

# Upper airway cough syndrome may be the main cause of chronic cough in Japan: a cohort study

Kimihiko Yasuda (✉ [kimihiko@yasuda-clinic.jp](mailto:kimihiko@yasuda-clinic.jp))

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## Research

**Keywords:** cough, chronic cough, postnasal drip syndrome, rhinosinusitis, sinusitis, upper airway cough syndrome

**Posted Date:** June 22nd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-17507/v2>

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**Version of Record:** A version of this preprint was published at Family Practice on June 11th, 2021. See the published version at <https://doi.org/10.1093/fampra/cmab046>.

# Abstract

## *Background*

Upper airway cough syndrome (UACS) is generally considered a common cause of chronic cough but remains poorly recognised in Japan.

## *Objective*

This study aimed to assess whether UACS was a common cause of chronic cough in Japan, as is true in other countries. Interview and examination items were evaluated for their potential use in UACS diagnosis.

## *Methods*

All patients with chronic cough were preliminarily diagnosed with bronchial asthma, UACS, gastroesophageal reflux disease, or post-infectious prolonged cough, based on interviews and examinations. Treatment centred on nasal steroids was administered to the UACS group and standard treatment to the other groups. The observation period lasted 4 weeks. The subjective cough score at first diagnosis was set at 10, and the final diagnosis was made based on the treatment administered at the time the cough score had decreased to  $\leq 2$ . The associations between the presence or absence of UACS and interview and examination items were statistically evaluated.

## *Results*

Among 230 patients with chronic cough, 146 were diagnosed with UACS-only. Multivariate logistic regression revealed that the assessment items 'awareness of mucus accumulating in the back of the throat', 'presence of abnormal echography findings', 'absence of associated coughing when exercising' and 'presence of coughing persisting after onset' were significantly correlated with the presence or absence of UACS ( $p < 0.05$ ).

## *Conclusions*

UACS may be the most common cause of chronic cough in Japan and may be effectively treated with nasal corticosteroids. Diagnosing UACS might be possible by selecting appropriate interview and examination items.

# Key Messages

## **Key messages**

- Upper airway cough syndrome may be the main cause of chronic cough in Japan

- Upper airway cough syndrome may be effectively treated with nasal corticosteroids
- Interview and appropriate examination may help diagnose upper airway cough syndrome

## Lay Summary

Chronic cough that lasts more than 8 weeks is often a symptom that plagues the patient and the physician. In general, postnasal drip (now defined as upper airway cough syndrome [UACS]) associated with rhinosinusitis, cough variant asthma, and gastroesophageal reflux are known causes of chronic cough.

The cough guidelines by the Japanese Respiratory Society state sinusitis as the cause of cough, and it is categorised as sino-bronchial syndrome. Thus, the recognition of UACS is extremely low. UACS is not considered a cause of cough in Japan, but it is unlikely that Japan is the only exception. Based on these findings, I investigated the causes of chronic cough in patients who visited my clinic. As a result, UACS accounted for at least 60% of chronic cough cases. This study showed that UACS might be the most common cause of chronic cough in Japan. This study also showed that the treatment centred on nasal steroids was highly effective against UACS and that some interview and examination items might be useful in the diagnosis of UACS. This is an unprecedented finding and may contribute to the diagnosis of chronic cough.

## Background

Cough is one of the most common complaints of patients visiting both the respiratory and the general medicine departments. When cough episodes last >8 weeks, it is considered chronic [1-4].

In 1998, the American College of Chest Physicians (ACCP) stated that postnasal drip syndrome was the most common cause of chronic cough [5]. However, considering that the cough associated with postnasal drip syndrome is not merely due to mechanical irritation caused by postnasal drip [6-8], it was termed as upper airway cough syndrome (UACS) associated with rhinosinusitis in 2006. According to the ACCP, UACS is the most common cause of chronic cough, and treatments for UACS are recommended for chronic cough of unknown aetiology [1,4]. Of the 15 cough-related clinical practice guidelines systematically evaluated, the ACCP guidelines scored the highest and were 'strongly recommended' for clinical practice [9]. UACS is a concept centred on rhinosinusitis [1,4,5], and the European Respiratory Society (ERS) promoted the use of the term 'rhinosinusitis' to UACS [2,10]. However, UACS as a disease is now widely accepted rather than rhinosinusitis because merely rhinosinusitis (postnasal drip) does not explain the symptoms of cough [6,7]; moreover, the pathogenesis of cough without nasal symptoms,

which is responsive to UACS treatment, has been presented [11,12]. Medical societies in various countries support UACS as a concept [12]. Hence, the use of the term UACS was maintained in this study.

