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Original Article

Clinical impact of gastroesophageal reflux disease in patients with subacute/chronic cough

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AC, atopic cough; AS, acid-reflux symptoms;
CVA, cough-variant asthma; DS, dysmotility
symptoms; FSSG, the Frequency Scale for
Symptoms of Gastroesophageal reflux;
GERD, gastroesophageal reflux disease; J-
LCQ, the Japanese version of the Leicester
Cough Questionnaire; PIC, post-infectious
cough; PPIs, proton pump inhibitors;
QoL, quality of life; SBS, sinobronchial
syndrome; UADs, upper airway diseases

ABSTRACT

Background: While gastroesophageal reflux disease (GERD) is one of the commonest causes of subacute/chronic cough along with cough-variant asthma (CVA) and rhinosinusitis, its clinical impact remains unknown. Therefore, we sought to investigate the impact of GERD in patients with subacute/chronic cough.

Methods: Between April 2012 and March 2018, a total of 312 patients presenting subacute or chronic cough lasting for ≥ 3 weeks [median cough duration, 4.9 (0.7–434) months] underwent diagnostic tests. GERD symptoms and cough-specific QoL were evaluated through the Frequency Scale for Symptoms of Gastroesophageal reflux (FSSG) and the Japanese version of the Leicester Cough Questionnaire (J-LCQ). According to the FSSG domains, patients with GERD were arbitrarily categorized into 3 groups; acid-reflux predominant, dysmotility predominant, and pauci-symptoms groups, respectively.

Results: The average scores of J-LCQ was 12.5 (SD3.7). One hundred-forty three were diagnosed as having GERD-related cough based on classical reflux symptoms including heartburn and characteristic triggers of cough such as phonation, rinsing, lying, and eating. Most of them (89.8%) had other causative diseases including CVA. Cough lasted longer ($p = 0.019$) and required a longer time until alleviation ($p = 0.003$) in patients with GERD than in those without GERD. They also scored lower J-LCQ than counterpart group ($p < 0.0001$). In terms of symptom stratification, dysmotility predominant group showed significant more response to specific GERD treatments than the remnants ($p = 0.002$).

Conclusions: These results indicate that GERD is associated with the aggravation of other causes including CVA. Particularly, dysmotility symptoms may be potential therapeutic target for GERD-related cough.

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Introduction

Cough is the most common complaint and troublesome symptom leading patients to seek medical care worldwide.^{1–4} In European or American countries, gastroesophageal reflux disease (GERD) is the most common cause of subacute/chronic cough along

with allergic disorders such as asthma and rhinosinusitis.^{5–7} In Asian countries, on the contrary, GERD-related cough has been considered rare, with a prevalence of 0%–12%.^{8–10} Meanwhile, in both Asian and European or American countries, the prevalence of GERD itself has been increasing,^{11,12} thus giving more importance to cough alleviation in clinical practice.¹³ Similar to European or American countries, in Asia, the prevalence of GERD-related cough may not be as rare as previously assumed.¹⁴

Cough is often attributed to multiple causes,⁷ and it has been previously reported that 69% of the patients presenting with GERD-related cough had comorbid conditions such as asthma or post nasal drip.⁷ In the United Kingdom, gut dysmotility conditions, such as regurgitation and irritable bowel syndrome, were found to

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comprise significant risk factors of chronic cough, in addition to smoking and low social class.¹⁵ The impact of GERD symptoms on cough-specific quality of life (QoL) in patients with cough-variant asthma (CVA) has also been shown.¹⁶ GERD and cough may therefore aggravate each other, with their interaction potentially leading to the development of treatment refractoriness.¹⁷ Despite this evidence, the clinical impact of GERD on subacute/chronic cough remains to be established.

The present study aimed to investigate the prevalence and impact of GERD in patients with subacute/chronic cough. Furthermore, we addressed the impact of GERD treatment on cough, upon patient stratification arbitrarily according the Frequency Scale for the Symptoms of GERD (FSSG), validated subjective measurement of GERD symptoms.

