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COUGH

Baseline Cohort Profile of the Korean Chronic Cough Registry: A Multicenter, Prospective, Observational Study

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Abstract

Purpose The Korean Chronic Cough Registry study was initiated to characterize patients with chronic cough (CC) and investigate their outcomes in real-world clinical practice. This report aims to describe the baseline cohort profile and study protocols.

Methods This multicenter, prospective observational cohort study included newly referred CC patients and those already being treated for refractory or unexplained chronic cough (RUCC). Cough status was assessed using a visual analog scale, the Leicester Cough Questionnaire (LCQ), and the Cough Hypersensitivity Questionnaire (CHQ).

Results A total of 610 patients (66.9% women; median age 59.0 years) were recruited from 18 centers, with 176 being RUCC patients (28.9%). The median age at CC onset was 50.1 years, and 94.4% had adult-onset CC (≥19 years). The median cough duration was 4 years. Compared to newly referred CC patients, RUCC patients had a longer cough duration (6.0 years vs. 3.0 years) but had fewer symptoms and signs suggesting asthma, rhinosinusitis, or gastroesophageal acid reflux disease. Subjects with RUCC had lower LCQ scores (10.3 ± 3.3 vs. 11.6 ± 3.6; $P < 0.001$) and higher CHQ scores (9.1 ± 3.9 vs. 8.4 ± 4.1; $P = 0.024$). There were no marked differences in the characteristics of cough between refractory chronic cough and unexplained chronic cough.

Conclusions Chronic cough typically develops in adulthood, lasting for years. Cough severity and quality of life impairment indicate the presence of unmet clinical needs and insufficient cough control in real-world clinical practice. Longitudinal follow-up is warranted to investigate the natural history and treatment outcomes.

Keywords Cough · Registries · Prospective studies · Patient outcome assessment

Introduction

Cough is a physiological defense reflex to protect the lower airways. However, it is one of the most frequent symptoms for which patients seek medical care [1, 2]. Chronic cough (CC), typically defined as a cough lasting for longer than 8 weeks in adults [3–5], is a prevalent medical condition, affecting approximately 5–10% of the general adult populations [6–9]. CC is often refractory to treatments and can substantially impair quality of life (QoL) [10–12].

Despite recent advances in understanding the pathophysiology of CC and the development of novel antitussive drugs [13, 14], the epidemiology of CC remains largely understudied, especially regarding its natural progression and long-term outcomes in real-world settings [14]. Most current knowledge has been obtained from simple questionnaire-based population surveys, retrospective analyses of routinely collected data, or single-centered studies [2, 7, 8, 15–20]. In this background, we have initiated a multicenter, prospective, observational cohort study on patients with CC. The primary objectives are as follows: (1) to evaluate the clinical characteristics, treatment responses, and longitudinal courses of CC; (2) to quantify the disease burden; (3) to investigate the prevalence of refractory or unexplained chronic cough (RUCC) among referred CC patients and identify predictive factors; and (4) to establish an infrastructure for studying novel biomarkers and therapeutic targets

Extended author information available on the last page of the article

in CC. This report aims to outline the baseline cohort profile and study protocols, as well as to compare the baseline characteristics of patients with RUCC vs. newly referred CC patients.

Materials and Methods

Study Design and Participants

The Korean Chronic Cough Registry study is a multicenter, prospective observational cohort study involving CC patients receiving care at referral allergy, pulmonology, or cough clinics. The study network initially consisted of 12 centers during the first wave (from July 2019 to March 2022) and extended to 18 centers during the second wave of the study (since April 2022) (Fig. 1). A part of the cross-sectional data focused on health-related QoL (HRQoL) among 200 subjects was previously reported [21].

Subjects were included if they were Korean adults aged ≥ 19 years and had active CC (either newly referred with CC or being treated for RUCC). Patients were excluded if they (1) had a red-flag sign, such as hemoptysis, severe dyspnea, fever, weight loss, peripheral edema, dysphagia, vomiting, or history of recurrent pneumonia; (2) had abnormal findings on physical examination or chest X-rays suggesting a serious condition other than CC; or (3) had active major medical conditions other than CC, such as malignancy, heart failure, stroke, or other severe respiratory diseases.

RUCC was defined as CC of unknown etiology (unexplained chronic cough, UCC) or CC refractory to treatment (refractory chronic cough, RCC), despite diagnostic and therapeutic trials per current international and national cough guidelines [3–5]. Briefly, these investigations and therapeutic trials included those for common cough-triggering conditions, such as cigarette smoking, angiotensin enzyme (ACE) inhibitor use, rhinitis, rhinosinusitis, asthma, eosinophilic bronchitis, and gastroesophageal reflux disease (GERD), as well as for rare cough-triggering conditions. CC controlled only by central cough neuro-modulatory drugs, such as codeine or gabapentin, was also considered RUCC.

