Could cough hypersensitivity symptom profile differentiate phenotypes of chronic cough?

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The symptoms of cough hypersensitivity may not distinguish between asthmatic cough and refractory chronic cough. Cough reflex hypersensitivity may underlie chronic cough across different phenotypes, despite having different treatable traits. https://bit.ly/45kgwBm

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Abstract

Background Recently, cough reflex hypersensitivity has been proposed as a common underlying feature of chronic cough in adults. However, symptoms and clinical characteristics of cough hypersensitivity have not been studied amongst phenotypes of chronic cough. This study aimed to compare symptom features, such as cough triggers and associated throat sensations, of cough hypersensitivity in patients with asthmatic chronic cough and those with refractory chronic cough (RCC).

Methods Patients with chronic cough from the Korean Chronic Cough Registry were prospectively evaluated over 6 months. Physicians determined the aetiological diagnosis based on clinical evaluations and responses to treatment at the 6-month follow-up visit. Symptoms of cough hypersensitivity and cough-specific quality of life were assessed using the Cough Hypersensitivity Questionnaire (CHQ) and the Leicester Cough Questionnaire (LCQ), respectively.

Results The analysis included 280 patients who completed the follow-up: 79 with asthmatic cough (cough variant asthma or eosinophilic bronchitis) and 201 with RCC. Baseline CHQ scores were similar between the groups (8.3±3.7 in asthmatic cough *versus* 8.9±3.9 in RCC; p=0.215, adjusted for age, sex and LCQ score). There were no significant between-group differences in the LCQ and cough severity Visual Analog Scale scores. Both groups showed a similar negative correlation with LCQ scores (asthmatic cough: r=−0.427, p<0.001; RCC: r=−0.306, p<0.001).

Conclusions The symptoms of cough hypersensitivity may not distinguish between asthmatic cough and RCC. This suggests that chronic cough is the primary diagnosis in both phenotypes. It indicates a shared mechanism in their cough pathogenesis, despite having potentially different treatable traits.

Introduction

Cough is a vital reflex that protects the lower airways. However, when dysregulated, it may become a disease [1]. It is one of the most common reasons patients seek medical care [2–4]. Chronic cough, persisting for more than 8 weeks, is prevalent in the general adult population and significantly impacts quality of life (QoL) [5–10].

Cough reflex hypersensitivity has been recently proposed as a shared mechanism underlying chronic cough in adults [11]. This hypersensitivity can manifest as an exaggerated cough response to trivial stimuli such as cold air, perfume, talking or eating (referred to as allotussia); an increased cough response upon tussigen inhalation (hypertussia); or abnormal throat sensations like itching or tickling (laryngeal paraesthesia) [11, 12]. Studies using tussigen inhalation tests have reported an enhanced cough reflex in patients with different respiratory conditions such as asthma, bronchiectasis, COPD or idiopathic pulmonary fibrosis [13–16]. However, the differences in cough hypersensitivity across these various disease conditions remain under-explored.

In this study, we aimed to compare the profiles of cough hypersensitivity symptoms, including cough triggers and throat sensations associated with cough, between two major chronic cough phenotypes in our patient registry: asthmatic cough, including cough variant asthma and eosinophilic bronchitis, and refractory chronic cough (RCC). Additionally, the study examined the correlations between these cough hypersensitivity symptoms and cough-specific QoL within each phenotype to determine the clinical relevance of cough hypersensitivity symptoms.

Methods

Study participants

Patients with chronic cough were enrolled from the Korean Chronic Cough Registry, a prospective multicentre observational cohort of adult patients recruited from referral allergy, pulmonology or cough clinics across South Korea. The baseline cohort profile and study protocols have been previously described [17]. Inclusion criteria were adults aged ⩾19 years with active chronic cough (newly referred for chronic cough or already diagnosed with RCC). Exclusion criteria were 1) a “red flag sign”, such as haemoptysis, severe dyspnoea, fever, weight loss, peripheral oedema, dysphagia, vomiting or history of recurrent pneumonia; 2) abnormal findings on physical examination or chest radiography suggesting a serious condition other than chronic cough; or 3) active major medical conditions other than chronic cough, such as malignancy, heart failure, stroke or other severe respiratory diseases such as severe asthma. The study protocols were approved by the Institutional Review Boards (IRBs) of all participating institutions (IRB no. 2019–0754). All participants provided written informed consent and patient anonymity was preserved.

