



Exploring the concept of disease control in chronic cough

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Disease control in chronic cough represents a distinct concept that is not fully captured by conventional patient-reported outcome measures for cough. There is a need to develop both a consensus on this concept and specific measurement tools. <https://bit.ly/3woOUxT>

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Abstract

Background Disease control in chronic diseases is an overarching concept that reflects the degree to which the goals of therapy are met. However, to date, there is no consensus on the definition of disease control in chronic cough. This study aimed to provide a conceptual exploration of patient-reported cough control in chronic cough.

Methods This research is comprised of two subanalyses. First, patients with chronic cough receiving care at referral clinics were evaluated. Correlation analyses were performed between patient-reported cough control (a 5-point Likert scale), cough-specific patient-reported outcomes (PROs) and generic health PRO scores. Second, a survey was conducted among patients with refractory chronic cough and physicians to identify factors pertinent to cough control.

Results The analysis of 341 patients (mean age: 55.5±15.1 years; female: 66.6%) revealed that cough control rating was moderately correlated with cough severity visual analogue scale and Leicester Cough Questionnaire scores, while demonstrating weaker correlations with cough-associated throat symptoms, cough-related complications or general health-related quality of life (QoL). In the survey of patients and physicians, both groups considered certain factors, such as cough frequency, severity and impact on QoL, to be relevant to the concept of cough control. However, patients rated “need for cough rescue drug” notably higher than physicians.

Conclusion Patient-reported cough control was associated with cough severity or impact on QoL; however, cough control may not be fully captured by conventional cough PRO measurement tools. Further studies are warranted to define the consensus and tools to measure disease control in chronic cough.



Introduction

Cough, while primarily a physiological reflex aimed at protecting the lower airways, also stands as one of the most prevalent symptoms prompting patients to seek medical consultation [1, 2]. Chronic cough, defined as a persistent cough enduring beyond 8 weeks in adults [3, 4], manifests in ~5–10% of individuals within the general population [5, 6]. It is often refractory to treatment, persisting for several years and detrimentally affecting quality of life (QoL) [7–10].

Disease severity typically encompasses the extent of impact, impairment or treatment requisites induced by a disease [11–13]. Conversely, disease control denotes the objective of treatment, delineating the efficacy with which a disease is managed through interventions, encompassing preventative measures and curative approaches [14]. Thus, disease control embodies a broader scope than disease severity. In chronic cough, the concept of cough severity has been advanced as a multidimensional construct, encompassing parameters such as cough intensity, frequency, disruption and the sensation of the urge to cough [15, 16]. However, to date, there is no consensus on the definition of disease control in chronic cough.

In this study, we investigated the correlations between patient-rated cough control status and patient-reported outcomes (PROs) concerning both cough and general health status, utilising a database from a prospective registry of patients with chronic cough. Additionally, we endeavoured to identify the specific elements associated with cough control that are valued by both patients and physicians. Through this analysis, our objective was to gain deeper insights into the concept of cough control among patients with chronic cough.

Methods

This study encompassed two distinct subanalyses: 1) an examination of the correlations between patient-reported cough control and cough-specific and general health-related PRO scores; and 2) a survey administered to patients and physicians regarding items pertinent to cough control.

Study participants

The study enrolled participants aged 19 years and older who were receiving care for chronic cough at referral clinics and participated in the Korean Chronic Cough Registry study [17]. Exclusion criteria included: 1) presentation of “red flag signs”, such as haemoptysis, severe dyspnoea, fever, weight loss, peripheral oedema, dysphagia, vomiting or a history of recurrent pneumonia; 2) detection of abnormal findings during physical examination or chest radiograph indicative of serious conditions other than chronic cough; or 3) presence of active major medical conditions other than chronic cough, such as malignancy, heart failure, stroke or other severe respiratory diseases. The study protocols were approved by the Institutional Review Boards of all participating institutions, and all participants provided written informed consent.

Assessment of PROs and cough control status

Demographic and clinical characteristics, including age, sex, smoking history, cough duration and medical history, were recorded. Baseline diagnostic assessments, such as chest radiograph, spirometry and exhaled nitric oxide fraction (F_{ENO}), were reviewed. Chest radiograph results were defined as abnormal formal interpretation by a radiologist that revealed any grossly abnormal parenchymal lesions.

