, quality of life

Gastroesophageal reflux disease (GERD) is a chronic, relapsing disorder characterized by recurrent symptoms of acid reflux with esophageal injury; that is, reflux esophagitis.⁽¹⁾ It also manifests a variety of extra-esophageal complications including cough, laryngitis, asthma and dental erosion.⁽¹⁾ The prevalence of GERD began to increase from the end of the 1990s, and is now very common, especially in the elderly population in Japan, ranging from 1.4% to 52.1% in the literature.⁽²⁾ Furthermore, GERD often accompanies many chronic diseases such as diabetic mellitus (DM), chronic liver disease, obstructive sleep apnea syndrome (OSAS), and bronchial asthma.⁽²⁾ Patients with chronic autoimmune conditions, such as scleroderma and systemic sclerosis, also have a relatively high prevalence of GERD.^(3,4)

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that mostly affects the synovial joints of the extremities, but also manifests many extra-articular symptoms, including gastrointestinal (GI) ones, with high prevalence.⁽⁵⁾ An evaluation of the relationship between GI symptoms and quality of life (QOL) in patients with RA or osteoarthritis (OA) demon-

strated that QOL measures were significantly impaired in patients with GI symptoms compared with those without.⁽⁶⁾ Of all the GI symptoms, dyspepsia and upper abdominal/epigastric pain were common and more strongly related to QOL measures than other symptoms.⁽⁶⁾

GI events induced by corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been reported and are considered to be a complication of the treatment of RA.^(7,8) It is also recognized that disease-modifying anti-rheumatic drugs (DMARDs) may sometimes cause GI adverse events.⁽⁹⁾ Moreover, assessment of GI risk factors was reported as important in the treatment of osteoporosis, especially in RA patients.⁽¹⁰⁾ However, those previous reports focused predominantly on gastric ulcer, and GERD has not been well recognized in RA patients.

In this study, we examined the prevalence of GERD symptoms in patients with RA, using the Frequency Scale for the Symptoms of GERD (FSSG) questionnaire, a non-invasive assessment tool of GERD symptoms that is used widely in Japan with relatively high sensitivity and specificity.⁽¹¹⁾ We also investigated whether GERD symptoms correlate with several clinical factors of RA, including medications and patients' functional status as evaluated by the Modified Health Assessment Questionnaire (MHAQ),⁽¹²⁾ to identify the potential risk factors of GERD symptoms in RA patients.

Patients and Methods

We enrolled 278 outpatients with RA (50 males, 228 females; mean age, 61.2 years (range, 18–84)). RA was diagnosed according to the American College of Rheumatology 1987 classification criteria of RA.⁽¹³⁾ Prednisolone was prescribed to 169 patients (60.8%), DMARDs to 222 (79.9%), NSAIDs to 162 (58.3%), proton pump inhibitors (PPI) to 59 (21.2%), histamine 2 receptor-antagonists (H2RA) to 50 (18%), gastromucosal protective agents (GMP) to 149 (53.6%), bisphosphonate to 127 (45.7%), and other anti-osteoporosis agents to 83 (29.9%).

All patients were interviewed for GERD symptoms using the FSSG (Table 1), which comprises 12 questions regarding typical symptoms recognized in GERD, to which patients answered accordingly with the frequency of symptoms: never, 0; occasionally, 1; sometimes, 2; often, 3; always, 4. GERD symptoms were considered as present when the total FSSG score was ≥ 8 .⁽¹¹⁾

The presence or absence of GERD symptoms and the total

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This work was carried out at Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine.

Table 1. Frequency scale for the symptoms of GERD questionnaire

Question	Never	Occasionally	Sometimes	Often	Always
1 [†] Do you get heartburn?	0	1	2	3	4
2 [‡] Does your stomach get bloated?	0	1	2	3	4
3 [‡] Does your stomach ever feel heavy after meals?	0	1	2	3	4
4 [†] Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
5 [‡] Do you ever feel sick after meals?	0	1	2	3	4
6 [†] Do you get heartburn after meals?	0	1	2	3	4
7 [†] Do you have an unusual (e.g., burning) sensation in your throat?	0	1	2	3	4
8 [‡] Do you feel full while eating meals?	0	1	2	3	4
9 [†] Do some things get stuck when you swallow?	0	1	2	3	4
10 [†] Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
11 [†] Do you burp a lot?	0	1	2	3	4
12 [†] Do you get heartburn if you bend over?	0	1	2	3	4

GERD, gastroesophageal reflux disease; [†]questions regarding reflux symptom; [‡]questions regarding acid-related dyspepsia.