Methods

Subjects

We retrospectively reviewed 312 consecutive patients with subacute/chronic cough persisting for 3 weeks or longer, who were referred to the asthma and chronic cough clinic of Nagoya City University Hospital from April 2012 to March 2018. All patients underwent a meticulous diagnostic investigation, including a medical history checked by cough specialists (Y.K., M.T. and A.N.), chest radiograph, physiological examinations such as spirometry and airway hyperresponsiveness test, blood test, and fractional nitric oxide measurement,¹⁸ and therapeutic trials. Patients who met some exclusion criteria were not incorporated into this analysis. Exclusion criteria were as follows: (1) abnormal chest radiograph findings, likely to explain the cough, (2) current and former smokers of more than 10 pack-years or those who quit within 6 months prior to the first visit, or (3) patients with chest tightness, shortness of breath or wheezing. Four hundred and fourteen patients visited our hospital because of subacute/chronic cough during the follow-up period. Of these, 35 patients had current or ex-smokers of more than 10 pack-years, and wheezes were audible on auscultation in 67 patients. Thus, the remaining 312 patients were eligible for the present analysis. The causes of cough were determined based on the guidelines of the Japanese Respiratory Society Cough Guideline, with slight modifications.¹ The diagnosis of CVA was based on the following criteria: (1) isolated prolonged cough without shortness of breath or wheezing and no wheezes audible on auscultation, (2) the presence of airway hyperresponsiveness (AHR) to inhaled methacholine, as assessed by the continuous methacholine inhalation method (Dmin: an index for airway sensitivity defined by the cumulative dose of inhaled methacholine at the inflection point at which baseline respiratory resistance began to increase ≤ 12.5 units) (Asthograph[®]; Chest, Tokyo, Japan)^{19,20} and symptomatic improvement of cough with the use of short-acting β_2 agonists and (3) no past history of asthma.²¹ GERD-related cough was suspected by the presence of classic reflux symptoms, such as heartburn, indigestion, chest discomfort, throat clearing, dysphonia, dysphagia and belching and/or typical characteristics of cough triggered by phonation, rising, lying, eating and intake of certain foods.²² When the cough was improved through specific GERD treatments [proton pump inhibitor (PPIs) and/or prokinetic agents], a diagnosis of GERD-related cough was confirmed.^{22,23} A diagnosis of upper airway diseases (UADs) such as sinobronchial syndrome (SBS) and allergic rhinosinusitis were based on a positive result of sinus images (checked by otolaryngology specialist, M.S.) and improvement of cough, as well as symptoms of chronic sinusitis with macrolide antibiotics and/or histamine H1 antagonists.¹ A diagnosis of post-infectious cough (PIC) was based on a preceding history of acute

upper airway respiratory tract infection and spontaneous resolution of cough.¹ A diagnosis of atopic cough (AC) was based on chronic, bronchodilator-resistant, non-productive cough with atopic predisposition but without non-specific bronchial hyper-responsiveness, where the cough could be successfully treated with histamine H1 antagonists and/or glucocorticoids.²⁴ Psychogenic cough was suspected if cough was aggravated by emotional stress and social activity and was absent during sleep, and unresponsive to conventional therapy.²⁵ Diagnosis was based on successful treatment with psychological therapy and anti-anxiety agents or tricyclic antidepressants. All causes of subacute/chronic cough were confirmed by the response to disorder-specific therapies. When patients reported the improvement or resolution of cough symptoms, to the extent of no longer hampering their QoL, they were considered as treatment responders.⁶ On the contrary, patients reporting a slight cough reduction were categorised as partial responders. Unexplained chronic cough was only accepted as a diagnosis upon failed examinations and intensive therapeutic trials for CVA, GERD, SBS, AC and psychogenic cough including inhaled corticosteroids, PPIs, macrolide antibiotics, histamine H1 antagonists and psychological therapy.

This study was approved by the ethical board of the Nagoya City University Hospital (Approval number: 60-17-0025).

Subjective measures of GERD symptoms and cough-specific QoL

In addition to physical and physiological examinations, the patients were asked to complete questionnaires of GERD symptoms and cough-specific QoL.

GERD symptoms were evaluated using the original version of the Frequency Scale for the Symptoms of GERD (FSSG) questionnaire, a useful tool for objective evaluation of GERD symptoms (Table 1),²⁶ which focuses on the 12 most prevalent GERD symptoms, including 7 questions (No. 1, 4, 6, 7, 9, 10, 12) associated with acid-reflux symptoms (AS) and 5 questions (No. 2, 3, 5, 8, 11) associated with gastroesophageal dysmotility symptoms (DS). The frequency of each symptom was scored as follows: 0 = never, 1 = occasionally, 2 = sometimes, 3 = often, and 4 = always, with low scores indicating less GERD symptoms. This GERD questionnaire was previously validated by endoscopic findings.²⁶ According to the FSSG domains, patients with GERD were arbitrarily stratified into 3 groups. Firstly, we defined pauci-GERD symptoms group (AS ≤ 3 , DS ≤ 1). These cut-off values were determined based on the quartile values of AS and DS in patients with GERD, respectively. Among the remaining patients, they were considered to be the DS predominant-symptoms group when DS scores were higher than AS scores (DS $\geq$ AS). Otherwise, AS predominant-symptoms group (AS $>$ DS).