Patient self-rated cough control status was assessed at 6-month follow-up visits within the registry study. The assessment utilised a 5-point Likert scale (1–5), with participants responding to the question, “Is your cough currently under control?” A higher score denoted a better cough control status. On the same day, the following cough-related parameters were also recorded: presence of cough-related complications, visual analogue scale (VAS) for cough severity in the past week (0–100), VAS for throat sensation severity in the past week (0–100), Leicester Cough Questionnaire (LCQ) to evaluate cough-specific QoL over the preceding 2 weeks and Cough Hypersensitivity Questionnaire (CHQ) to assess the degree of cough triggers and cough-related laryngeal sensations experienced over the past 2 weeks [18, 19]. Self-reported cough-related complications included fatigue, urinary incontinence, chest pain, syncope, headache, hernia or others (yes or no) [17]. The cough severity VAS was rated without anchors, using the question “How would you rate the severity of cough in the past week?” [17] The Korean version of the LCQ, validated for measuring cough-specific QoL, yielded scores ranging from 3 to 21, with a lower score indicating poorer cough-specific QoL status [18]. The CHQ comprised six questions regarding cough-related laryngeal sensations and 16 questions pertaining to cough triggers, with a total score of 22; a higher score signified a greater manifestation of hypersensitivity symptom features [19].

General health-related QoL was assessed using the five-level EuroQoL five-dimension (EQ-5D-5L) questionnaire and EQ-VAS [20]. The EQ-5D index spans from less than 0 (where 0 denotes a health state comparable to death; negative values indicate a health state worse than death) to 1 (representing perfect health). Meanwhile, the EQ-VAS gauges self-reported health status on a scale from 0 (denoting the poorest state of health) to 100 (indicating best imaginable health).

Survey of patients and physicians on items related to cough control

A survey was conducted among a group of patients with refractory chronic cough (persistent cough despite etiological management; n=50) and physicians actively engaged in clinical practice (n=38) to evaluate their assessment of items pertinent to cough control. A total of 14 survey items were selected for their potential relevance to disease control. The selection process involved: 1) a comprehensive review of research on chronic cough PROs; 2) an examination of the existing literature on the disease control of chronic airway diseases, including asthma and chronic rhinosinusitis; and 3) the expertise and clinical experience of specialist clinicians. Participants were requested to assess the relevance of each item to the concept of cough control, with responses recorded on a 5-point Likert scale (5=extremely relevant, 1=irrelevant).

Statistical analysis

Continuous variables are presented as mean±SD or medians with interquartile range (IQR), while categorical variables are expressed as percentages with numbers. Spearman's correlation test was employed to evaluate the associations between cough control and other PRO measures or item scores. Data analysis was conducted using Stata software (Version 18.0, Stata Corp., College Station, TX, USA). p-values of <0.05 were considered statistically significant.

Results

Study participants

A total of 341 patients with chronic cough were analysed. An overview of their demographic and clinical characteristics is provided in table 1. The mean age of the participants was 55.5±15.1 years, with females constituting 66.6% of the study population. The median cough duration was 60 months (IQR: 18–120).

TABLE 1 Baseline characteristics of study participants (n=341)

Age years	55.5±15.1
Female sex	66.6
Smoking status	
Never-smoker	74.4
Ever-smoker	25.6
Cough duration months	60 (18–120)
Cough-related complications	
Fatigue	34.8
Incontinence	20.7
Headache	14.6
Chest pain	11.2
Syncope	0.0
Hernia	0.0
Others	5.0
Number of cough-related complications	1 (0–1)
FEV₁ % of predicted	89.8±17.4
FVC % of predicted	88.1±16.0
FEV₁/FVC ratio %	79.5±7.6
F_{ENO} ppb	20 (12–28)
Abnormal chest radiograph	10.2
Cough control rating (1–5)	3.6±1.1
Cough severity VAS (0–100)	34.9±25.8
Throat sensation VAS (0–100)	32.4±28.6
LCQ total score (3–23)	14.1±3.9
LCQ physical domain score	5.0±1.1
LCQ psychological domain score	4.5±1.5
LCQ social domain score	4.6±1.6
CHQ total score (0–22)	7.5±4.5
CHQ laryngeal sensation score	2.8±1.7
CHQ cough trigger score	4.7±3.2
EQ-5D index (0–1.00)	0.87±0.12
EQ-VAS (0–100)	70.8±15.9

Data are presented as %, mean±SD or median (IQR). FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: exhaled nitric oxide fraction; VAS: Visual Analogue Scale; LCQ: Leicester Cough Questionnaire; CHQ: Cough Hypersensitivity Questionnaire; EQ-5D: EuroQoL 5-dimension.