Table 2. Modified Health Assessment Questionnaire (MHAQ)⁽¹²⁾

Are you able to:	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
Dress yourself, including tying shoelaces and doing buttons?	___ 0	___ 1	___ 2	___ 3
Get in and out of bed?	___ 0	___ 1	___ 2	___ 3
Lift a full cup or glass to your mouth?	___ 0	___ 1	___ 2	___ 3
Walk outdoors on flat ground?	___ 0	___ 1	___ 2	___ 3
Wash and dry your entire body?	___ 0	___ 1	___ 2	___ 3
Bend down to pick up clothing from the floor?	___ 0	___ 1	___ 2	___ 3
Turn regular faucets on and off?	___ 0	___ 1	___ 2	___ 3
Get in and out of a bus, car, train, or airplane?	___ 0	___ 1	___ 2	___ 3

FSSG scores were studied in relation to clinical factors, such as age, sex, height, weight, body mass index (BMI), and medications, including prednisolone, DMARDs, NSAIDs, PPI, H2RA, GMP, bisphosphonate, and other anti-osteoporosis agents, as well as each patient's QOL evaluated by MHAQ.

MHAQ is the modification and simplification of the original Health Assessment Questionnaire (HAQ),⁽¹⁴⁾ and consists of 8 questions regarding disabilities in the activities of daily living over the last week before the questionnaire (Table 2). Patients are asked to answer each question by rating the degree of disability from '0; without any difficulty' to '3; unable to do', and the average of 8 ratings is calculated as MHAQ score. From its unique rating system, the higher MHAQ score is, the worse the patient's functional status is.

The Mann-Whitney *U* test was used for comparing continuous variables among two groups, and the chi-square test was used for comparing categorical variables such as sex and intake or not of medications. The correlations between variables were examined by Spearman's rank correlation coefficient analysis.

Both univariate and multivariate analyses were used to examine the relationship between GERD symptoms and the clinical factors, after adjusting the variables to normal distribution by transformation into logarithmic function if necessary. First, univariate regression analysis was performed for all variables to obtain the odds ratio for the risk of GERD symptoms and then multivariate logistic regression analysis was performed for the predictor variables with a statistical level of $p < 0.1$ in the univariate analysis, in order to examine the determinants of GERD symptoms at the individual level. Odds ratios with their 95% confidence intervals

(CI) are presented as a measure of association. All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS11.5J for Windows, SPSS Inc, Chicago, IL). $p < 0.05$ was considered as statistically significant.

Results

Prevalence of GERD symptoms. The mean FSSG score for all 278 patients was 5.6 ± 6.0 (0–28), and 82 patients were considered to have GERD symptoms (FSSG score ≥ 8). As a result, the prevalence of GERD symptoms in this study group was 29.5%.

Comparison of the patients with and without GERD symptoms. Patients with GERD symptoms had significantly lower height ($p = 0.023$) and higher MHAQ score ($p < 0.0001$), and were significantly more likely to take oral prednisolone ($p = 0.0017$) (Table 3).

Correlation between FSSG score and clinical factors.

A significant positive correlation was recognized only for MHAQ score ($r = 0.425$, $p < 0.0001$) and a significant negative correlation only for height ($r = 0.167$, $p = 0.0064$) (Fig. 1). As for prednisolone, which is recognized as a significant characteristic of patients with GERD symptoms, no statistically significant correlation was demonstrated in this study between daily dose and FSSG score ($r = 0.037$, $p = 0.6283$).