The cough-specific QoL was assessed by the Japanese version of the Leicester Cough Questionnaire (J-LCQ).¹⁶ LCQ is a valid and reliable health status measure for patients with cough.²⁷ This questionnaire contains 19 items with a 7-point Likert response scale and consists of 3 subdomains: physical, social and psychological. Scores within each domain ranging from 1 to 7, while the total scores range from 3 to 21. High scores indicate a better cough-specific QoL.²⁷ The questionnaire was translated to Japanese using the forward and backward translation method, according to the standard validated protocol,²⁸ and we recently confirmed a high internal consistency of the J-LCQ,¹⁶ in line with that of the original version.²⁷

Statistical analysis

Statistical analysis was performed using the JMP system, version 11 (SAS Institute Japan, Tokyo, Japan). Results are presented as

Table 1The original version of the frequency scale for the symptoms of GERD (FSSG) questionnaire.²⁶

Question	Frequency				
	Never	Occasionally	Sometimes	Often	Always
1 Do you get heartburn?	0	1	2	3	4
2 Does your stomach 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

mean [standard deviation (SD)] or median (range). Between-group comparisons were performed using an unpaired-*t* test or analysis of variance, as appropriate. Log-transformation was performed to evaluate the difference in AHR because Dmin, an index for airway sensitivity, was not normally distributed. A multivariate regression analysis was applied to determine the characteristics of multiple causes of subacute/chronic cough. Receiver operating characteristic (ROC) analysis was performed to clarify whether significant indices on a multivariate analysis could be available for the detection of the cough caused by multiple disorders. The correlation between cough-specific QoL and GERD-related symptoms was investigated through the Pearson's correlation test. A level of $p < 0.05$ was considered statistically significant.

Results

Prevalence of subacute/chronic cough causative diseases

The characteristics of the 312 patients with subacute/chronic cough are presented in Table 2. According to the diagnostic and therapeutic trials, 190 patients had an isolated cause for the cough, and 119 had multiple causes, while 3 patients were considered to have unexplained cough. Among the 312 patients, 249 (78.1%) were considered as treatment responders based on their self-reported cough symptoms following therapeutic interventions. Patients with isolated cause and those with multiple causes for the cough presented similar characteristics, except for the J-LCQ and FSSG scores (Table 2).

Table 2

Characteristics of patients with subacute/chronic cough.

	Whole patients (n = 312)	Isolated cause (n = 190)	Multiple causes (n = 119)	p value
Sex, Females (%)	207 (66.3)	121 (63.7)	84 (70.6)	0.21
Age, years	50.3 (17.2)	48.8 (17.6)	52.5 (16.6)	0.065
Body mass index, kg/m ²	22.5 (4.1)	22.3 (4.1)	22.7 (4.1)	0.39
Smoking, never (%)	263 (84.3)	163 (85.8)	97 (81.5)	0.32
Treatment responders, n (%)	249 (79.8)	152 (80.0)	97 (81.5)	0.74
Cough duration, months [†]	4.9 (0.7–433.8)	4.0 (0.7–433.8)	6.5 (0.8–300)	0.081
Time required cough alleviation, months [†]	1.1 (0.17–20.8) [‡]	0.9 (0.17–20.8) [§]	1.6 (0.3–18.0) [¶]	0.095
FEV ₁ , %predicted	99.8 (16.6)	98.7 (16.2)	101.3 (17.2)	0.19
Fractional exhaled nitric oxide, ppb	24.7 (20.3)	25.1 (21.1)	24.2 (19.2)	0.70
AHR to inhaled methacholine (Dmin), units [†]	21.5 (0.036–50) ^{‡‡}	25.2 (0.036–50) ^{‡‡}	15.8 (0.18–50) ^{§§}	0.98
J-LCQ ^{¶¶} total scores, points	12.5 (3.7)	13.0 (3.7)	11.7 (3.5)	0.004
FSSG ^{†††} total scores, points	8.5 (7.3)	7.1 (7.0)	10.5 (7.4)	0.0001
acid reflux symptoms, points	4.7 (4.3)	4.0 (4.2)	5.8 (4.4)	0.0004
dysmotility symptoms, points	3.7 (3.8)	3.1 (3.6)	4.6 (3.9)	0.0007

[†]Median (range), [‡]n = 249, [§]n = 152, [¶]n = 97, ^{‡‡}n = 163, ^{§§}n = 94, ^{¶¶}n = 68, AHR, Airway hyperresponsiveness. AHR was considered positive if Dmin was ≤ 12.5 units.²⁰ ^{¶¶}The Japanese version of the Leicester Cough Questionnaire, ^{†††}The Frequency Scale for the Symptoms of GERD. Treatment responders were defined when patients reported the improvement or resolution of cough symptoms, to the extent of no longer hampering their QoL.⁶ On the contrary, patients reporting a slight cough reduction were categorised as partial responders.

We conducted a multivariate analysis to clarify the characteristics of multiple causes of subacute/chronic using variables of $p < 0.10$ of Table 2. Cough alleviation time was not adapted as a variable because cough alleviation time was obtained only on treatment responders. A multivariate analysis has revealed that elder age, lower cough-specific QoL, and higher dysmotility symptoms are significant characteristics of multiple causes of subacute/chronic cough (Supplementary Table 1). Meanwhile, their AUCs are low according to the ROC analysis (Age; 0.56, J-LCQ; 0.60, and FSSG dysmotility symptoms; 0.63, Figures not shown).

