

# Different gastroesophageal reflux symptoms of middle-aged to elderly asthma and chronic obstructive pulmonary disease (COPD) patients

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**Symptomatic differences and the impact of gastroesophageal reflux disease (GERD) have not been clarified in patients with asthma and chronic obstructive pulmonary disease (COPD). The purpose of this study is to assess the differences of GERD symptoms among asthma, COPD, and disease control patients, and determine the impact of GERD symptoms on exacerbation of asthma or COPD by using a new questionnaire for GERD. A total of 120 subjects underwent assessment with the frequency scale for the symptoms of GERD (FSSG) questionnaire, including 40 age-matched patients in each of the asthma, COPD, and disease control groups. Asthma and control patients had more regurgitation-related symptoms than COPD patients ( $p < 0.05$ ), while COPD patients had more dysmotility-related symptoms than asthma patients ( $p < 0.01$ ) or disease control patients ( $p < 0.01$ ). The most distinctive symptom of asthma patients with GERD was an unusual sensation in the throat, while bloated stomach was the chief symptom of COPD patients with GERD, and these symptoms were associated with disease exacerbations. The presence of GERD diagnosed by the total score of FSSG influences the exacerbation of COPD. GERD symptoms differed between asthma and COPD patients, and the presence of GERD diagnosed by the FSSG influences the exacerbation of COPD.**

**Key Words:** GERD, asthma, COPD, FSSG, dysmotility

Gastroesophageal reflux (GER) is a potential trigger for supra-esophageal manifestations of asthma and chronic obstructive pulmonary disease (COPD).<sup>(1,2)</sup> The prevalence of gastroesophageal reflux disease (GERD) in asthma patients was 42% to 69% according to the questionnaire for the diagnosis of reflux disease (QUEST).<sup>(3,4)</sup> In COPD patients, the prevalence was 37% according to the Mayo clinic GERD questionnaire.<sup>(5,6)</sup> GER is common in patients with pulmonary disease and is involved in the pathophysiology of exacerbation of asthma and COPD, but proton pump inhibitors (PPIs) show limited efficacy for improvement of pulmonary function and respiratory symptoms in asthma or COPD patients with GERD.<sup>(7-9)</sup> Failure of PPI therapy is observed in patients who are diagnosed as having GERD by endoscopy, pH testing and esophageal impedance.<sup>(10)</sup> Therefore, another mechanism that has attracted attention is gastric motor activity.<sup>(11)</sup> In contrast, QUEST covers more typical symptoms of acid regurgitation, the frequency scale for the symptoms of GERD (FSSG) is a recently developed questionnaire that covers 12 symptoms, including not only typical regurgitation symptoms such as “heartburn” but also dysmotility symptoms such as “heavy stomach”.<sup>(12)</sup> GERD also changes with age,<sup>(13)</sup> and there have been no reports about the prevalence and features of GERD symptoms in age-

matched asthma and COPD patients with GERD diagnosed by the FSSG.

The aims of this study were to compare the prevalence of GERD and the symptoms of GERD among asthma, COPD, and disease control patients. The impact of GERD (evaluated by the FSSG) on exacerbation of asthma and COPD was also examined.

## Subjects and Methods

**Subjects.** A total of 120 subjects underwent the FSSG, including 40 patients with asthma, 40 patients with COPD, and 40 disease control subjects without asthma or COPD. The characteristics of the subjects enrolled in this study are shown in Table 1. The diagnosis of asthma was established according to the Global Initiative for Asthma report (GINA),<sup>(14)</sup> as described previously,<sup>(4)</sup> while a diagnosis of COPD was established according to the Global Initiative for Chronic obstructive Lung disease report (GOLD).<sup>(15)</sup> The disease control patients had hypertension ( $n = 26$ ), hyperlipidemia ( $n = 11$ ), insomnia ( $n = 1$ ), prostatomegaly ( $n = 1$ ), and cervical spondylosis ( $n = 1$ ) without respiratory symptoms and without receiving respiratory medications. Patients were excluded if they had a history of esophageal, gastric, or duodenal surgery, were using acid-suppressing drugs of PPI, H<sub>2</sub> receptor antagonist or gastroprokinetic agents such as selective serotonin (5HT<sub>4</sub>) agonists, were mentally incompetent, or were being treated with an angiotensin-converting enzyme (ACE) inhibitor. Since COPD occurs rather older than young, less than 50 years old were excluded.

