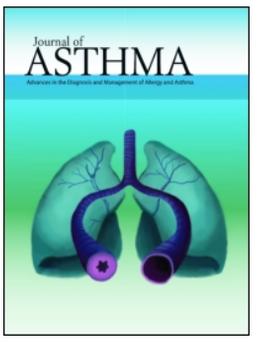


Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: https://www.tandfonline.com/loi/ijas20

The diagnostic utility of the Frequency Scale for the Symptoms of Gastroesophageal reflux disease questionnaire (FSSG) for patients with subacute/chronic cough

Ryota Kurokawa, Yoshihiro Kanemitsu, Kensuke Fukumitsu, Norihisa Takeda, Jennifer Maries Yap, Motohiko Suzuki, Yuta Mori, Satoshi Fukuda, Takehiro Uemura, Tomoko Tajiri, Hirotsugu Ohkubo, Ken Maeno, Yutaka Ito, Tetsuya Oguri, Masaya Takemura & Akio Niimi

To cite this article: Ryota Kurokawa, Yoshihiro Kanemitsu, Kensuke Fukumitsu, Norihisa Takeda, Jennifer Maries Yap, Motohiko Suzuki, Yuta Mori, Satoshi Fukuda, Takehiro Uemura, Tomoko Tajiri, Hirotsugu Ohkubo, Ken Maeno, Yutaka Ito, Tetsuya Oguri, Masaya Takemura & Akio Niimi (2020): The diagnostic utility of the Frequency Scale for the Symptoms of Gastroesophageal reflux disease questionnaire (FSSG) for patients with subacute/chronic cough, Journal of Asthma, DOI: 10.1080/02770903.2020.1805750

To link to this article: https://doi.org/10.1080/02770903.2020.1805750

The diagnostic utility of the Frequency Scale for the Symptoms of Gastroesophageal reflux disease questionnaire (FSSG) for patients with subacute/chronic cough

Ryota Kurokawa, MD[1], Yoshihiro Kanemitsu, MD, PhD[1], Kensuke Fukumitsu, MD, PhD[1], Norihisa Takeda, MD, PhD[1], Jennifer Maries Yap, MSc[1], Motohiko Suzuki, MD, PhD[2], Yuta Mori, MD[1], Satoshi Fukuda, MD, PhD[1], Takehiro Uemura, MD, PhD[1], Tomoko Tajiri, MD, PhD[1], Hirotsugu Ohkubo, MD, PhD[1], Ken Maeno, MD, PhD[1], Yutaka Ito, MD, PhD[1], Tetsuya Oguri, MD, PhD[1], Masaya Takemura, MD, PhD[1] and Akio Niimi, MD, PhD[1].

[1]Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University School of Medical Sciences, Aichi, Japan.

[2]Department of Neuro-otolaryngology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

R.K. and Y.K. contributed equally to this work

Running Head: Utility of subjective GERD questionnaire in cough

Corresponding author: Yoshihiro Kanemitsu, MD, PhD Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University School of Medical Sciences, 1, Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, Japan. **Tell:** +81-52-853-8216 **Fax:** +81-52-852-0849 **Email:** kaney32@med.nagoya-cu.ac.jp

Abstract

Background: The Frequency Scale for the Symptoms of GERD (FSSG) questionnaire, which originally consists of acid-reflux and dysmotility symptom domains, is a succinct questionnaire to evaluate gastroesophageal reflux disease (GERD) symptoms.

Objectives: To evaluate the utility of subjective questionnaire of GERD for the diagnosis of GERD-related cough by using FSSG questionnaire.

Methods: We recruited 256 patients with subacute/chronic cough between April 2012 and March 2018, who were analyzed using FSSG questionnaire and blood eosinophil counts. GERD-related cough was inferred through the presence

of classic reflux symptoms including heartburn and/or typical coughing trigger (e.g. phonation, rising, lying, eating, and intake of certain food). The diagnosis was confirmed by response to specific treatments for GERD. Receiver operating characteristic curve analysis was performed to determine the cut-off score for the diagnosis.

Results: One-hundred ten patients (43%) were diagnosed as having GERD-related cough. FSSG questionnaire was relevant for diagnosing GERD-related cough, with the area under the curve (AUC) of 0.70 ($p < 0.0001$, cut-off score 7 points, sensitivity 75%, specificity 62%). When limited to patients with blood eosinophils of ≤150/μL or those with sputum eosinophils of ≤3%, sensitivity and specificity of the diagnosis was increased, respectively (sensitivity and specificity; 79% and 65% for blood eosinophils and 82% and 68% for sputum eosinophils. $p < 0.0001$, AUC 0.74 for both).

Conclusions: The subjective questionnaire of GERD (FSSG) would be helpful in diagnosing GERD-related cough, particularly in patients with low blood or sputum eosinophil counts.

Key Words Subacute/chronic cough, gastroesophageal reflux disease, FSSG questionnaire, blood/sputum eosinophil count

Introduction

Subacute/chronic cough is a recurrent clinical problem reported to cause a decline in patients' quality of life (QoL) and labor difficulties(1). Gastroesophageal reflux disease (GERD) is one of the most common causes of subacute/chronic cough worldwide, including Japan(2-5). It is generally known that GERD-related cough has many triggers such as phonation, eating, rising, front bending of upper body, and can be accompanied by pharyngolaryngeal symptoms such as hoarseness or dysphagia(6). Meanwhile, the character, timing, or complications were not beneficial in diagnosing GERD-related cough in a previous study(7). Indeed, the American College of Chest Physicians guidelines still recommends that the diagnosis of GERD-related cough should be made on the basis of response to empiric medication such as proton pump inhibitors (PPIs) with or without prokinetics(2).