Baseline assessment

The baseline assessment included 1) demographic and clinical characteristics, including age, sex, body mass index (BMI), comorbidities and smoking history; 2) cough characteristics, including cough duration, cough severity Visual Analog Scale (VAS), Leicester Cough Questionnaire (LCQ) for cough-specific QoL [18, 19] and Cough Hypersensitivity Questionnaire (CHQ). Comorbidity was assessed by a physician.

The CHQ was originally developed based on qualitative patient interviews to evaluate cough-associated laryngeal sensations and cough triggers [20]. It consists of 6 questions on cough-related laryngeal sensations and 16 on cough triggers. Patients were asked to respond to each symptom-related item within 2 weeks [21]. The number of items answered “yes” totalled the score of each domain (cough-related laryngeal sensation domain (0–6 points), cough trigger domain (0–16 points) and CHQ total score (0–22 points)). In anchor-based method analysis, the change of CHQ total score that corresponds to the minimal clinically important difference of LCQ total score (1.3) [22, 23] was estimated to be 3.77 (unpublished data). The intra-class correlation coefficient of CHQ score was 0.780 in chronic cough patients with Δ LCQ<1.3 during 6 months (unpublished data).

Baseline diagnostic test results were reviewed for chest radiography, spirometry, bronchodilator response (BDR), methacholine challenge, fractional exhaled nitric oxide (F_{ENO}), induced sputum and blood eosinophil count. Chest radiographs were defined as abnormal if the patient had any grossly abnormal parenchymal lesion upon formal interpretation by the radiologist. BDR(+) was defined as an increase of ⩾12% and ⩾200 mL from baseline. Methacholine airway hyperresponsiveness (AHR) was defined as

positive if the concentration of inhaled methacholine that reduced forced expiratory volume in 1 s (FEV_1) 20% from baseline (PC_{20}) was <16 mg·mL^{-1}.

Cough assessment and phenotyping at 6-month follow-up visits

Patients were followed up at 6 months and received care according to international and national cough guidelines [24–26]. The diagnostic investigations and therapeutic trials were conducted as part of clinical practice, but none was mandatory for the study inclusion. According to the registry study protocols [17], cough phenotypes were determined by attending physicians according to diagnostic evaluations and treatment responses.

For the diagnosis of asthmatic cough (cough variant asthma or eosinophilic bronchitis), objective test results were required, such as the presence of BDR, AHR and type 2 (T2) inflammation (F_{ENO} ⩾25 ppb, induced sputum ⩾3% or blood eosinophil count ⩾300·μL^{-1} [27, 28]), and the diagnosis was verified based on a clinically significant response to anti-asthmatic therapy, including inhaled or oral corticosteroids and/or bronchodilators, as determined by clinicians.

The diagnosis of RCC was made if a cough remained persistent and refractory to aetiological management [24]. This includes not only a chronic cough that persists in patients with a comorbid condition associated with cough, such as asthma, rhinosinusitis or gastro-oesophageal reflux disease, despite appropriate aetiology-specific therapy, but also a persistent cough that cannot be explained by such aetiology.

Sensitivity analysis

To further reduce the confounding effects of "RCC with comorbid asthma" on asthmatic cough, we conducted a sensitivity analysis comparing patients with asthmatic cough based on their cough status at the 6-month follow-up. The aim was to differentiate subjects whose cough remained well controlled with anti-asthmatic therapy from those experiencing fluctuating cough symptoms, because the latter might indicate characteristics of RCC. For this purpose, we classified subjects with asthmatic cough based on their LCQ score at 6 months. The cut-off for this classification was derived from the patient global impression of scale analysis [29]: having no-to-minimal cough (LCQ score >16) or moderate-to-severe cough (⩽16).

An additional sensitivity analysis was conducted to explore the effects of each treatable trait on the baseline CHQ scores: T2 inflammation (F_{ENO} ⩾25 ppb, induced sputum ⩾3% or blood eosinophil count ⩾300·μL^{-1}), airflow obstruction (FEV_1/forced vital capacity (FVC) <0.7), and airway reversibility (BDR or AHR positive).

Statistical analysis

Continuous variables are described as mean±SD or median (interquartile range (IQR)) and categorical variables are presented as percentages with numbers. Mann–Whitney U-tests or t-tests were used to compare continuous variables between two groups, while Pearson's chi-squared or Fisher's exact tests were used for categorical variables. Correlations between two continuous variables were analysed using Spearman's correlation tests. To adjust for confounders, ANCOVA (general linear model), multivariate linear regression or binary logistic regression analysis was conducted. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 27.0 (IBM Corporation, Armonk, NY, USA).