CVA was the most common isolated cause (n = 107, 34.3% of all patients), followed by GERD (n = 37, 11.9%) and UADs (n = 22, 7.1%) (Fig. 1). Among the 118 patients with multiple causes, 106 (89.8%) were diagnosed as having GERD. CVA was the most common disease comorbid with GERD (89 patients, Fig. 1). Through repeated counting of overlapping cases, CVA was present in 209 patients (67.0%), GERD in 143 (45.8%) and UADs in 47 (15.1%). GERD was thus found to be among the most prevalent causes of subacute/chronic cough in our cohort, especially as a contributor to multiple causes.

Association between cough-specific QoL and GERD symptoms

According to the subjective measurement of cough-specific QoL, the mean J-LCQ was scored as 12.5 (SD, 3.7), which is as low as that of previous reports, indicating a significant impairment of cough-specific QoL.^{16,29–31} The average of total, AS, and DS scores was 8.5 (7.3), 4.7 (4.3) and 3.7 (3.8), respectively. Patients with multiple

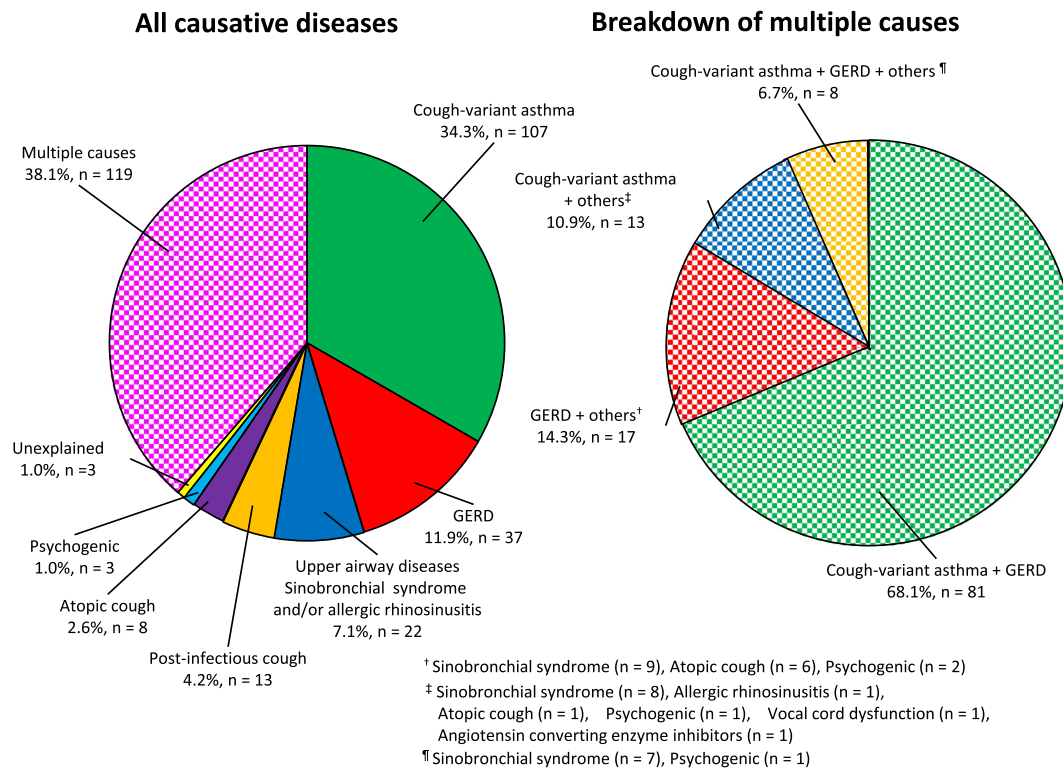


Fig. 1. The breakdown of causes of subacute/chronic cough. GERD, gastro-esophageal reflux disease.

causes scored lower in the J-LCQ and higher in the FSSG than those with an isolated cause (Table 2). Regarding the association between cough-specific QoL and GERD symptoms, a lower cough-specific QoL was associated with more GERD symptoms, as evaluated by the FSSG (Fig. 2, $r = -0.28$, $p < 0.0001$ for total, $r = -0.29$, $p < 0.0001$ for AS, and $r = -0.21$, $p = 0.0001$ for DS).

Association between GERD and cough-related variables

After excluding 3 patients diagnosed as having unexplained cough, 309 patients were used to evaluate the impact of GERD on the following cough-related variables: cough duration, cough-specific QoL, cough alleviation time and response to specific therapies. For that purpose, the 309 patients were stratified according to the presence or absence of GERD (Table 3, Fig. 3). Patients with GERD-related cough were lower rate of treatment response ($p = 0.040$), showed longer cough duration ($p = 0.019$), required more time until cough alleviation ($p = 0.003$) and had more impaired the cough-specific QoL than those without GERD ($p < 0.0001$) (Table 3, Fig. 3). On the contrary, FeNO was lower in patients with GERD than in those without GERD (Table 3, $p = 0.024$). Furthermore, GERD patients tended to be smaller number of concomitant CVA patients and higher value of Dmin than those without GERD (Table 3). The FSSG total, AS, and DS scores were, as expected, higher in patients with GERD-related cough (Table 3, $p < 0.0001$ for all). In patients with GERD-related cough, the cough-related variables were not affected by the presence of comorbid diseases, such as CVA (Fig. 4). Also, when the 309 patients were stratified according to the presence or absence of CVA, no significant differences were found for cough-related variables between the 2 groups (data not shown). These results indicate that GERD, but not other diagnosis, is profoundly involved in the pathogenesis of intractable chronic cough.

