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Original Article

Reflux-related symptoms reflect poor asthma control and the presence of airway neuronal dysfunction

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Abbreviations:

ACT, asthma control questionnaire; CVA, cough-variant asthma; FeNO, fraction of exhaled nitric oxide; FSSG, frequency scale for the symptoms of GERD; GERD, gastroesophageal reflux disease; HARQ, Hull airway reflux questionnaire; ICSs, inhaled corticosteroids; J-LCQ, the Japanese version of the Leicester cough questionnaire; LABAs, long-acting beta agonists; LPR, laryngopharyngeal reflux; QoL, quality of life; VAS, visual analogue scale

ABSTRACT

Background: Gastroesophageal reflux may be associated with the worsening of asthma by increasing cough reflex sensitivity. Hull Airway Reflux Questionnaire (HARQ) consists of 14 prevalent reflux-related symptoms. It may be useful in predicting the presence of cough reflex hypersensitivity in asthma.

Methods: From August 2018 to July 2020, 266 asthmatic patients completed the HARQ. They underwent blood analysis, spirometry, fraction of exhaled nitric oxide (FeNO) measurement, and the capsaicin cough challenge test. Patients were considered to have reflux-related symptoms if their HARQ scores were 13 points or higher. We evaluated the association between reflux-related symptoms and clinical asthma outcomes. Finally, we performed a multivariate analysis to determine the clinical significance of the HARQ for asthma. This study was registered in the University Hospital Medical Information Network (UMIN000040732).

Results: The mean HARQ scores were 13.1 (standard deviation 12.0). Patients in the high HARQ scores group (HARQ ≥ 13 , $n = 105$) showed a lower prevalence of atopic predisposition, lower levels of FeNO, heightened capsaicin cough reflex sensitivity, poorer asthma control, and more frequent admissions due to asthma than those in the low HARQ groups (all p values < 0.05). The HARQ was useful in selecting patients with poor controlled asthma and those with severe cough when the cut-off value was set at 13. Multivariate analysis revealed that heightened capsaicin cough reflex sensitivity affected reflux-related symptoms, as well as lower levels of FeNO and younger age.

Conclusions: Higher HARQ scores (≥ 13) may be useful in predicting not only poor asthma condition but also the presence of airway neuronal dysfunction in patients with asthma to some extent.

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Introduction

Asthma is often categorized into various phenotypes based on clinical information, such as the presence of atopic predisposition and eosinophilia¹ and age of onset and sex.² Recently, the

importance of airway neuronal dysfunction in the pathophysiology of asthma has been reported.^{3–5} Cough reflex hypersensitivity, often assessed using inhaled capsaicin, is considered an important component of the pathophysiology of severe asthma,⁶ particularly in non-atopic female patients.⁵ However, the capsaicin cough challenge test has only been performed for research purposes. Thus, we need to establish succinct tools that can easily evaluate heightened capsaicin cough reflex sensitivity in real-world clinical practice.

Laryngopharyngeal reflux (LPR) is a well-recognized extra-esophageal variant of gastroesophageal reflux disease (GERD).⁷ It is considered to cause respiratory symptoms such as chronic cough,

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hoarseness, vocal fatigue, excessive throat clearing, globus pharyngeus, postnasal drip, and dysphagia by mediating transient receptor potential channels on airway nerves.^{7,8} LPR differs from classical gastroesophageal reflux because most patients with reflux-related cough and LPR do not present with typical GERD symptoms such as heartburn and regurgitation.^{7,9} The latest European Respiratory Society guidelines on the management of chronic cough have clearly stated that reflux is a common feature of cough reflex hypersensitivity, along with esophageal dysmotility.¹⁰ The Hull Airway Reflux Questionnaire (HARQ), which consists of 14 prevalent gastroesophageal and extra-gastroesophageal reflux symptoms, is a validated questionnaire to aid the diagnosis of refractory chronic cough.⁹ Higher HARQ scores (≥ 13) could discriminate patients with refractory chronic cough from healthy subjects,⁹ suggesting that reflux may contribute to the worsening of chronic respiratory diseases. Indeed, the HARQ scores reflect cough frequency and impaired cough-specific quality of life (QoL) in other chronic respiratory diseases such as cystic fibrosis¹¹ and bronchiectasis.¹² Previous studies have revealed that reflux may decrease cough threshold and increase cough reflex sensitivity.^{13,14} Thus, we considered that increased cough reflex sensitivity caused by reflux is associated with the worsening of asthma. The HARQ may be useful in predicting the presence of cough reflex hypersensitivity in asthma.

This historical cohort study aimed to clarify the clinical significance of the HARQ in asthma. We hypothesized that higher HARQ scores indicate worse clinical outcomes and the presence of heightened capsaicin cough reflex sensitivity in asthma. We also validated the Japanese version of the HARQ.

Methods

Subjects

A total of consecutive 330 patients with asthma (including 80 cough-variant asthma [CVA] patients) who had received anti-asthma treatments, including inhaled corticosteroids (ICSs) at our asthma and chronic cough clinic, completed the HARQ from August 2018 to July 2020. Among these, we excluded 64 patients from the analysis because (1) 58 patients with current or former smoking history of more than 10 pack-years or those who quit smoking within 6 months prior to the evaluation, (2) five had abnormal chest radiograph findings that may affect asthma control, and (3) one female aged younger than 20 years. Thus, we retrospectively analyzed the remaining 266 patients (including 73 patients with CVA) to clarify the role of airway reflux on the clinical outcomes and pathophysiology of asthma. The diagnosis of asthma and CVA was made according to the American Thoracic Society criteria¹⁵ and the Japanese Respiratory Society Cough Guideline of Management for Chronic Cough issued in 2012 (unpublished in English). In brief, all patients had already been diagnosed with asthma based on asthma-related symptoms such as cough, dyspnea, chest tightness, and/or wheezing with the presence of clinical reversible airway obstruction or airway hyperresponsiveness to inhaled methacholine. Diagnosis was confirmed if asthma-related symptoms were relieved by commencing ICSs with or without inhaled β_2 agonists.⁵ 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, (3) symptomatic improvement of cough with the use of short-acting β_2 agonists, and (4) no past history of asthma.

This study was approved by the ethical board of the Nagoya City University Hospital (approval number: 60-20-0037) and registered in the University Hospital Medical Information Network (UMIN000040732). Written informed consent was exempted by

the ethical board due to a retrospective nature of this study. Instead, we posted an opt-out document regarding this study on the hospital website to offer patients the opportunity to deny the participation of this study.