There are some questionnaires available to help with diagnosis of GERD and are used heterogeneously based on clinician preference. The Frequency Scale for the Symptoms of GERD (FSSG) questionnaire is a succinct questionnaire to evaluate esophageal symptoms of GERD which is validated based on endoscopic esophagitis(8). The original version of FSSG consists of the most prevalent 7 acid-reflux related (No. 1, 4, 6, 7, 9, 10, 12) and 5 dysmotility-related symptoms (No. 2, 3, 5, 8, 11) of GERD with higher scores being more indicative of underlying GERD (Table 1). Each score was determined as follows: 0 = never, 1 = occasionally, 2 = sometimes, 3 = often, and 4 = always. This questionnaire was validated in 124 subjects with GERD based on the endoscopic findings(8). The Japanese version of FSSG has been widely used to investigate the relationship between GERD and respiratory disorders such as chronic obstructive pulmonary disease and

asthma(9, 10). In our previous study, we also found that dysmotility symptoms assessed by this questionnaire were associated with the impairment of cough-specific QoL in patients with cough-variant asthma (CVA)(11). Given that FSSG would be helpful to evaluate GERD symptoms in patients with subacute/chronic cough, it could also be applicable to detect GERD as a cause of subacute/chronic cough.

The purpose of this study is to evaluate whether FSSG questionnaire could help in the diagnosis of GERD-related cough and to examine whether it is useful to extract comorbid GERD-related cough in CVA, the most common cause of subacute/chronic cough in Japan, by conducting analysis limited to CVA patients(12). Furthermore, we would also verify whether sensitivity and specificity of this questionnaire could change in combination with the blood eosinophil count because blood eosinophils are widely used and available tool in clinical practice worldwide, to predict responsiveness of airway diseases such as asthma and chronic obstructive pulmonary disease(13, 14) to inhaled corticosteroid (ICS), the mainstay treatment of CVA. We also analyzed the effect of sputum eosinophils in a subset of patients.

Materials and Methods

Subjects

This is a post-hoc analysis of our previous study of the epidemiology of subacute/chronic cough in a tertiary cough center in Japan(4). Four hundred and fourteen patients visited the asthma and chronic cough clinic of Nagoya City University Hospital between April 2012 and March 2018 due to subacute or chronic cough without other respiratory symptoms(4). Subacute/chronic cough was defined as cough persisting for 3 weeks or longer. Patients underwent diagnostic and therapeutic trials by cough specialists (Y.K., M.T., and A.N.). Exclusion criteria of this study were as follows, as were in our original study(4); (1) patients with current or former smoking history of more than 10 pack-years or those who quitted smoking within 6 months prior to the first visit, (2) abnormal chest radiograph findings that may explain cough symptoms, and (3) symptoms of chest tightness, shortness of breath or wheezing that may suggest typical asthma rather than CVA. In the previous report, we excluded 102 patients due to smoking history of >10 pack-years (n = 35) or the presence of wheezes on auscultation (n = 67)(4). Among the remaining 312 patients, 56 patients did not undergo blood analysis. Therefore, 256 patients were analyzed in the present study.

Diagnosis

The diagnosis of subacute/chronic cough was made according to the Japanese Respiratory Society Cough Guideline of management for chronic cough issued with slight modification(15).

Causes of cough were confirmed when the therapeutic trials were effective for their cough. Detailed information for the methodology of the diagnosis of subacute/chronic cough including for GERD and CVA was described in our previous report(4). In brief, 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) airway hyperresponsiveness (AHR), (3) symptomatic improvement of cough with the use of short-acting β_2 agonists, and (4) no past history of asthma(15). GERD-related cough was inferred by the presence of classic reflux symptoms, such as heartburn, indigestion, chest discomfort, dysphagia and belching, laryngopharyngeal reflux symptoms such as throat clearing and dysphonia, and/or cough typically and characteristically triggered by phonation, rising, lying, and intake of alcohol, caffeine, fatty foods, chocolate, citrus juices and tomato products(6). When we alleged the presence of GERD-related cough, patients received treatment for GERD [PPIs with or without prokinetic agents] and continued for at least 12 weeks. We evaluated the efficacy of PPIs with or without prokinetic agents according to the patient's self-reporting when patients visited our hospital. If patients reported the improvement or reduction of cough symptoms after two to twelve weeks after commencing treatments, we confirmed the diagnosis of GERD as a cause of subacute/chronic cough. Besides treatment for GERD, we also treated for other causes of subacute/chronic cough if patients had comorbid causes of subacute/chronic cough [e.g. inhaled corticosteroids with or without long acting β_2 agonists for CVA] but were not started simultaneously (started one by one). Therefore, we consider that other medications did not affect the diagnosis of GERD. Detailed information of measurements and objective questionnaire are noted in the supplemental material.

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

Subjective questionnaire of GERD

Subjective questionnaire was completed to determine GERD symptoms. FSSG comprises the most prevalent 12 symptoms of GERD (Table 1). Total scores range from 0 to 48. Higher scores represent worse symptoms of GERD. According to the original article, its sensitivity and specificity for the diagnosis of erosive GERD were 62% and 59% if the cut-off value was set at 8 points(8).