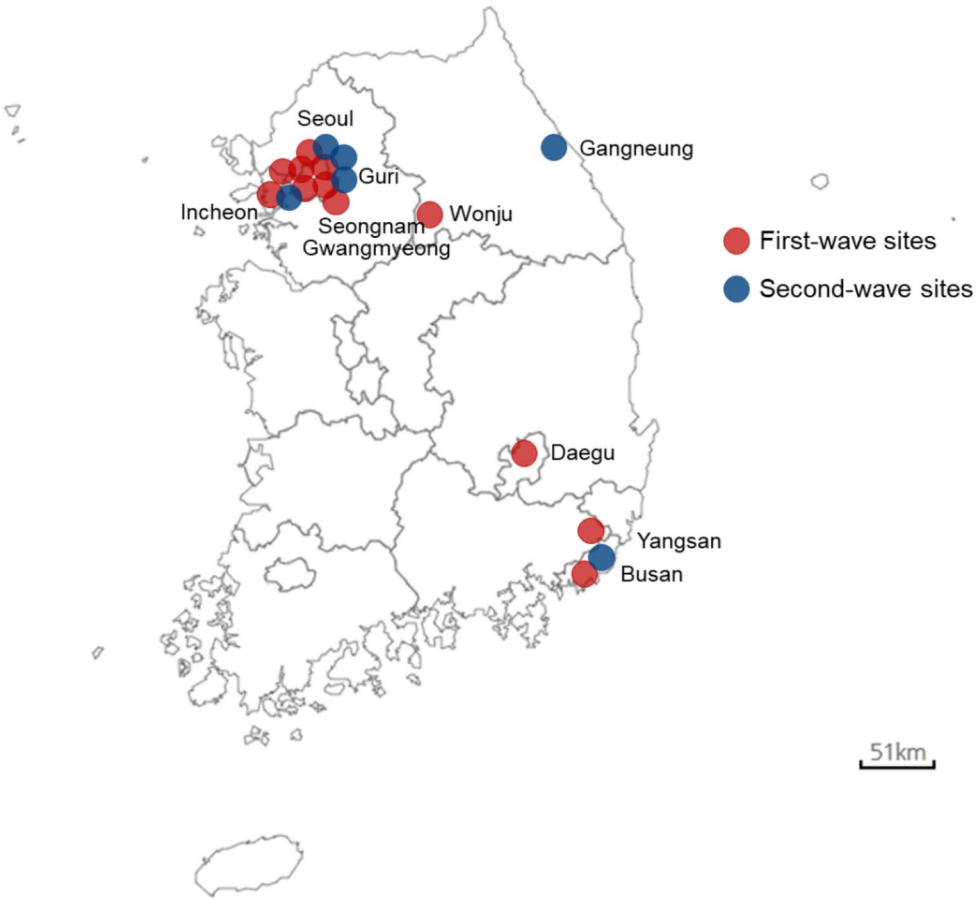


Fig. 1 Study network. First-wave sites involved in this analysis were colored in red. Second-wave sites as extended registry network were colored in blue

All study participants provided written informed consent. The study protocols were approved by the Institutional Review Board of each participating institution.

Baseline Assessment

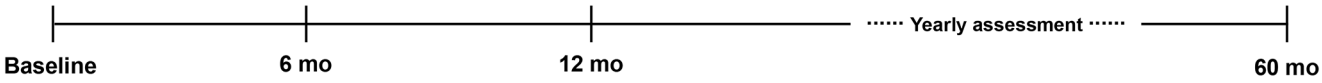
Baseline evaluation items and protocols are presented in Table 1; Fig. 2. Demographic and clinical characteristics included age, sex, body mass index (BMI), smoking history, previous medical history, comorbidities, and recent medication use. Cough characteristics included age at CC onset, family history, cough severity, cough-specific QoL, cough triggers, throat sensations, cough complications and associated symptoms, and general HRQoL and depression were investigated.

BMI was calculated as weight divided by height squared (kg/m^2). Comorbidity was defined by a physician-diagnosed history. Recent use of ACE inhibitors was asked. Onset of CC was defined by the onset age of the first CC episode. Family history of CC was defined as positive if any