Results

Study population

Among the 583 registry participants who reached the 6-month milestone after their baseline visit prior to July 2023, 365 (62.6%) returned for their 6-month follow-up visit. In comparing subjects who attended the 6-month follow-ups with those who missed them, there was no significant difference in baseline cough severity VAS, CHQ and LCQ scores (supplementary table 1). However, subjects who attended the 6-month follow-ups were older (56.4±15.2 *versus* 52.7±14.7 years, p=0.001) and had a higher prevalence of physician-diagnosed hypertension (29.5% *versus* 20.8%, p=0.022), compared with those who did not complete the follow-up visit.

Comparison of asthmatic cough versus RCC

Of the 365 patients who attended the 6-month follow-up, a cough phenotype was determined for 334. This analysis predominantly focused on two major cough phenotypes in the registry: asthmatic cough (n=79) and RCC (n=201). The process of subject selection is detailed in figure 1. The baseline characteristics of 280 study subjects are presented in table 1. Compared with those with RCC, patients with asthmatic cough

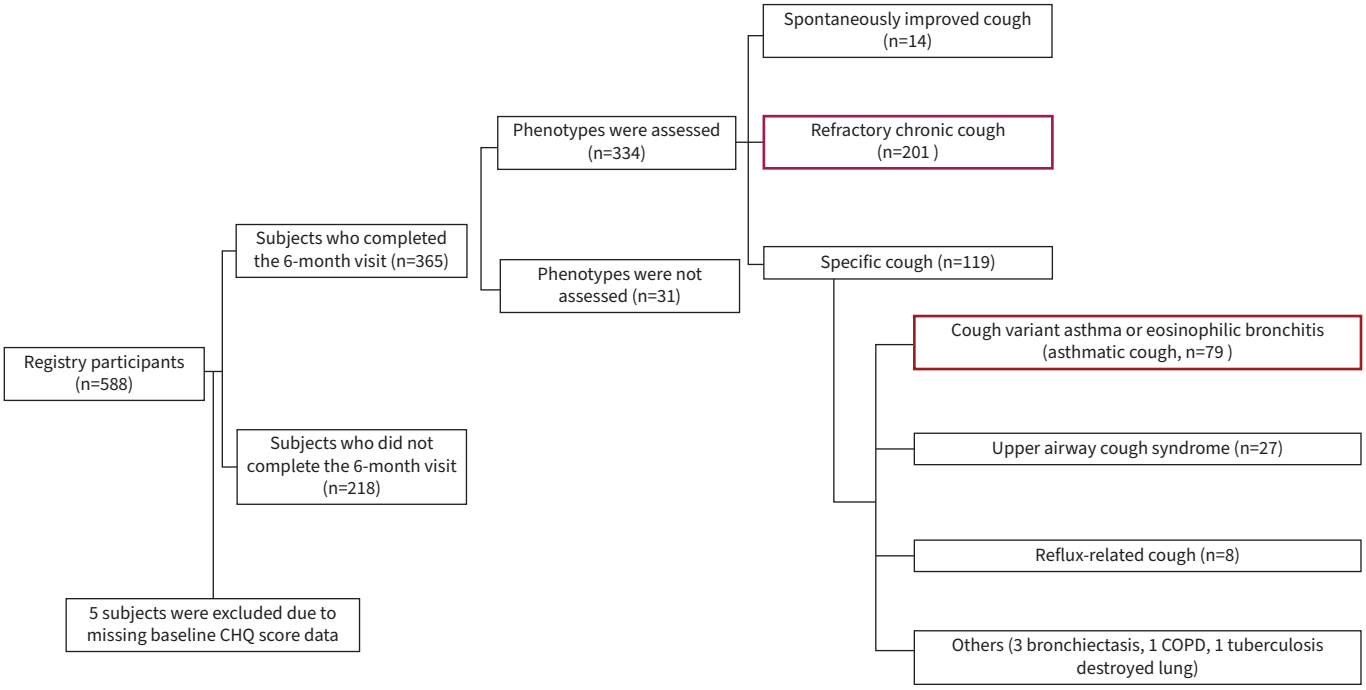

FIGURE 1 Flow diagram of study patient selection. CHQ: Cough Hypersensitivity Questionnaire.

had higher levels of F_{ENO} (median 27 ppb (IQR 17–37) *versus* 18 ppb (IQR 12–27); p<0.001). However, the baseline cough severity VAS, LCQ and CHQ scores were similar between the two groups.