Measurements

We evaluated patient characteristics such as age, sex, body mass index, smoking history, use of proton pump inhibitors or potassium-competitive acid blocker, and ICS dose. Patients underwent spirometry and measurements of fraction of exhaled nitric oxide (FeNO) and blood biomarkers, such as absolute eosinophil and neutrophil counts, when completing the HARQ. Among 266 patients, 21 underwent either FeNO measurement or blood analysis at the time of answering the HARQ ($n = 19$ for FeNO measurement only and $n = 2$ for blood analysis only). We also performed a capsaicin cough challenge test in 156 patients. The concentrations of capsaicin required to induce at least two (C2) and five coughs (C5) were recorded.¹⁶ C5 is generally used as an index of cough reflex sensitivity,^{17,18} we previously demonstrated the association between lower threshold of C2 and poorer response to ICS for the daytime asthmatic cough.¹⁹ Thus, lower values of both C2 and C5 indicate a heightened capsaicin cough reflex sensitivity. Detailed method of capsaicin cough challenge test is available in the [Supplementary files](#). Of these 156 patients, 149 underwent both FeNO measurement and blood analysis. The levels of serum IgE and specific IgE titers against eight aeroallergens [house dust mite, cat, dog dander, Japanese cedar pollen, mixed Gramineae pollens (orchard grass, sweet vernal grass, Bermuda grass, Timothy grass, and reeds), mixed molds (Penicillium, Cladosporium, Aspergillus, Candida, Alternaria), *Trichophyton rubrum*, and mixed weed pollen (ragweed, mugwort, goldenrod, dandelion, and oxeye daisy)] (ImmunoCAP® total IgE and ImmunoCAP® specific IgE, Phadia K.K., Tokyo, Japan) were used at the first visit to our hospital to determine atopic predisposition. Patients were considered non-atopic when all eight specific IgE antibodies were negative (<0.35 UA/mL).⁵

All patients completed the HARQ. The HARQ consists of 14 items to evaluate reflux-related symptoms, each rated between 0 and 5, where 0 = no problem and 5 = frequent/severe problem ([Supplementary Table 1](#)). If the HARQ score was 13 or more, patients were considered to have reflux-related symptoms positive.⁹

In addition to the HARQ, all patients also completed the Asthma Control Test (ACT), the Japanese version of the Leicester Cough Questionnaire (J-LCQ), and the Frequency Scale for the Symptoms of GERD (FSSG) were completed. Optimal cut-off values of ACT and FSSG were determined to be ≥ 20 (well control)²⁰ and ≥ 8 (the presence of erosive GERD),²¹ respectively. Cough severity visual analogue scale (VAS) were completed in 197 patients. If the cough severity VAS represents ≥ 40 mm or longer,²² patients are regarded as having severe cough in asthma. All measurements, except for HARQ, are described in the [Supplementary files](#).

Clinical features of uncontrolled asthma

Uncontrolled asthma was defined if patients met one or more of the criteria of the European Respiratory Society and American Thoracic Society severe asthma guidelines as follows: 1) poor symptom control: ACT < 20 ; 2) frequent exacerbations: ≥ 2 /year bursts of systemic corticosteroids (3 days each); 3) serious exacerbation (admissions): ≥ 1 /year; and 4) airflow limitation: Forced expiratory volume in 1 s $< 80\%$ predicted following withholding of both short-acting beta agonists and long-acting beta agonists (LABAs).²³ We counted the number of asthma exacerbations requiring oral and/or intravenous corticosteroids (≥ 3 days and ≥ 1

day, respectively) and hospitalization due to asthma attacks. In addition, post bronchodilator Forced expiratory volume in 1 s was applied in this study because we could not ask patients to withhold ICSs/LABAs combination in order to maintain ICSs adherence prior to spirometry.

Statistical analysis

Statistical analyses were performed using JMP version 11 (SAS Institute Japan, Tokyo, Japan). Values are expressed as mean (standard deviation) or median (25th percentile, 75th percentile) for continuous variables and n (%) for categorical variables. Base 10 log-transformation was performed to analyze all non-normally distributed data except for capsaicin cough reflex sensitivity. Base 2 logarithmic translation was applied when analyzing the capsaicin cough reflex sensitivity because the values of C2 and C5 were expressed as doubling concentrations of capsaicin. We divided patients into reflux-positive (R+ group, HARQ ≥ 13) and negative (R- group, HARQ < 13) to compare clinical variables between the two groups using unpaired t, chi-square, and Fisher's exact tests, as appropriate. We adopted the Pearson product-moment correlation coefficient test to analyze the correlation between HARQ scores and biomarkers. We also performed a receiver operating characteristic curve analysis to evaluate the optimal cut-off value of the HARQ in the Japanese population. Multivariate logistic regression analysis was performed in 149 patients who underwent the capsaicin challenge test, FeNO measurement, and blood analysis to determine the clinical significance of the HARQ in asthma. Variables with $p < 0.10$, on the comparison between the two groups were included in the multivariate analysis. The results are presented as estimates with 95% confidence intervals and standardized beta values. Statistical significance was set at $p < 0.05$, when α error was set to 5%.

We also quantified the reliability of the Japanese version of the HARQ using Cronbach's alpha coefficient. The value ranges from 0 to 1, and represents the degree of internal consistency within an instrument. The reliability of the Japanese version of the HARQ was acceptable if the Cronbach's α coefficient was 0.7 or greater.²⁴

Results

Characteristics of the study population

Patient characteristics are presented in Table 1. According to the HARQ score (≥ 13 points), 105 patients were considered to have reflux-related symptoms positive. The R+ group was younger than the R- group. CVA and non-atopic patients were more prevalent in the R+ group than in the R- group. The R+ group had poorer asthma control, worse gastroesophageal reflux-related symptoms, and more impaired cough-specific QoL than the R- group. These results were in accordance with the higher daily ICS dose and proportion of proton pump inhibitors used in the R+ group.

When patients were stratified according to daily dose of ICS, patients in the high dose of ICS ($\geq 1000 \mu\text{g}$ a daily) had higher HARQ scores than counterpart group (Supplementary Table 2). Similar result was obtained when stratified according to asthma severity defined by GINA 2020 guidelines (Supplementary Table 3).

The association of reflux-related symptoms with clinical asthma outcomes and biomarkers

We also evaluated the prevalence of reflux-related symptoms in patients with uncontrolled and well-controlled asthma. Reflux-related symptoms were more prevalent in patients with uncontrolled asthma, as determined by the European Respiratory Society and American Thoracic Society severe asthma guidelines than in those with well-controlled asthma (Fig. 1A), particularly in those with poor asthma control (ACT < 20) and those requiring admission due to asthma (Fig. 1B and D). Similar results were observed even if CVA were excluded ($n = 193$, data not shown). When biomarkers were compared between the two groups (Table 2), the levels of FeNO were significantly lower in the R+ group than in the R- group. Conversely, capsaicin cough reflex sensitivity was more heightened in the R+ group than in the R- group. The concentrations of C2 and C5 showed weak but significant correlations with the HARQ scores (Fig. 2, $r = -0.28$, $p = 0.003$ for C2, $r = -0.27$, and $p = 0.006$ for C5, respectively). Collectively, reflux-related

Table 1

Patient's characteristics and comparison between the reflux-related symptoms positive (R+) and negative (R-) groups.

	All patients (n = 266)	Reflux positive (n = 105, 39.5%)	Reflux negative (n = 161, 60.5%)	p value
Age, years	55.1 (15.6)	50.8 (15.8)	57.9 (14.8)	0.0003
Age above 60 years old, presence (%)	110 (41)	28 (27)	82 (51)	<0.0001
Sex, females (%)	186 (70)	80 (76)	106 (66)	0.07
Smoking history, never (%)	232 (87)	91 (87)	141 (88)	0.82
Pack-years	0.4 (1.4)	0.4 (1.3)	0.4 (1.5)	0.78
Body mass index, kg/m ²	23.5 (4.4)	23.9 (5.1)	23.2 (3.8)	0.22
Body mass index 25 or more, presence (%)	82 (31)	34 (32)	48 (30)	0.66
Non-atopic, n (%)	91 (34)	44 (42)	47 (29)	0.03
Cough variant asthma, n (%)	73 (27)	36 (34)	37 (23)	0.04
Step 4/5 of asthma treatment, n (%)	187 (70)	86 (82)	101 (63)	0.0008
Dose of ICS, low/medium/high	49/146/71	7/55/43	42/91/28	<0.0001
ICSs equivalent to 1000 μg /day or more of fluticasone, n (%)	71 (26)	43 (41)	28 (17)	<0.0001
Use of PPIs or P-CAB when filling in HARQ, n (%)	73 (27)	46 (44)	27 (17)	<0.0001
HARQ, points	13.1 (12.0)	25.0 (10.5)	5.4 (4.0)	<0.0001
Leicester cough questionnaire, points	16.8 (3.8)	13.5 (3.7)	18.9 (2.3)	<0.0001
Asthma control test, points	20.2 (4.9)	16.7 (5.2)	22.6 (2.9)	<0.0001
Cough VAS, mm	21.7 (24.9) [†]	36.0 (28.4) [‡]	11.2 (14.8) [§]	<0.0001
Cough VAS over 40 mm, n (%)	41 (21) [†]	35 (42) [‡]	6 (5) [§]	<0.0001
Frequency scale for the symptoms of GERD total, points	7.9 (8.2)	13.2 (9.4)	4.4 (4.9)	<0.0001
Acid reflux-related symptoms, points	4.0 (4.3)	6.8 (4.8)	2.2 (2.6)	<0.0001
Functional dyspepsia symptoms, points	3.9 (4.5)	6.4 (5.4)	2.2 (2.9)	<0.0001