Table 1 Study protocols: cough and health status assessment items

	Assessment tool and question	Responses and scoring
Baseline and follow-up visits		
Cough severity	• VAS on paper: "How would you rate the severity of cough in the past week (0–100)?"	• 0–100 (higher score indicates more severe cough)
Cough-specific quality of life	• LCQ	• Total LCQ score: 3–21 (lower score indicates a greater impact of cough on QoL)
Cough hypersensitivity	• CHQ	• Total CHQ score: 0–22 (sum of laryngeal sensations [0–6] and cough triggers [0–16]; higher score indicates more features of hypersensitivity)
General health-related QoL	• EQ-5D-5 L questionnaire	• The EQ-5D index ranges from less than 0 to 1 (0 is a health state equivalent to death, 1 is perfect health, and negative values indicate a health state worse than death).
	• EQ-VAS	• 0–100 (lower score indicates poorer QoL)
Depression	• CES-D scale questionnaire	• 0–60 (higher score indicates a greater degree of depression)
Follow-up visits only		
Treatment response	• Physician assessment of treatment response	• Cough spontaneously improved without treatment • Cough improved following specific treatments based on anatomic diagnostic protocols • Cough did not respond to the anatomic diagnostic protocols but improved by treatment with central neuro-modulatory drugs (such as codeine and gabapentin) • Cough remained refractory to all currently available treatments
Cough control	• Self-reported question: "Is your cough currently under control?"	5-point Likert scale: • Strongly agree • Agree • Neither agree nor disagree • Disagree • Strongly disagree
Telephone survey (for follow-up assessments)		
Treatment status	• Self-reported question: "How have you managed your cough after the last hospital visit?"	• No treatments needed • Over-the-counter drugs • Physician prescribed medication (name of drug)
Treatment effectiveness	• Self-reported question: "How effective is your current cough treatment?"	• No effect at all • Slightly effective • Very effective
Cough severity	• VAS: "How would you rate the severity of cough in the past week between 0 (not at all) and 100 (worst)?"	• 0–100 (higher score indicates more severe cough)
Cough control	• Self-reported question: "Is your cough currently under control?"	• Strongly agree • Agree • Neither agree nor disagree • Disagree • Strongly disagree
Duration of troublesome cough	• Self-reported question: "How long have you experienced discomfort from coughing in the past 6 months?"	• Not at all • Less than 1 month • Between 1 and 3 months • Between 3 and 6 months

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CHQ, Cough Hypersensitivity Questionnaire; EQ-5D-5 L, EuroQoL 5-Dimension 5-Level; EQ-VAS, EuroQoL-visual analog scale; LCQ, Leicester Cough Questionnaire; QoL, quality of life; VAS, visual analog scale



	Baseline visit	Follow-up visits (6, 12, 24, 36, 48, 60 months)
Demographics and clinical information	V	
Cough characteristics	V	V
Patient-reported outcomes		
Cough severity VAS	V	V
LCQ	V	V
CHQ	V	V
EuroQoL	V	V
CES-D	V	V
Physician assessment		
Cough phenotype		V
Physician-assessed treatment response		V
Electronic medical record review	V	V
Blood sample	V	

Fig. 2 Study protocols: baseline assessment and follow-up plan. Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CHQ, Cough Hypersensitivity Questionnaire; LCQ, Leicester Cough Questionnaire; VAS, visual analog scale

grandparent, parent, or sibling had CC. Cough-associated symptoms were defined as self-reported rhinorrhea, nasal obstruction, hyposmia/anosmia, wheezing, breathlessness, heartburn, acid regurgitation, or sputum (yes or no). Self-reported cough-related complications included fatigue, urinary incontinence, chest pain (or rib fracture), syncope, headache, hernia, or others (yes or no).

Cough-specific patient-reported outcomes (PROs) included cough severity visual analog scale (VAS) during the previous week, the Leicester Cough Questionnaire (LCQ) to assess cough-specific QoL [22], and the Cough Hypersensitivity Questionnaire (CHQ) to evaluate cough triggers and cough-related laryngeal sensations [23]. HRQoL was measured using the five-level EuroQoL five-dimension (EQ-5D-5 L) questionnaire [21] and EQ-VAS [24]. Depression was assessed using the Korean version of the Center for Epidemiological Studies Depression scale (CES-D) questionnaire [25].

Blood samples were collected to measure biomarkers and targets of specific treatments. A 5 mL aliquot of whole blood was collected from each subject in an EDTA-containing tube and centrifuged to yield plasma and cell samples, from which genomic DNA was isolated. The aliquoted samples were stored in a -80℃ freezer.

Items Collected from Medical Record

The medical records of each subject were retrieved for cough-related medications; H1-receptor antihistamine (H1RA), inhaled corticosteroid (ICS), oral corticosteroid, H2-receptor antihistamine, proton pump inhibitor, leukotriene receptor antagonist (LTRA), inhaled long-acting beta2-agonist, inhaled long-acting muscarinic antagonist, codeine, codeine-containing combination drugs, neuro-modulators (such as gabapentin, pregabalin, or amitriptyline), macrolides, and other drugs.

The baseline diagnostic tests were reviewed for chest X-rays, spirometry, bronchodilator response (BDR), methacholine challenge test, fractional exhaled nitric oxide (FeNO), induced sputum, and blood eosinophil count. Chest X-rays were defined as abnormal if the subject had any grossly abnormal parenchymal lesion in the radiologist's formal interpretation. BDR was defined as an increase of $\geq$12% and $\geq$200 mL from baseline. Methacholine airway hyper-responsiveness (AHR) was defined as positive if the concentration of inhaled methacholine that reduced FEV_1 20% from baseline was less than 16 mg/mL. T2 inflammation was defined as positive if FeNO levels were $\geq$25 ppb, induced sputum eosinophils were $\geq$3%, or peripheral blood eosinophil counts were $\geq$300 cells/μL.

Longitudinal Follow-up and Assessment Plan

Participants are being followed up for 5 years and will be evaluated at 6 months, 1 year, and then annually for up to 5 years after their baseline visit in order to assess long-term responses (Fig. 2). To assess early responses to treatment, newly referred CC patients will be additionally evaluated at 1 month. All participants will receive usual care according to current international and national cough guidelines [3–5].