Meanwhile, according to the 'cough guidelines' published by the Japanese Respiratory Society, cough variant asthma (CVA) was listed as the most common cause of chronic cough followed by gastroesophageal reflux disease (GERD), sino-bronchial syndrome (SBS), and atopic cough (AC) [3]. Few reports have shown that upper respiratory inflammation, such as UACS or rhinosinusitis, are the major causes of chronic cough in Japan. Niimi contested that racial differences may account for the low prevalence of UACS in Japan [13]. However, numerous studies on UACS have been carried out in Asian countries, indicating that UACS is a major cause of chronic cough in Asia [14-18].

The aim of this study was to evaluate the prevalence of UACS in Japan by identifying the cause of chronic cough and to evaluate whether the ACCP statement that 'UACS is the major cause of chronic cough' is considerable in Japan. The ACCP also stated that 'the symptoms and signs of UACS are nonspecific, and definitive diagnosis of UACS cannot be made based on the medical history and physical examination alone' [11]. It was hypothesised that certain interview and examination items associated with rhinosinusitis could be useful in the UACS diagnosis. To evaluate this hypothesis, these items were compared between patients with and without UACS.

## Results

Patients with a chronic cough who visited my clinic between March 2016 and July 2018 were included. Patients who were using angiotensin-converting enzyme inhibitors or who had radiographic findings showing the probable cause of chronic cough were excluded. Patients available for follow-up were treated, and the final diagnosis was evaluated. The associations between interview and examinations items and UACS diagnosis were examined. Interviews and examinations on the first visit Interviews (including questionnaire form shown in Table 1), pharynx and nasal cavity assessments, auscultation of the chest, chest radiography, pulmonary function tests, nasal discharge eosinophilic count, and maxillary sinus echography were performed at the first visit. The questionnaire was directly completed by the patients themselves. All items in the list presented in Table 1 were checked. Diagnosis on the first visit A preliminary diagnosis was delivered as shown in Fig. 1-A, B. First, the presence or absence of bronchial asthma (BA) was diagnosed based on the diagnostic criteria in accordance with the Global Initiative for Asthma [19]. The diagnostic criteria for UACS remain unclear [1]. In this study, since rhinosinusitis can be considered to exhibit the same conditions as UACS [2,11], patients with symptoms of rhinosinusitis, such as postnasal drip, nasal discharge, and nasal congestion, or with abnormal findings on sinus echography (see Supplementary File; Figure S1), were diagnosed with UACS. Patients who were not diagnosed with BA or UACS and had obvious gastric symptoms, such as acid reflux, a feeling of weight in the stomach, or diet-related coughing, were diagnosed with GERD. Patients who were not diagnosed with BA, UACS, or GERD were diagnosed with post-infectious prolonged cough (PIPC). In view that CVA is a BA subtype, diagnosis of BA included both classical BA and CVA. Even if multiple diagnoses were possible, each patient was diagnosed with a single disease at the initial assessment to accurately evaluate the cause of

the cough by clarifying the therapy effect of a single diagnosis. However, patients with both BA and UACS were diagnosed with combined conditions according to the concept of 'one airway, one disease' [20].

**Treatments** Treatment was initiated based on the preliminary diagnosis (Fig. 1-C). Patients with BA received standard treatment according to the severity grade by combining inhaled corticosteroids, fluticasone furoate 100–200 µg and long-acting β-2 agonist, vilanterol 25 µg, once daily, and leukotriene receptor agonist, montelukast 10 mg, once daily. Patients with UACS were treated with nasal corticosteroids, beclomethasone dipropionate 50 µg, twice daily, or mometasone furoate 200 µg, once daily; oral carbocysteine 500 mg thrice daily; herbal medicines, Kakkonto-ka-senkyu-shin-i or Shin-i-seihai-to 2.5 g, thrice daily. Oral bepotastine, 10 mg twice daily, was added only for patients with strong symptoms of allergic rhinitis, including sneezing, nasal discharge, and nasal congestion, and pallor of the middle or lower turbinates observed with a nasal speculum. In patients whose cough score did not decrease to  $\leq 2$  on first evaluation and whose eosinophilic count in nasal discharge was  $\geq 1+$ , nasal levocabastine was additionally administered at a dose of 0.2 mg, thrice daily, and/or nasal corticosteroid administration was changed to several drops of betamethasone (0.1%), twice daily as needed. Nasal betamethasone was not administered for more than 2 weeks. Famotidine 10 mg or rabeprazole 10 mg, twice daily, was administered to patients with GERD. Metoclopramide 5 mg, thrice daily, and domperidone 10 mg, thrice daily, were administered as needed. Codeine phosphate 10 mg and Bakumondo-to 3 g, thrice daily, were administered to patients with PIPC. In cases where chronic cough was thought to be exacerbated by infection, antibiotics were administered concurrently as needed.

