Cough Presentation and Cough-Related Healthcare Utilization in Tertiary Care: Analysis of Routinely Collected Academic Institutional Database

Jin An¹,² · Ji-Hyang Lee¹ · Ha-Kyeong Won¹,³ · Yewon Kang¹,⁴ · Hyouk-Soo Kwon¹ · Jae-Seung Lee⁵ · Sei Won Lee⁵ · Tae-Bum Kim¹ · Yeon-Mok Oh² · You Sook Cho¹ · Sang-Do Lee⁵ · Hee-Bom Moon¹ · Woo-Jung Song¹

Received: 3 May 2022 / Accepted: 26 June 2022 / Published online: 9 July 2022
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Abstract
Purpose Routinely collected data (RCD) from electronic health records (EHR) are useful for studying disease epidemiology in the real world. We examined cough presentation and cough-related healthcare utilization using an academic institutional EHR database in Korea.

Methods In this retrospective cohort study, patients with subacute (3–8 weeks) or chronic cough (> 8 weeks in duration) referred to allergy and asthma clinics were studied. Cases were identified using the search term “cough” or “coughing,” which is the chief complaint, in the data fields. Structured data, including demographics, medical history, symptoms, and diagnostic tests, were analyzed. Healthcare utilization was assessed for drug prescriptions, additional tests, or outpatient visits for 1 year.

Results Cough was the chief complaint in 13,223 cases (46.7%) among 28,312 new referrals for 8 years. A total of 3810 subacute and 7150 chronic cough patients were analyzed. The common demographic profile was middle-aged woman (mean age 52.1 years), reported in 63% of the cases. Cough was frequently accompanied by anterior nasal (about 50%), lower airway (30%), or acid reflux disease symptoms (20%), and by test abnormalities in chest X-rays (14%), spirometry (23%), or T2 inflammation markers (40%). Chronic cough patients frequently required additional tests (chest CT scan: 24%), drug prescriptions (codeine: 21.5% and oral steroids: 9.9%), and long-term healthcare utilization (16.0%) for 1 year.

Conclusions Cough is a common chief complaint at allergy and asthma clinics, but the clinical presentation may be heterogeneous. Further studies are needed to understand long-term outcomes and reduce the disease burden.

Keywords Cough · Electronic health record · Epidemiology

Abbreviations
COPD Chronic obstructive pulmonary disease
RCD Routinely collected data
EHR Electronic health record
ICD International Statistical Classification of Diseases
CRF Case report form
PND Postnasal drip
ILD Interstitial lung disease
GERD Gastro-esophageal reflux disease
DM Diabetes mellitus
ACEi Angiotensin-converting enzyme inhibitor
FeNO Fractional exhaled nitric oxide
FEV1 Forced expiratory volume in 1 s
FVC Forced vital capacity
CT Computed tomography
ICS Inhaled corticosteroid
PPI Proton pump inhibitor
OCS Oral corticosteroids
IQR Interquartile range

Introduction

Cough is an essential airway defense mechanism but also one of the symptoms for which patients seek frequent medical consultation [1]. In particular, chronic cough is a clinically important condition, with high population prevalence, and has a substantial impact on the quality of life of patients [2–4].

Most current knowledge on cough epidemiology has been obtained from large-scale general populations using simple questionnaire surveys, or small focused studies on patients visiting specialist cough clinics. Routinely collected data (RCD) from electronic health records (EHRs) or health administrative data contain comprehensive data, including records of health services, medical procedures, prescriptions, and diagnoses, and may offer useful sources for studying disease epidemiology in the real world [5]. However, because of the lack of a diagnostic code for chronic cough in the International Classification of Diseases (ICD)-9 or ICD-10 systems [6], the use of RCD has been very limited in cough research.