**Protocol.** This study is retrospective cohort-study. Pulmonary function tests [% vital capacity (% VC), forced vital capacity (FVC), and forced expiratory volume in 1 sec (FEV<sub>1.0</sub>)] were measured with a CHESTAC -55V (CHEST MI, Tokyo, Japan) at Gunma University and with a CHESTAC -5500 or -8800 (CHEST MI, Tokyo, Japan) at Jobu Hospital. Pulmonary function in disease control was not measured because this study is retrospective study and measuring pulmonary function was not approved by institute committee. Sputum was obtained after inhaling 3 ml of 3% saline via a nebulizer, and cells were counted. If a patient could not expectorate the sputum, 3 ml of 6% saline were nebulized repeatedly. Definition of adequate sputum was one in which there were fewer than 20% squamous cells and where viability was <50%.<sup>(16)</sup> The eosinophil count was determined by Hansel stain.<sup>(17)</sup> For calculation of the dose of inhaled steroid, fluticasone was assumed to be about twice the strength of

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**Table 1.** Characteristics of asthma, COPD, and disease control

	Asthma	COPD	Disease control
Age, year	65.5 ± 9.4	69.8 ± 10.2	65.0 ± 9.9
Sex (male/female)	19/21	38/2	22/18
Body mass index, kg/m <sup>2</sup>	23.1 ± 3.8	20.3 ± 2.6*.#	23.8 ± 4.0
Smoking, pack-years	7.1 ± 19.5	27.1 ± 17.0*.#	5.4 ± 8.3
Smoking, cur-, ex-, never-	5, 5, 30	17, 22, 1	8, 5, 27
Eosinophil of peripheral blood, %	3.8 ± 2.1	1.6 ± 0.3*	
Sputum, %			
neutrophil	55.2 ± 30.7	84.4 ± 12.1*	
eosiniphil	34.7 ± 32.8	8.3 ± 6.0*	
basophil	0.58 ± 1.3	0.7 ± 1.6	
macrophage	9.6 ± 11.1	6.7 ± 7.3	
Pulmonary function			
%VC, %	99.7 ± 22.0	88.7 ± 25.2	
FVC, L	2.9 ± 1.0	2.6 ± 1.1	
FEV 1.0, L	1.7 ± 0.8	1.4 ± 0.9	
FEV1.0/FVC % pred	78.5 ± 27.0	62.2 ± 22.9	
FEV1.0/FVC, %	65.9 ± 21.2	50.2 ± 13.9	
Medication			
Oral corticosteroids	20	2	
Oral theophyllines	13	15	
Oral expectrants	2	8	
Oral anti-histamines	2	0	
Leukotrienes	13	0	
Tulobuterol patches	9	11	
Inhaled steroids	13	6	
Inhaled β2 agonists	4	4	
Inhaled steroids/β2 agonists	17	12	
Inhaled anticholinergics	1	16	

\*Statistically significance between asthma patients and COPD patients. #Statistically significance between COPD patients and disease control patients.

**Table 2.** Questions of FSSG\*

Questions
q1 Do you get heartburn?
q2 Does your stomach get bloated?
q3 Does your stomach ever feel heavy after meals?
q4 Do you sometimes subconsciously rub your chest with your hand?
q5 Do you ever feel sick after meals?
q6 Do you get heartburn after meals?
q7 Do you have an unusual (e.g. burning) sensation in your throat?
q8 Do you feel full while eating meals?
q9 Do some things get stuck when you swallow?
q10 Do you get bitter liquid (acid) coming up into your throat?
q11 Do you burp a lot?
q12 Do you get heartburn if you bend over?

\*FSSG: The frequency of scale for the symptoms of GERD.

budesonide.<sup>(18)</sup> Exacerbation of asthma and COPD was defined as worsening that required an unscheduled visit to the local doctor, emergency department, or hospital, or else needed treatment with oral or intravenous corticosteroids at least one episode during the past two years.<sup>(6,19)</sup> The FSSG has been proven to be a useful questionnaire for the assessment of GERD, and it was used to determine the prevalence and symptoms of GERD.<sup>(12)</sup> This questionnaire is composed of 12 questions (Table 2), which are scored to indicate the frequency of symptoms as follows: never =

0, occasionally = 1, sometimes = 2, often = 3, and always = 4. The cut-off score for diagnosis of GERD was defined as 8 points. The unique feature of the FSSG is that the questions cover both acid regurgitation-related symptoms (questions 1, 4, 6, 7, 9, 10, and 12) and gastric dysmotility-related symptoms (questions 2, 3, 5, 8, and 11). This study was conducted according to the Declaration of Helsinki, and all patients gave informed consent before enrollment. The Human Research Committee of Gunma University and the Human Research Committee of Jobu Hospital for Respiratory Disease both approved this study.