Data collected at each follow-up visit includes (1) cough characteristics, (2) general HRQoL and depression, (3) patient's assessment of cough control, and (4) physician-assessed treatment responses (Table 1; Fig. 2). Treatment responses include (1) spontaneously improved cough, (2) cough improved by specific treatments based on anatomic diagnostic protocols, (3) cough unresponsive to the anatomic diagnostic protocols but improved by treatment with central neuro-modulatory drugs (such as codeine or gabapentin), and (4) cough refractory to any treatments. Subjects will be classified as RUCC if their cough does not respond to the anatomic diagnostic protocols (criteria (3) and (4) above).

In case of follow-up loss, telephone surveys are conducted to assess (1) current cough treatment status, (2) treatment effectiveness, (3) cough severity VAS, (4) cough control status, and (5) duration of bothersome cough during the previous 6 months (Table 1).

Electronic Data Collection

The study data was collected and managed using the Research Electronic Data Capture (REDCap) tools, hosted at Asan Medical Center, Seoul, Korea. The REDCap-based Clinical Data Management Application will facilitate the electronic collection of data in a transparent manner.

Statistical Analyses

Descriptive data were presented as mean ± standard deviation, median with interquartile range (IQR), or percentages, depending on the type and distribution of each parameter. Group differences were assessed using *t*-tests, Mann-Whitney tests, or chi-square tests. All statistical analyses were performed using SPSS software (ver. 27.0 for Windows; SPSS Inc., Chicago, IL, USA), with two-sided *P*-values < 0.05 considered statistically significant.

Results

Baseline Characteristics

Among 616 subjects with CC recruited until February 2023, 610 were finally included for analysis, after excluding 5 withdrawals and 1 ineligible subject. The baseline characteristics of the study participants (66.9% women; median age 59.0 years [IQR 43.8–67.0]) are presented in Table 2, with 434 (71.1%) being newly referred CC patients. The median age at CC onset was 50.1 years (IQR 34.0–61.0), and 94.4% of patients had adult-onset CC (≥ 19 years). The median duration of CC from the first onset to the study enrollment was 4 years (IQR 1–10), with 80% of patients experiencing cough for more than one year. Family history of CC was present in 31% of participants. The proportions of obese patients (BMI ≥ 25 kg/m^2 per Korean guidelines [26]), current smokers, and current ACE inhibitor users were 40.4%, 4.6%, and 0.7%, respectively. Sputum was the most frequently associated symptom (59.4%), followed by rhinorrhea (37.8%), breathlessness (21.6%), wheezing (16.2%), and acid regurgitation (16.2%).

Subjects with RUCC were significantly older (median 62.0 years [IQR 49.5–69.0] vs. 58.0 years [IQR 41.8–65.0]; $p = 0.001$) and had a longer cough duration (median 6.0 years [IQR 3.0–10.0] vs. 3.0 [IQR 1.0–10.0]; $p < 0.001$) and a higher rate of physician-diagnosed hypertension (32.8% vs. 23.8%; $p = 0.023$) and asthma (13.9% vs. 7.1%; $p = 0.009$), but had fewer cough-associated symptoms such as nasal obstruction (13.2% vs. 23.6%; $p = 0.004$), acid regurgitation (9.7% vs. 18.9%; $p = 0.005$), or heartburn (8.6% vs. 16.4%; $p = 0.012$), compared to those with newly referred CC. In baseline diagnostic tests, subjects with RUCC had significantly lower signs of T2 inflammation (24.0% vs. 40.1%; $p < 0.001$), represented by FeNO levels or eosinophil counts (Table 2).

Baseline Cough and Health PRO Scores

In all participants, the mean weekly cough severity VAS score was 56.5 ± 25.0, the mean LCQ score was 11.2 ± 3.6, and the mean CHQ score was 8.6 ± 4.0 (Table 3). In the CHQ assessment, approximately 95% of subjects reported at least one throat abnormal sensation or at least one cough trigger. When comparing subjects newly referred with CC to those with RUCC, it was found that those with RUCC had significantly lower LCQ scores (10.3 ± 3.3 vs. 11.6 ± 3.6; $p < 0.001$) and higher CHQ scores (9.1 ± 3.9 vs. 8.4 ± 4.1; $p = 0.024$; Table 3). In the LCQ assessment, psychological and social domains were more affected in subjects with RUCC. Cough-related complications were generally similar, but headache was more frequent in subjects with