Univariate logistic regression analysis of the risk factors for GERD symptoms. Univariate logistic regression analysis showed that statistically significant factors for the risk of GERD symptoms were lower height (odds ratio for a SD (= 8.0 cm) increase in height, 0.960; 95% CI, 0.927–0.995; $p = 0.0211$),

Table 3. Comparison of the characteristics of patients with or without GERD symptoms

Variable factors	With GERD symptoms (N = 82)	Without GERD symptoms (N = 196)	p value
Age (years)	63.1 ± 11.1	60.5 ± 12.4	0.3029
Gender (male/female)	14/68	36/160	0.9323
Height (cm)	154.3 ± 8.7	156.7 ± 7.6	0.023
Weight (kg)	53.0 ± 9.3	51.5 ± 9.7	0.224
BMI (kg/m ²)	20.9 ± 4.7	21.5 ± 3.5	0.2907
MHAQ (mean ± SD)	1.024 ± 0.739	0.474 ± 0.566	<0.0001
Medication drugs:			
Prednisolone	62/20	107/89	0.0017
DMARDs	10/72	27/169	0.7471
NSAIDs	51/31	111/85	0.4689
PPI	23/59	36/160	0.0772
H2RA	19/63	31/165	0.1989
GMP	3/79	1/195	0.2301
Bisphosphonate	44/38	83/113	0.0842
Anti-osteoporosis agents (ex. bisphosphonate)	27/55	56/140	0.5619

GERD, gastroesophageal reflux disease; BMI, body mass index; MHAQ, Modified Health Assessment Questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs; PPI, proton pump inhibitor; H2RA, histamine 2 receptor-antagonists; GMP, gastro-mucosal protective agents.

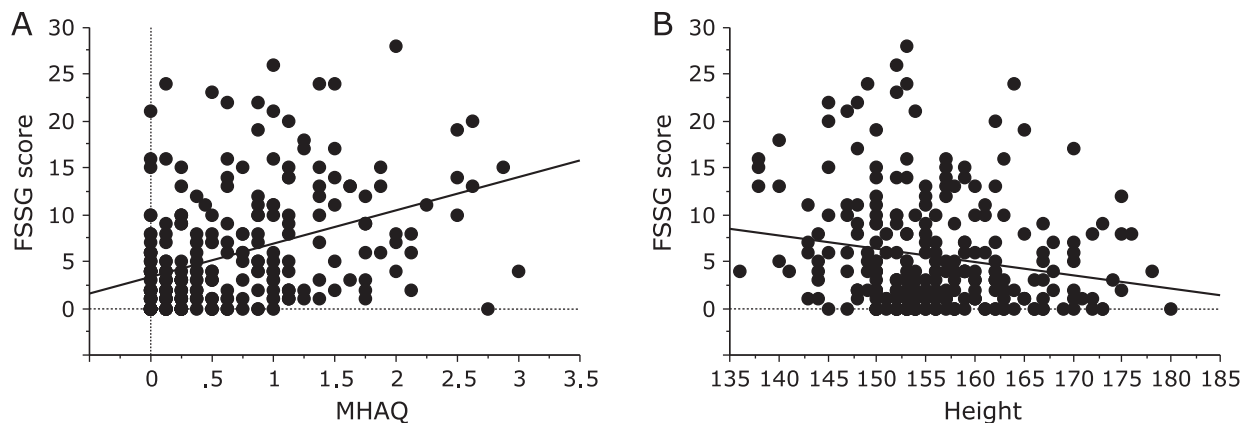


Fig. 1. Correlation between FSSG and MHAQ scores (A), and that between FSSG score and height (B). A significant positive correlation was recognized with MHAQ score ($r = 0.425$, $p < 0.0001$) and a significant negative correlation with height ($r = -0.167$, $p = 0.0064$). Other than MHAQ score and height, no other variables demonstrated a significant correlation with FSSG. FSSG, Frequency Scale for the Symptoms of gastroesophageal reflux disease; MHAQ, Modified Health Assessment Questionnaire.

higher MHAQ score (odds ratio for a SD (= 0.67) increase in MHAQ, 3.428; 95% CI, 2.242–5.243; $p < 0.0001$), and prednisolone intake (odds ratio, 2.579; 95% CI, 1.448–4.592; $p = 0.0008$) (Table 4).