Baseline CHQ response profiles in two patient groups are presented in figure 2. The CHQ score distribution was similar between asthmatic cough and RCC; CHQ total score was 8.3±3.7 in asthmatic cough and 8.9±3.9 in RCC (p=0.505, adjusted for age, sex and LCQ score). More than 95% of patients in each group reported one or more laryngeal sensations and cough triggers. The domain scores for laryngeal sensation and cough trigger were also comparable. There was no significant difference between each item response except for one item: "noticeable urge to cough before coughing starts"; 55.7% in asthmatic cough *versus* 69.7% in RCC (p=0.028, odds ratio 1.8, 95% confidence interval (CI) 1.1–3.1, adjusted for age and sex; figure 3).

Among other clinical parameters, the CHQ score was weakly correlated with age (r=−0.183, p=0.002) and BMI (r=0.156, p=0.009) and the score was higher in females (*versus* males; p=0.004) and nonsmokers (*versus* ex-smokers; p=0.003).

Correlations between the CHQ and LCQ scores

The baseline CHQ score was modestly correlated with the LCQ score in all subjects (r=−0.350, p<0.001), in patients with asthmatic cough (r=−0.427, p<0.001) and in those with RCC (r=−0.306, p<0.001) (figure 4). In multivariate linear regression analysis, the LCQ score was significantly associated with CHQ score, independently from demographic parameters (age, sex, BMI and smoking history) and cough phenotypes (asthmatic cough *versus* RCC) (correlation coefficient, −0.293; 95% CI, −0.395 to −0.190; p<0.001; data not shown).

Sensitivity analysis

We compared subjects with asthmatic cough based on their LCQ score at 6 months: those whose cough remained well controlled with anti-asthmatic therapy (likely having "pure asthmatic cough") *versus* those whose cough was not fully controlled at 6 months (potentially having "RCC with comorbid asthma"). Among 79 asthmatic cough subjects, 62 completed the LCQ at 6 months; 30 had no or minimal cough (LCQ score >16), while 32 experienced mild to very severe cough (LCQ score ⩽16) [29]. However, their baseline CHQ scores were comparable, as illustrated in figure 5. Their baseline characteristics were also generally similar (supplementary table 2).

TABLE 1 Baseline characteristics of study participants

	Asthmatic cough	RCC	p-value
Subjects, n	79	201	
Age, years	55.9±14.9	58.3±14.7	0.118
Sex, female, %	60.8	66.7	0.351
BMI, kg·m^{-2}	24.9±4.7	24.5±3.6	0.831
Smoking history, %			0.625
Nonsmoker	69.6	75.0	
Ex-smoker	25.3	21.5	
Current smoker	5.1	3.5	
Cough duration, remote, months (IQR)	72 (36–120)	72 (36–168)	0.313
Cough duration, recent, months (IQR)	5 (3–16)	12 (5–42)	0.001
Comorbidities, %			
Hypertension	28.0	34.5	0.306
Diabetes mellitus	10.7	12.8	0.638
Post-tuberculosis lung sequelae	9.3	5.6	0.271
Thyroid disease	5.4	7.1	0.787
Arrhythmia	4.0	2.0	0.400
Heart failure	1.3	0.5	0.479
Chest radiography abnormality, % (n)	20.0 (14 of 70)	11.5 (21 of 182)	0.082
Pulmonary function test			
FEV_1, % of predicted value	89.4±12.4	91.2±14.1	0.227
FVC, % of predicted value	86.9±12.1	87.9±12.7	0.488
FEV_1/FVC ratio	79.5±7.3	79.6±7.2	0.913
Methacholine AHR (+), % (n)	9.5 (2 of 21)	13.2 (7 of 53)	0.662
BDR (+), % (n)	10.0 (2 of 20)	1.4 (1 of 73)	0.053
F_{ENO}, ppb (IQR)	27 (17–37) (n=68)	18 (12–27) (n=184)	<0.001
Induced sputum eosinophils, % (IQR)	2.7 (0–5.5) (n=8)	0 (0–2) (n=17)	0.175
Blood eosinophils, µL (IQR)	125 (59–189) (n=43)	119 (73–207) (n=106)	0.730
Cough severity VAS	58.2±22.0	58.3±25.3	0.935
LCQ score	11.75±3.25	10.89±3.54	0.058

Data are presented as mean±SD, median with interquartile range (IQR) or % (and numbers where necessary). The most common chest radiography abnormalities were nodular opacities (three cases) in asthmatic cough and atelectasis (four cases) in RCC. Other abnormal findings included bronchiectasis, bronchial wall thickening and costophrenic angle blunting. Methacholine AHR was defined as positive if the PC_{20} was <16 mg·mL^{-1}. BDR was defined as positive if FEV_1 increased by ⩾12% and ⩾200 mL from baseline. RCC: refractory chronic cough; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; AHR: airway hyperresponsiveness; BDR: bronchodilator response; F_{ENO}: fractional exhaled nitric oxide; VAS: Visual Analog Scale; LCQ: Leicester Cough Questionnaire.