Considering this background, this study investigated cough presentation and cough-related healthcare utilization using an academic institutional EHR database of a tertiary hospital in Seoul, Korea. The institutional EHR database has a risk of selection bias (as it may consist of more severe cases than primary or secondary clinics) but has strength in case identification, longitudinal structured data collection, and analysis of prescriptions and diagnostic tests in a large scale. We constructed a retrospective cohort of patients with subacute and chronic cough and analyzed their clinical characteristics and healthcare utilization during the first year of management using the database.

Materials and Methods

Study Population

This retrospective cohort analysis reviewed the tertiary institutional EHR of patients with subacute or chronic cough referred to allergy and asthma clinics, routinely collected between January 2010 and August 2018. A structured case report form (CRF) has been used to collect baseline information of every new referral. This form includes the chief complaint and duration, present illness, concomitant symptoms, past medical history, and demographics. The CRF was filled by specialist nurses and physicians (allergists or pulmonologists) at the clinics, which is the routine procedure introduced to facilitate patient management and to collect the data in a standard format.

Target populations were newly referred patients with subacute (3–8 weeks in duration) or chronic cough (> 8 weeks in duration) [7, 8]. Cough cases were first identified using the search term “cough” or “coughing” (either in English or Korean) in the EHR data field of the chief complaint. Then, the data field for the duration of the chief complaint was retrieved to verify cases with subacute or chronic cough. For subsequent analyses, subjects were excluded if (1) cough duration was missing, (2) duration was less than 3 weeks, or 3) other symptoms, such as hemoptysis, fever, chest discomfort, or pain, were indicated as co-chief complaints. Study population selection is presented in Fig. 1A. Structured data collected during the first year were retrieved for analysis.

Fig. 1 Study algorithm. A Patient selection. B Study design. A total of 3810 subacute cough and 7150 chronic cough patients were included in this retrospective cohort (2010–2018). Baseline parameters including demographics, clinical information, and initial diagnostic workups were retrieved from case report forms collected at baseline visits. Healthcare utilizations were analyzed during the first 1 year since the baseline visit.
of healthcare utilization (Fig. 1B). The study protocol was approved by the hospital institutional review board (IRB No. 2019-0511).

Baseline Clinical Information

Baseline parameters were retrieved from the structured EHR data. A total of 12 concurrent symptoms were routinely recorded in a dichotomous fashion (yes or no), including sputum, rhinorrhea, nasal obstruction, sneeze, postnasal drip (PND)/throat clearing, abnormal throat sensation (globus, tickling, or dryness), hoarseness, throat pain, dyspnea, wheeze, heartburn, and acid regurgitation. Cigarette smoking was classified into never, former, or current. A physician-diagnosed history defined past medical history. It included allergic rhinitis, chronic rhinosinusitis, asthma, COPD, bronchiectasis, pulmonary tuberculosis, interstitial lung disease (ILD), gastroesophageal reflux disease (GERD), heart failure, malignancy, hypertension, and diabetes mellitus (DM). The current use of an angiotensin-converting enzyme inhibitor (ACEi) was also recorded.

We retrieved the information of baseline diagnostic workups if conducted: chest X-rays, spirometry (and/or bronchodilator testing), and T2 marker tests (such as induced sputum eosinophils, blood eosinophils, or fractional exhaled nitric oxide [FeNO]). For analytic purpose, we used the following definitions: (1) chest X-rays were defined as abnormal if the patient had bronchiectasis, tuberculosis, malignancy, or any other grossly abnormal parenchymal lesion in the radiologist’s formal interpretation; (2) airflow obstruction was defined as positive if the ratio of forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) was less than 0.7 [9]; and (3) T2 inflammation marker was defined as positive if induced sputum eosinophils ≥ 3%, a blood eosinophil count ≥ 300 cells/µl, or FeNO level ≥ 30 ppb [8].

Healthcare Utilization During the First Year of Management

Healthcare utilization was assessed during the first year since the index date (baseline visit) in each subject. It included additional diagnostic workups, prescribed medications, and the number of outpatient visits and hospitalizations. We retrieved the information of additional diagnostic tests if prescribed by specialist physicians at the clinics: methacholine bronchial challenge test, nasal endoscopy, laryngoscopy, and chest computed tomography (CT) scan.