Statistical analysis

Statistical analysis was performed with JMP system version 11 (SAS Institute Japan, Tokyo, Japan). Values were expressed as mean [standard deviation (SD)] or median (range). The utility of FSSG for the diagnosis of subacute/chronic cough was evaluated by comparing the total points between patients with and without GERD-related cough using unpaired t test. The same evaluation was also performed by limiting the patients to those with lower blood eosinophil count, lower fractional exhaled nitric oxide (FeNO) levels, and also to those with CVA. For the 2 former variables, we assumed that the utility of FSSG for the diagnosis of GERD may increase in the setting with less

eosinophilic inflammation because GERD is a cause of subacute/chronic cough associated with non-type2 inflammation(16, 17). The latter analysis was conducted because CVA was the most common cause of subacute/chronic cough worldwide, and the presence or absence of comorbid GERD-related cough worldwide is prevalent(4), respectively(12). We defined lower blood eosinophil count as 150/μL or less with reference to the relationship between blood eosinophils and sputum eosinophils as an indicator of lower airway eosinophilic inflammation in a clinical trial for asthma medication(25). Similarly, we also defined lower FeNO as 29.2 ppb or less, the optimal cut-off value of FeNO to distinguish asthmatic cough from non-asthmatic cough(26). Furthermore, we confined patients to lower sputum eosinophils (≤3%)(18), lower total IgE (≤50 IU/mL)(19), and non-atopic patients cohorts for the similar subanalysis. Receiver operating characteristic curves were examined to determine the optimal cut-off score of FSSG for the diagnosis of GERD-related cough. We adopted maximum Youden's Index, the value of "(sensitivity) - (1 - specificity)", as the optimal cut-off scores. Sensitivity and specificity of the analysis were also calculated.

Clinical variables such as blood eosinophil counts, forced expiratory volume in 1 second (FEV1), FeNO, and scores of the Japanese version of Leicester cough questionnaire (J-LCQ) were also compared between patients with and without GERD-related cough using an unpaired-t test, and Chi square test as appropriate. If data were not normally distributed, test was performed after log-transformation. These were also applied when limiting the patients to those with lower blood eosinophil (≤150/μL), lower FeNO (≤29.2 ppb), and CVA. A level of $p < 0.05$ was considered statistically significant.

Results

Characteristics of the study population

The demographics and baseline characteristics of 256 patients who met the criteria were summarized in Table 2. There was no significant difference between the characteristics of these 256 patients and the excluded 56 patients (data not shown). Among these 256 patients, 110 were diagnosed as having GERD-related cough (including 74 with GERD-related but multifactorial cough; 56 comorbid with CVA, 6 with upper airway cough syndrome, 3 with atopic cough, 7 with CVA and upper airway cough syndrome, 2 with CVA and atopic cough). The average score of FSSG and J-LCQ of whole patients ware 8.6 (7.1) points and 12.6 (3.7), respectively. There was no significant difference between the two groups in terms of age, sex, smoking history and body mass index. The duration of cough and time required for cough alleviation were significantly longer in patients with GERD-related cough than in those without GERD-related cough (Table 2). Similarly, as expected, there was significant difference in the scores of FSSG between the two groups [11.4 (7.6) *vs* 6.5 (5.9), p value <0.001]. Blood eosinophil counts and FEV_1 were similar between the two groups, while levels of FeNO were a significantly higher in patients without GERD-related cough as compared to those with GERD-related cough ($p = 0.03$).

Diagnostic utility of FSSG questionnaire for GERD-related cough

We evaluated the diagnostic utility of FSSG questionnaire for GERD-related cough. When the cut-off score was set at 7 points, the total FSSG scores showed the best sensitivity of 75% and specificity of 62% for diagnosis [Figure 1A, area under the curve (AUC) 0.70, p <0.0001]. The sensitivity and specificity of FSSG for the diagnosis of GERD were similar if we excluded 52 patients with subacute cough from the analysis (p <0.0001, sensitivity 74%, specificity 66%, and AUC 0.71). If 8 points was adapted as the cut-off score according to the original report(8), sensitivity was 68% and specificity was 67% (AUC 0.70).

When the patients were limited to those with blood eosinophils of 150/μL or less (n = 170, Table E1), and those with FeNO of 29.2 ppb or less (n = 176, Table E2), cough duration and time until cough alleviation in both populations had almost similar trend with those in the whole study population (Table E1 and E2). The sensitivity and specificity for diagnosis by FSSG in the lower blood eosinophils population were increased up to 79% and 65%, respectively if the cut-off score was set at 7 points (Figure 1B, AUC 0.74, and p value <0.0001). Meanwhile, the utility of FSSG at the same cut-off point for diagnosis of GERD-related cough in patients who have blood eosinophils of 150 or more (n = 86) was also significant, but lower (sensitivity 65%, specificity 44%, AUC 0.63, and p <0.0001). The sensitivity and specificity of diagnosis in the lower FeNO population were 78% and 60% (Figure 1C, AUC 0.71, and p value <0.0001), which was similar with that in the whole study population (Figure 1A).

The sensitivity and specificity of FSSG for the diagnosis of GERD-related cough in lower IgE (n = 112), lower sputum eosinophils (n = 120), and non-atopic patients (n = 111) cohorts are shown in Figure E1. Sensitivity and specificity in lower sputum eosinophils cohort was increased as compared to those in whole patients (Figure E1A, p <0.0001, AUC 0.74, sensitivity 82%, and specificity 68%). Meanwhile, their values in lower IgE and non-atopic cohorts were similar with those in whole patients (Figure E1B,1C).

Comparison between CVA patients with and without GERD-related cough

Additionally, we sought to investigate whether FSSG could detect comorbid GERD as a cause of subacute/chronic cough from patients with CVA because we have shown that 64 out of 74 patients with GERD-related cough who had multiple causes had comorbid CVA (Table 2). Serum IgE levels were significantly higher in patients with CVA (n = 151) than those without (n = 74) [p = 0.04, 61.6 (5 - 2797) IU/L *vs* 38.4 (5 - 1490) IU/L, data were analyzed after log transformation]. The prevalence of atopic predisposition was greater in patients with CVA than in those without [p = 0.046, 103 (61%) patients *vs* 42 patients (41%)]. Meanwhile, either blood or sputum eosinophil counts were similar between patients with and without CVA (data not shown). The characteristics of 168 CVA patients were summarized in Table 3. When we set the cut-off score at 7 point, the

evaluation of total FSSG score showed the best sensitivity of 83% and specificity of 60% for diagnosis of comorbid GERD-related cough (Figure 2, AUC 0.74, and $p < 0.0001$).