**Assessment of cough improvement** The cough score in the initial diagnosis was set to 10. Thereafter, the degree of cough improvement was evaluated by the subjective cough score after the treatment. This assessment method has been shown to be highly correlated with the visual analogue scale score [21,22].

**Evaluation and final diagnosis** The observation period was set at 4 weeks. The first evaluation was performed 2 weeks after the start of treatment. Treatment was completed, continued, intensified, added, or changed based on the cough score (Fig. 1-D). The last evaluation was performed at week 4, and the final diagnosis was made based on the administered treatment at the time the cough score had decreased to  $\leq 2$  (Fig. 1-E). Patients who did not respond to any treatment and had a cough score  $\geq 8$  were diagnosed with cough of unknown aetiology. In some patients who had achieved a cough score  $\leq 2$  prior to week 4, treatment was completed early, and a final diagnosis was made based on the administered treatment at that time. Patients with cough scores of 3–7 on week 4 were excluded because they were few ( $n = 4$ ) and required continued treatment due to which it was considered impossible to accurately assess them within the pre-set 4-week follow-up period.

**Statistical analysis** The items listed in Table 1 were compared between the groups with a final diagnosis of UACS-only and the group without UACS. Medians and 25th and 75th percentiles were obtained for continuous variables, and the Mann–Whitney U test was used to determine the statistical significance of differences between the groups. The frequencies of the categorical variables were obtained, and a Fisher's exact test was used to determine the statistical significance of differences between the groups. Predictive models were generated to determine whether the final diagnosis of UACS could be predicted by the interview and examination items. Univariate logistic regression models, with the final diagnosis of UACS as the dependent variable and individual items as explanatory variables, were generated. A multivariate logistic regression model was generated by

incorporating explanatory variables that achieved  $p < 0.1$  in the univariate analyses. Model selection based on Akaike's information criterion was performed using the variable-reduction method. To evaluate the discriminatory ability of the generated models, receiver operating characteristic analysis was performed, and the area under the curve was calculated. All statistical analyses were performed using R version 3.3.3 (R Core Team 2017, Vienna, Austria).  $p$ -values  $< 0.05$  were considered statistically significant.

## Discussion

UACS is widely recognised as a cause of chronic cough. However, its prevalence is considered low in Japan [3,13]. Since it is unlikely that Japan constitutes the only exception, this study was conducted to examine the actual UACS prevalence in Japan. In this study, UACS was the most common cause of chronic cough. It was effectively treated by nasal corticosteroids. Certain interview and examination items were useful for UACS diagnosis.

According to the ACCP guidelines, antihistamines/decongestants are recommended for UACS treatment, and the diagnosis should be based on the response to antihistamines in addition to symptoms and examinations [1]. The concept of 'silent UACS', without nasal symptoms, diagnosed only by the effectiveness of antihistamine treatment has also been presented [11,12]. First-generation antihistamines are recommended for UACS treatment [1]. The mechanism of action is considered to be mainly anticholinergic (suppression of cholinergic vagal reflex), and their binding affinities at histamine receptors may not be highly correlated with the suppression of cough; however, no definite conclusion has been reached [23]. This medication may have strong sedative-hypnotic side effects, which could cause antitussive activity [6].

Therefore, instead of first-generation antihistamines, treatment focused on nasal steroids recommended in the European and American guidelines for rhinosinusitis was carried out in this study [24-28]. Since UACS and rhinosinusitis share the same pathophysiological status, nasal steroid-based treatment for UACS is appropriate and has been reported in previous studies [29,30]. In this study, in 110 (75.3%) of the 146 patients with the final UACS-only diagnosis, cough scores showed significant improvement (from 10 to  $\leq 2$ ) within only 2 weeks of treatment with mainly nasal steroids. This finding unlikely reflects a natural course; although ERS cough guidelines state that there is no evidence of the effectiveness of a localised treatment against UACS [31], this finding indicates that inflammation in the nasal cavity plays a pivotal role in the pathophysiology of UACS. Compared with antihistamines, nasal corticosteroids constitute a potent therapeutic option for UACS in terms of effectiveness, side effects, and interpretation of the location of the primary pathophysiology. The effectiveness and mechanism of action of herbal medicines for the treatment of rhinosinusitis have been demonstrated in Japan, China, and Korea [32-34].