Cough-related parameters and associations with cough control status

In Spearman's correlation analyses, the cough control rating score exhibited moderate correlations with the cough severity VAS ($r = -0.713$, $p < 0.001$) and LCQ scores ($r = 0.587$, $p < 0.001$). Weaker correlations were observed with the throat sensation VAS ($r = -0.389$, $p < 0.001$), CHQ score ($r = -0.329$, $p < 0.001$), the number of cough-related complications ($r = -0.302$, $p < 0.001$), EQ-VAS index ($r = 0.258$, $p < 0.001$) and EQ-5D index ($r = 0.189$, $p = 0.004$). However, no significant correlation was observed with lung function parameters or F_{ENO} levels (table 2).

Among the LCQ domains, the cough control rating score exhibited stronger correlations with the psychological and social domain scores compared with the physical domain score (table 2). Moreover, within the LCQ items, the cough control score displayed higher correlations with the following items: "Feeling in control of one's cough (LCQ4, psychological domain; $r = 0.632$)", "Feeling embarrassed (LCQ5, psychological domain)", "Feeling fed up (LCQ13, psychological domain)", "Feeling anxious (LCQ6, psychological domain)" and "Frequent coughing bouts (LCQ11, physical domain)" (figure 1). In the CHQ, the correlation of the cough control rating score was stronger with the laryngeal sensation score ($r = -0.352$) compared with the cough trigger score ($r = -0.286$; table 2). Regarding the EuroQoL questionnaire items, although the correlations were predominantly weak with the cough control score, anxiety/depression and pain/discomfort displayed some correlations (table 2).

Patient and physician ratings of item relevance to cough control

A total of 50 patients with refractory chronic cough (mean age: 58.8 ± 13.9 years; 74.0% female; 80% nonsmokers; and cough severity VAS: 45.1 ± 31.0) participated in the item rating survey. They were tasked with assessing the relevance of items to the concept of cough control using a 5-point Likert scale (5=extremely relevant, 1=irrelevant). Figure 2a presents the ratings assigned to each item concerning cough control. Items with the highest average scores included "need for cough rescue drug" (4.38 ± 0.90) and "overall health quality of life" (4.38 ± 0.88), followed by "cough frequency" (4.36 ± 0.75), "cough severity" (4.30 ± 0.76) and "impact of cough on usual activity" (4.30 ± 0.97).

Meanwhile, a survey involving 38 clinicians evaluating the same items revealed high scores for "cough frequency" (4.53 ± 0.76), "cough severity" (4.39 ± 0.82), "impact of cough on usual activity" (4.24 ± 0.68)

TABLE 2 Correlations between cough control rating and other parameters

	Correlation coefficient	p-value
Cough severity VAS	-0.713	<0.001
LCQ total score	0.587	<0.001
LCQ psychological domain score	0.626	<0.001
LCQ social domain score	0.547	<0.001
LCQ physical domain score	0.459	<0.001
Throat sensation VAS	-0.389	<0.001
CHQ total score	-0.329	<0.001
CHQ laryngeal sensation score	-0.352	<0.001
CHQ cough trigger score	-0.286	<0.001
Number of cough-related complications	-0.302	<0.001
EQ-VAS	0.258	<0.001
EQ-5D index	0.189	0.004
Anxiety/depression	-0.220	<0.001
Pain/discomfort	-0.185	0.005
Usual activities	-0.156	0.017
Mobility	-0.041	0.531
Self-care	-0.006	0.930
FEV₁ % predicted	-0.071	0.224
FVC % predicted	-0.041	0.479
FEV₁/FVC ratio	-0.006	0.923
F_{ENO} ppb	-0.006	0.924

VAS: Visual Analogue Scale; LCQ: Leicester Cough Questionnaire; CHQ: Cough Hypersensitivity Questionnaire; EQ-5D: EuroQoL 5-dimension; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: exhaled nitric oxide fraction.