Mean (standard deviation), HARQ: Hull airway reflux questionnaire, reflux positive: patients with HARQ score higher than 13, reflux negative: patients with HARQ score of 13 or less, non-atopic: patients without all eight specific IgE antibodies (house dust mite, cat, dog dander, Japanese cedar pollen, mixed Gramineae pollens, mixed molds, *Trichophyton rubrum*, and mixed weed pollen), step 4/5: patients who receive treatment step 4 or 5 according to the GINA 2020 guideline. ICSs, inhaled corticosteroids; PPIs, proton pump inhibitors; P-CAB, potassium-competitive acid blocker; VAS, visual analogue scale; GERD, gastroesophageal reflux disease.

[†]n = 197, [‡]n = 84, [§]n = 113.

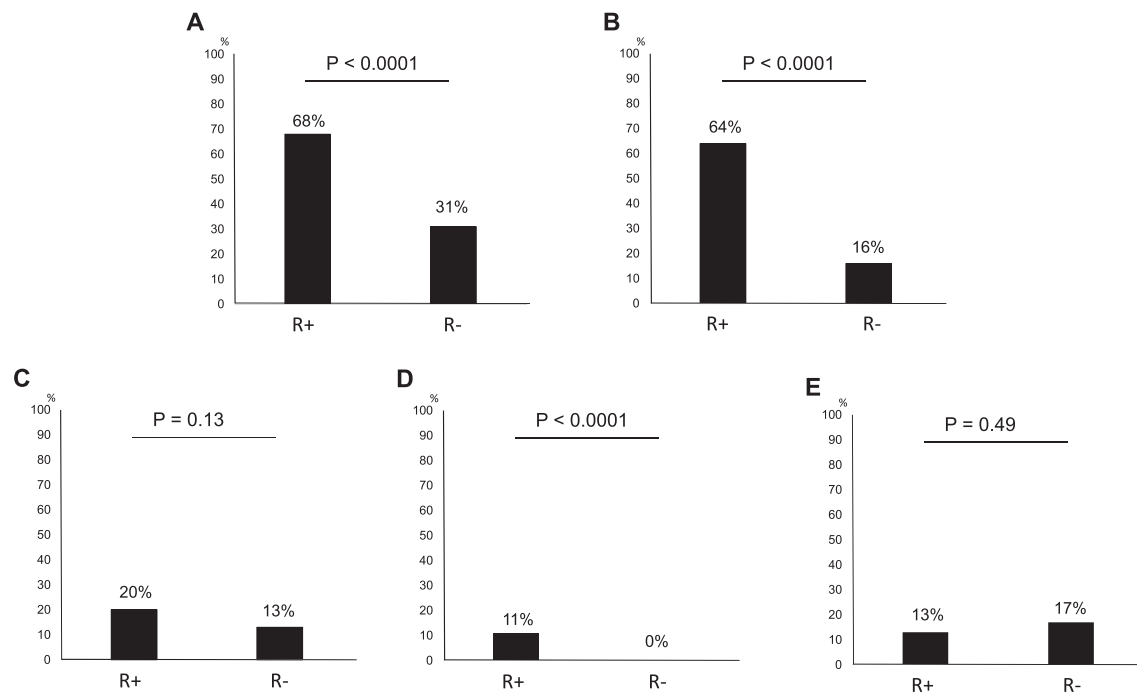


Fig. 1. Comparison of percentages of patients with each characteristic of uncontrolled asthma between reflux-related symptoms positive (R+) and negative (R-) groups. (A) uncontrolled asthma (one or more of the criteria of severe asthma), (B) poor control (asthma control questionnaire < 20), (C) frequent exacerbations (≥ 2 /year) (D) admissions (≥ 1 /year), (E) airflow limitation (forced expiratory volume in 1 s <80% predicted).

symptoms are important symptoms in patients with uncontrolled asthma. These may be refractory to ICS/LABA.

Similar analysis was performed when stratified according to the FSSG scores. When we divided patients into GERD-positive (G+ group, FSSG ≥ 8) and negative (G-group, FSSG < 8)^{21,25} most of results analyzed using the FSSG questionnaire were comparable to those using the HARQ (Supplementary Table 4, 5 and Supplementary Fig. 1). Meanwhile, we did not show the difference of capsaicin cough reflex sensitivity between the two groups when analyzed using the FSSG questionnaire (Supplementary Table 5).

The evaluation of the reliability of the Japanese version of the HARQ

We assessed the reliability of the Japanese version of the HARQ using Cronbach's alpha coefficient (Supplementary Table 6). The Cronbach's alpha coefficient for the total HARQ scores examined for all 266 patients was 0.87, and that for each item ranged from 0.85 to 0.88. This indicated good internal consistency for the Japanese version of the HARQ (Supplementary Table 1). The HARQ scores were significantly correlated with ACT, J-LCQ, cough severity VAS and FSSG scores ($r = -0.65$, $p < 0.0001$ for ACT, $r = -0.77$,

$p < 0.0001$ for J-LCQ, $r = 0.54$ for cough severity VAS, and $r = 0.62$, $p < 0.0001$ for FSSG, respectively) (Fig. 3). We found that a HARQ score of 13 was the optimal value for selecting patients with poorly controlled asthma (ACT < 20), those with severe cough (cough severity VAS ≥ 40), and those with GERD symptoms (FSSG ≥ 8) when performing the receiver operating characteristic curve analysis (area under curve, sensitivity and specificity: 0.82, 77%, and 76% for ACT, 0.82, 85% and 66% for cough severity VAS, and 0.83, 80% and 77% for the FSSG, respectively). Thus, higher HARQ scores (≥ 13) reflect poorer asthma control, more impaired cough-related QoL, and worse GERD symptoms in the Japanese population.

The clinical meaning of the HARQ in asthma

We performed multivariate logistic regression analysis to identify the clinical significance of the HARQ for asthma (Table 3). We found that heightened capsaicin cough reflex sensitivity significantly affected the higher HARQ scores (≥ 13), as well as lower levels of FeNO and younger age. Thus, higher HARQ scores indicate the presence of heightened capsaicin cough reflex sensitivity in asthma to some extent.

Table 2

Comparison of biomarkers and lung function between the reflux-related symptoms positive (R+) and negative (R-) groups.