Table 2 Baseline characteristics of subjects with newly referred CC and RUCC

	Total (n = 610)	Newly referred CC (n = 434)	RUCC (n = 176)	*P* value*
Females, %	66.9%	65.4%	70.5%	0.233
Age, years	59.0 (IQR 43.8–67.0)	58.0 (IQR 41.8–65.0)	62.0 (IQR 49.5–69.0)	0.001
Age at cough onset, years	50.1 (IQR 34.0–61.0)	49.0 (IQR 34.0–60.6)	51.0 (IQR 33.0–62.0)	0.530
Cough duration, years	4.0 (IQR 1.0–10.0)	3.0 (IQR 1.0–10.0)	6.0 (IQR 3.0–10.0)	< 0.001
Family history of chronic cough	31.0%	30.0%	33.3%	0.424
BMI, kg/m^2	24.6 ± 4.4	24.7 ± 4.6	24.5 ± 3.8	0.814
Smoking status, %				
Non-smoker	75.7%	75.1%	77.3%	0.573
Ex-smoker	19.7%	19.4%	20.5%	0.757
Current smoker	4.6%	5.5%	2.3%	0.090
Recent ACE inhibitor use, %	0.7%	1.0%	0%	0.327
Comorbidity, %				
Hypertension	26.5%	23.9%	32.8%	0.026
GERD	20.0%	20.8%	17.9%	0.424
Diabetes mellitus	10.4%	10.2%	11.0%	0.767
Asthma	9.1%	7.1%	13.9%	0.009
Thyroid diseases	5.9%	6.2%	5.2%	0.647
Post-tuberculosis lung sequelae	5.2%	5.7%	4.0%	0.417
Arrhythmia	2.4%	2.4%	2.3%	1.000
Heart failure	1.2%	1.2%	1.2%	1.000
Autoimmune diseases	0.7%	0.5%	1.2%	0.584
Associated symptom, %				
Sputum	59.4%	59.4%	59.4%	0.998
Rhinorrhea	37.8%	37.5%	38.5%	0.812
Nasal obstruction	20.6%	23.6%	13.2%	0.004
Hyposmia/anosmia	6.5%	7.3%	4.6%	0.224
Breathlessness	21.6%	21.0%	22.9%	0.620
Wheezing	16.2%	17.9%	12.0%	0.075
Acid regurgitation	16.2%	18.9%	9.7%	0.005
Heartburn	14.1%	16.4%	8.6%	0.012
Chest X-ray abnormality, % (n = 490)	11.6%	12.4% (40/323)	10.2% (17/167)	0.471
Spirometry (n = 492)				
FEV_1% of predicted	91.3 ± 13.1	91.2 ± 13.4	91.4 ± 12.6	0.897
FVC% of predicted	89.4 ± 13.6	90.0 ± 14.4	88.3 ± 11.7	0.165
FEV_1/FVC ratio	81.3 ± 8.8	80.9 ± 8.7	82.1 ± 9.1	0.366
BDR, % (n = 151)	5.3%	6.6% (6/91)	3.3% (2/60)	0.479
Methacholine AHR, % (n = 178)	5.1%	6.5% (9/139)	0%	0.103
FeNO ≥ 25 ppb, % (n = 494)	32.0%	37.2% (125/336)	20.9% (33/158)	< 0.001
Sputum eosinophils ≥ 3%, % (n = 45)	24.4%	27.3% (9/33)	16.7% (2/12)	0.699
Blood eosinophils ≥ 300 cells/μL, % (n = 323)	12.7%	15.5% (35/226)	6.2% (6/97)	0.021
T2 inflammation (n = 521)†	34.9%	40.1% (142/354)	24.0% (40/167)	< 0.001

Results are expressed as percentage, median (interquartile range), or mean ± standard deviation

Abbreviations: ACE, angiotensin-converting enzyme; AHR, airway hyper-responsiveness; BDR, bronchodilator response; BMI, body mass index; CC, chronic cough; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; IQR, interquartile range; RUCC, refractory or unexplained chronic cough

**P* values for comparing newly referred CC versus RUCC.

†T2 inflammation was defined as positive if FeNO levels were ≥ 25 ppb, induced sputum eosinophils were ≥ 3%, or peripheral blood eosinophil counts were ≥ 300 cells/μL

Table 3 Baseline cough and health status in subjects with newly referred CC and RUCC

	Total (n = 610)	Newly referred CC (n = 434)	RUCC (n = 176)	*P value*
LCQ total score (3–21)	11.2 ± 3.6	11.6 ± 3.6	10.3 ± 3.3	< 0.001
Physical domain	4.3 ± 1.1	4.4 ± 1.1	4.2 ± 1.1	0.082
Psychological domain	3.3 ± 1.3	3.5 ± 1.3	3.0 ± 1.2	< 0.001
Social domain	3.5 ± 1.5	3.7 ± 1.6	3.1 ± 1.4	< 0.001
CHQ total score (0–22)	8.6 ± 4.0	8.4 ± 4.1	9.1 ± 3.9	0.024
Throat sensations (0–6)	3.4 ± 1.6	3.4 ± 1.7	3.6 ± 1.5	0.252
Cough triggers (0–16)	5.2 ± 3.1	5.0 ± 3.1	5.6 ± 3.1	0.029
Cough severity VAS (0–100)	56.5 ± 25.0	55.2 ± 25.2	59.8 ± 24.2	0.071
Cough complications, %				
Fatigue	36.6%	34.7%	41.4%	0.124
Urinary incontinence	28.6%	26.4%	34.1%	0.058
Headache	25.9%	28.2%	20.1%	0.039
Chest pain or rib fracture	25.4%	26.6%	22.4%	0.282
Syncope	1.2%	0.9%	1.7%	0.416
Hernia	0.5%	0.5%	0.6%	1.000
General health status				
EQ-5D-5 L index (0–1)	0.85 ± 0.14	0.86 ± 0.14	0.83 ± 0.15	0.067
EQ-VAS score (0–100)	67.5 ± 18.0	67.7 ± 17.9	67.2 ± 18.2	0.805
CES-D score (0–60)	11.2 ± 10.7	11.0 ± 10.4	11.7 ± 11.3	0.785