Discussion

GERD is an important cause of subacute/chronic cough worldwide, but its diagnosis is often difficult. Classically, 24 hours pH monitoring and more recently multi-channel intraluminal impedance-pH monitoring are the most reliable tests to determine GERD as a cause of subacute/chronic cough(2, 20). However, these methods are invasive, and not generally available in clinical practice. Therefore, more simple and feasible diagnostic methods are required. In this study, we have indicated objectively for the first time with significant statistical analysis that FSSG, a validated questionnaire of esophageal symptom of GERD, is a useful diagnostic tool of GERD-related cough in patient with subacute/chronic cough when a cut-off value is set at 7 points. We have also shown that FSSG may be more useful when patients are limited to those with blood eosinophils counts of 150/μL or less. This indicates the importance of the assessment of GERD symptoms in patients with subacute/chronic cough. This study is strengthened by its simplicity and feasibility of the diagnostic methods we applied because FSSG and blood eosinophil test are available even to general practitioners.

A modified version of FSSG is now available which consists of 12 original symptoms (7 with acid-related symptoms and 5 with dysmotility one) and 2 additional dysmotility symptoms, the latter two of which are newly combined as dyspepsia symptoms(21). In the present study, we used the original one as the modified one was not yet available when we started this survey. In the original version, 8 points was the optimal cut-off value for predicting diagnosis of GERD(8), and the cut-off that we have identified (7 points) is different from the original one. Although the cut-off value of FSSG for the diagnosis was almost similar between erosive GERD and GERD-related cough, discordance of the cut-off value might reflect the predominance of non-erosive reflux disease in the pathophysiology of GERD-related cough. GERD-related cough is considered predominantly due to non-erosive reflux disease (NERD) or based on non-acid reflux mechanism(3). Baldi et al. have demonstrated that the presence of erosive reflux disease (ERD) accounts for only 15% in a group of 45 patients with cough while over 50% of the group had pH-metry positive and PPIs test positive without erosive findings(22), suggesting that GERD-related cough could occur without erosion of the esophagus mucosa. In our previous study. we found that 24 of 37 patients (65%) with GERD-related cough had NERD(17), which was comparable to the report of Baldi, et al. Additionally, some epidemiological studies have reported that NERD is more frequent than ERD worldwide(23-25). Indeed, both plasma and sputum substance P levels were significantly decreased by PPIs and prokinetic agents in GERD-related cough irrespective of the presence or absence of erosive findings(17). Although we did not confirm findings of acid-reflux with the use of endoscopy or pH monitoring methods, FSSG would be a sensitive questionnaire for the diagnosis of GERD-related cough in patients with subacute/chronic cough. Validation studies using

impedance-pH monitoring may be necessary to further clarify the accuracy of subjective measures of GERD including FSSG as its diagnosis.

Diagnostic ability of FSSG was increased when patients were limited to low blood eosinophil counts (≤150/μL), as expected (Figure 1B). Blood eosinophil counts are the most available biomarker when patients visit medical care centers due to subacute/chronic cough together with chest X-ray. In general, blood eosinophil counts are higher in patients with cough predominant asthma than in those with non-asthmatic cough(26). In patients with mild to moderate asthma, blood eosinophil was the best marker that reflects sputum eosinophilia (≥3%)(18). We also demonstrated high diagnostic ability of FSSG for GERD-related cough in lower sputum eosinophils cohort as compared to whole patients (Figure E1A). This suggests that GERD-related cough is the major cause of subacute/chronic cough caused by non-type2 inflammation. Indeed, airway neutrophilic inflammation but not eosinophilic inflammation was related to the pathophysiology of GERD-related cough, along with neurogenic inflammation(17). Maniscalco et al, also demonstrated that FeNO levels were significantly lower in patients with GERD than in those with eosinophilic airway disorders(16). We observed that low level of FeNO was one of the significant characteristics of GERD-related cough (Table 2). However, the diagnostic accuracy did not increase when patients were confined to low FeNO group (Figure 1C). One possible reason may be explained through the use of ICSs in CVA patients at the fist referral. Some patients were referred to our hospital after commencing ICSs treatment. Levels of FeNO reduces rapidly before symptoms relief when ICS was commenced to patients with asthma(27). Conversely, as far as we have searched, there are no evidences that blood eosinophil counts decline by ICSs in patients with CVA. Although the diagnostic utility of blood eosinophil counts in subacute/chronic cough remained unsolved, at the least, the present findings indicate that GERD is the most important causes of less-type2 inflammation in patients with subacute/chronic cough.

CVA is the most common cause of subacute/chronic cough and it is often comorbid with GERD(28, 29). Concomitant GERD-related cough in patients with subacute/chronic cough is thought to be involved in cough prolongation and the difficulty of its treatment(4). Indeed, CVA patients with more severe dysmotility symptoms had more impaired cough-specific QoL(11). Therefore, the assessment of GERD symptoms in CVA patients is important because potential GERD-related cough may be expected to lead to the exacerbation of cough symptoms in patients with CVA. FSSG would also be useful for detecting the coexistence of GERD-related cough in CVA patients according to the present study (Table 3, Figure 2).

Although we have already discussed the characteristics of GERD-related cough in original cohort, patients with GERD-related cough had lower levels of FeNO and AHR as compared to those without. Lower values of FeNO and AHR could be explained by the difference in the number of CVA patients between patients with and without GERD (Table 2). Additionally, some of patients with GERD-related cough had already been diagnosed as having CVA and received treatments including ICSs before the referral to our hospital. ICSs lead to decline in levels of FeNO and

improve AHR in GERD-related cough patients with comorbid CVA. The use of ICSs for CVA before the referral may also be associated with lower values of FeNO and AHR in patients with GERD-related cough.