UACS is described only briefly in cough guidelines by the Japanese Respiratory Society [3] and is poorly recognised [13]. These guidelines state that CVA, SBS, AC, and GERD are the major causes of chronic cough [3]. SBS, which is defined as chronic recurrent neutrophilic inflammation of the upper and lower

airways, is described as a cause of chronic cough solely in the Japanese guidelines. Although the concept of SBS differs from that of UACS in the presence of lower-airway as well as upper-airway lesions (rhinosinusitis), its clinical condition largely overlaps with that of UACS [12]. However, the treatment of SBS involves macrolide administration as recommended for sinusitis in Japan, and the therapeutic effect is determined based on improvement within 4–8 weeks after administration [3]. AC has been reported mostly in Japan [35-37]. The condition has been defined as a dry cough that can be effectively treated using inhalation corticosteroids or antihistamines and is characterised by eosinophilic central airway inflammation [3,36,37]. The concept of AC pathophysiologically overlaps with that of CVA and non-asthmatic eosinophilic bronchitis. However, the condition of AC as an independent disease remains controversial [2,12,13,38]. Niimi and Yu et al. noted that AC may overlap with silent UACS, which is not associated with nasal symptoms, and the associated cough symptoms could be improved by antihistamine administration [12,13]. Additionally, UACS associated with allergic rhinitis that could be ameliorated by antihistamines may overlap with AC. Since these diseases overlapping with UACS are recognised as causes of chronic cough, UACS may not be recognised as the sole cause in Japan.

The ACCP reported that ‘the symptoms and signs of UACS are nonspecific, definitive diagnosis cannot be made based on the medical history and physical examination alone’ [1]. Several interview and examination items associated with rhinosinusitis were useful in diagnosing UACS in this study. The questions shown in Table 1 refer to common cough-related patient complaints and the major rhinosinusitis guidelines in the United States and Europe [24-28]. These guidelines utilise both clinical symptoms and objective findings for rhinosinusitis diagnosis. Considering that UACS shares the same status as rhinosinusitis, it is reasonable to refer to the features of rhinosinusitis for the diagnosis of UACS. All the guidelines recommend computed tomography. However, echography could be a useful diagnostic tool since it is economical, convenient, and does not involve radiation exposure [39,40].

The present study had several limitations. First, the treatment method in this study was not placebo-controlled. Second, the detailed conditions of rhinosinusitis were not confirmed. Third, more patients were diagnosed with UACS than with BA in this study. In general, outpatients often consult a physician before their cough becomes chronic. CVA is generally recognised among general practitioners because the Japanese guidelines specify CVA as a major cause of chronic cough [3]. Therefore, in many cases, inhaled corticosteroids had been empirically administered before the patients visited the clinic (data not shown). This could have inflated the prevalence of UACS over CVA as a cause of chronic cough encountered in the clinic. In addition, most patients with BA presented with nasal symptoms or abnormal echography findings and received UACS treatment. Although some patients should have been diagnosed with BA only, they may have been over-diagnosed as complicated UACS. Thus, the diagnosis of BA and UACS should have been separated. However, even when all these patients were diagnosed with BA only, the prevalence of UACS in patients with a chronic cough would be 63.5%. This result indicates that UACS was the most common cause of chronic cough in the study. Fourth, the large difference in the number of patients with UACS-only and those without UACS could have introduced a bias in the statistical results regarding the diagnostic items. This could be avoided by standardising the number of patients, which

would increase the accuracy of the statistical analyses. Last, while assessing the prevalence of a chronic cough in Japan, it may be difficult to draw conclusions based on a single institution survey. Similar studies on chronic cough within Japanese populations are warranted in the future.

In conclusion, based on our findings, the statement 'UACS is the most common cause of chronic cough', as stated by the ACCP, appears to also apply to the Japanese population. It could be effectively treated with nasal steroids. Certain interview and examination items could increase the diagnostic accuracy of UACS.