The impact of treatment response on GERD symptoms in patients with GERD-related cough

Finally, we assessed the response to specific therapies in patients with GERD-related cough. Among the 143 patients, 110 were treated with both PPIs and prokinetic agents. According to the FSSG scores, 69 in AS predominant-symptoms, 52 in DS predominant-symptoms, and 22 in pauci-symptoms groups, respectively. Although no obvious differences in treatment response were observed among the 3 groups [Fig. 5A, 69.6 (46.4) % for AS predominant-symptoms group, 84.6 (36.4) % for DS predominant-symptoms group, and 72.7 (45.6) % for pauci-symptoms group, $p = 0.16$ by ANOVA], patients with DS predominant-symptoms group showed significant more response to specific therapies as compared with the remaining groups [Fig. 5B, 84.6 (36.4) % for DS predominant-symptoms group vs 70.3 (45.9) % for others, $p = 0.043$]. Forty-three out of 52 DS predominant patients were used prokinetic agents in addition to PPIs. On the contrary, treatment response was similar when it was compared between AS predominant group-symptoms and others, and pauci-symptoms groups and others, respectively.

Discussion

In European or American countries, GERD is the most common cause of subacute/chronic cough, along with asthma and rhinosinusitis. The present study showed that, in Japan, GERD is much more common as a cause of subacute/chronic cough than was assumed previously, and more prevalent as a comorbid disease than as an isolated cause of subacute/chronic cough. The presence of GERD was associated with longer cough duration, longer time until cough alleviation and lower cough-related QoL. Furthermore, when stratified according to GERD symptoms, more dysmotility symptoms but less acid-reflux symptoms may be a sign to predict

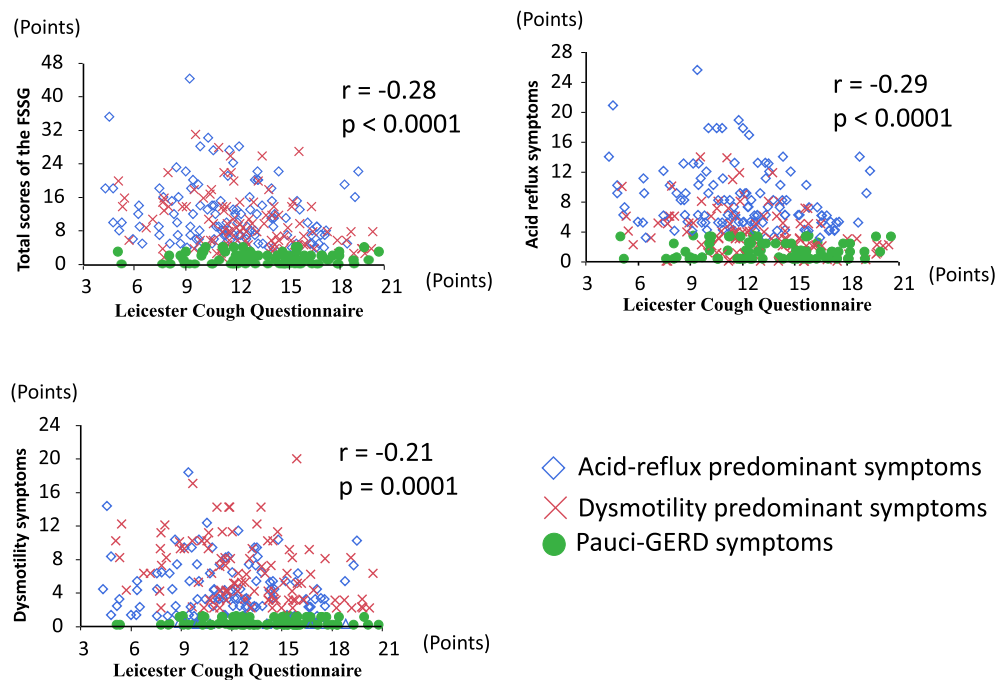


Fig. 2. The association of GERD symptoms with cough specific QoL. Total, acid reflux and dysmotility symptoms scores of the FSSG are shown. Open diamond: acid-reflux predominant symptom group, Cross marks: dysmotility predominant symptom group, Closed circle: pauci-GERD symptom group.

Table 3

Characteristics of patients with or without GERD.