**Statistics.** Data are expressed as the mean (SD). Comparison of parameters between two groups was done by Student's *t* test. Comparisons among three groups were done by one-way ANOVA with Bonferroni's multiple comparison test. Differences in frequency between regurgitation and dysmotility symptoms were assessed by the chi-square test. A *p* value of less than 0.05 was considered significant. Comparison of exacerbation number of patients between GERD positive and negative were performed by Fisher's exact test.

## Results

The characteristics of each group are shown in Table 1. Age did not differ among the asthma, COPD, and disease control patients. The body mass index (BMI) of the COPD group was lower than that of the other two groups (*p*<0.05). Regular treatments given for asthma patients were oral corticosteroids, inhaled steroids/long-acting β2 agonists, oral theophyllines, leukotrienes and inhaled steroids. Regular treatments given for COPD patients were

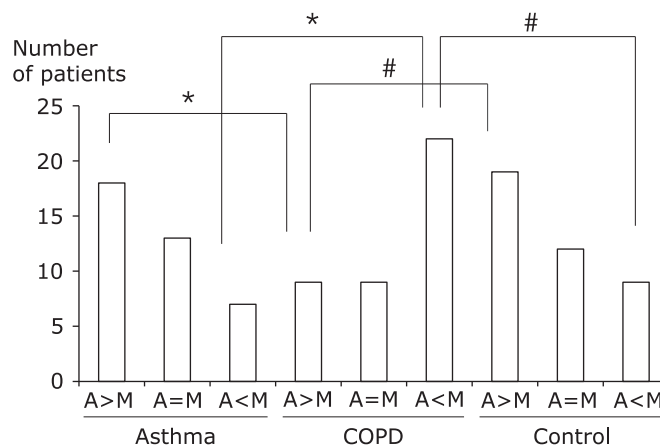
**Table 3.** Characteristics of asthma, COPD, and disease control having GERD

	Asthma	COPD	Disease control
Frequency of GERD, %, GERD pt/total pt	25.0, 10/40	32.5, 13/40	27.5, 11/40
Age, year	64.2 ± 9.8	72.2 ± 7.5*	64.3 ± 7.5
Sex (male/female)	2/8	13/0*	4/7
Body mass index, kg/m <sup>2</sup>	22.8 ± 4.4	20.7 ± 3.6	22.7 ± 2.6
Smoking, pack-years	10.0 ± 31.6	28.9 ± 16.5*	4.1 ± 8.3#
Smoking, cur-, ex-, never-	0, 0, 10	4, 9, 0	2, 2, 8
Eosinophil of peripheral blood, %	3.4 ± 1.1	0.3 ± 1.1*	
Sputum, %			
neutrophils	59.1 ± 32.4	92.5 ± 5.8*	
eosiniphils	33.1 ± 34.5	6.4 ± 5.5*	
metachromatic cells (basophils)	0.29 ± 0.76	0	
macrophages	7.1 ± 7.4	1.1 ± 0.85*	
Pulmonary functions			
%VC, %	93.2 ± 18.5	67.0 ± 17.1*	
FVC, L	2.1 ± 0.40	1.9 ± 0.66	
FEV 1.0, L	1.5 ± 0.4	0.93 ± 0.3*	
FEV 1.0% pred, %	81.9 ± 28.1	52.9 ± 16.1	
FEV 1.0/FVC, %	72.2 ± 22.3	50.8 ± 10.1	
Regular use of medication			
Oral corticosteroids	2	0	
Oral theophyllines	6	5	
Oral expectrants	2	2	
Oral anti-histamines	1	0	
Leukotrienes	4	0	
β2 agonist patches	8	3	
Inhaled steroids	2	6	
Inhaled β2 agonists	0	0	
Inhaled steroids/β2 agonists	6	1	
Inhaled anticholinergics	0	8	