The main limitation of the present study is with regards to the diagnosis of GERD-related cough. The diagnosis of GERD was made by symptoms and responsiveness to specific treatment without objective examinations such as manometry, pH/impedance monitoring and endoscopy. This could lead to bias. However, the diagnosis based on the medical history and response to GERD-specific therapy is recommended by international guidelines, which also admit the limitations of objective measurements(2). Second, our cohort included not only chronic cough but also subacute cough (n = 52, 20.3%). According to a study evaluated causes of subacute cough, cough was self-limiting without any treatments in almost one-thirds of patients, and they were diagnosed as having postinfectious cough(30, 31). Therefore, a cause of cough in some patients might not be specific causes such as GERD and CVA but postinfectious cough. We cannot preclude that cough might improve spontaneously because response to specific treatments was made on the basis of self-reporting by patients. However, we did diagnostic workup such as the presence of preceding respiratory infection and typical cough triggers of GERD when patients visited our hospital(6). Indeed, all patients but those diagnosed as having postinfectious cough did not have either a preceding history of acute upper respiratory tract infection or purulent sputum. Furthermore, physician's assessment for treatments based on self-reporting by patients reflect its response and patient's health-related QoL well(32). Thus, we judged that cough was alleviated not spontaneously but by specific treatments. Additionally, the frequency of postinfectious cough in this study (n =9, 3.5%) is similar to that in the previous multicenter study conducted in Japan (6.7%)(12). Third, we cannot diagnose GERD-related cough using FSSG alone. Among 110 patients diagnosed as having GERD-related cough, 28 cases showed less than 7 points by FSSG. Non-acid reflux not detectable by pH monitoring may have triggered cough in such patients(33). Laryngopharyngeal reflux is also a large aspect of GERD-related cough(34). Therefore, it may be necessary to establish other questionnaires that can detect non-acid reflux and laryngopharyngeal reflux. Questionnaires such as Hull Airway Reflux Questionnaire (HARQ) that assess the reflux of the upper airway including features found in GERD-related cough may be useful for detecting such conditions(35). Last, we did not replicate the diagnostic utility of FSSG using a new population. The utility of FSSG for the diagnosis of GERD should be clarified in future prospective studies involving larger cohorts.

In conclusion, evaluating GERD symptoms using subjective questionnaires of GERD such as FSSG could help the diagnosis of GERD-related cough in patients with subacute/chronic cough. The utilization of FSSG is more viable when patients show low blood eosinophils of ≤150/μL. Although FSSG is also useful when FeNO levels show 29.2 ppb or less, we emphasize the utility of FSSG for the diagnosis of GERD-related cough in low blood eosinophil cohort since blood eosinophils are the most commonly available biomarker. A vast majority of clinicians can utilize both FSSG and blood eosinophils in clinical practice even if they are not cough specialists. It may

also be useful for finding out concomitant GERD-related cough in patients with CVA. Meanwhile, there is still remaining room for improvement of the diagnostic accuracy of GERD-related cough. Further studies are necessary to establish other biomarkers or questionnaires to improve the accuracy for the diagnosis of GERD-related cough.

Abbreviations:

AUC: Area under the curve, CVA: cough-variant asthma, FSSG: the Frequency Scale for the Symptoms of GERD, GERD: Gastroesophageal reflux disease, J-LCQ: The Japanese version of the Leicester cough questionnaire, QoL: quality of life, SD: standard deviation

Acknowledgement: None.

Financial support: None.

COI statement:

Y.K. reports research grants from Novartis Pharma, Sanofi, MSD and Kyowa-Kirin corporations outside the submitted work. K.F. reports research grants from GSK and Novartis Pharma outside the submitted work. S.F. reports personal fees from AstraZeneca, personal fees from Eli Lilly Japan outside the submitted work. H.O reports research grant from Boehringer Ingelheim outside the submitted work. K.M. reports personal fees from Pfizer and Chugai Pharmaceutical outside the submitted work. T.O reports personal fees from AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Pfizer, Chugai Pharmaceutical, MSD, Daiichi Sankyo, and Asahi Kasei Pharma, and research grants and personal fees from Kyowa Hakko Kirin, Boehringer Ingelheim, Ono Pharmaceutical, and Novaltis outside the submitted work. M.T reports research grant from Pfizer outside the submitted work. A.N. reports personal fees from Astellas, AstraZeneca, Kyorin, GSK, Sanofi and Boehringer Ingelheim, and research grants from Astellas, Kyorin, Boehringer Ingelheim, Novartis, MSD, Daiichi Sankyo, Taiho, Teijin, Ono, Takeda, and Sanofi Pharmaceutical outside the submitted work.

Authorship:

RK: contributed to the performance of diagnostic tests, the collection of data, the acquisition and interpretation of data, and drafting the manuscript. 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. 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, YM, SF, HO, TU, TT, KM, YI, and TO: contributed to the diagnostic tests, the collection of data, and management of patients. JY: contributed to the diagnostic tests and the collection of data. AN: contributed to the recruitment of patients, disease diagnosis and management, interpretation of data, and revision of the manuscript.