We conducted another sensitivity analysis to explore the effects of individual traits, such as T2 inflammation (F_{ENO} ⩾25 ppb, induced sputum ⩾3% or blood eosinophil count ⩾300·µL^{-1}), airflow obstruction (FEV_1/FVC <0.7) and airway reversibility (BDR or AHR positive). However, there were no significant differences according to the presence of each trait (supplementary table 3).

Discussion

This study evaluated the symptom profiles related to cough hypersensitivity in two major cough phenotypes in our patient registry: asthmatic cough and RCC. We found that symptoms of cough hypersensitivity, such as cough-associated laryngeal sensations and cough triggers, which were measured using the CHQ, were comparable in both groups with similar cough severity VAS and LCQ scores. The findings were also verified in our sensitivity analyses according to the 6-month LCQ score or the presence of baseline treatable traits of asthma. This finding supports the notion that cough hypersensitivity is a shared feature underlying chronic cough in adults, at least between asthmatic cough and RCC.

In the literature, only a few studies have reported cough hypersensitivity symptom profiles in patients with chronic cough. In a study of 53 patients with RCC in Australia, most reported abnormal sensations in the throat (*e.g.* blocked throat, tightness or irritation) and nontussive triggers of coughing [30]. Hilton *et al.* [31] described the sensations and triggers associated with the urge to cough in a sample of 100 patients with chronic cough recruited from a specialist cough clinic in the United Kingdom. Our previous cross-sectional