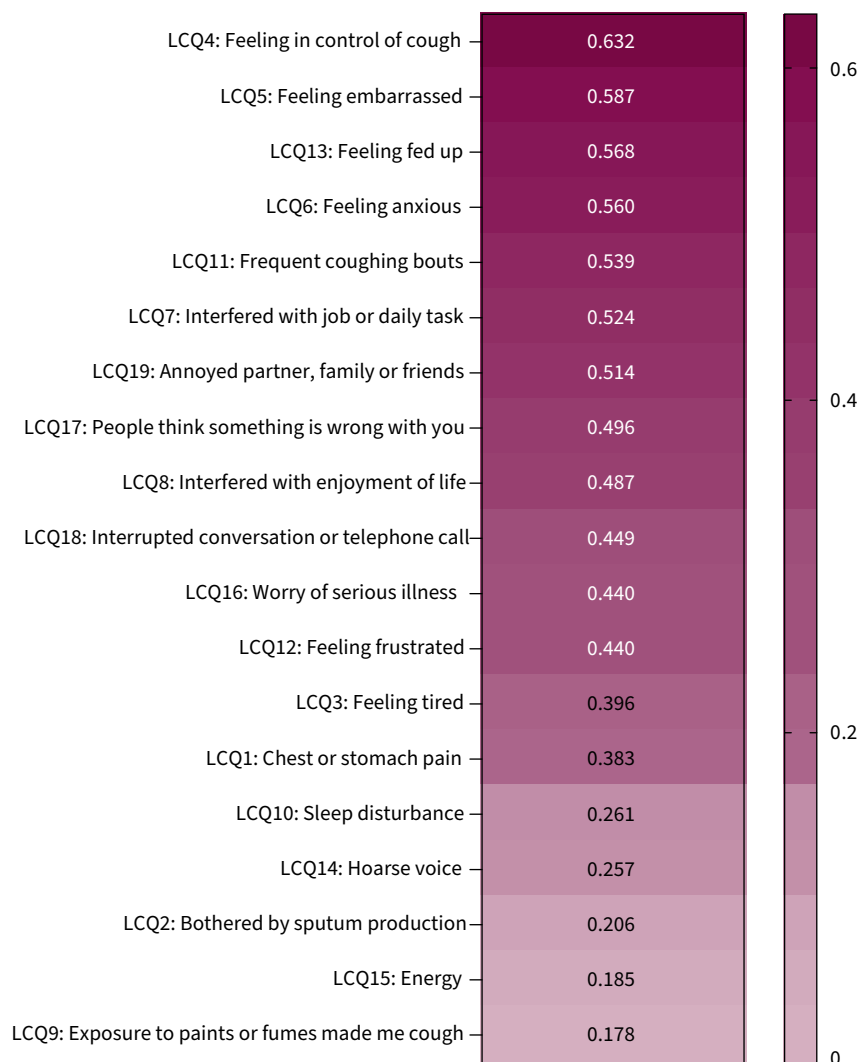


FIGURE 1 Correlation of the cough control rating with Leicester Cough Questionnaire (LCQ) items.

and “overall health quality of life” (3.95 ± 0.73). However, in contrast to the patients’ responses, “need for cough rescue drug” received a lower rating (3.45 ± 0.83) (figure 2b).

The ratings provided by patients and physicians were depicted in a scatter dot plot, with each point representing the average score. While there was a general concordance on many items such as “cough frequency”, “cough severity”, “impact on usual activity” and “physical complications”, there were specific instances where patient and physician ratings diverged. Notably, patients found certain items, such as “need for cough rescue drug”, “throat sensation”, “drug side-effects”, “phlegm” and “hoarseness”, more relevant than physicians did (figure 3).

Discussion

The present study explored the concept of cough control among patients with chronic cough. First, leveraging data from a prospective registry, we identified statistically significant but moderate correlations between patient-rated cough control and both cough severity and cough-specific QoL impairment (LCQ score), suggesting that conventional cough PROs may not fully encapsulate the multifaceted nature of cough control. Furthermore, correlations with cough-associated throat symptoms, cough-related