Multivariate logistic regression analysis of the risk factors for GERD symptoms. The six variables that showed a significant ($p < 0.05$) or marginally significant ($0.05 \leq p < 0.1$) association with the risk of GERD symptoms in univariate analysis were tested as predictor variables in multivariate logistic regression analysis (Table 5). High MHAQ score alone demonstrated a significant association with increased risk of GERD symptoms (odds ratio for a SD (= 0.67) increase in MHAQ, 2.864; 95% CI, 1.775–4.620; $p < 0.0001$). Prednisolone intake also had a tendency of association, but did not reach statistical significance (1.710; 0.890–3.285; $p = 0.1075$). Age, height and drugs such as PPI and bisphosphonate did not show any significant association with GERD symptoms.

Discussion

GERD is caused by reflux of stomach contents, with a variety of symptoms and complications.^(1,2) Typical symptoms of esophageal injury because of acid regurgitation are known as ‘heartburn’, but it is often that patients are absent from these typical symptoms but present with a variety of other ones, not limited to the esophageal or upper GI region.^(1,2) Furthermore, patients with dyspepsia are reported to have an increased risk not only of GERD, but also of irritable bowel syndrome and peptic ulcer disease.⁽¹⁵⁾

In this study, we evaluated GERD symptoms using the FSSG questionnaire. It is important which rating system is used in an evaluation of clinical symptoms, and the FSSG questionnaire can be regarded as a reasonable tool, because its sensitivity, specificity and accuracy have been proven equal to those of another structured questionnaire for GERD symptoms, QUEST (questionnaire in the assessment of symptomatic gastroesophageal reflux dis-

Table 4. Univariate logistic regression analysis of the risk factors for GERD symptoms

Variable factors	Odds ratio	95% CI	p value	
Age (years)	1.019	0.997–1.043	0.0891	
Gender (male)	0.915	0.464–1.805	0.797	
Height (cm)	0.96	0.927–0.995	0.0211	
Weight (kg)	0.982	0.954–1.011	0.2173	
BMI (kg/m ²)	0.965	0.902–1.032	0.294	
MHAQ (mean)	3.428	2.242–5.243	<0.0001	
Medication drugs	Prednisolone	2.579	1.448–4.592	0.0008
	DMARDs	0.855	0.455–1.608	0.6291
	NSAIDs	1.26	0.743–2.137	0.3896
	PPI	1.733	0.949–3.165	0.0772
	H2RA	1.605	0.846–3.046	0.1529
	GMP	1.425	0.845–2.404	0.1817
	Bisphosphonate	1.576	0.939–2.647	0.0846
	Anti-osteoporosis agents (ex. bisphosphonate)	1.227	0.704–2.138	0.4716

GERD, gastroesophageal reflux disease; BMI, body mass index; MHAQ, Modified Health Assessment Questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs; PPI, proton pump inhibitor; H2RA, histamine 2 receptor-antagonists; GMP, gastro-mucosal protective agents.

Table 5. Multivariate logistic regression analysis of risk factors for GERD symptoms

Variable factors	Odds ratio	95% CI	p value	
Age (years)	0.997	0.971–1.023	0.7979	
Height (cm)	0.987	0.949–1.028	0.5181	
MHAQ (mean)	2.864	1.775–4.620	<0.0001	
Medication drugs:	Prednisolone	1.710	0.890–3.285	0.1075
	PPI	1.247	0.629–2.474	0.5283
	Bisphosphonate	1.116	0.610–2.041	0.7222

GERD, gastroesophageal reflux disease; MHAQ, Modified Health Assessment Questionnaire; PPI, proton pump inhibitor.

ease).⁽¹⁶⁾ Also, compared with QUEST, FSSG is better for distinguishing GERD from other conditions and its score is known to rise with increasing endoscopic severity of GERD.⁽¹⁷⁾ Furthermore, the FSSG comprises 12 questions about the most commonly experienced symptoms in GERD, concerning not only reflux symptoms (7 questions) but also acid-related dyspepsia (5 questions).⁽¹⁸⁾