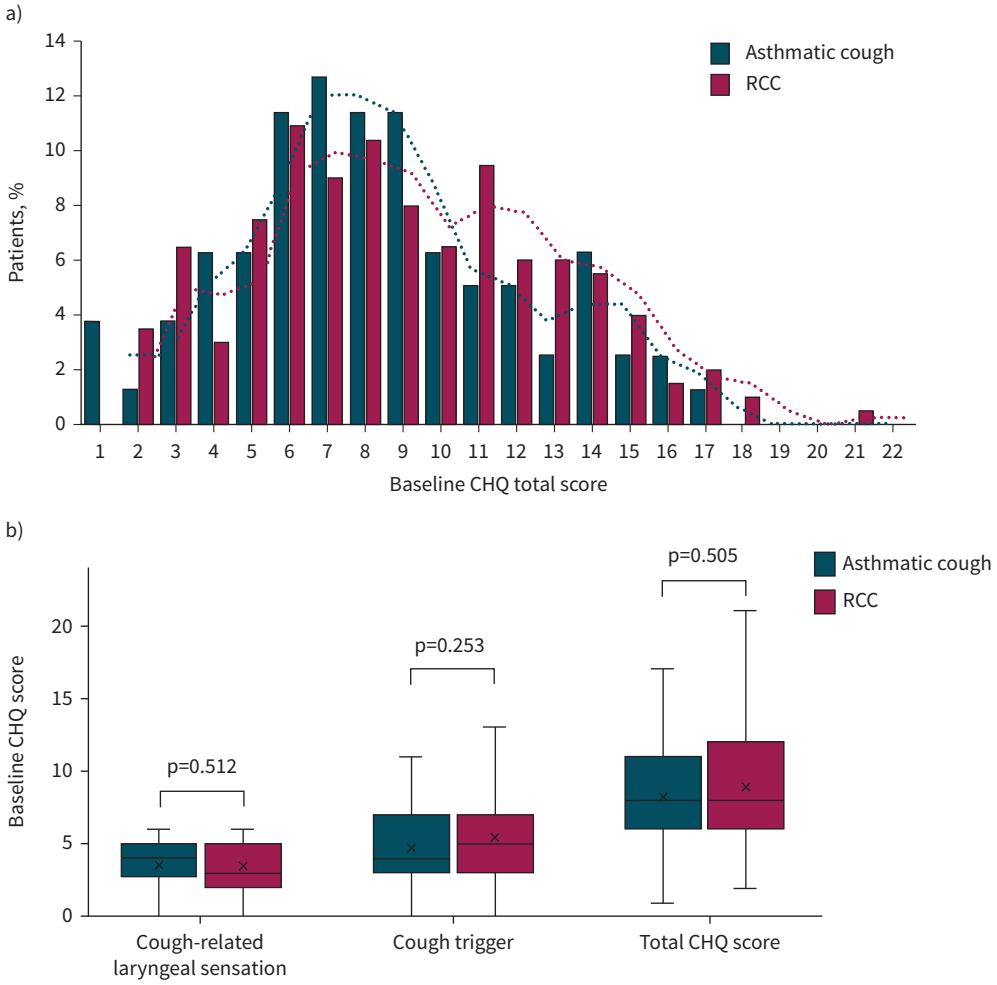

FIGURE 2 a) Comparison of baseline CHQ score distributions in asthmatic cough and RCC and b) Comparison of CHQ scores between asthmatic cough and RCC (box-and-whisker plot). CHQ: Cough Hypersensitivity Questionnaire; RCC: refractory chronic cough.

study using the CHQ found that 62 patients with RCC had higher scores for cough triggers (6.9±2.6 *versus* 5.0±2.8; p<0.001) and associated throat sensations (4.4±1.5 *versus* 3.9±1.9; p=0.049) than 416 newly referred patients with chronic cough; however, the previous study had a cross-sectional design and lacked information on cough severity and specific aetiologies [21]. In this regard, the present study is a valuable addition to the literature as it longitudinally evaluated cough phenotypes and compared the relevance of cough hypersensitivity symptoms between RCC and asthmatic chronic cough. Our findings may serve as clinical guidance, indicating that cough hypersensitivity symptom features before initiating treatment are unlikely to be helpful in predicting RCC from asthmatic cough.

Interestingly, as suggested by the distribution of CHQ scores (figure 2), the interindividual difference in symptom profiles was greater than the intergroup difference (*e.g.* asthmatic cough *versus* RCC). This substantial interindividual variability is in line with the observations from capsaicin inhalation challenge studies [32]. Female sex is a major factor associated with cough reflex hypersensitivity [21, 33, 34], as we also observed the association with CHQ score. However, the reasons behind this interindividual variability warrants further investigation.

The LCQ score showed similar correlations with CHQ score in both individuals with asthmatic cough and RCC. The findings support the notion that cough hypersensitivity is one of the factors affecting QoL [6, 18, 35, 36]. In a Finnish community population study by Koskela *et al.* [36] the number of cough triggers was significantly higher in a patient cluster with more severe cough. The findings align with

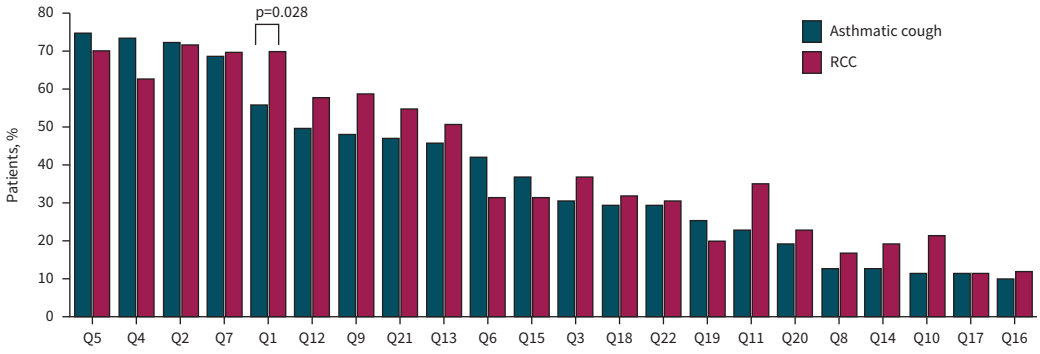

FIGURE 3 Response to Cough Hypersensitivity Questionnaire items in patients with asthmatic cough and RCC. Items are presented in descending order of positive responses. RCC: refractory chronic cough; Q1: noticeable urge to cough before coughing starts; Q2: tickle in throat; Q3: itchy throat; Q4: dry throat; Q5: irritation in throat; Q6: cough originating from a sensation in the chest; Q7: cold air; Q8: hot air; Q9: dry air; Q10: damp; Q11: perfumes and scents; Q12: smoke or smoky atmosphere; Q13: talking; Q14: laughing; Q15: eating or drinking; Q16: heartburn; Q17: indigestion; Q18: change in body position; Q19: exercise; Q20: brushing teeth; Q21: sputum; Q22: post-nasal drip.

clinical observations that the frequent complaints of patients are throat irritation/tickling and unpredictable and uncontrollable coughing triggered by talking, eating or temperature. The findings also underscore the importance of managing cough hypersensitivity in treatment strategies to improve patients' cough-specific QoL change.