Results are expressed as percentage or mean ± standard deviation

Abbreviations: CC, chronic cough; CES-D, Center for Epidemiologic Studies Depression Scale; CHQ, Cough Hypersensitivity Questionnaire; EQ-5D-5 L, EuroQoL 5-Dimension 5-Level; EQ-VAS, EuroQoL-visual analog scale; LCQ, Leicester Cough Questionnaire; RUCC, refractory or unexplained chronic cough; VAS, visual analog scale

Table 4 Cough-related medications being prescribed to subjects with RUCC

Drug	%
Narcotic antitussives	79.5%
Codeine	53.2%
Codeine-containing combination drugs	35.5%
H1-receptor antihistamines	40.4%
Leukotriene receptor antagonists	36.5%
Inhaled corticosteroids	29.2%
Inhaled long-acting beta2-agonists	28.2%
Neuro-modulators drugs (gabapentin, pregabalin, or amitriptyline)	21.1%
Oral corticosteroids	19.3%
Macrolides	17.0%
Acid suppressants (proton-pump inhibitors or H2-receptor antihistamines)	15.9%
Proton-pump inhibitors	11.2%
H2-receptor antihistamines	5.8%
Intranasal corticosteroids	7.6%
Levodropropizine	7.1%
Theobromine	6.5%
Dry ivy leaf	4.1%
Inhaled antimuscarinic agents	2.9%
Non-macrolide antibiotics	1.2%
Others*	9.4%

*Others: ambroxol (n = 3), theophylline/doxofylline (n = 3), pseudoephedrine (n = 3), erdosteine (n = 3), mosapride (n = 3), acetylcystine (n = 1)

newly referred CC (28.2% vs. 20.1%; p = 0.039). The baseline cough severity VAS score, EQ-5D-5 L index, EQ-VAS score, and CES-D score did not significantly differ between the two groups.

Cough-related Medications Prescribed to Subjects with RUCC at the Time of Enrollment

Cough-related medications prescribed to subjects with RUCC at the time of enrollment are summarized in Table 4. The median number of cough medications was 3 (IQR 2–4; range: 0–11). The most prescribed medications were narcotic antitussives, such as codeine or codeine-containing combination drugs (79.5%), followed by H1RA (40.4%), LTRA (36.5%), and ICS (29.2%); 9.2% of patients were prescribed with both codeine and codeine-containing combination drugs with either drug being prescribed as an 'as-needed' medication. Cough neuro-modulatory drugs, such as gabapentin, pregabalin, or amitriptyline, were being prescribed to 21.1% of subjects.

Comparison Between RCC and UCC

Among the 176 patients with RUCC, 96 (54.5%) had RCC (Table 5). Asthma/eosinophilic bronchitis was the most common cough-associated condition in RCC patients, observed in 66.7% of cases, followed by rhinitis/rhinosinusitis (50.0%), GERD (14.6%), and bronchiectasis (6.3%). A predominance of elderly females was commonly observed (70.5% women; median age 60.5 year). The age at CC onset was younger and the cough duration was slightly longer in UCC patients; however, no significant differences were noted in age and cough PRO scores, including LCQ, CHQ, and VAS, between the two groups (Table 5 and Fig. 3).

Table 5 Comparison of baseline characteristics and cough status between RCC and UCC patients

	RCC (n = 96)	UCC (n = 80)	*P* value
Females, %	71.9%	68.8%	0.651
Age, years	62.5 (IQR 53.3–69.0)	61.5 (IQR 41.3–69.0)	0.348
Age at cough onset, years	54.0 (IQR 43.4–62.5)	47.7 (IQR 26.3–61.6)	0.023
Cough duration, years	5.0 (IQR 2.5–10.0)	8.3 (IQR 3.1–16.5)	0.087
Family history of chronic cough	38.5%	27.5%	0.129
BMI, kg/m^2	25.0 ± 3.7	23.9 ± 3.8	0.009
Smoking status, %			
Non-smoker	76.0%	78.8%	0.669
Ex-smoker	19.8%	21.3%	0.811
Current smoker	4.2%	0%	0.127
LCQ total score (3–21)	10.3 ± 3.4	10.5 ± 3.3	0.655
Physical domain	4.2 ± 1.1	4.3 ± 1.1	0.628
Psychological domain	3.0 ± 1.3	3.0 ± 1.2	0.995
Social domain	3.1 ± 1.4	3.2 ± 1.4	0.400
CHQ total score (0–22)	9.0 ± 3.9	9.3 ± 3.9	0.745
Throat sensations (0–6)	3.4 ± 1.6	3.7 ± 1.5	0.272
Cough triggers (0–16)	5.6 ± 3.1	5.6 ± 3.2	0.902
Cough severity VAS (0–100)	58.0 ± 24.4	61.9 ± 24.0	0.331