Our results showed that the prevalence of GERD symptoms in the present group of RA patients was 29.5% (82/278). In a review by Fujiwara and Arakawa, the prevalence of GERD symptoms in Japanese patients with chronic liver disease and OSAS evaluated by the FSSG was 15.3–19.3% and 30.4–31.5%, respectively.⁽²⁾ Moreover, when patients were evaluated by QUEST, the prevalence of GERD symptoms was 25.3–53.1% in DM, 9.5–33.6% in chronic liver disease, 34.2–42.1% in OSAS and 38.5–75.6% in bronchial asthma.⁽²⁾ Compared with those data, the prevalence of GERD symptoms in the present RA patients (almost 30%) can be considered as high as in other chronic diseases. On the other hand, Myasoedova *et al.*⁽¹⁹⁾ studied the prevalence of GI lesions including GERD in RA patients using Bowel Disease Questionnaire. They compared RA with age and sex matched non-RA subjects, reporting that abdominal pain/discomfort, postprandial fullness, nausea were significantly more common in RA, but that the prevalence of GERD was not significantly different. The discrepancy between this report and our results might have been resulted from the difference of the questionnaire used to evaluate the GERD symptoms.

The mechanism of GERD symptoms in RA patients is unclear. A well known histological disorder in GI system in RA should be amyloidosis, in which excessive serum amyloid, an acute phase reactant protein produced by liver in chronic inflammatory diseases, deposit within GI mucosa causing dysfunction of GI tract. This condition is rather well known in lower GI tract, which often manifests severe diarrhea, but can also be observed in upper GI tract in RA,⁽²⁰⁾ and significantly associated with reflux esophagitis in chronic renal failure patients.⁽²¹⁾ GI amyloidosis in RA, including upper GI lesion, has recently been reported to be improved by treatment with such biologics as infliximab and tocilizumab.^(22,23) Since the prevalence of GI amyloidosis was reported around 10% by histological evaluation of stomach and duodenum biopsy,^(24,25) patients with upper GI amyloidosis could have been included in our study. Unfortunately, however, we did not perform endoscopy and biopsy in this study, and it is unclear whether such histological disorders as amyloidosis were included and whether they associated with GERD symptoms.

In our results, MHAQ score, height and prednisolone intake were associated with GERD symptoms by univariate logistic regression analysis, but only MHAQ score was recognized as a significant risk factor for GERD symptoms by multivariate logistic regression analysis. Decreased QOL has been reported previously in patients with GERD, in accordance with the severity of symptoms.⁽²⁶⁾ Also, in RA and OA patients, QOL evaluated by HAQ was reported to be a significant risk factor for hospitalization because of GI events, with one unit increase (worsening) in HAQ

score resulting in an incidence ratio of 1.77.⁽⁷⁾ Higher HAQ was also significantly associated with occurrence of GERD in RA patients in Myasoedova's report.⁽¹⁹⁾

Which condition comes first, high MHAQ or presence of GERD symptoms? Since the prevalence of GERD symptoms in RA patients was much higher than general healthy population, it could be that dysfunction and poor QOL in RA patients come first and then lead to GERD symptoms. Also, since MHAQ is focused on the dysfunction in activities in daily living which are often due to musculoskeletal disorders, it would not be straightforward to think that GERD symptoms do impair these activities. However, these two conditions may associate with each other and both symptoms should be worsened. At any rate, the presence or absence of GERD symptoms should always be considered in the clinical management of RA patients, especially of those with a relatively low QOL.

Miyakoshi *et al.*⁽²⁷⁾ studied patients with osteoporosis and reported that GERD symptoms were significantly associated with increases in the angle of lumbar kyphosis and the number of vertebral fractures. Moreover, multiple vertebral fractures, together with hiatus hernia, were reported to be very strongly associated with refractory reflux esophagitis, presumably by increased intra-abdominal pressure caused by lumbar kyphosis.⁽²⁸⁾ In this study, we did not investigate the relationship between GERD symptoms and osteoporosis itself or such osteoporotic disorders as lumbar kyphosis and vertebral fractures. However, because the patients with GERD symptoms were with significantly lower height, there might have been patients with osteoporosis among those with GERD symptoms in this study. Loss of 2.0 cm or more in height over 3 years has been reported as a clinical sign of new vertebral fractures, with a specificity of 93.6%.⁽²⁹⁾