	Patients with GERD (n = 143)	Patients w/o GERD (n = 166)	p value
Sex, Females (%)	94 (65.7)	111 (66.9)	0.83
Age, years	50.9 (17.1)	49.6 (17.4)	0.49
Body mass index, kg/m ²	22.7 (4.5)	22.2 (3.7)	0.38
Smoking, never (%)	118 (82.5)	142 (85.5)	0.47
Treatment Responders, n (%)	108 (75.5)	141 (84.9)	0.040
Cough duration, months [†]	6.3 (0.8–433.8)	4.1 (0.7–317.8)	0.019
Time required cough alleviation, months [†]	1.6 (0.2–20.8) [‡]	0.9 (0.2–14.3) [§]	0.003
The number of cough-variant asthma, n (%)	89 (62.2)	120 (72.3)	0.060
FEV ₁ , %predicted	99.4 (17.9)	100.0 (15.4)	0.74
Fractional exhaled nitric oxide, ppb	22.0 (14.6)	27.1 (24.0)	0.024
AHR to inhaled methacholine (Dmin), units [†]	26.4 (0.18–50) [¶]	11.3 (0.036–50) ^{††}	0.073
J-LCQ [#] total scores, points	11.5 (3.5)	13.4 (3.6)	<0.0001
FSSG [#] total scores, points	11.3 (8.0)	6.0 (5.6)	<0.0001
acid reflux symptoms, points	6.3 (4.9)	3.4 (3.2)	<0.0001
dysmotility symptoms, points	5.0 (4.0)	2.6 (3.2)	<0.0001

Patients with unexplained cough were excluded. w/o: without, [†]Median (range), [‡]n = 108, [§]n = 141, [¶]n = 74, ^{††}n = 88, AHR, Airway hyperresponsiveness. AHR was considered positive if Dmin was ≤12.5 units.²⁰ Treatment responders were defined when patients reported the improvement or resolution of cough symptoms, to the extent of no longer hampering their QoL.⁶ [#]The Japanese version of the Leicester Cough Questionnaire, [#]The Frequency Scale for the Symptoms of GERD.

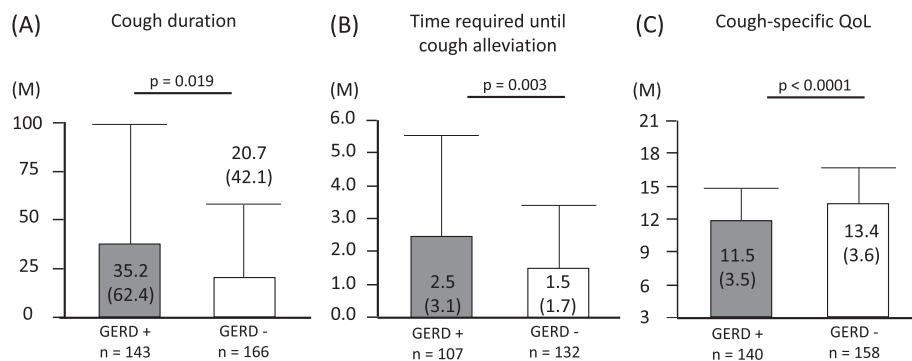


Fig. 3. The impact of GERD on cough duration (A), time required until cough alleviation (B), and cough-specific QoL (C) in patients with subacute/chronic cough. GERD +, patients with GERD-related cough; GERD -, patients without GERD-related cough.

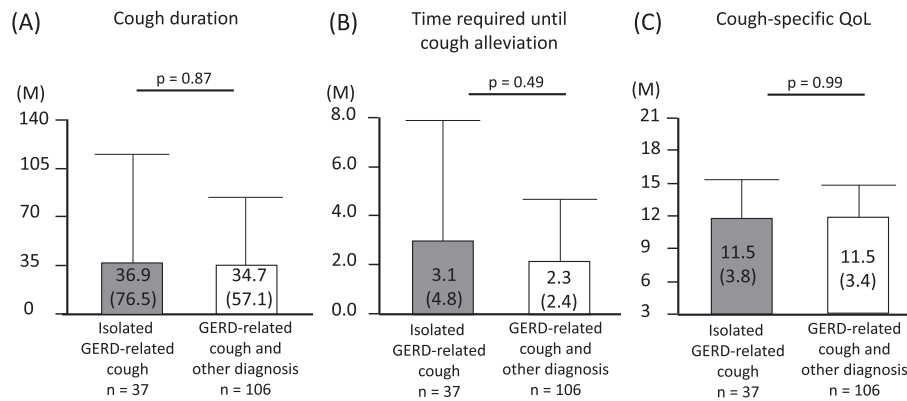


Fig. 4. The influence of comorbidity on cough duration (A), time required until cough alleviation (B), and cough-specific QoL (C) in patients with GERD-related cough.