	All patients (n = 266)	Reflux positive (n = 105, 39.5%)	Reflux negative (n = 161, 60.5%)	p value
Absolute neutrophil count, μl^*	3434 (2484, 4291) [†]	3529 (2593, 4637) [‡]	3336 (2372, 4114) [§]	0.08
Absolute eosinophil count, μl^*	138 (70, 258) [†]	127 (66, 219) [‡]	141 (71, 277) [§]	0.59
Serum IgE at the first visit, IU/ml*	103 (31, 304)	64 (23, 222) [¶]	140 (46, 455) ^{††}	0.001
FEV ₁ , %predicted	97.0 (19.4)	98.1 (19.3)	96.5 (19.5)	0.62
Fraction of exhaled nitric oxide, ppb*	22.2 (15.1, 34.1) ^{‡‡}	20.0 (14.0, 26.6) ^{§§}	25.8 (16.1, 40.2)	0.0006
Capsaicin cough reflex sensitivity				
C2, μM^*	4.88 (2.44, 19.5)	2.44 (1.22, 19.5) ^{¶¶}	9.76 (2.44, 39.0) ^{†††}	0.0005
C5, μM^*	9.76 (2.44, 39.0)	9.76 (1.22, 19.5) ^{¶¶}	19.5 (4.88, 78.1) ^{†††}	0.002

Mean (standard deviation), *median (25 percentile, 75 percentile), HARQ: Hull airway reflux questionnaire, reflux positive: patients with HARQ score of higher than 13, reflux negative: patients with HARQ score of 13 or less. IgE, Immunoglobulin E; FEV₁, forced expiratory volume in 1 s.

[†]n = 247, [‡]n = 100, [§]n = 147, ^{||}n = 249, [¶]n = 96, ^{††}n = 153, ^{‡‡}n = 264, ^{§§}n = 103, ^{||||}n = 156, ^{¶¶}n = 58, ^{†††}n = 98.

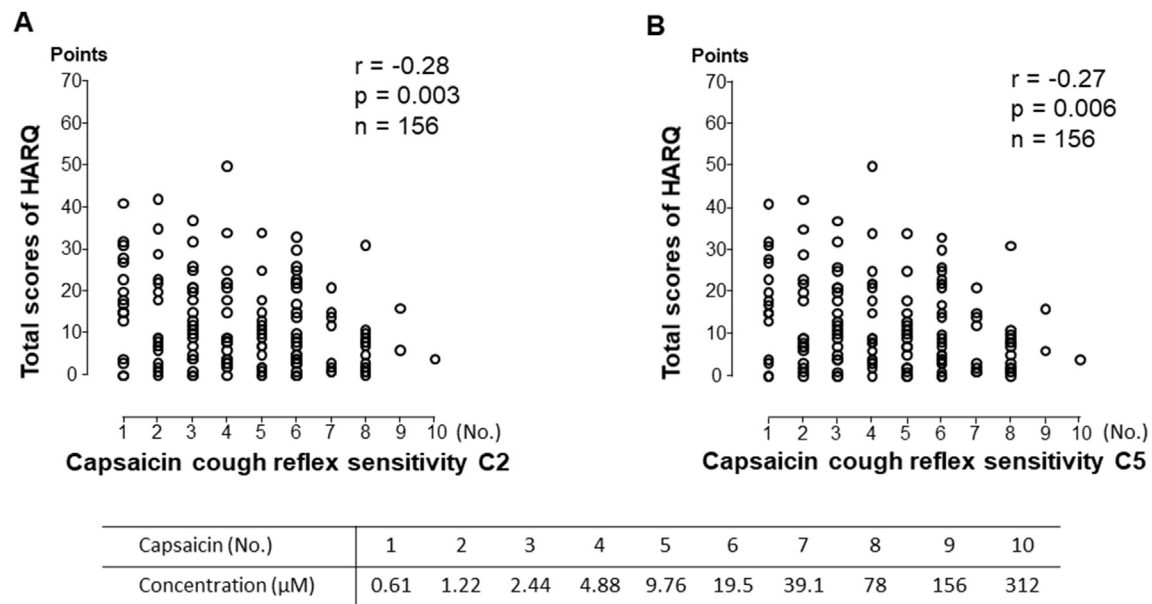


Fig. 2. Correlation of Hull airway reflux questionnaire with factors capsaicin cough reflex sensitivity. (A) Capsaicin cough reflex sensitivity C2, (B) Capsaicin cough reflex sensitivity C5. They are represented as doubling dose concentrations of capsaicin where range from 1 (0.61 μM) to 10 (312 μM).

Discussion

To the best of our knowledge, this study demonstrates for the first time that reflux-related symptoms assessed by the HARQ are important symptoms in patients with uncontrolled asthma. Furthermore, higher HARQ scores (≥ 13) indicated poor asthma condition including severe cough and the presence of heightened capsaicin cough reflex sensitivity in patients with asthma. In other words, reflux-related symptoms are a sign of the presence of airway neuronal dysfunction in asthma. Lower levels of FeNO are also associated with higher HARQ scores, suggesting that reflux-related symptoms may be refractory to ICS/LABA. In addition, we confirmed the validity of the Japanese version of the HARQ in the present study.

There are several reports regarding the association of reflux-related symptoms assessed by the HARQ, mainly composed of LPR-related symptoms, with the pathophysiology of chronic respiratory diseases. LPR is caused by the reflux of gastric components into the airway, but has a different manifestation from that of GERD.⁷ In patients with non-cystic fibrosis bronchiectasis, higher HARQ scores are associated with not only the frequency of exacerbation but also cough severity.¹² In a small cohort study, 68% of patients with idiopathic pulmonary fibrosis were considered positive for reflux-related symptoms (HARQ ≥ 13).²⁶ Meanwhile, the levels of pepsin in exhaled breath condensate and the infection rate of *Helicobacter pylori* were comparable between the two groups.²⁶ Thus, acid regurgitation may be independent of reflux-related symptoms. Indeed, respiratory symptoms, such as cough and wheezing, are not always triggered by gastroesophageal reflux in patients with asthma²⁷ and chronic cough.²⁸ This suggests the presence of factors other than acid reflux for the development of reflux-related respiratory symptoms. The HARQ consists of 14 prevalent gastroesophageal and extra-gastroesophageal reflux symptoms, which may be similar with the FSSG questionnaire. Indeed, The HARQ scores were significantly correlated with the FSSG scores ($r = 0.62$). Although most of indices such as asthma control and FeNO showed similar both when stratified according to the HARQ (≥ 13) and the FSSG (≥ 8) scores, the difference of

capsaicin cough reflex sensitivity was shown only when factors were analyzed using the HARQ. This suggests that HARQ would reflect not only merely gastroesophageal reflux symptoms but also cough reflex sensitivity. Therefore, the HARQ may be useful in predicting the presence of cough reflex hypersensitivity in asthma. The present study revealed that heightened capsaicin cough reflex sensitivity may be an important factor in the development of reflux-related respiratory symptoms, which leads to worse clinical outcomes in chronic respiratory diseases, including asthma.

Airway neuronal dysfunction is one of the asthma phenotypes. The capsaicin cough challenge test, a transient receptor potential channels V1 agonist, is often used to assess airway neuronal dysfunction in clinical research. Capsaicin cough reflex sensitivity is heightened in patients with asthma, particularly in females, non-atopic patients, and poorly controlled patients than in healthy subjects.³ Furthermore, exposure to allergens can augment heightened capsaicin cough reflex sensitivity by triggering airway hyperresponsiveness and airway eosinophilic inflammation in mild asthma.⁴ We have also demonstrated that heightened capsaicin cough reflex sensitivity is related to poor asthma control and asthma exacerbations, including admission due to asthma, in patients with non-atopic severe asthma.⁵ However, the assessment of capsaicin cough reflex sensitivity in real-world clinical practice is extremely limited. Thus, we need to establish a succinct tool that can be used to assess capsaicin cough reflex sensitivity in clinical practice. The present study showed that higher HARQ scores indicate the presence of heightened capsaicin cough reflex sensitivity in patients with asthma to some extent. The HARQ may be a well-established tool for detecting asthmatic patients with heightened capsaicin cough reflex sensitivity in real-world clinical practice.