## Declarations

***Ethics approval and consent to participate.*** This clinical study was performed in accordance with the Declaration of Helsinki, with the approval of the Yasuda Clinic Ethics Review Board (#15-06-01). Informed consent was not required as instead of obtaining direct consent from patients, information regarding research purposes, methods, and the handling of personal information was posted in the clinic and on the website. Participants were provided with an opportunity to opt-out of the study at any time. The waiver of informed consent was approved by the Ethics Committee. I ensured that patient anonymity was respected by removing any details that may have led to patient identification.

***Funding.*** This study was not funded by any specific project grant.

***Consent for publication:*** Not applicable.

***Competing interests:*** The author declares that he has no competing interests.

***Acknowledgements:*** I would like to express my greatest appreciation to Yoshiaki Tanaka, M.D., and Masako Yasuda, M.D., whose comments and suggestions were immensely valuable throughout the course of my study. I would also like to extend my appreciation to the staff at the clinic who helped me organise the data.

Data Availability Statement: The datasets used and/or analysed during the current study are obtainable from the corresponding author on reasonable request.

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# Tables

**Table 1:** Checklist used at the time of the initial visit: characteristics, examination findings, and questionnaire items

<b>Characteristics</b>	<b>Assessment items</b>	<b>Standard</b>
Age	Age	Year(s)
Sex	Male or female	M/F
History of smoking	Is there a history of smoking?	Y/N
History of asthma	Has there ever been a diagnosis of asthma?	Y/N
<b>Physical and laboratory examination findings</b>		
Auscultation	Can wheezing, rhonchi, or squawking be heard on auscultation?	Y/N
Pharyngeal examination	Are there findings of postnasal drip in the oropharynx?	Y/N
Nasal cavity observation	Is there swelling or purulent nasal discharge in the middle or lower turbinates as observed using a nasal speculum?	Y/N
Pulmonary function test	Are there findings indicative of obstructive changes, such as decreases in FEV1, %FEV1, V50, and V25 or a convex curve below the FVC?	Y/N
Radiographic findings	Are there any findings that may cause coughing?	Y/N
Maxillary sinus echography	<b>Can the posterior wall bone be observed in the maxillary sinus echography?</b>	Y/N
Assessment of eosinophilic count in nasal discharge	Are there at least 1+ eosinophils in nasal swab specimens fixed onto glass slides?	Y/N
<b>[Questionnaire form]</b>		
<b>Regarding nasal symptoms</b>	<b>Assessment items</b>	<b>Standard</b>
Awareness of rhinorrhoea	Are you aware of a runny nose?	Y/N

Awareness of nasal congestion	Are you aware of nasal congestion?	Y/N
Awareness of postnasal drip	Are you aware of postnasal drip?	Y/N
History of nasal symptoms	If there are no nasal symptoms, were you aware of runny nose, nasal congestion, or postnasal drip prior to the onset of coughing?	Y/N

### Regarding coughing

Duration of coughing	How many weeks has it been since you started coughing?	Week(s)
Coughing at night	Does coughing occur at night?	Y/N
Coughing at bedtime	Does coughing occur at bedtime or when lying down?	Y/N
Coughing at dawn	Does coughing occur at dawn?	Y/N
Choking coughing	When you are coughing, does it feel as if you are choking?	Y/N
Coughing that persists after onset	Do you experience coughing that does not stop for a while after it begins?	Y/N
Coughing after infection	Were there subjective symptoms of infection that triggered coughing (fever, cough, phlegm, runny nose, etc.)?	Y/N
Diet-related coughing	Was coughing particularly frequent before and after or during meals?	Y/N
Coughing upon speaking	Is coughing induced by speaking?	Y/N
Coughing associated with atmospheric changes	Do atmospheric changes induce coughing?	Y/N
Coughing associated with changes in temperature	Do temperature differences (e.g. indoor to outdoor) induce coughing?	Y/N
Coughing upon exercising	Does exercise induce coughing?	Y/N
Coughing associated with warming of the body	Does warming the body induce coughing?	Y/N

### Regarding conditions other than coughing

Presence of phlegm	Are you aware of phlegm?	Y/N
Awareness of	Are you aware of feeling of phlegm or mucus accumulating	Y/N

mucus accumulating in the back of the throat in the back of your throat?