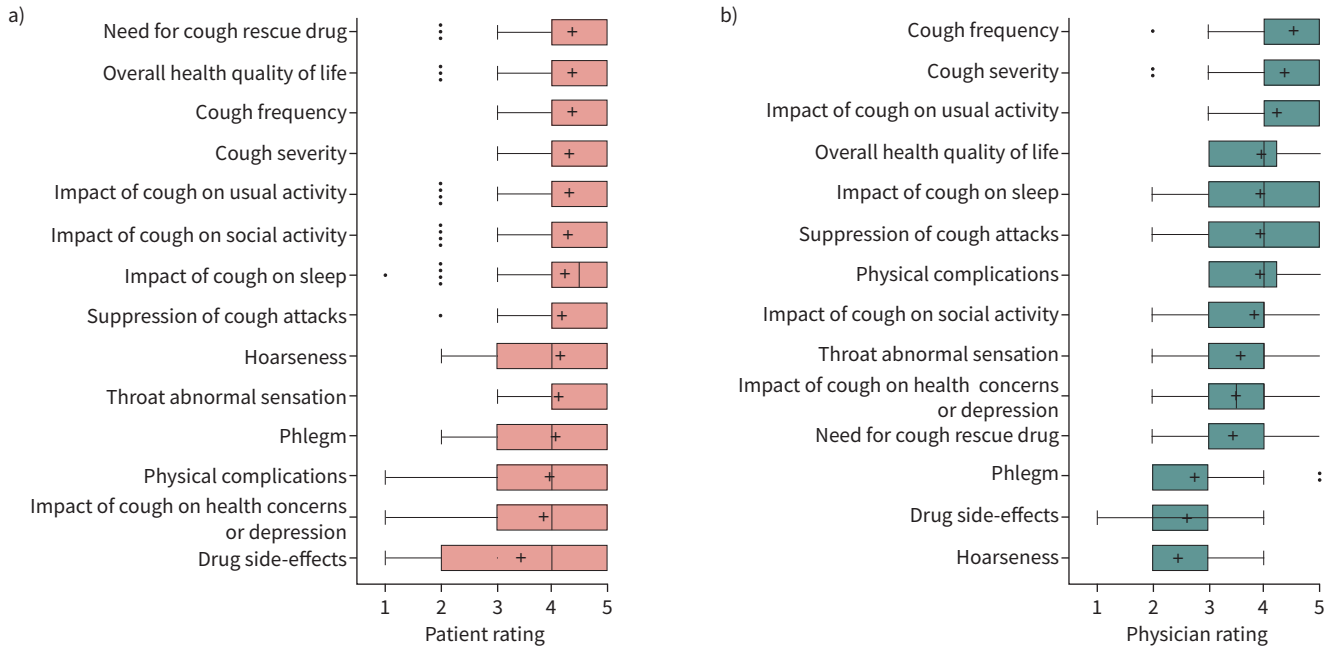


FIGURE 2 a) Patient and b) physician ratings of item relevance to cough control.

complications or general health-related QoL were comparatively weaker, suggesting that patients’ perception of cough control primarily considers the cough itself rather than its associated symptoms or complications. Second, in the survey of patients and physicians, we observed generally congruent ratings regarding items pertinent to cough control, such as cough frequency, cough severity and impact on QoL. However, notable discordance emerged for items such as “need for cough rescue drug”, “drug side-effects”, “phlegm” and “hoarseness”, with patients assigning higher relevance to these factors than physicians. This underscores the importance of integrating patients’ treatment needs and cough-associated symptoms into the concept of cough control.

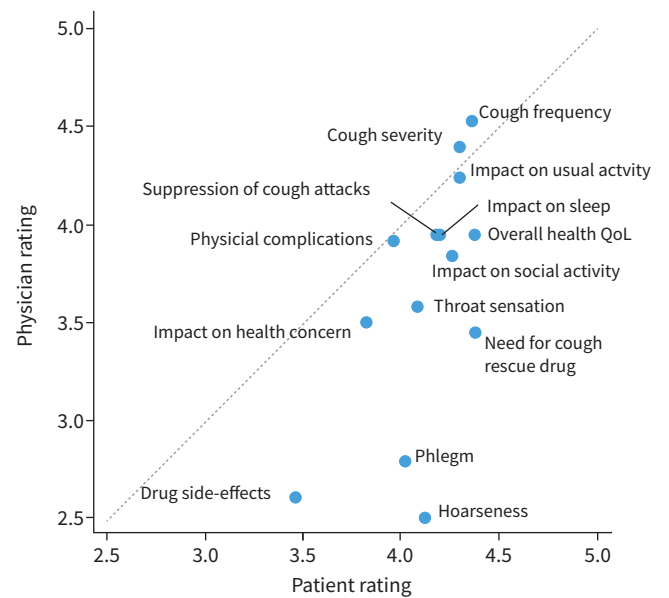


FIGURE 3 Scatter dot plot illustrating the mean score of patient and physician ratings. QoL: quality of life.

Disease control has emerged as a pivotal outcome measure in the evaluation and management of chronic diseases, for which curative care is not an option. It pertains to the extent to which the manifestations of a disease are within acceptable limits [21, 22]. Notably, the concept of disease control has been extensively employed in asthma management, denoting the extent to which the various manifestations of asthma have been reduced or eliminated through treatment. The establishment of clear definitions for different levels of control has facilitated the development of standardised approaches to asthma treatment, consequently improving patient outcomes [23–26]. In chronic rhinosinusitis, it is characterised by the absence of bothersome symptoms and the presence of a healthy nasal mucosa without the need for systemic medication [27]. Conversely, the understanding of chronic cough control and its determinants remains unexplored, despite chronic cough being considered as a distinct disease entity. To our knowledge, this study represents the first attempt to elucidate factors associated with the control of chronic cough.