Lower levels of FeNO are associated with reflux-related symptoms. This may be caused by the high doses of ICS in the R+ group. In other words, reflux-related symptoms are refractory to ICS/LABA. In a study of chronic cough, patients with reflux-related cough had lower FeNO levels than those with CVA.²⁹ Furthermore, we have previously demonstrated that patients with GERD-related cough often have comorbid CVA.³⁰ Thus, reflux-related symptoms may be

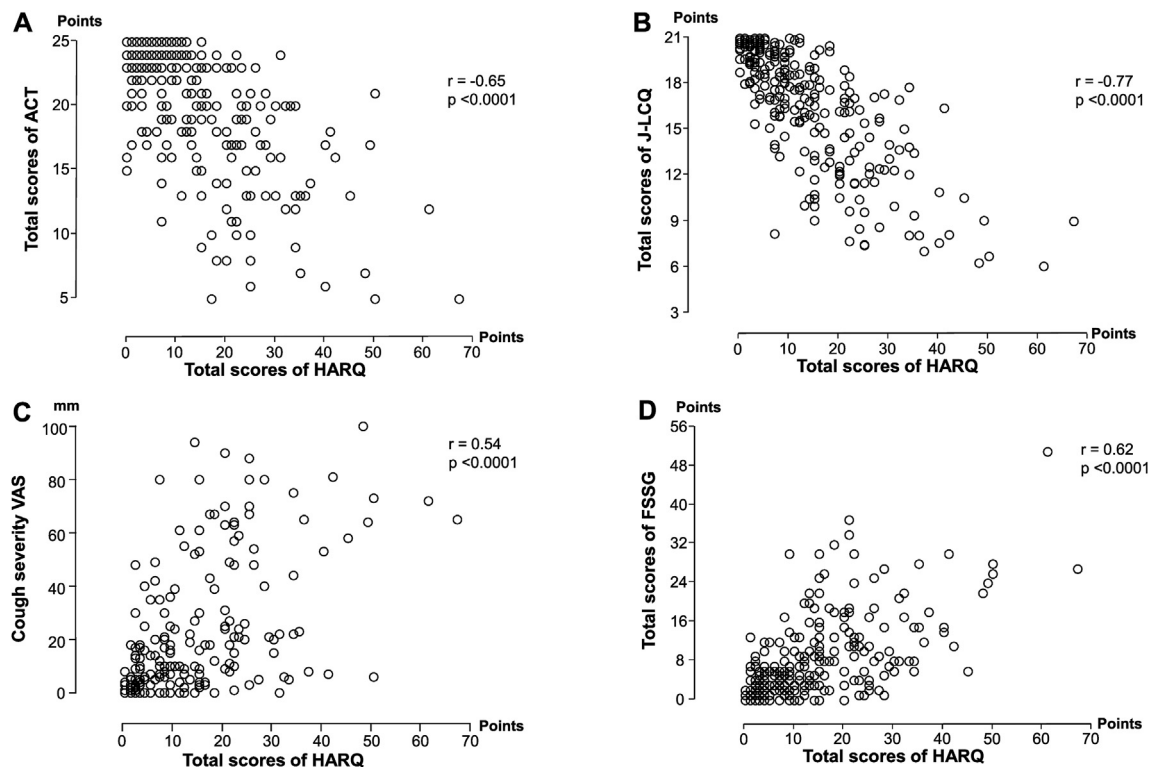


Fig. 3. Correlation between the Hull airway reflux questionnaire scores and (A) asthma control test, (B) Japanese version of Leicester cough questionnaire, (C) cough severity visual analogue scale*, and (D) frequency scale for the symptoms of GERD. *n = 197, no asterisk: n = 266.

Table 3

The multivariate logistic regression assessing the clinical meaning of the higher HARQ scores (≥ 13) in asthma (n = 149).

Variables	Estimates	95% C.I.	Standardized β	p value
Age	-0.58	-1.11; -0.04	-0.17	0.035
Sex, females	4.99	-3.85; 13.8	0.09	0.27
Atopic predisposition, non-atopic	4.46	-3.91; 12.8	0.09	0.29
Absolute neutrophil counts/ μ l	0.00043	-0.0053; 0.0062	0.02	0.88
Log 10 FeNO, ppb	-25.8	-51.1; -0.49	-0.16	0.046
Log 2 Capsaicin cough reflex sensitivity CS	-4.12	-7.48; -0.76	-0.20	0.017

HARQ: Hull airway reflux questionnaire, 95% C.I.: 95% confidence interval, non-atopic: patients without all eight specific immunoglobulin E antibodies (house dust mite, cat, dog dander, Japanese cedar pollen, mixed Gramineae pollens, mixed molds, *Trichophyton rubrum*, and mixed weed pollen). FeNO, fraction of exhaled nitric oxide.

a common feature and troublesome symptoms in patients with asthma, particularly those with uncontrolled asthma. The present findings indicate that reflux-related symptoms are independent of type2 airway inflammation.

Age affected the perception of reflux-related symptoms in asthma, along with heightened capsaicin cough reflex sensitivity and lower levels of FeNO. According to a multi-center prospective study, subjective reflux-related symptoms assessed by the reflux symptom index were lower in elderly patients (≥ 60 years old) than in younger patients.³¹ The younger age group was more refractory to empiric treatment for reflux (pantoprazole and diet recommendations for 3 months) than the older age group.³¹ In patients who were endoscopically diagnosed with reflux esophagitis, younger age was a predictor of LPR, along with the presence of a hiatus hernia and hoarseness.³² Recently, aging has been associated with reduced contraction of the upper esophageal sphincter and

esophageal body pressure responses.³³ They might be related to less perception of reflux-related symptoms in elderly patients by reducing the frequency of transient esophageal sphincter relaxation. However, we could not evaluate this relationship with asthma in the present study. Further investigations are warranted to clarify this.

The present study has some limitations. First, this was a single-center, cross-sectional, retrospective study. We did not evaluate esophageal manometry or 24-h esophageal pH monitoring. Therefore, the association between reflux of gastric contents and the perception of reflux-related symptoms in patients with asthma remains unknown. Meanwhile, higher HARQ scores were significantly correlated with higher FSSG scores. This suggests that the perception of reflux-related symptoms is exacerbated in parallel with typical GERD symptoms to some extent. Second, it also remains unclear whether treatments against GERD, such as proton pump inhibitors and prokinetic agents, are effective in attenuating capsaicin cough reflex sensitivity and reflux-related symptoms in patients with asthma. Further longitudinal studies are necessary to evaluate the efficacy of treatments against GERD for airway reflux-related symptoms in patients with asthma. Third, we could not determine the optimal cut-off value of the HARQ to distinguish between patients with asthma and healthy subjects. However, the HARQ (≥ 13) was effective in selecting patients with poorly controlled asthma and severe cough in the Japanese population. Forth, although hoarseness is one of symptoms of LPR, it may also be caused by ICS. Indeed, a score regarding hoarseness (Question 1 of the HARQ) was higher in patients who receive higher doses of ICS (≥ 1000 μ g a daily) than in those without (Supplementary Table 2). Similar results were obtained when compared between patients with severe (treatment step 4 or 5 according to the GINA 2020 guideline) and non-severe asthma (Supplementary Table 3). Thus, higher doses of ICS may affect HARQ scores, resulting in

overestimation of reflux-related symptoms. However, scores of most other questions of the HARQ were also higher in such patients (e.g. Q2, Q4, Q5, Q6, Q7, Q11, Q13). Although we cannot exclude the possibility that some of reflux-related symptoms assessed by the HARQ scores might be caused by ICS, reflux itself is associated with the pathophysiology of uncontrolled asthma. Therefore, we believe that HARQ is a good subjective measurement to assess reflux-related symptoms in patients with asthma. Finally, 110 patients did not undergo the capsaicin cough challenge test. In addition, more than half of the patients (64%) with reflux-related symptoms did not show heightened capsaicin cough reflex sensitivity. We should explore more suitable biomarkers or subjective questionnaires that reflect heightened capsaicin cough reflex sensitivity in future studies.