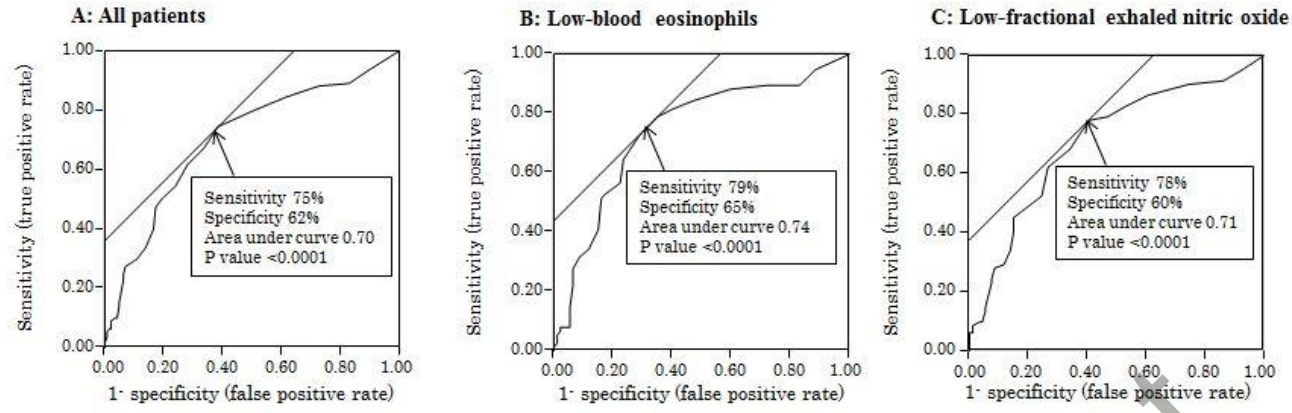
References:

1. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, Boon MH, Kantar A, Lai K, McGarbey L, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020;55(1).
2. Kahrilas PJ, Altman KW, Chang AB, Field SK, Harding SM, Lane AP, Lim K, Mcgarvey L, Smith J, Irwin RS, et al. Chronic Cough Due to Gastroesophageal Reflux in Adults: CHEST Guideline and Expert Panel Report. Chest. 2016;150(6):1341-60.
3. Niimi A. Cough associated with gastro-oesophageal reflux disease (GORD): Japanese experience. Pulm Pharmacol Ther. 2017;47:59-65.
4. Kanemitsu Y, Kurokawa R, Takeda N, Takemura M, Fukumitsu K, Asano T, Yap J, Suzuki M, Fukuda S, Ohkubo H, et al. Clinical impact of gastroesophageal reflux disease in patients with subacute/chronic cough. Allergol Int. 2019;68(4):478-85.
5. Zeiger RS, Schatz M, Butler RK, Weaver JP, Bali V, Chen W. Burden of Specialist-Diagnosed Chronic Cough in Adults. J Allergy Clin Immunol Pract. 2020;8(5):1645-57.e7.
6. Morice A, Fowles H. Acute and Chronic Cough. In: Hart S, Greenstone M, editors. Foundations of Respiratory Medicine. 1st ed. Cottingham (UK): Springer, Cham; 2018. p. 73-86.
7. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med. 1996;156(9):997-1003.
8. Kusano M, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, Kuribayashi S, Higuchi T, Zai H, Ino K, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. J Gastroenterol. 2004;39(9):888-91.
9. Shirai T, Mikamo M, Tsuchiya T, Shishido Y, Akita T, Morita S, Asada K, Fujii M, Suda. Real-world effect of gastroesophageal reflux disease on cough-related quality of life and disease status in asthma and COPD. Allergol Int. 2015;64(1):79-83.
10. Takada K, Matsumoto S, Kojima E, Iwata S, Okachi S, Ninomiya K, Morioka H, Tanaka K, Enomoto Y. Prospective evaluation of the relationship between acute exacerbations of COPD and gastroesophageal reflux disease diagnosed by questionnaire. Respir Med. 2011;105(10):1531-6.
11. Kanemitsu Y, Niimi A, Matsumoto H, Iwata T, Ito I, Oguma T, Inoue H, Tajiri T, Nagasaki T, Izuhara Y, et al. Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. Allergol Int. 2016;65(3):320-6.
12. Niimi A, Ohbayashi H, Sagara H, Yamauchi K, Akiyama K, Takahashi K, Inoue H, Wakayama T, Kobayashi H, Hasegawa M, et al. Cough variant and cough-predominant asthma are major causes of persistent cough: a multicenter study in Japan. J Asthma. 2013;50(9):932-7.
13. Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax. 2016;71(2):118-25.
14. Meijer RJ, Postma DS, Kauffman HF, Arends LR, Koeter GH, Kerstjens HA. Accuracy of eosinophils and eosinophil cationic protein to predict steroid improvement in asthma. Clin Exp Allergy. 2002;32(7):1096-103.