\*Statistically significance between asthma patients and COPD patients. #Statistically significance between COPD patients and disease control patients.

inhaled anticholinergics, oral theophyllines, inhaled steroids/long acting β2 agonists, inhaled steroids and β2 agonist patches. The prevalence of GERD (detected by the FSSG) was not significantly different among the three groups of asthma patients (10/40, 25%), COPD patients (13/40, 32.5%) and disease control patients (11/40, 27.5%), as shown in Table 3. Among patients with GERD, the COPD patients were older than the asthma and disease control patients ( $p < 0.05$ ). BMI was not statistically different among the groups with GERD. Of the 13 GERD-positive COPD patients, some of the patients received inhaled steroid only or inhaled steroid and long acting β2 agonists patches without inhaled anticholinergics because of having glaucoma or dry mouth due to adverse event of anticholinergics.

The unique feature of the FSSG is that the questions are divided into those covering acid regurgitation-related symptoms (questions 1, 4, 6, 7, 9, 10, and 12) and those for gastric dysmotility-related symptoms (questions 2, 3, 5, 8, and 11). When regurgitation- and dysmotility-related symptoms were compared among each group, the number of patients showing predominance of regurgitation-related symptoms was higher in the asthma group ( $p < 0.005$ ) and the disease control group ( $p < 0.01$ ) than in the COPD group (Fig. 1). The number of patients showing predominance of dysmotility-related symptoms was higher in the COPD group than in the asthma group ( $p < 0.005$ ) and the disease control group ( $p < 0.01$ ). Among GERD-positive patients, the number of patients showing predominance of regurgitation-related symptoms was higher in the asthma group ( $p < 0.01$ ) and the disease control group

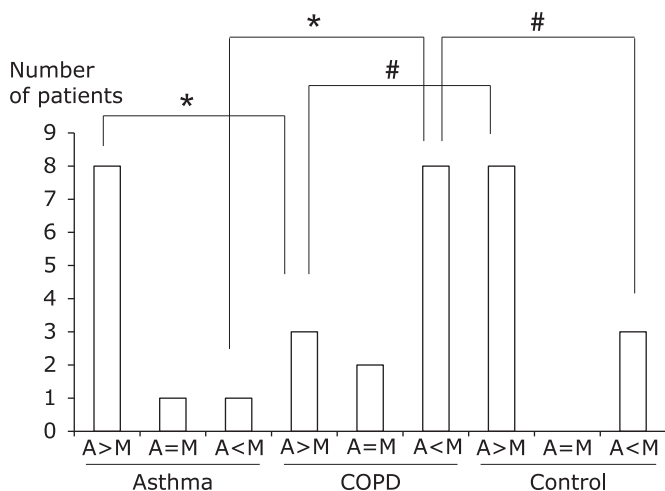


**Fig. 1.** Chief symptoms of asthma patients ( $n = 40$ ), COPD patients ( $n = 40$ ), and disease control patients ( $n = 40$ ). The total score for acid regurgitation-related symptoms (questions 1, 4, 6, 7, 9, 10, and 12) and the total score for dysmotility-related symptoms (questions 2, 3, 5, 8, and 11) were compared. The number of patients in each group with a higher score for acid regurgitation symptoms (A>M), the same score for both symptoms (A = M), or a higher score for dysmotility symptoms (A<M) was determined. \*Significant difference between asthma and COPD. #Significant difference between COPD and disease controls.

( $p < 0.01$ ) than in the COPD group, while the number with predominance of dysmotility-related symptoms was higher in the COPD group than in the asthma group ( $p < 0.01$ ) or the disease control group ( $p < 0.01$ ), as shown in Fig. 2. Presence GERD evaluated by FSSG was the risk of COPD exacerbation (OR = 4.8, 95% CI 1.25–18.5,  $p < 0.05$ ), however not in asthma (OR = 3.0,

95% CI 0.69–13.1) (Table 4).

When the scores for each question of patients with GERD were compared among the groups, the mean scores for question 7 (unusual sensation in the throat) was significantly higher in asthma patients and disease control patients with GERD ( $p < 0.01$ ) than in COPD patients with GERD. The mean score for question 2 (bloating stomach) was significantly higher in COPD patients than in disease control patients ( $p < 0.05$ ), but was not significantly different from asthma patients (Figs. 3 a–c). Each data expressed by mean (SD) was shown in Table 5. The score for question 2 was higher in COPD patients with GERD having a history of exacerbation of COPD during the past 2 years than in COPD patients with GERD without having a history of exacerbation ( $p < 0.01$ ) (Fig. 4a). Also, the score for question 7 was higher in asthma patients with GERD having a history of exacerbation during the past 2 years than in asthma patients with GERD without having a history of exacerbation ( $p < 0.01$ ) (Fig. 4b).