In conclusion, reflux-related symptoms are associated with worse clinical outcomes in patients with asthma, particularly in those with uncontrolled asthma. The HARQ would be useful in predicting the presence of heightened capsaicin cough sensitivity in asthma to some extent. Meanwhile, there are no adequate subjective or objective markers that reflect the presence of airway neuronal dysfunction in asthma in real-world clinical practice. Although the relationship between lower levels of FeNO and reflux-related symptoms may be an epiphenomenon of the use of high ICS doses, reflux-related symptoms might be a common feature of the type2-low inflammatory phenotype of asthma. Further studies are necessary to establish the utility of the HARQ in the management of asthma in real-world clinical practice.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.12.003>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

YK established the conception of the study and 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 and immunohistochemistry, data collection, and data acquisition and interpretation. KF, NT, TT, HN, JMY, and KI contributed to the performance of diagnostic tests, data collection, and data acquisition and interpretation. SF, TU, HO, KM, YI, and TO contributed to the diagnostic tests, data collection, and interpretation. MT and AN contributed to the recruitment of patients, disease diagnosis and management, interpretation of data, and revision of the manuscript.

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Supplementary file:

Reflux-related symptoms reflect poor asthma control and the presence of airway neuronal dysfunction

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Supplementary Methods

The diagnosis of asthma and cough-variant asthma

The diagnosis of asthma and cough-variant asthma was made according to the American Thoracic Society criteria¹ and the Japanese Respiratory Society Cough Guideline of Management for Chronic Cough issued in 2012 (unpublished in English). In brief, all patients had already been diagnosed with asthma based on asthma-related symptoms such as cough, dyspnea, chest tightness, and/or wheezing with the presence of clinical reversible airway obstruction or airway hyperresponsiveness to inhaled methacholine. Diagnosis was confirmed if asthma-related symptoms were relieved by commencing inhaled corticosteroids with or without inhaled β_2 agonists². The diagnosis of cough-variant asthma 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, (3) symptomatic improvement of cough with the use of short-acting β_2 agonists, and (4) no past history of asthma.

Subjective measures

All 266 patients completed the asthma control test (ACT), the Leicester cough questionnaire (LCQ), and Frequency Scale for the Symptoms of GERD (FSSG) in addition to the Hull Airway Reflux Questionnaire (HARQ). The cough severity visual analog scale (VAS) was also completed in 197 patients.

The HARQ consists of 14 items to evaluate airway reflux, each rated between 0 and 5,

where 0 = no problem and 5 = frequent/severe problem (Table 1). This is objectively made based on the findings of positive acid reflux on 24-hour pH manometry³. If the HARQ score was 13 or more, patients were considered to have reflux-related symptoms positive³.

The ACT is a self-report questionnaire regarding asthma control, which includes five items: the frequency of shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control. Total scores range from 1 to 5, with higher scores reflecting better asthma control⁴. Patients were considered poorly controlled if their ACT scores were <20⁴.

The LCQ contains 19 items with three subdomains: physical, social, and psychological, and ranges from 3 to 21⁵. Higher scores indicate better cough-specific quality of life. This questionnaire was translated from English into Japanese using the international protocol of the International Quality of Life Assessment translation protocol⁶. The validity and reliability of the Japanese version of the LCQ^{E5} have been confirmed in a previous study⁶.

The cough VAS is a 100 mm-line scale where its length represents the severity of cough: 0 mm means no cough, and 100 mm means worst cough imaginable⁷. If cough severity VAS represents ≥ 40 mm or longer⁸, patients were regarded as having severe cough in asthma.

The FSSG consists of the 14 most prevalent symptoms of GERD (seven acid-reflux related symptoms and seven functional dyspepsia-related symptoms). Each score was determined as follows: 0 = never, 1 = occasionally, 2 = sometimes, 3 = often, and 4 = always, indicating that lower

scores indicate less symptoms of GERD^{9, 10}. According to the original article, sensitivity and specificity for the diagnosis of erosive GERD were 62% and 59% if the cut-off value of the FSSG was set at 8 points^{E9}.

Measurement of lung function and inflammatory biomarkers

Patients underwent spirometry and measurements of fraction of exhaled nitric oxide (FeNO) and blood biomarkers, such as absolute eosinophil and neutrophil counts, when completing the HARQ. Among 266 patients, 21 underwent either FeNO measurement or blood analysis at the time of answering the Hull Airway Reflux Questionnaire (n = 19 for FeNO measurement only and n = 2 for blood analysis only). Therefore, 245 patients underwent both FeNO measurements and blood analyses. We also performed a capsaicin cough challenge test in 156 patients, and 149 patients underwent both FeNO measurement and blood analysis.

Spirometry was performed using a Chest-Graph HI-701 spirometer (Chest MI Corp, Tokyo, Japan) according to the current guidelines¹¹.

FeNO levels were measured at an expiratory flow rate of 50 mL/s using a chemiluminescence analyzer (NOA 280; Sievers, Boulder, CO, USA) according to the current guidelines¹².

The capsaicin cough challenge test was performed using Astograph® (Chest, Tokyo, Japan). Briefly, 10 doubling concentrations of capsaicin (0.61 to 312.5 µM) were inhaled for 15 s for each concentration at 1-minute intervals in increasing order, following physiological saline inhalation for

1 min. Saline was inhaled for 45 s during the interruption of capsaicin inhalation to increase patient blindness. When patients coughed five times or more, the capsaicin challenge test was completed after the end of the following 45 s of saline inhalation, and short-acting β_2 agonists were inhaled for 2 min immediately afterwards^{13, 14}. The concentrations required to induce at least two (C2) and five coughs (C5) were used as an index of C-CRS. C5 is generally used as an index of cough reflex sensitivity^{15, 16}, we previously demonstrated the association between a lower threshold of C2 and poorer response to ICS for daytime asthmatic cough¹⁷. Thus, lower values of both C2 and C5 indicate heightened capsaicin cough reflex sensitivity.

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Within the last month, how did the following problems affect you? (0 = no problem and 5 = severe/frequent problem)						
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess mucus in the throat, or drip down the back of your nose	0	1	2	3	4	5
Retching or vomiting when you cough	0	1	2	3	4	5
Cough on first lying down or bending over	0	1	2	3	4	5
Chest tightness or wheeze when coughing	0	1	2	3	4	5
Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)	0	1	2	3	4	5
A tickle in your throat, or a lump in your throat	0	1	2	3	4	5
Cough with eating (during or soon after meals)	0	1	2	3	4	5
Cough with certain foods	0	1	2	3	4	5
Cough when you get out of bed in the morning	0	1	2	3	4	5
Cough brought on by singing or speaking (for example, on the telephone)	0	1	2	3	4	5
Coughing during the day rather than night	0	1	2	3	4	5
A strange taste in your mouth	0	1	2	3	4	5
Total score	70					

This is self-administered and has 14 items. Responses to each question can vary from 0 to 5

Supplementary Table 1. The original version of the Hull Airway Reflux Questionnaire

Supplementary Table 2. Comparison of scores of the HARQ in each question between patients who receive high dose of ICS ($\geq 1000 \mu\text{g}$ a daily) and those without.