Drug records were retrieved for the following prescriptions: inhaled bronchodilators, inhaled corticosteroids (ICS), anti-leukotrienes, H1-antihistamines, proton pump inhibitors (PPIs), codeine (or codeine-containing drugs), amitriptyline, gabapentin, pregabalin, antibiotics, and oral corticosteroids (OCS). Drug exposure was defined as positive if a drug or drugs were prescribed at least once during the first year since the index date. In the case of OCS, cumulative dose (prednisolone equivalent) was also calculated, as the risk of complications may increase in a dose-dependent manner [10].

To quantify the proportion of patients who need repeated outpatient visits over a period, we arbitrarily defined “long-term healthcare utilization” by using the number and timing of subsequent outpatient visits during the first 1 year in each subject. It was defined positive if a patient had one or more outpatient visits during the first 6 months since the baseline visit and had at least one more visit during the next 6 months (Supplementary Figure S1 in Online Repository). The definition is based on our usual clinical practice pattern.

Statistical Analysis

Descriptive data were calculated as mean ± standard deviation, median, or percentages, depending on the type of distribution of each parameter. Group differences (subacute vs. chronic cough) were assessed using t tests or χ²-square tests. Multiple correspondence analyses were used to visualize and explore inter-relationships between concomitant symptoms for dichotomous variables. All calculations were performed using the Stata 15.1 software (Stata Corp, College Station, TX, USA). A two-sided p value of < 0.05 was considered statistically significant. The jvenn was used to draw a Venn diagram (http://jvenn.toulouse.inra.fr/app/example.html).

Results

Study Population

From a total of 28,312 new referrals to the clinics between January 2010 and August 2018, cough was the chief complaint in 13,223 patients (46.7%). A total of 10,960 subjects were included in the cohort for analysis (Fig. 1A); based on the cough duration, 3,810 patients were classified as to have subacute cough and 7510 patients as chronic cough at baseline visit. Patients were excluded for the following reasons: cough duration was missing (n = 20) or was less than 3 weeks (n = 827), or if patients had co-chief complaints, such as hemoptysis, fever, chest discomfort, or pain (n = 1416). The distribution of cough duration at baseline visit is presented as a histogram in Fig. 2.

Baseline Characteristics

Baseline demographic and clinical characteristics were compared between subacute and chronic cough patients (Table 1). Cough duration was median 1 month (IQR: 0.8 to 1 month) in subacute cough and median 6 months (IQR: 3
to 30 months) in chronic cough patients. Women commonly predominated in both patient groups. Patients with chronic cough were significantly older than those with subacute cough (52.9 ± 15.6 vs. 50.5 ± 15.9 years; p < 0.001). Patients with chronic cough had more physician-diagnosed histories of respiratory or non-respiratory diseases, such as allergic rhinitis, asthma, COPD, ILD, GERD, hypertension, or DM.

Among 12 concomitant symptoms recorded at baseline, patients with subacute and chronic cough had a median three accompanying symptoms (IQR: 2–5). An abnormal throat sensation was the most frequent (about 70%) in both groups. However, patients with chronic cough had significantly more sneeze, dyspnea, wheeze, heartburn, and acid regurgitation but had less PND/throat clearing, sputum production, hoarseness, and throat pain than those with subacute cough (Table 2).

The multiple correspondence analyses revealed that the symptom co-localization pattern was similar to the anatomic locations of the symptoms (Fig. 3A). The localization of the symptoms suggestive of acid reflux disease, such as heartburn and acid regurgitation, was distinct from that of nasal, lower airway, or throat symptoms. Symptom co-localization patterns between chronic cough and subacute cough patients were not different (data not presented).