**Fig. 2.** Chief symptoms in asthma patients ( $n = 10$ ), COPD patients ( $n = 13$ ) and disease control patients ( $n = 11$ ) who were diagnosed as having GERD by the FSSG survey in each group. The total score for acid regurgitation-related symptoms (questions 1, 4, 6, 7, 9, 10, and 12) and the total score for dysmotility-related symptoms (questions 2, 3, 5, 8, and 11) were compared. The number of patients in each group with a higher score for acid regurgitation symptoms (A > M), the same score for both symptoms (A = M), or a higher score for dysmotility symptoms (A < M) was examined. \*Significant difference between asthma and COPD. #Significant difference between COPD and disease controls.

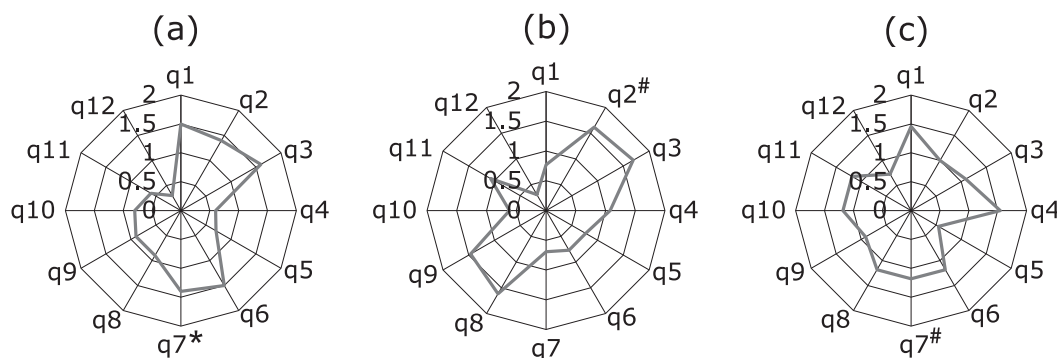
## Discussion

A previous survey using the FSSG revealed that the prevalence of GER was 27.4% among asthma patients,<sup>(20)</sup> and that its prevalence was higher among COPD patients (26.8%) than among age-matched healthy controls (12.5%).<sup>(21)</sup> The prevalence of GERD detected in the present study was similar to that in other studies using the FSSG, but the prevalence of GERD in the control group was higher in the present study (32.5% vs 27.5%) compared with a previous study.<sup>(21)</sup> A previous FSSG survey of metabolic syndrome patients, revealed that hypertension or hyperlipidemia were independent risk factors for GERD and metabolic syndrome patients showed high score of FSSG.<sup>(22)</sup> A possible reason for the different prevalences in the control groups was different background factors, i.e., healthy versus diseased subjects including those with hypertension and hyperlipidemia, and also this was the one of the reason that no statistical difference in prevalence among asthma, COPD and control groups in present study.

**Table 4.** Associations between exacerbations and presence of GERD symptoms in asthma and COPD patients

	Exacerbation (+)	Exacerbation (-)	$p$ value	OR	95% CI
Asthma GERD (+)	6	4			
Asthma GERD (-)	10	20	0.16	3	0.69–13.1
COPD GERD (+)	8	5			
COPD GERD (-)	9	27	0.038*	4.8	1.25–18.5

The number of patients having a history of disease exacerbations (+) or not having a history of exacerbation (-) were compared in presence of GERD (+) symptoms or without presence of GERD (-) symptoms. \*Statistically significance between GERD (+) and GERD (-) patients in COPD. Data are presented as odds ratios (ORs) and % 95% confidence interval (CI).