	All patients (n = 266)	High dose (n = 71, 27%)	Medium or low dose (n = 195, 73%)	p value
Q1 “Hoarseness or a problem with your voice”, points	1.4 (1.6)	2.0 (1.7)	1.1 (1.5)	0.0002
Q2 “Clearing your throat”, points	1.8 (1.5)	2.3 (1.5)	1.6 (1.5)	0.004
Q3 “Excess mucus in the throat, or drip down the back of your nose”, points	0.5 (1.2)	0.6 (1.2)	0.5 (1.2)	0.62
Q4 “Retching or vomiting when you cough”, points	0.6 (1.1)	0.9 (1.4)	0.4 (1.0)	0.006
Q5 “Cough on first lying down or bending over”, points	0.6 (1.2)	1.0 (1.5)	0.5 (1.0)	0.005
Q6 “Chest tightness or wheeze when coughing”, points	0.7 (1.2)	1.2 (1.5)	0.5 (1.0)	0.0001
Q7 “Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)”, points	1.5 (2.1)	2.2 (2.3)	1.2 (2.0)	0.002
Q8 “A tickle in your throat, or a lump in your throat”, points	0.9 (1.4)	0.9 (1.3)	0.9 (1.4)	0.86
Q9 “Cough with eating (during or soon after meals)”, points	0.7 (1.2)	0.8 (1.2)	0.6 (1.2)	0.24
Q10 “Cough with certain foods”, points	0.4 (1.1)	0.6 (1.2)	0.4 (1.1)	0.20
Q11 “Cough when you get out of bed in the morning”, points	0.8 (1.4)	1.2 (1.6)	0.6 (1.2)	0.003
Q12 “Cough brought on by singing or speaking (for example, on the telephone)”, points	1.4 (1.5)	1.9 (1.6)	1.2 (1.4)	0.001
Q13 “Coughing during the day rather than night”, points	1.4 (1.6)	1.5 (1.6)	1.3 (1.6)	0.28
Q14 “A strange taste in your mouth”, points	0.6 (1.3)	0.7 (1.4)	0.6 (1.3)	0.81
Total score, points	13.1 (12.0)	17.8 (12.1)	11.4 (11.5)	0.0002

Mean (standard deviation), HARQ: Hull airway reflux questionnaire, ICSs: Inhaled corticosteroids, High dose: Patients who receive high dose of ICS ($\geq 1000 \mu\text{g}$ a daily), Medium or low dose: Patients who receive medium or low dose of ICS ($< 1000 \mu\text{g}$ a daily)

Supplementary Table 3. Comparison of scores of the HARQ in each question between patients with high step treatment (defined by treatment step 4 or 5 according to the GINA 2020 guideline) and those without.

	All patients (n = 266)	High step (n = 187, 70%)	Not high step (n = 79, 30%)	p value
Q1 “Hoarseness or a problem with your voice”, points	1.4 (1.6)	1.5 (1.6)	1.1 (1.5)	0.04
Q2 “Clearing your throat”, points	1.8 (1.5)	2.0 (1.5)	1.4 (1.3)	0.005
Q3 “Excess mucus in the throat, or drip down the back of your nose”, points	0.5 (1.2)	0.6 (1.2)	0.4 (1.1)	0.31
Q4 “Retching or vomiting when you cough”, points	0.6 (1.1)	0.7 (1.2)	0.3 (0.7)	0.0002
Q5 “Cough on first lying down or bending over”, points	0.6 (1.2)	0.7 (1.3)	0.4 (0.9)	0.007
Q6 “Chest tightness or wheeze when coughing”, points	0.7 (1.2)	0.7 (1.2)	0.4 (1.0)	0.04
Q7 “Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)”, points	1.5 (2.1)	1.7 (2.2)	0.9 (1.8)	0.003
Q8 “A tickle in your throat, or a lump in your throat”, points	0.9 (1.4)	0.9 (1.3)	0.9 (1.4)	0.73
Q9 “Cough with eating (during or soon after meals)”, points	0.7 (1.2)	0.8 (1.3)	0.4 (0.9)	0.005
Q10 “Cough with certain foods”, points	0.4 (1.1)	0.4 (1.1)	0.4 (1.3)	0.70
Q11 “Cough when you get out of bed in the morning”, points	0.8 (1.4)	0.9 (1.4)	0.4 (1.3)	0.007
Q12 “Cough brought on by singing or speaking (for example, on the telephone)”, points	1.4 (1.5)	1.6 (1.5)	0.9 (1.2)	<0.0001
Q13 “Coughing during the day rather than night”, points	1.4 (1.6)	1.6 (1.6)	0.8 (1.3)	<0.0001
Q14 “A strange taste in your mouth”, points	0.6 (1.3)	0.7 (1.4)	0.5 (1.1)	0.28
Total score, points	13.1 (12.0)	14.7 (12.6)	9.3 (9.5)	0.0001

Mean (standard deviation), HARQ: Hull airway reflux questionnaire, ICSs: Inhaled corticosteroids, High step: Patients who receive treatment step 4 or 5 according to the GINA 2020 guideline, Not high step: Patients who receive treatment step 3 and below according to the GINA 2020 guideline

Supplementary Table 4. Patient's characteristics and comparison between the gastroesophageal symptoms positive (G+) and negative (G-) groups

	All patients (n = 266)	GERD positive (n = 89, 33.5%)	GERD negative (n = 177, 66.5%)	p value
Age, years	55.1 (15.6)	51.4 (15.8)	56.9 (15.3)	0.006
Age above 60 years old, presence (%)	110 (41)	23 (26)	87 (49)	0.0003
Sex, females (%)	186 (70)	72 (81)	114 (64)	0.006
Smoking history, never (%)	232 (87)	78 (88)	154 (87)	0.88
, pack-years	0.4 (1.4)	0.4 (1.6)	0.4 (1.3)	0.84
Body mass index, kg/m ²	23.5 (4.4)	23.8 (5.3)	23.3 (3.9)	0.45
Body mass index 25 or more, presence (%)	82 (31)	27 (30)	55 (31)	0.90
Non-atopic, n (%)	91 (34)	35 (39)	56 (32)	0.21
Cough variant asthma, n (%)	73 (27)	28 (31)	45 (25)	0.30
Step 4/5 of asthma treatment, n (%)	187 (70)	68 (76)	119 (67)	0.12
Dose of ICS, low/medium/high	49/146/71	12/44/33	37/102/38	0.02
ICSs equivalent to 1000 µg/day or more of fluticasone, n (%)	71 (26)	33 (37)	38 (21)	0.01
Use of PPIs or P-CAB when filling in HARQ, n (%)	73 (27)	43 (48)	30 (17)	<0.0001
HARQ, points	13.1 (12.0)	21.7 (12.7)	8.8 (9.0)	<0.0001
Leicester cough questionnaire, points	16.8 (3.8)	14.9 (4.0)	17.8 (3.6)	<0.0001
Asthma control test, points	20.2 (4.9)	17.9 (5.5)	21.5 (4.1)	<0.0001
Cough VAS, mm	21.7 (24.9)*	29.1 (27.4) [†]	17.8 (22.6) [‡]	0.004
Cough VAS over 40 mm, n (%)	41 (21)*	22 (32) [†]	19 (15) [‡]	0.004
Frequency scale for the symptoms of GERD total, points	7.9 (8.2)	17.2 (7.7)	3.2 (2.5)	<0.0001
acid reflux-related symptoms, points	4.0 (4.3)	8.5 (4.3)	1.7 (1.7)	<0.0001
functional dyspepsia symptoms, points	3.9 (4.5)	8.7 (4.6)	1.5 (1.6)	<0.0001