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Throat irritation	Is there an irritating sensation in your throat?	Y/N
Dry throat	Does your throat feel dry?	Y/N
Difficulty breathing	Is there any difficulty in breathing or a feeling of tightness in the anterior chest?	Y/N
Wheezing	Are you aware of wheezing?	Y/N
Clearing the throat	Are you aware of throat clearing?	Y/N
Hoarse throat	Are you aware of a hoarse throat?	Y/N
Gastric symptoms	Are you aware of gastric symptoms, such as heartburn, stomach ache, or nausea?	Y/N

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FEV1, forced expiratory volume in 1 second; %FEV1, percentage predicted forced expiratory volume in 1 second; V50, flow rate at 50% forced vital capacity; V25, flow rate at 25% forced vital capacity; FVC, flow volume curve

**Table 2** Comparison of patient characteristics in the UACS-only group with those in the without-UACS group (2016-2018)

Characteristics	UACS-only (n=146)	without-UACS (n=18)	P- value
Swelling of the middle and lower turbinate (Yes)	92 (63.0%)	6 (33.3%)	0.021*
Awareness of rhinorrhoea (Yes)	70 (47.9%)	3 (16.7%)	0.012*
Existence of a possible trigger for infection (Yes)	86 (58.9%)	4 (22.2%)	0.005*
Awareness of postnasal drip (Yes)	43 (29.5%)	1 (5.6%)	0.045*
Presence of abnormal maxillary sinus echography findings (Yes)	144 (98.6%)	15 (83.3%)	0.010*
Cough that persists after onset (Yes)	99 (67.8%)	7 (38.9%)	0.020*
Feeling of mucus accumulating in the back of the throat (Yes)	92 (63.0%)	4 (22.2%)	0.002*
Awareness of wheezing (Yes)	13 (8.9%)	5 (27.8%)	0.031*

\* $p < 0.05$

UACS, upper airway cough syndrome

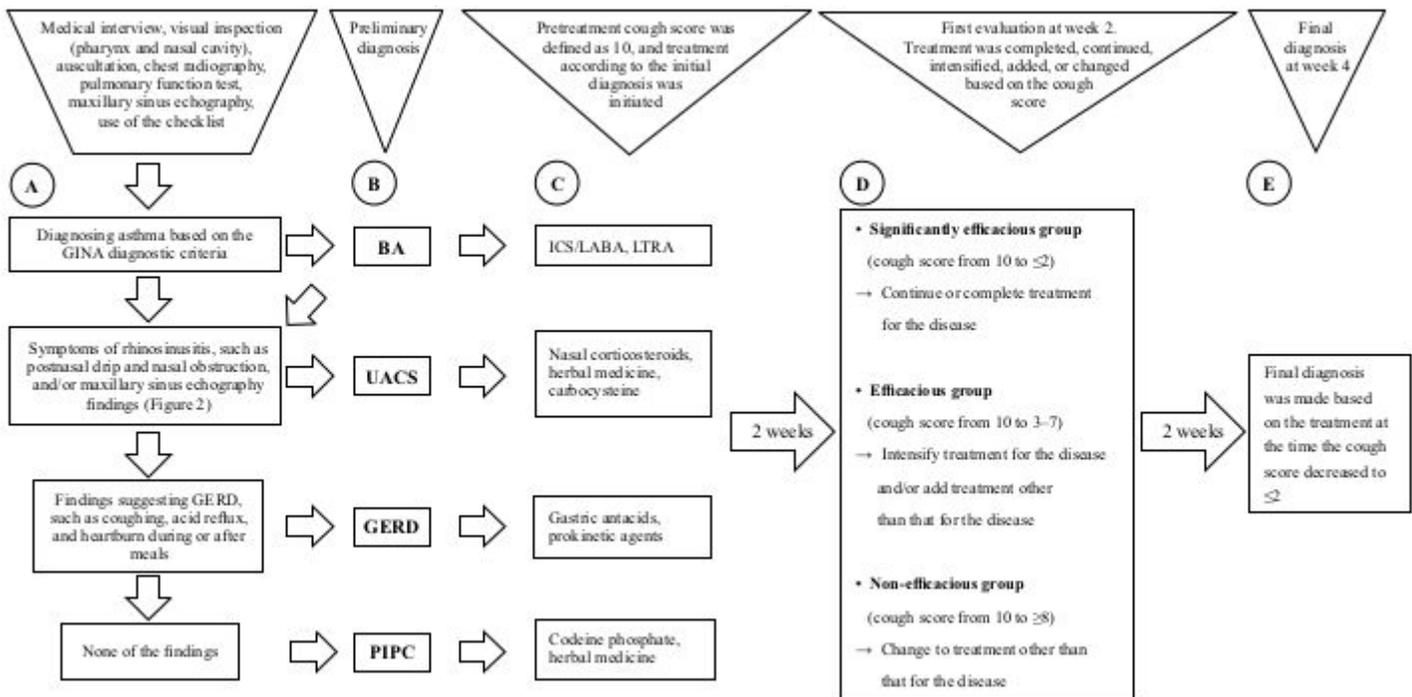
**Table 3** Results of the binomial logistic regression model analysis to determine the causes of cough in Japanese patients (2016-2018)