15. Kohno S, Ishida T, Uchida Y, Kishimoto H, Sasaki H, Shioya T, Takuyama K, Niimi A, Nishi K, Fujimura M, et al. The Japanese Respiratory Society guidelines for management of cough. Respirology. 2006;11 Suppl 4:S135-86.
16. Maniscalco M, Faraone S, Sofia M, Molino A, Vatrella A, Zedda A. Extended analysis of exhaled and nasal nitric oxide for the evaluation of chronic cough. Respir Med. 2015;109(8):970-4.
17. Takeda N, Takemura M, Kanemitsu Y, Hijikata H, Fukumitsu K, Asano T, Yamaba Y, Suzuki M, Kubota E, Kamiya K et al. Effect of anti-reflux treatment on gastroesophageal reflux-associated chronic cough: Implications of neurogenic and neutrophilic inflammation. J Asthma. 2019; Jul 15:1-9.
18. Wagener AH, de Nijs SB, Lutter R, Sousa AR, Weersink EJ, Bel EH, Sterk PJ. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. Thorax. 2015;70(2):115-20.
19. Kanemitsu Y, Matsumoto H, Oguma T, Nagasaki T, Ito I, Izuhara Y, Tajiri T, Iwata T, Mishima M, Niimi A. Independent Factors Contributing to Daytime and Nighttime Asthmatic Cough Refractory to Inhaled Corticosteroids. J Investig Allergol Clin Immunol. 2019;29(1):30-9.
20. Smith JA, Abdulqawi R, Houghton LA. GERD-related cough: pathophysiology and diagnostic approach. Curr Gastroenterol Rep. 2011;13(3):247-56.
21. Kusano M, Hosaka H, Kawada A, Kuribayashi S, Shimoyama Y, Kawamura O, Moki F. Development and evaluation of a modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease to distinguish functional dyspepsia from non-erosive reflux disease. J Gastroenterol Hepatol. 2012;27(7):1187-91.
22. Baldi F, Cappiello R, Cavoli C, Ghersi S, Torresan F, Roda E. Proton pump inhibitor treatment of patients with gastroesophageal reflux-related chronic cough: a comparison between two different daily doses of lansoprazole. World J Gastroenterol. 2006;12(1):82-8.
23. Murao T, Sakurai K, Mihara S, Marubayashi T, Murakami Y, Sasaki Y. Lifestyle change influences on GERD in Japan: a study of participants in a health examination program. Dig Dis Sci. 2011;56(10):2857-64.
24. Min YW, Lim SW, Lee JH, Lee HL, Lee OY, Park JM, Choi MG, Rhee PL. Prevalence of Extraesophageal Symptoms in Patients With Gastroesophageal Reflux Disease: A Multicenter Questionnaire-based Study in Korea. J Neurogastroenterol Motil. 2014;20(1):87-93.
25. Savarino E, de Bortoli N, De Cassan C, Della Coletta M, Bartolo O, Furnari M, Ottonello A, Marabotto E, Bodini G, Savarino V. The natural history of gastro-esophageal reflux disease: a comprehensive review. Dis Esophagus. 2017;30(2):1-9.
26. Asano T, Takemura M, Fukumitsu K, Takeda N, Ichikawa H, Hijikata H, Kanemitsu Y, Uemura T, Takakuwa O, Ohkubo H, et al. Diagnostic utility of fractional exhaled nitric oxide in prolonged and chronic cough according to atopic status. Allergol Int. 2017;66(2):344-50.
27. Bates CA, Silkoff PE. Exhaled nitric oxide in asthma: from bench to bedside. J Allergy Clin Immunol. 2003;111(2):256-62.
28. Irwin RS, Madison JM. The persistently troublesome cough. Am J Respir Crit Care Med. 2002;165(11):1469-74.

29. Poe RH, Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. Chest. 2003;123(3):679-84.
30. Kwon NH, Oh MJ, Min TH, Lee BJ, Choi DC. Causes and clinical features of subacute cough. Chest. 2006;129(5):1142-7.
31. Lai K, Lin L, Liu B, Chen R, Tang Y, Luo W, Chen Q. Eosinophilic airway inflammation is common in subacute cough following acute upper respiratory tract infection. Respirology. 2016;21(4):683-8.
32. Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, Pilette C, Lee CS, Gurdain S, Vancayzeele S, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study. Respir Med. 2009;103(11):1633-42.
33. Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. Lung. 2010;188 Suppl 1:S87-90.
34. Houghton LA, Lee AS, Badri H, DeVault KR, Smith JA. Respiratory disease and the oesophagus: reflux, reflexes and microaspiration. Nat Rev Gastroenterol Hepatol. 2016;13(8):445-60.
35. Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM. Cough hypersensitivity syndrome: a distinct clinical entity. Lung. 2011;189(1):73-9.

Figure 1. Receiver operating characteristic curves for diagnosis of GERD-related cough using FSSG



(A) Total FSSG scores in all patients (B) Total FSSG scores in patients with low blood eosinophil counts of ≤150/μL (C) Total FSSG scores in patients with low FeNO of ≤29.2 ppb

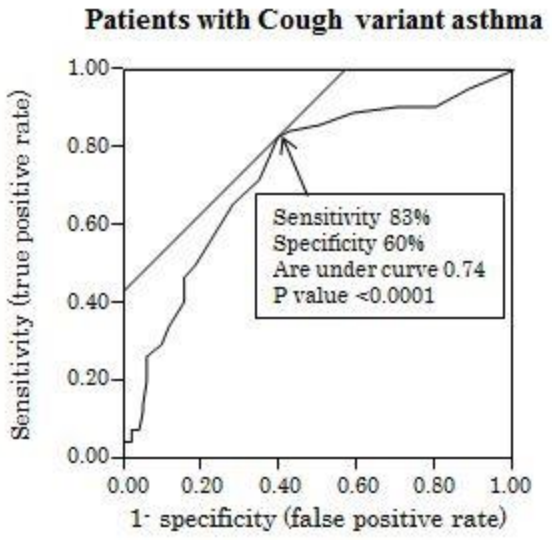


Figure 2. Receiver operating characteristic curves for diagnosis of GERD-related cough using FSSG in CVA patients

Table 1. The original version of the frequency scale for the symptoms of GERD (FSSG) questionnaire(8)