Mean (standard deviation), GERD: Gastroesophageal reflux disease, GERD positive: Patients with Frequency scale for the symptoms of GERD (FSSG) score higher than 8, GERD negative: Patients with FSSG score of 8 or less, Non-atopic: Patients without all eight specific immunoglobulin E antibodies (house dust mite, cat, dog dander, Japanese cedar pollen, mixed Gramineae pollens, mixed moulds, Trichophyton rubrum, and mixed weed pollen), Step 4/5: Patients who receive treatment step 4 or 5 according to the GINA 2020 guideline, ICSs: Inhaled corticosteroids, PPIs: Proton pump inhibitors, P-CAB: Potassium-competitive acid blocker, HARQ: Hull airway reflux questionnaire, VAS: visual analogue scale, *n=197, [†]n=68, [‡]n=129

Supplementary Table 5. Comparison of biomarkers and lung function between the

	All patients (n = 266)	GERD positive (n = 89, 33.5%)	GERD negative (n = 177, 66.5%)	p value
Absolute neutrophil count, / μ l*	3434 (2484, 4291) [†]	3539 (2573, 4724) [‡]	3342 (2442, 4102) [§]	0.08
Absolute eosinophil count, / μ l*	138 (70, 258) [†]	106 (58, 226) [‡]	146 (76, 276) [§]	0.04
Serum IgE at the first visit, IU/ml*	103 (31, 304)	72 (22, 275) [¶]	119 (36, 319) ^{**}	0.09
FEV ₁ , %predicted	97.0 (19.4)	99.0 (17.7)	96.0 (20.2)	0.21
Fraction of exhaled nitric oxide, ppb*	22.2 (15.1, 34.1) ^{††}	20.6 (14.2, 27.5) ^{‡‡}	24.6 (15.5, 38.2)	0.0004
Capsaicin cough reflex sensitivity				
C2, μ M*	4.88 (2.44, 19.5) ^{§§}	4.88 (1.22, 19.5)	9.76 (2.44, 19.5) ^{¶¶}	0.14
C5, μ M*	9.76 (2.44, 39.0) ^{§§}	9.76 (2.44, 19.5)	19.5 (4.88, 39.0) ^{¶¶}	0.20

gastroesophageal symptoms positive (G+) and negative (G-) groups

Mean (standard deviation), *Median (25 percentile, 75 percentile), GERD: Gastroesophageal reflux disease, GERD

positive: Patients with Frequency scale for the symptoms of GERD (FSSG) score higher than 8, GERD negative:

Patients with FSSG score of 8 or less, IgE: Immunoglobulin E, FEV₁: Forced expiratory volume in one second,

[†]n=247, [‡]n=85, [§]n=162, ^{||}n=249, [¶]n=83, ^{**}n=166, ^{††}n=264, ^{‡‡}n=87, ^{§§}n=156, ^{|||}n=54, ^{¶¶}n=102

Supplementary Table 6. Reliability of the Japanese version HARQ

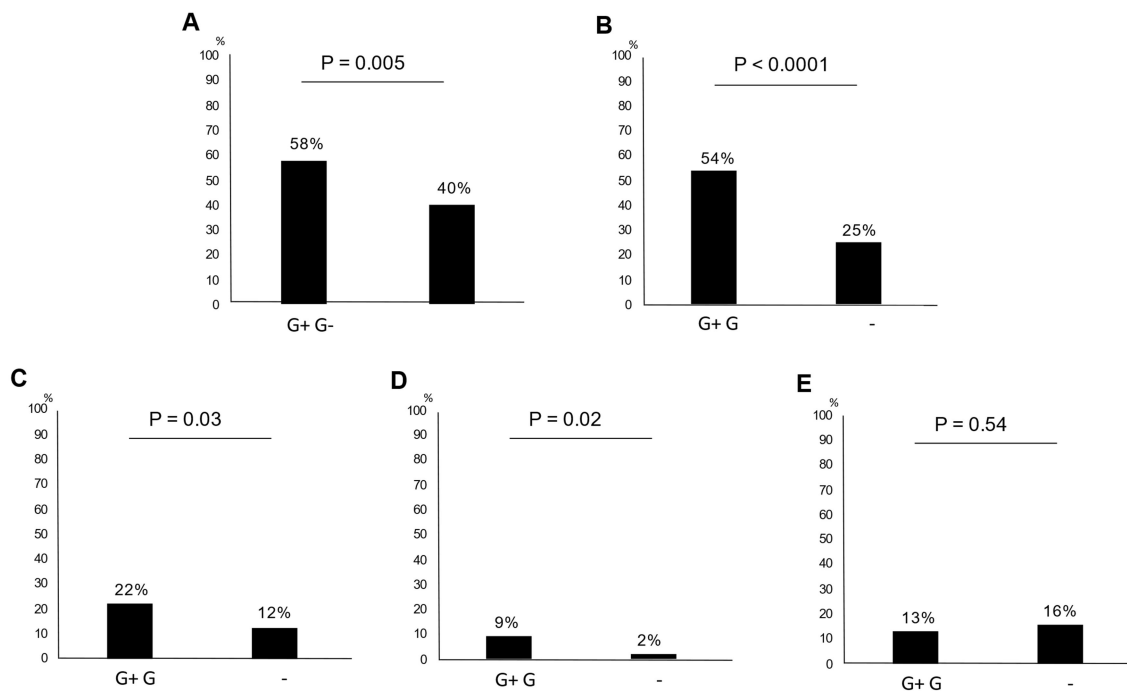
Questions	Score	Cronbach's coefficient alpha
Hoarseness or a problem with your voice	1.4 (1.6)	0.87
Clearing your throat	1.8 (1.5)	0.86
Excess mucus in the throat, or drip down the back of your nose	0.5 (1.2)	0.87
Retching or vomiting when you cough	0.6 (1.1)	0.86
Cough on first lying down or bending over	0.6 (1.2)	0.86
Chest tightness or wheeze when coughing	0.7 (1.2)	0.86
Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)	1.5 (2.1)	0.88
A tickle in your throat, or a lump in your throat	0.9 (1.4)	0.86
Cough with eating (during or soon after meals)	0.7 (1.2)	0.86
Cough with certain foods	0.4 (1.1)	0.87
Cough when you get out of bed in the morning	0.8 (1.4)	0.86
Cough brought on by singing or speaking (for example, on the telephone)	1.4 (1.5)	0.85
Coughing during the day rather than night	1.4 (1.6)	0.86
A strange taste in your mouth	0.6 (1.3)	0.87
Total	13.1 (12.0)	0.87

Mean (Standard deviation), HARQ: Hull airway reflux questionnaire

Supplementary Figure 1

Comparison of percentages of patients with each characteristic of uncontrolled asthma

between gastroesophageal symptoms positive (G+) and negative (G-) groups.



(A) Uncontrolled asthma (one or more of the criteria of severe asthma), (B) Poor control (ACT < 20),

(C) Frequent exacerbations (≥ 2 /year) (D) Admissions (≥ 1 /year), (E) Airflow limitation ($FEV_1 < 80\%$

predicted)