In animal models of asthma, allergic inflammation induced a phenotypic switch in tracheal neurons to express TRPV1 more in guinea pigs [37], suggesting that cough reflex can be sensitised by peripheral inflammation (such as in the asthmatic airways). This may explain the common cough hypersensitivity symptoms observed in patients with asthmatic cough. Conversely, persistent cough hypersensitivity, in the absence of such peripheral triggers, may indicate a vicious cycle of peripheral neuropathy or central sensitisation. Thus, the presence of cough hypersensitivity symptoms might not indicate whether the hypersensitivity is an aetiology or a consequence, and a single measurement might not be useful in making a differential diagnosis, as we observed in this study. Meanwhile, among the CHQ items, the urge to

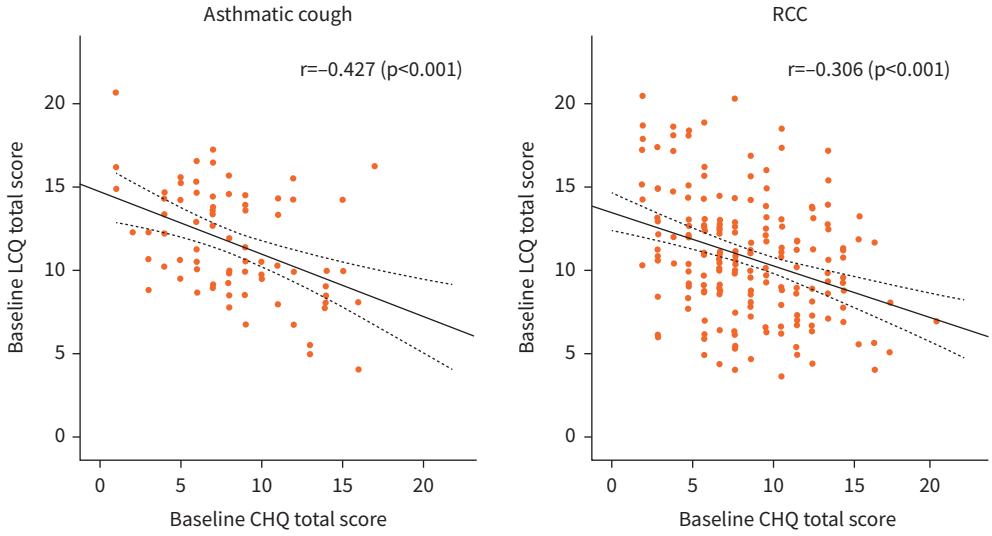

FIGURE 4 Scatter-plots showing Spearman correlations between baseline LCQ and CHQ score in asthmatic cough and RCC. LCQ: Leicester Cough Questionnaire; CHQ: Cough Hypersensitivity Questionnaire; RCC: refractory chronic cough.

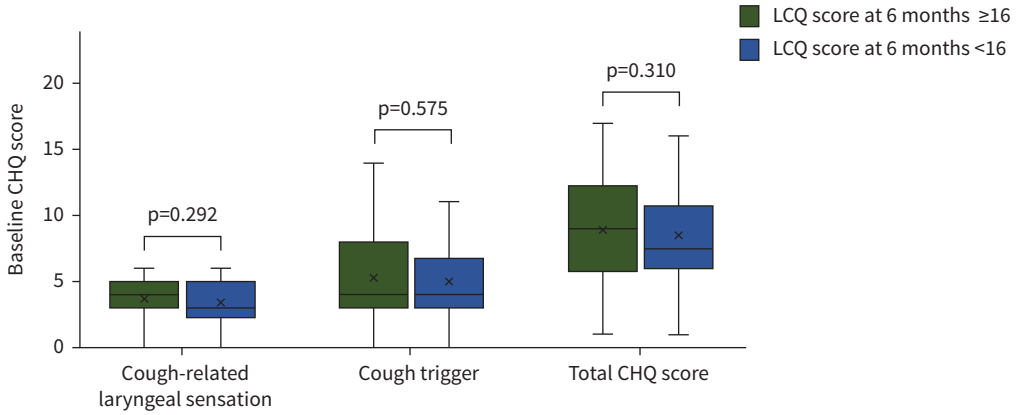

FIGURE 5 Comparison of baseline CHQ scores between patients with 6-months follow-up LCQ score ⩾16 points and <16 points in asthmatic cough. Age, sex and baseline LCQ score were adjusted by ANCOVA (general linear model). CHQ: Cough Hypersensitivity Questionnaire; LCQ: Leicester Cough Questionnaire.

cough sensation (Q1) was noticeably more frequent in patients with RCC, which might suggest a possibly different pattern of sensitisation in RCC (*versus* asthmatic cough). However, our registry study is limited in its observational nature.