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

Table 2. Characteristics of patients with subacute/chronic cough

	Whole patients (n = 256)	GERD+ (n = 110)	GERD- (n = 146)	p value
Sex, females (%)	168 (66)	71 (65)	97 (66)	0.79
Age, years	51.7 (17.2)	51.0 (16.7)	52.2 (17.5)	0.57
Body mass index, kg/m^2	22.6 (4.2)	22.8 (4.7)	22.5 (3.8)	0.60
Smoking, never (%)	216 (84)	88 (80)	128 (88)	0.12
Atopic predisposition, n (%)	145 (57)	63 (57)	82 (56)	0.90
Multiple causes, n (%)	83 (32)	74 (67)	9 (6)	<0.001
Subacute cough, n (%)	52 (20)	16 (15)	36 (25)	0.06
Cough duration, months *	4.3 (0.7 - 433.8)	6.3 (0.8 – 433.8)	3.7 (0.7 – 317.8)	0.005
Time required for cough alleviation, months *	1.0 (0.2 - 20.8) †	1.5 (0.2 – 20.8) ‡	0.9 (0.2 – 6.3) §	0.001
Prevalence of cough variant asthma	168 (65.6)	64 (58.1)	104 (71.2)	0.03
Blood eosinophil counts, /μL *	102 (0 - 936)	100 (0 - 600)	109 (0 - 936)	0.12
Low blood eosinophil (≤150 /μl), n (%)	170 (66)	76 (69)	94 (64)	0.50
Sputum eosinophils, %*	0 (0 – 42) ‖	0 (0 - 4) ¶	0 (0 – 42) **	0.11
Serum total immunoglobulin E, IU/L *	50.6 (5.0 – 2797.0) ††	49.7 (5.0 – 2797.0) ‡‡	53.6 (5.0 – 2510.0) §§	0.76
FEV_1, %predicted	99.6 (15.6)	98.8 (15.5)	100.2 (15.6)	0.48
Fractional exhaled nitric oxide, ppb	25.3 (21.5) ‖‖	22.1 (14.9) ¶¶	27.8 (25.3) ****	0.03
AHR to inhaled methacholine (Dmin), units *	21.5 (0.04 – 50.0) ††††	28.2 (0.4 – 50.0) ‡‡‡‡	11.4 (0.04 – 50.0) §§§§	0.12
J-LCQ total scores, points	12.6 (3.7)	11.4 (3.7)	13.5 (3.6)	<0.001
FSSG total scores, points	8.6 (7.1)	11.4 (7.6)	6.4 (5.9)	<0.001
acid reflux symptoms, points	5.3 (4.6)	6.5 (4.7)	3.8 (3.5)	<0.001
dysmotility symptoms, points	3.6 (3.5)	4.9 (3.9)	2.7 (3.0)	<0.001

*Median (range): Data are analyzed after log transformation, †n = 208, ‡n = 86, §n = 122, ‖n = 130, ¶n = 49, **n = 81, ††n = 225, ‡‡n = 192, §§n = 133, ‖‖n = 241, ¶¶n = 106, ****n =135, ††††n = 125, ‡‡‡‡n = 54, §§§§n = 71, GERD+: Patients with GERD-related cough, GERD-: Patients without GERD-related cough, FEV_1: Forced expiratory volume in one second, AHR: Airway hyperresponsiveness. AHR was considered positive if Dmin, the cumulative dose of inhaled methacholine at the inflection point at which baseline respiratory resistance began to increase, represented ≤12.5 units, J-LCQ: The Japanese version of the Leicester cough questionnaire, FSSG: The Frequency scale for the symptoms of GERD

Table 3. Characteristics of patients with CVA

	Whole CVA patients (n = 168)	GERD+ (n = 64)	GERD- (n = 104)	p value
Sex, females (%)	110 (66)	45 (70)	65 (63)	0.32
Age, years	49.8 (16.1)	50.9 (15.8)	49.1 (16.3)	0.46
Body mass index, kg/m^2	22.6 (4.0)	22.4 (4.3)	22.7 (3.8)	0.70
Smoking, never (%)	138 (82)	49 (77)	89 (86)	0.15
Atopic predisposition, n (%)	103 (61)	40 (63)	63 (61)	0.87
Multiple causes, n (%)	72 (43)	64 (100)	8 (8)	<0.001
Subacute cough, n (%)	30 (18)	8 (13)	22 (21)	0.21
Cough duration, months *	4.2 (0.8 - 317.8)	5.5 (0.8 – 300.0)	4.0 (0.8 – 317.8)	0.08
Time required for cough alleviation, months *	1.1 (0.2 – 18.0) †	2 (0.3 – 17.8) ‡	0.9 (0.2 – 6.3) §	0.001
Blood eosinophil counts, /μL *	102 (0 - 936)	100 (5 - 600)	1 (0 - 936)	0.16
Low blood eosinophil (≤150 /μl), n (%)	110 (66)	44 (70)	65 (63)	0.32
Sputum eosinophils, %*	0 (0 – 42) ‖	0 (0 - 4) ¶	0 (0 – 42) **	0.28
Serum total immunoglobulin E, IU/L *	61.6 (5.0 – 2797.0) ††	62.9 (5.0 – 2797.0) ‡‡	55.3 (5 - 2510) §§	0.64
FEV_1, %predicted	100.0 (15.3)	99.5 (15.8)	100.3 (15.1)	0.76
Fractional exhaled nitric oxide, ppb	27.3 (24.7) ‖‖	23.5 (17.2) ¶¶	29.7 (28.2) ****	0.08
AHR to inhaled methacholine (Dmin), units *	10.0 (0.04 – 50.0) ††††	21.6 (0.4 – 50.0) ‡‡‡‡	9.0 (0.04 – 50.0) §§§§	0.20
J-LCQ total scores, points	12.8 (3.6)	11.3 (3.4)	13.7 (3.4)	<0.001
FSSG total scores, points	8.3 (6.7)	11.6 (6.8)	6.3 (5.8)	<0.001
acid reflux symptoms, points	4.7 (4.0)	6.6 (4.3)	3.6 (3.4)	<0.001
dysmotility symptoms, points	3.6 (3.4)	5.0 (3.5)	2.7 (3.1)	<0.001

*Median (range): Data are analyzed after log transformation, GERD+: Patients with GERD-related cough, GERD-: Patients without GERD-related cough, †n = 137, ‡n = 53, §n = 84, ‖n = 87, ¶n = 30, **n = 57, ††n = 151, ‡‡n = 56, §§n = 95, ‖‖n = 162, ¶¶n = 62, ****n = 100, ††††n = 90, ‡‡‡‡n = 37, §§§§n = 53, CVA: cough variant asthma, FEV_1: Forced expiratory volume in one second, AHR: Airway hyperresponsiveness. AHR was considered positive if Dmin, the cumulative dose of inhaled methacholine at the inflection point at which baseline respiratory resistance began to increase, represented ≤12.5 units, J-LCQ: The Japanese version of the Leicester cough questionnaire, FSSG: The Frequency scale for the symptoms of GERD