Results are expressed as percentage, median (interquartile range), or mean ± standard deviation

Abbreviations: BMI, body mass index; LCQ, Leicester Cough Questionnaire; CHQ, Cough Hypersensitivity Questionnaire; VAS, visual analogue scale; IQR, interquartile range; RCC, refractory chronic cough; UCC, unexplained chronic cough

Discussion

The present study described the registry protocol and the baseline cohort profile in the Korean Chronic Cough Registry study. To our knowledge, this is the first multi-center, prospective observational cohort of CC patients reported in the literature to date. We recruited patients with active cough from referral allergy, pulmonology, and cough clinics. Therefore, this cohort profile may represent the characteristics of CC patients with unmet clinical needs at referral clinics. Consistent with previous findings [16, 18, 27, 28], the present study found that CC was frequently severe and persistent for several years and was associated with QoL impairment. The baseline demographic profile showed an older female predominance (66.9% women; median age 59.0 years [IQR 43.8–67.0]), which is similar to observations from a worldwide survey of cough clinics (66.0% women; mean age 55.5 ± 15.0 years) [29] and phase 3 clinical trials with gefapixant (75.0% women; mean age 58 ± 12.0 years) [30].

In our registry, RUCC patients exhibited a longer cough duration (median 6 years [IQR 3.0–10.0]) compared to newly referred CC patients, who had a median of 3 years (IQR 1.0–10.0) ($p < 0.001$). Furthermore, RUCC patients exhibited a lower LCQ score (10.3 ± 3.3) than in newly referred CC patients (11.6 ± 3.6; $p < 0.001$), although the difference in LCQ scores did not exceed the minimum clinically important difference of 1.3 [31]. These findings underscore the persistence of unmet clinical needs in RUCC patients, even when they are receiving care at referral

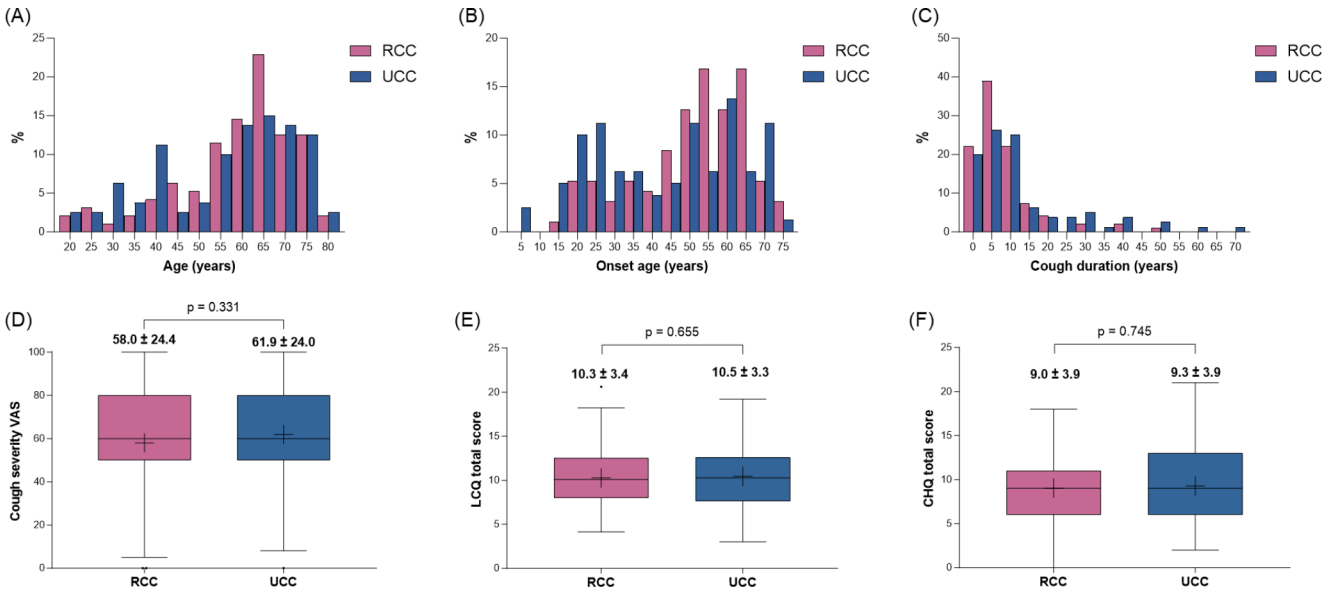


Fig. 3 Distribution of baseline cough characteristics and scores in patients with RCC and UCC: (A) age at recruitment, (B) age at chronic cough onset, (C) duration of chronic cough, (D) cough severity VAS, (E) LCQ total score, and (F) CHQ total score. Abbreviations: VAS, visual analogue scale; CHQ, Cough Hypersensitivity Questionnaire; LCQ, Leicester Cough Questionnaire; RCC, refractory unexplained chronic cough; UCC, unexplained chronic cough; VAS, visual analog scale

clinics. In addition, subjects with RUCC had higher CHQ score and had less symptoms and signs suggesting cough-triggering conditions, such as nasal obstruction, acid reflux symptoms, or T2 inflammation, compared to newly referred CC patients, suggesting that treatable traits beyond the disease triad asthma, rhinitis, and GERD may be relevant to RUCC.