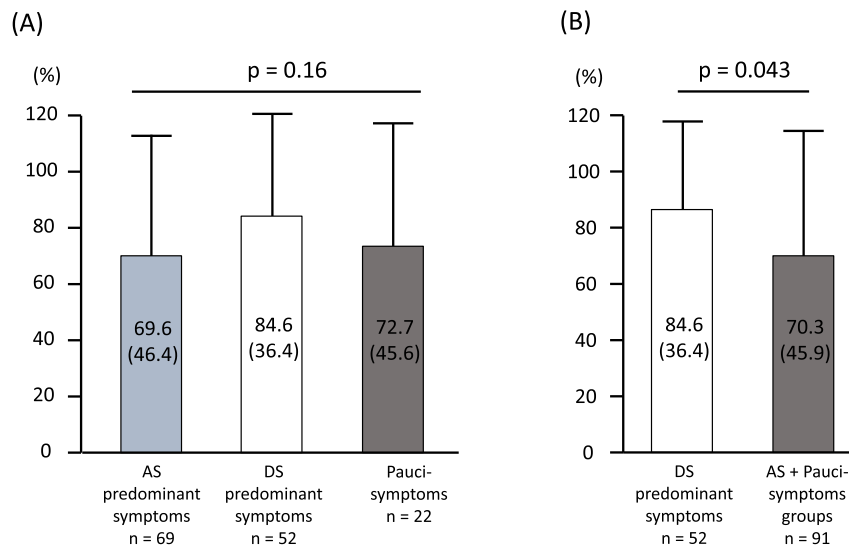


Fig. 5. The impact of GERD symptoms on treatment response to specific treatments against GERD in patients with GERD-related cough. Patients were arbitrarily categorized into 3 groups according to the FSSG questionnaire; AS-predominant symptoms, DS-predominant symptoms, and pauci-symptoms, respectively. Analysis of variance was used to compare among the 3 groups (A). Unpaired-t test was adopted to compare between DS-predominant symptoms group and the remaining groups (B). The rate of treatment responders after proton pump inhibitors with or without prokinetic agents is shown. AS, Acid-reflex related symptoms; DS, Dysmotility related symptoms.

patients who are likely to respond to specific treatment such as PPIs and/or prokinetic agents.

The prevalence of endoscopically diagnosed and/or symptomatic GERD in general population has been lower in Japan (16–18%)^{32,33} than in European or American countries (21–59%).³⁴ Although the prevalence of chronic cough in patients with GERD in Japanese has not been reported in statistics, the prevalence of GERD-related cough has been increasing from 2% to 12% for two decades as corresponded with the increase in GERD in general population.^{12,14} Indeed, a recent review of epidemiology of GERD in Japan surveyed on 2011 has reported that the prevalence of at least weekly reflux symptoms in seven studies closely defined by the Montreal definition was 6.5–9.5%, which is approaching the prevalence reported in European or American countries (10–20%).³⁵ Similarly, the prevalence of GERD-related cough in Japan is also coming close to that in European or American countries.¹⁴ The increase in the prevalence of GERD itself in Japan may be explained by an increase in gastric acid secretion,³⁶ a decrease in the *Helicobacter pylori* infection among younger aged population,³⁷ and more attention being paid to GERD by clinicians.¹² These factors may affect the difference in the prevalence of GERD-related cough between Japanese and

European or American population. The present results showed that almost half of patients with subacute/chronic cough presented GERD symptoms, as evaluated by the original version of the FSSG consisting of the 12 most common symptoms, indicating that GERD symptoms are related to multiple causes of subacute/chronic cough.

We have indicated that GERD and its symptoms affect cough duration and time to cough alleviation following the start of specific therapies, and impair cough-specific QoL. Two mechanisms are thought to underlie GERD-related cough: the vagally mediated esophageal-tracheobronchial reflex caused by distal esophageal exposure to gastric contents (reflex theory), and the micro-aspiration of gastric contents into the proximal airways (reflux theory).²² Transient lower esophageal sphincter relaxation (TLESR) caused by gastric distension is involved in the development of cough.³⁸ Because TLESR occurs more frequently during daytime than night-time, GERD-related cough is likely to exert a strong impact on QoL. In fact, a diagnosis of GERD-associated cough can be suspected when the cough is exacerbated by postural changes, food intake and talking.^{22,39} As triggers of GERD-related cough is closely related to daily life, its diagnosis and treatment may be difficult for many clinicians.

According to the guidelines of the American College of Chest Physicians and the British Thoracic Society, intensive treatment of GERD including PPIs therapy should be undertaken for at least 3 months upon suspicion of GERD-related cough.^{3,23} Meanwhile, it remains to be controversial about the efficacy of prokinetic agents in GERD-related cough because any randomised clinical trials regarding the treatment of GERD-related cough did not mention of the use of prokinetic agents with or without antireflux therapy. However, the association between gut dysmotility and the pathophysiology of chronic cough have been established. A study using esophageal manometry has demonstrated that esophageal dysmotility was present in 38% out of the patients with GERD-related cough. From other studies including ours, gut dysmotility symptoms, but not acid-reflex symptoms, found to be attributed to the development of chronic cough in general population¹⁵ and the impairment of cough-specific QoL in patients with CVA.¹⁶ The present study demonstrated for the first time that gut dysmotility symptoms such as abdominal bloating and burping may be a potential therapeutic target against GERD-related cough. Indeed, the latest expert panel report clearly mentioned that the use of PPIs alone is not recommended for patients suspected of reflux-cough, unless heartburn or regurgitation is evident.⁴⁰ Further research would be indispensable to confirm the importance of gut dysmotility as a therapeutic target of GERD-related cough.