We found that both patients and physicians consider cough frequency a key factor contributing to cough control. This finding aligns well with recent chronic cough guidelines and clinical trials, where objective cough frequency is a core outcome in decision-making and demonstrating the treatment efficacy of antitussive drugs [3, 28]. However, it remains to be determined how objective cough frequency should be measured and how it can be incorporated into the definition of cough control. Further studies are warranted to correlate cough control with the degree of, or longitudinal changes in, objective cough frequency.

It is noteworthy that the patients rated “need for cough rescue drug” as the highest-scoring factor. This aspect may serve as a crucial determinant of cough control status among patients, despite being poorly perceived by physicians. Notably, there have been no specific tools or attempts to evaluate patients’ medication needs or to ascertain whether therapy adjustments are warranted for chronic cough. This gap partly stems from the lack of a well-established concept of “rescue medication” for chronic cough. Nevertheless, the findings suggest that patient-reported control status is indicative of their perception regarding the adequacy of medical management or other interventions aimed at ameliorating disease processes or clinical manifestations [23]. For any given level of severity, the need to initiate, modify or escalate treatment is proportional to the control status [21]. Therefore, further investigation is warranted to establish the relationships between cough control and the requirement for rescue drug medications.

This study is subject to several limitations. First, objective cough measures were not incorporated into our study due to the pragmatic nature of the clinical practice setting in which the study was conducted [17]. Nonetheless, the determinants of cough control were identified by both patients and physicians in real-world practice. Second, we examined several conventional cough-specific and general health-related PROs as potential determinants of cough control status. These included the cough severity VAS, LCQ, CHQ and EuroQoL questionnaires, along with their individual items. While these factors are significant, additional factors might also be relevant from the patients’ perspectives on cough control. To explore this, we surveyed both patients and physicians and evaluated their views on additional items such as the impact on sleep, suppression of cough attacks and drug side-effects. Moreover, given the examples from severe asthma [29], the risk of future adverse health outcomes, such as the incidence of comorbidities or mortality, might also be worth consideration. However, the long-term health consequences of having chronic cough remain largely unknown. Third, we utilised a Likert scale for assessing cough control status, while maintaining the original scales for conventional PROs. A response scale or the use of anchors may affect the degree of correlations. However, the correlation between the VAS (a continuous scale) and the Patient Global Impression of Severity (a categorical scale) regarding cough severity was reported to be as high as 0.81 [30]. Finally, the sample size of the item rating survey was relatively small, potentially limiting the generalisability of our findings. It is noteworthy that the concept of cough control may exhibit variability depending on individual patient’s or physician’s experiences. Thus, specific components underlying cough control necessitate further investigation based on the inputs from both patients and clinicians.

Despite these limitations, this research represents the first exploration into the concept of cough control. Our findings indicate that cough control is not fully captured by conventional PRO measurement tools. Given the treatment demands and prolonged disease duration associated with chronic cough, there is a compelling need to develop a tailored tool to delineate disease control as a treatment outcome in this patient population.

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Ethics statement: The study protocols were approved by the Institutional Review Boards of all participating institutions and all participants provided written informed consent.

Author contributions: Woo-Jung Song is the full guarantor of this manuscript. Jin Young Park and Woo-Jung Song contributed to the study conception and design, and data interpretation. Seung-Eun Lee, Ha-Kyeong Won, Sung-Yoon Kang, Noeul Kang, Ji-Yoon Oh, Young-Chan Kim, So-Young Park, Jin An, Youngsang Yoo, Mi-Yeong Kim, Hwa Young Lee, Ji-Su Shim, Min-Hye Kim, Sae-Hoon Kim, Sang-Heon Kim, Yoon-Seok Chang, Sang-Hoon Kim, Byung-Jae Lee and Woo-Jung Song have made contributions to the data acquisition. Jin Young Park and Woo-Jung Song performed formal analysis. Jin Young Park and Woo-Jung Song drafted the first version of the manuscript. Haesung Jun, Surinder S. Biring and Woo-Jung Song revised the manuscript. All authors approved this version of the manuscript for submission.

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