A strong association of NSAIDs with GI lesions, including GERD, has long been reported in non-arthritic patients,^(30,31) as well as in patients with RA or OA.^(7,8,32) In contrast, Janssen⁽⁵⁾ stated that NSAID intake was not a risk factor for upper GI symptoms in patients with RA, and Miyakoshi *et al.*⁽²⁷⁾ also reported that NSAIDs did not affect GERD symptoms evaluated by FSSG in patients with osteoporosis. Moreover, prednisolone has been reported as a more potent risk factor for GI events than NSAIDs in RA as well as OA patients.⁽⁷⁾

In this study, intake of NSAIDs was not associated with GERD symptoms and the only significant risk factor for GERD symptoms was prednisolone among the several drugs studied. Our finding can be considered reasonable, as it is not so different from past reports, even though it might be because patients taking COX-2 inhibitors were included in this study that the association of NSAIDs intake with GERD symptoms was estimated as relatively weak. Cryer *et al.*⁽³³⁾ studied the persistence of NSAID prescription in OA and RA patients with concomitant GERD, comparing non-selective NSAID and celecoxib, a selective COX-2 inhibitor, and reported that significantly more patients treated with celecoxib were persistent than non-selective NSAIDs. From the results of our study along with Cryer's report, COX-2 inhibitors could be prescribed more safely than non-selective NSAID with regard to GI lesions including GERD.

Another reason that NSAID intake did not affect the prevalence of GERD symptoms could be the precaution by PPI and H2RA, which are often prescribed together with NSAID, though these medications themselves did not affect the prevalence of GERD in our study. Since PPI and H2RA are prescribed in patients with existing GERD symptoms, it should be difficult to determine the association of these medications with the prevalence of GERD symptoms. As for bisphosphonate, which demonstrated a weak correlation with the prevalence of GERD symptoms in our univariate logistic regression analysis, no statistically significant correlation was recognized either by univariate or by multivariate logistic regression analysis. Although we evaluated GERD

symptoms only by FSSG questionnaire and there might have been asymptomatic GI lesions caused by medications, our results clearly demonstrated that only prednisolone should be regarded as a potent risk factor among medication drugs for GERD symptoms in RA patients. When it comes to the dose of steroid, however, no statistical significant difference was recognized between the patients with GERD symptoms and those without (data not shown). The pathomechanism of GERD in the patients with steroid intake is unclear. One reason might be gastric ulcer and gastritis caused by steroids, but the association of these disorders with GERD is still controversial, especially regarding those with *Helicobacter pylori* infection.⁽¹⁾ Some researchers have pointed out negative correlation of GERD with *Helicobacter pylori* infection,^(34,35) while others reported no or positive correlation.⁽³⁶⁻³⁸⁾ Since we did not perform endoscopy nor *Helicobacter pylori* examination in this study, it is unclear whether patients with these conditions were included in our study and whether they associated with GERD symptoms.

Among three conditions which showed significant association with the prevalence of GERD by univariate logistic regression analysis, only MHAQ demonstrated a significant, strong association by multivariate regression analysis, while height and prednisolone intake failed to reach statistical significance. Because there was a significant correlation between MHAQ score and height, as well as between MHAQ and prednisolone intake (data not shown), however, height and prednisolone intake might have been statistically dependent on the MHAQ score, resulting in a significant association with GERD symptoms by univariate logistic regression analysis. It has also been reported that use of corticosteroids does not prevent worsening of the HAQ score, even in patients with low disease activity.⁽³⁹⁾ We speculate that both lower height, presumably as the result of osteoporosis, and prednisolone intake, presumably as the result of insufficient control of disease activity of RA, contribute to dysfunction and worsened QOL characterized as higher MHAQ score, which demonstrated a strong association with the prevalence of GERD symptoms and was affected still more adversely by GERD symptoms.

In conclusion, prevalence of GERD symptoms was considerably high in RA patients, and there was an association with higher MHAQ score, lower height and prednisolone intake. Among these, the most significant factor related to GERD symptoms was MHAQ score, which demonstrates the patient's functional status as well as QOL. We believe that clinicians should always be aware of GERD symptoms in patients with RA, especially those with relatively low functional status or poor QOL.

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Conflict of interest

No financial support or other benefits in any form have been or will be received from commercial sources, directly or indirectly for the work reported in this manuscript. Also, none of the authors have had or will have any financial interests which could create a potential conflict of interest, with regard to the work reported in this manuscript.

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