To date, no drugs have received global approval for the treatment of CC and RUCC, although the use of codeine or gabapentin may be common in real-world practice [2, 15]. Recent analyses based on routine data collection in South Korea and the US found that over 50% of patients with CC at referral clinics were prescribed narcotic anti-tussive drugs [15, 32], which is similar to the findings of the present study (79.5%). In a recent analysis of CC patients in community-based populations, the use of codeine or hydrocodone-containing drugs was reported by 11.9% respondents in South Korea and 28.2% in Taiwan [33]. However, there are conflicting guideline recommendations regarding the use of opiates, such as codeine or morphine, between continents or countries [4, 5, 34]. The main issues associated with narcotic anti-tussive drugs include the lack of high-quality evidence on their efficacy and concerns about long-term overuse or addiction [35]. Unfortunately, there are also concerns about the efficacy and tolerability of gabapentin or pregabalin [5, 34]. Furthermore, despite their frequent prescriptions, there is no robust evidence or biomarker to guide the precise use of H1RA, ICS, or acid suppressants in patients with CC [36–38]. Thus, there is a pressing need for novel antitussives and treatment strategies, as drugs targeting neuronal pathways are showing promising [39].

Interestingly, 94.4% of the subjects in the registry reported that the onset age of CC was ≥19 years, and the age at onset was similar between RUCC and newly referred CC patients. These findings suggest that early-life factors may play a minor role in developing CC in adults. Meanwhile, the present study reported that 31% of adult patients had a family history of CC. A previous retrospective cohort study in South Korea found that a family history of CC was significantly associated with cough persistence [18]. A Finnish community population study also found that family history was a risk factor for acute, subacute, and chronic cough [40]. Additionally, genetic polymorphisms were found to be associated with the risk of cough in some patients [41–44]. However, it is important to note that these findings do not confirm the large effects of genetic factors, as environmental risk factors such as passive smoking and air pollution, diet, and comorbidity may be shared within families. Specifically, obesity is a known risk factor for CC [19]; shared dietary habits and lifestyle within a family could contribute to the development of CC. Further investigation is needed to determine the contribution of genetic and environmental factors to the development of CC and RUCC in adults.

Our comparison of RCC and UCC patients revealed no significant differences in overall baseline characteristics, even in the presence of cough-associated comorbidities in RCC. Notably, CHQ scores, which indicate the degree of laryngeal sensations and cough triggers, were similar in both groups, suggesting a possible common mechanism underlying RCC and UCC. These findings are consistent with the COUGH-1 and COUGH-2 clinical trials, which showed similar efficacy of gefapixant in treating both RCC and UCC [13].

This study has limitations. First, the findings may have limited external validity as the subjects were recruited from referral clinics, which could result in an overrepresentation of patients with difficult-to-treat coughs in the cohort. Second, objective measures of cough frequency and cough reflex sensitivity were not included in the study. However, this limitation is inherent to the study's nature, which is based on routine clinical practice. Third, while this study described cross-sectional differences in the characteristics of RUCC patients versus newly referred CC patients, it is important to note that the findings may be subject to time bias, and the phenotype of CC can change over time. Therefore, the characteristics of RUCC patients should be assessed in follow-up studies.

Despite the limitations, the present study provides valuable baseline clinical profiles of patients with CC prospectively recruited from 18 centers in real-world settings. These profiles will serve as a reference for longitudinal follow-up studies. Additionally, the findings will be useful for comparisons with clinical trial populations or international patient registries.

In conclusion, chronic cough typically develops in adulthood and can persist for years. The severity of cough and the impairment in QoL highlight the existence of unmet clinical needs and insufficient control of cough in real-world settings. Further longitudinal studies are required to gain insights into the natural progression of cough, long-term treatment outcomes, and the development of more effective management strategy for refractory cough.

Author Contributions WJS is the full guarantor of this manuscript. WJS, BJL, and EJJ contributed to the study conception and design, and data interpretation. EJJ, JHL, HKW, NK, SYK, SEL, JHL, MYK, JSS, JA, YY, SYP, BKK, JYM, HKP, MHK, HSK, SHK, SHK, YSC, SHK, BJL and WJS have made contributions to the data acquisition. EJJ and WJS performed formal analysis and interpretation of data. EJJ and WJS drafted the first version of the manuscript. WJS, BJL, and SSB supervised and revised the manuscript. All authors approved this version of the manuscript for submission.

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Declarations

Conflict of interests SSB declares grants from Merck Sharp & Dohme Corp., consulting fees from Merck, Shionogi, Bayer, Nerre, Genentech/Roche and Bellus. WJS declares grants from Merck Sharp & Dohme Corp. and AstraZeneca, consulting fees from Merck, AstraZeneca, Shionogi and GSK, and lecture fees from Merck, AstraZeneca, GSK, Sanofi, and Novartis. Other authors declare that they have no competing interests.

Competing Interests The authors declare no competing interests.

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