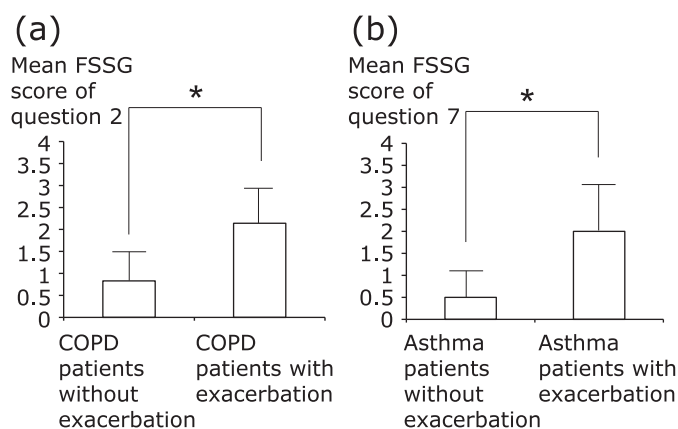


**Fig. 3.** Mean score for each FSSG question in asthma (a), COPD (b), and disease control (c) patients with GERD. Asthma patients ( $n = 10$ ), COPD patients ( $n = 13$ ), and disease control patients were diagnosed as having GERD by the FSSG survey in each group. Vertical bars from 0 to 2 show the mean score for each question. \*Significant difference between asthma and COPD. #Significant difference between COPD and disease controls.

**Table 5.** Scores for questions of FSSG on patients with GERD

FSSG question number	Asthma with GERD	COPD with GERD	Control
q1	1.0 (1.1)	0.8 (1.1)	1.4 (1.3)
q2	1.5 (0.8)	1.6 (1.0) <sup>#</sup>	1.0 (1.3)
q3	1.3 (1.4)	1.7 (1.0)	1.1 (1.2)
q4	0.8 (0.8)	1.1 (0.8)	1.6 (1.2)
q5	0.5 (0.5)	0.8 (0.2)	0.6 (1.0)
q6	1.3 (1.5)	0.7 (1.0)	1.2 (1.3)
q7	1.5 (1.4) <sup>*</sup>	0.5 (1.1)	1.5 (1.5) <sup>#</sup>
q8	0.5 (0.8)	1.5 (1.1)	1.5 (1.4)
q9	0.7 (0.8)	1.3 (0.8)	0.9 (1.2)
q10	0.7 (0.8)	0.5 (0.7)	1.2 (1.4)
q11	0.5 (0.5)	1.1 (0.9)	1.1 (1.4)
q12	0.2 (0.4)	0.2 (0.4)	1.2 (0.4)

FSSG was composed by 12 questions (q1 to q12), and each score was indicated mean (SD) in asthma with GERD ( $n = 10$ ), COPD with GERD ( $n = 13$ ) and disease control with GERD ( $n = 11$ ). Statistically significance between asthma and COPD is indicated  $*p < 0.05$ . Statistically significance between COPD and disease control is indicated  $\#p < 0.05$ .



**Fig. 4.** The mean scores for questions 2 and question 7 in COPD or asthma patients with GERD having a history of disease exacerbation vs patients without having a history of exacerbation. The scores of COPD patients with GERD for question 2 (bloated stomach) (a). Scores are compared between COPD patients with GERD having a history vs without having a history of exacerbation. Scores of asthma patients with GERD for question 7 (unusual sensation of the throat) (b). Scores are compared between asthma patients with GERD having a history vs without having a history of exacerbation. \*Significant difference between groups.

Dysmotility-related symptoms were prominent in the COPD patients. A survey using the Rome II criteria for irritable bowel syndrome showed that 14% of COPD patients fulfilled these criteria.<sup>(23)</sup> A physiological study using manometry showed a 35% decrease of peristalsis in COPD patients.<sup>(24)</sup> To our knowledge, there has only been this study about esophageal motility, and there have been no studies of intestinal peristalsis in COPD patients. A decrease of lower esophageal sphincter pressure is related to the mechanism of GER in both asthma and COPD patients,<sup>(25-27)</sup> while dysmotility from the esophagus to intestines seemed to contribute to GER symptoms in COPD. Dysmotility symptoms are frequently induced by rather functional dyspepsia (FD) than GERD. Rome III consensus for diagnosis of FD needs the absence of organic disorder, such as esophagitis, gastric atrophy or erosive gastroduodenal lesions on endoscopy.<sup>(28)</sup> Present study was questionnaire based survey, and did not include the endoscopic examination. Therefore it was difficult to discriminate between GERD and FD patients. The FSSG contains questions about dysmotility

symptoms, in addition to acid-reflux-related symptoms, allowing it to detect GERD symptoms widely. However, the FSSG was inferior to QUEST for the diagnosis of reflux esophagitis in distinguishing between GERD and other condition, such as FD, gastric ulcer (GU) and duodenal ulcer (DU).<sup>(29)</sup> Further analysis is needed to proportion of FD in COPD patients.