	Odds ratio	95% CI lower limit	95% CI upper limit	P-value
Existence of a possible trigger for infection (Y/N)	4.011	0.984	16.355	0.052
Awareness of mucus accumulating in the back of the throat (Y/N)	4.613	1.124	18.928	0.034*
Presence of abnormal maxillary sinus echography findings (Y/N)	15.725	1.445	171.101	0.024*
Coughing upon exercise (Y/N)	0.212	0.055	0.813	0.024*
Cough that persists after onset (Y/N)	6.47	1.755	23.843	0.005*
Awareness of postnasal drip (Y/N)	4.627	0.43	49.774	0.206
Swelling of the middle and lower turbinates (Y/N)	2.543	0.712	9.088	0.151

\*P<0.05

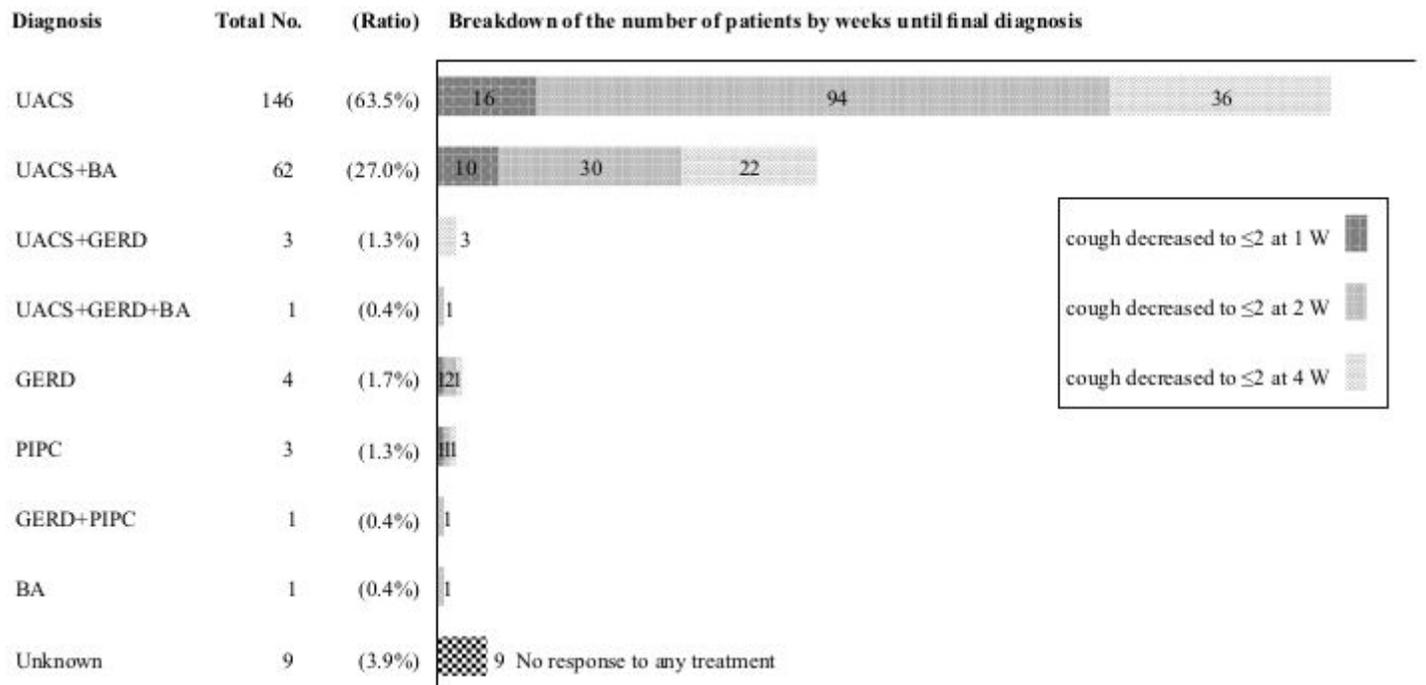
CI, confidence interval; UACS, upper airway cough syndrome