Patients with GERD-related cough have significantly lower levels of FeNO than those without GERD in the present study. This could be explained by the difference in the number of CVA patients between patients with and without GERD. According to a study of the utility of measurement of FeNO for differentiating eosinophilic airway disorders such as CVA and nonasthmatic eosinophilic bronchitis from GERD and UADs in patients with chronic cough, FeNO was significantly higher in patients with CVA than in patients with GERD [54.0 (21.0) vs 18.1 (13.5), $p < 0.001$].⁴¹ We have also revealed that FeNO levels were significantly higher in patients with CVA than in those with non-asthmatic cough, particularly when patients had atopic predisposition.¹⁸ Indeed, Dmin, an index for airway sensitivity, of non-GERD coughers, majority of whom were CVA patients, tended to be low as compared to that of patients with GERD-related cough. Additionally, some of patients with GERD-related cough had already been diagnosed as having CVA and took treatment for it including inhaled corticosteroids before the referral to our hospital. Treatment intervention for CVA before the referral might also have affected the difference in FeNO levels between patients with and without GERD-related cough.

This study had several limitations. First, patients who smoked currently and had smoking history of more than 10 pack-years were excluded from this analysis. Additionally, this study may be biased by the studied population in the single university hospital of tertiary cough care clinic in Japan. Indeed, the frequency of allergic rhinosinusitis as a cause of subacute/chronic cough was low. One possible explanation is that patients may not be referred to respiratory specialists but to otorhinolaryngology specialists when they had nasal symptom together with cough. Therefore, our result might not be thoroughly applicable in real-world clinical practices. Second, treatment efficacy was judged retrospectively, according to the patients' reports. Thus, the outcome may involve self-reporting bias, although the patients' perception of treatment efficacy is critical for disease management in clinical practice. Third, we did not use intensive objective methods for GERD evaluation, such as 24-h intraesophageal pH monitoring, manometry or impedance monitoring. Hence, the diagnosis of GERD may be equivocal in such patients. We confirmed GERD-related symptoms in patients diagnosed with GERD using the FSSG questionnaire instead of PH monitoring, which was previously validated through endoscopic findings. Lastly, it remains unclear why acid-reflux symptoms are

associated with the refractoriness to PPIs with or without prokinetic agents. Other anti-acid suppressants such as potassium competitive acid blockers (e.g., vonoprazan fumarate) might be effective for a subset of patients. Therefore, further studies are needed to elucidate refractoriness mechanism of anti-GERD treatments.

In conclusion, the second most frequent cause of subacute/chronic cough in Japan is GERD next to CVA, which is often comorbid with other causes. GERD may be associated with the aggravation of other causes of subacute/chronic cough including asthmatic cough. Evaluation of GERD symptoms using succinct questionnaires such as FSSG may be helpful to detect patients likely to experience difficulties in the treatment of cough and who can potentially show good response to prokinetic agents. Further studies are needed to establish a treatment strategy for GERD-related cough and to elucidate the impact of GERD on other causes of subacute/chronic cough including asthma.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.04.011>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

YK: contributed to the performance of diagnostic tests, the collection of data, the recruitment of patients, disease diagnosis and management, the acquisition and interpretation of data, and drafting the manuscript. RK: contributed to the performance of diagnostic tests, the collection of data, the acquisition and interpretation of data, and drafting the manuscript. MT, and TA: contributed to the recruitment of patients, disease diagnosis and management, and revision of the manuscript. MS: contributed to help disease diagnosis. NT, KF, SF, HO, KM, YI, and TO: contributed to the diagnostic tests, the collection of data, and management of patients. JY: contributed to the diagnostic tests, the collection of data, and the proofreading of manuscript. AN: contributed to the recruitment of patients, disease diagnosis and management, interpretation of data, and revision of the manuscript.

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Supplementary Table 1. Characteristics of multiple causes of subacute/chronic cough in a multivariate analysis

	Estimates	95 % confidence interval	p value
Age	0.02	0.002; 0.30	0.030
Cough duration, months	0.004	-0.001; 0.008	0.13
J-LCQ [*] total scores, points	-0.07	-0.14; -0.003	0.043
FSSG [†] acid reflux symptoms, points	0.04	-0.04; 0.11	0.33
FSSG [†] dysmotility symptoms, points	0.08	0.002; 0.17	0.045

A multivariate analysis was conducted to clarify the characteristics of multiple causes of subacute/chronic using variables of $p < 0.10$ of Table 2. Cough alleviation time was not adapted as a variable because cough alleviation time was obtained only treatment responders. ^{*}The Japanese version of the Leicester Cough Questionnaire, [†]The Frequency Scale for the Symptoms of GERD.