There are several limitations to this study. First, the study population consisted of patients visiting referral clinics in South Korea; hence, our findings may have limited external validity. Patients in the community could have less-severe cough symptoms, and the relevance of cough hypersensitivity symptoms might be different. Available treatment options for RCC might be different across countries. In South Korea, speech pathology therapy is not available for chronic cough, whereas pharmacological treatments, such as codeine, gabapentin or pregabalin, are readily accessible. However, accessibility to asthma treatment is supposed to be the same as in most developed countries in other continents. Second, we did not utilise objective tussigen inhalation challenge tests due to the routine clinical practice setting of our study. However, our questionnaire-based findings could have better applicability to clinical practice. In a previous study of 32 subjects with pulmonary sarcoidosis, a modest-to-weak correlation was observed between CHQ score and capsaicin C5 ($r=-0.36$, $p=0.045$) [38]. Third, the follow-up rate at 6 months was relatively low (62.6%), although we tried to address the risk of selection bias by comparing those who completed the follow-up visit and those who did not (supplementary table 1). Fourth, there could be a risk of misclassification of cough phenotypes, as our classifications were determined by a physician, based on the diagnostic evaluations and treatment responses. The aetiological diagnosis of cough has an intrinsic risk of misclassification, even in the presence of objective markers supporting the diagnosis, because cough is prone to regression to the mean or placebo effects [39]. In our registry, the diagnostic investigations and therapeutic trials were conducted as part of clinical practice, and accordingly, not every subject in the registry underwent all the tests. Nevertheless, the attending physicians were allergists, pulmonologists or cough specialists at referral hospitals, and they were instructed to follow chronic cough guidelines in the identification and management of causes [24, 26]. Also, our diagnosis of asthmatic cough was corroborated by the presence of at least one objective marker, such as T2 inflammation and/or variable airflow obstruction. In addition, we conducted a subgroup analysis of asthmatic cough patients according to their 6-month LCQ score, to reduce possible confounding effects from subjects with possible RCC and comorbid asthma (supplementary table 2). Finally, our definition of asthmatic cough was broad. This limitation is related to the lack of an agreed-upon single diagnostic test and also to the subjectiveness in defining asthma [24]. Different markers may indicate different pathophysiology or treatable traits, such as T2 inflammation, AHR or airflow limitation; to address the possibility, we conducted a sensitivity analysis to explore the effect of each asthmatic trait (supplementary table 3). Due to these limitations, our approach should be viewed as pragmatic, based on data collected from routine clinical practice settings.

Despite the limitations, this study represents the first evaluation of the clinical relevance of cough hypersensitivity symptom profiles in relation to cough phenotypes (asthmatic cough *versus* RCC) in a longitudinal cohort of patients with chronic cough. Our findings indicate a shared mechanism in their cough pathogenesis, despite having potentially different treatable traits. Additionally, our data may suggest that “asthma-variant cough” is a more appropriate term than “cough variant asthma”, given that cough

hypersensitivity symptoms are the chief complaints, while asthmatic features act as triggers and treatable traits of chronic cough in these patients. We also found that interindividual differences in hypersensitivity symptoms exceeded the intergroup differences, a phenomenon that warrants further investigation.

Provenance: Submitted article, peer reviewed.

Ethics statement: The study protocols were approved by the IRBs of all participating institutions (IRB number 2019-0754). All participants provided written informed consent and patient anonymity was preserved.

Author contributions: Mi-Yeong Kim and Woo-Jung Song designed the study and wrote the manuscript. Ha-Kyeong Won, Ji-Yoon Oh, Ji-Hyang Lee, Eun-Jung Jo, Sung-Yoon Kang, Ji-Ho Lee, Seung-Eun Lee, Noeul Kang, Young-Chan Kim, Hwa Young Lee, Jin An, Youngsang Yoo, Ji-Su Shim, So-Young Park, Han-Ki Park, Min-Hye Kim, Sae-Hoon Kim, Sang-Heon Kim, Yoon-Seok Chang, Sang-Hoon Kim and Byung-Jae Lee contributed data collection. All authors, including Surinder S. Birring, revised the manuscript and approved its final submitted version.

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