## Figures



**Figure 1**

Flow chart of diagnosis and treatment BA, bronchial asthma; GERD, gastroesophageal reflux disease; GINA, global initiative for asthma; ICS, inhaled corticosteroids; LABA, long-acting  $\beta$ -2 agonist; LTRA, leukotriene receptor agonist; PIPC, post infectious prolonged cough; UACS, upper airway cough syndrome



**Figure 2**

Final diagnosis and breakdown of the number of patients in each disease group by the period until final diagnosis (2016-2018) UACS, upper airway cough syndrome; BA, bronchial asthma; GERD,

gastroesophageal reflux disease; PIPC, post infectious prolonged cough

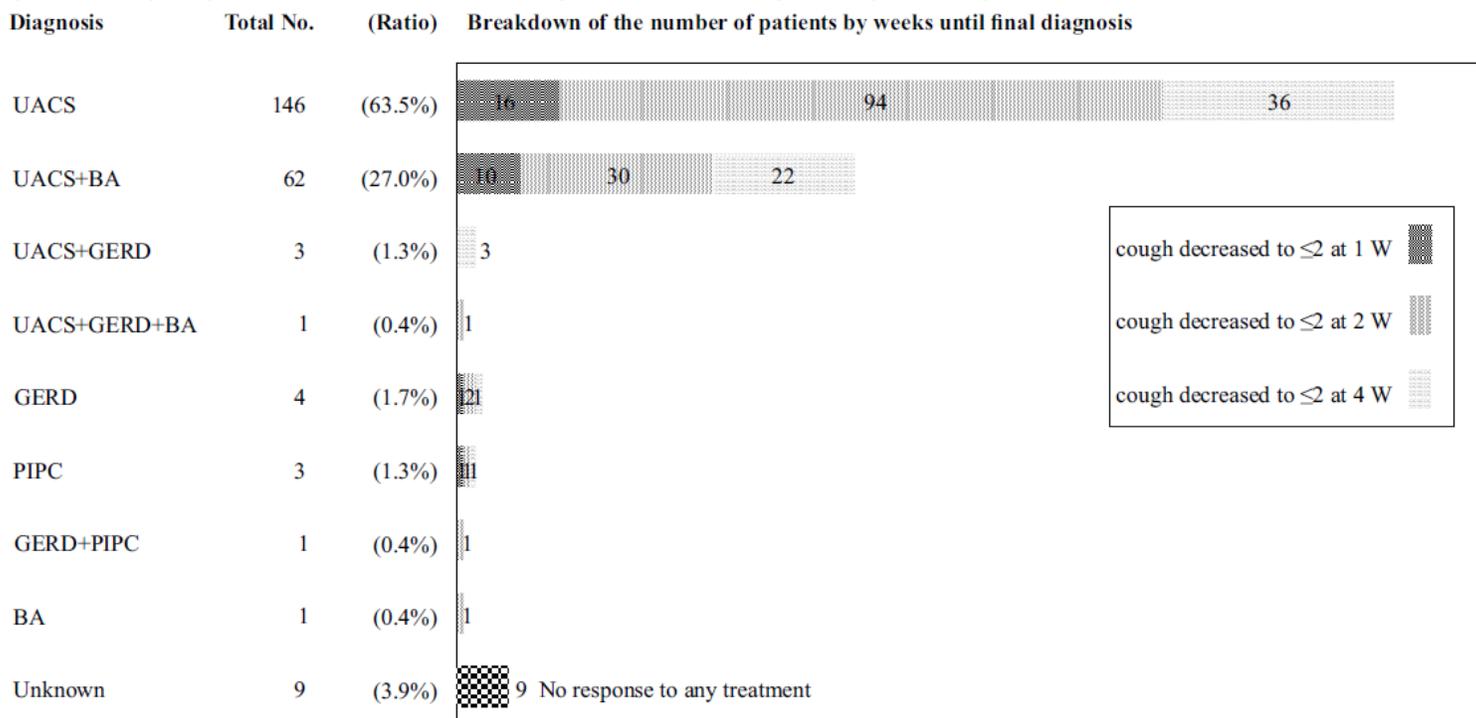


Figure 3

Diagnosis and breakdown of patient number in each disease group by period till final diagnosis. UACS, upper airway cough syndrome; BA, bronchial asthma; GERD, gastroesophageal reflux disease; PIPC, post infectious prolonged cough

### Supplementary Files

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