In asthma patients, the typical symptom detected by the FSSG was an unusual sensation in the throat. Bloated stomach also showed a high score, but it was not statistically different from the other items. There is an increase of tonsillitis, pharyngitis, and laryngitis among respiratory tract diseases in patients with GERD, and GERD is also considered to play a role in 55% of hoarseness.<sup>(2,30)</sup> Possible mechanisms leading to an unusual sensation in the throat are direct acid reflux or acidic gas reflux.<sup>(31)</sup> Another mechanism is stimulation of esophageal or laryngeal sensory nerves by gastric acid, because some sensory nerves from these sites terminate in the same region of the central nervous system.<sup>(32)</sup> The limitation of this result is that factors of patients in this study might affect the unusual sensation in throat. Medications such as  $\beta_2$  agonists and oral theophyllines might aggravate GERD, and use of inhaled steroids might have been a cause of "unusual sensation in throat".<sup>(33)</sup> Eosinophil ratio was actually high in asthma patients, and several patients received oral corticosteroids which indicated those patients were severe asthma, and this might affect on unusual sensation in the throat in asthma patients.

In COPD patients, the typical symptom detected by the FSSG was bloated stomach. As mentioned above, dysmotility of the esophagus has been speculated to have an association with COPD,<sup>(23)</sup> but there has not been enough investigation. It is known that the severity of atrophic gastritis increases with a longer duration of COPD, as well as with the severity of hypoxia and bronchial obstruction.<sup>(34)</sup> Ventilation affects both gastric mucosal blood flow and gastric mucosal pH.<sup>(35)</sup> Thus, COPD can influence the mucosa and blood flow of the stomach, and changes of the mucosal integrity or blood flow may have an effect on GER.

Recently published longitudinal study showed that a history of gastroesophageal reflux or heartburn is associated with frequent-exacerbation phenotype in COPD patients.<sup>(36)</sup> Patients who had GER symptoms of reflux or heartburn had significantly more hospitalizations related to their COPD.<sup>(6)</sup> In present study, COPD patients had more dysmotility symptoms than reflux or heartburn symptoms, and presence of GERD evaluated by total score of FSSG was the risk of COPD exacerbations. Therefore, dysmotility to esophagus to intestine possibly affects COPD exacerbation. In asthma patients, presence of GERD evaluated by total score of FSSG did not affect the asthma exacerbations. Asthma patients

had more reflux symptoms than dysmotility symptoms, and FSSG total score was inferior to QUEST for the detection of reflux symptoms.<sup>(29)</sup> This might affect the negative result for the detecting an increased risk of asthma exacerbation by FSSG. The scores for questions 2 and 7 were higher in GERD patients with a history of exacerbation of asthma or COPD than in GERD patients without a history of exacerbation. These questions were useful for detecting an increased risk of exacerbation. Previous reviews have indicated an association of GERD with the risk of exacerbation of asthma and COPD, but the potential effect of anti-reflux therapy, (PPIs, etc.) on this relationship has not been determined.<sup>(7,37)</sup> Multi-drug therapy may be important in asthma and COPD patients with GERD. In conclusion, dysmotility-related symptoms were common in COPD patients, and useful questions from the FSSG were an “unusual sensation in the throat” for asthma patients or “bloated stomach” for COPD patients. GERD is considered to be a risk factor for the exacerbation of COPD, but the efficacy of PPI therapy is limited. The efficacy of PPIs may differ between regurgitation-related symptoms and dysmotility-related symptoms in asthma patients and COPD patients with GERD.

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## Conflict of Interests

The authors declare that they have no competing interests.

## Author's Contributions

Shimizu Y. MD., PhD and head of internal medicine of Jobu Hospital for Respiratory Disease designed the study, collected the data, analysed the data, and wrote the manuscript. Dobashi K. MD., PhD and Prof. designed the study and collected the data, Kusano M. MD., PhD and Associate Prof. gave useful suggestions for FSSG and GERD, and Mori M. MD., PhD and Prof. gave useful suggestions for the design of this study.

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