Major symptoms were classified into anterior nasal (rhinorrhea, sneezing, or nasal obstruction), lower airway (dyspnea or wheeze), and acid reflux (heartburn or acid regurgitation), based on their anatomic locations and co-occurrence patterns. Anterior nasal symptoms were commonly found in patients with subacute and chronic cough (48.9% and 51.8%, respectively), followed by lower airway (30.2% and 33.6%, respectively) and acid reflux symptoms (21.3% and 25.8%, respectively). A total of 28.0% of subacute cough and

Table 1  Baseline characteristics of study participants

| Characteristic                                  | Subacute cough (n = 3810) | Chronic cough (n = 7150) | P value |
|------------------------------------------------|---------------------------|--------------------------|---------|
| Median cough duration (months)                  | 1 (IQR: 0.8–1)            | 6 (IQR: 3–30)            | < 0.001 |
| Age (years)                                     | 50.5 ± 15.9               | 52.9 ± 15.6              | < 0.001 |
| Gender, female, %                               | 62.5                      | 63.6                     | 0.243   |
| Smoking history, %                              |                           |                          | 0.487   |
| Never smoker                                    | 71.0                      | 71.6                     |         |
| Former smoker                                   | 21.0                      | 20.1                     |         |
| Current smoker                                  | 8.0                       | 8.3                      |         |
| Use of ACE inhibitor, %                         | 0.3                       | 0.4                      | 0.389   |
| Physician-diagnosed history ever                |                           |                          |         |
| Respiratory disease, %                          |                           |                          |         |
| Allergic rhinitis                               | 10.5                      | 11.8                     | 0.049   |
| Chronic rhinosinusitis                          | 19.8                      | 18.8                     | 0.008   |
| Asthma                                          | 14.8                      | 21.7                     | < 0.001 |
| COPD                                            | 1.1                       | 2.0                      | < 0.001 |
| Bronchiectasis                                  | 0.3                       | 0.5                      | 0.263   |
| Pulmonary tuberculosis                          | 0.2                       | 0.3                      | 0.138   |
| ILD                                             | 0.2                       | 0.5                      | 0.021   |
| Non-respiratory disease, %                      |                           |                          |         |
| GERD                                            | 7.0                       | 10.1                     | < 0.001 |
| Malignancy                                      | 8.0                       | 7.8                      | 0.618   |
| Heart failure                                   | 0.5                       | 0.4                      | 0.771   |
| Hypertension                                    | 19.3                      | 21.5                     | < 0.001 |
| DM                                              | 7.0                       | 8.8                      | 0.001   |

IQR interquartile range; ACE angiotensin-converting enzyme; COPD chronic obstructive pulmonary disease; ILD interstitial lung disease; GERD gastroesophageal reflux disease; DM diabetes mellitus

Fig. 2  Cough duration in all patients referred with cough to the clinics between 2010 and 2018
32.5% of chronic cough patients had multiple symptoms. However, 32.9% of subacute cough and 28.9% of chronic cough patients had none of these symptoms (Fig. 3B, C).

**Baseline Diagnostic Work-Up**

The number of patients who underwent baseline diagnostic work-up and their test results are summarized in Table 3 and Fig. 4, respectively. Chest X-rays were performed in 83.6% of patients during the first month, and about 13.8% of subacute cough and 14.8% of chronic cough patients had abnormal findings. Spirometry was significantly more frequently conducted, and airflow obstruction was also more positive in chronic cough than in subacute cough patients (56.5% vs. 42.7% in Table 3; and 12.8% vs. 9.7% in Fig. 4, respectively). T2 inflammation marker testing was done in 31.5% of subacute cough and 39.9% of chronic cough patients (Table 3). Sputum eosinophilia (≥ 3%) and blood eosinophilia (≥ 300 cells/μL) were significantly more frequent in chronic cough patients. The proportion of FeNO ≥ 30 ppb did not differ between subacute and chronic cough patients (Fig. 4).

**Healthcare Utilization During the First Year of Management**

Healthcare utilization is summarized in Table 3. The number of patients who underwent nasal endoscopy, laryngoscopy, methacholine challenge, or chest CT scan was higher in chronic cough than in the subacute cough group. Chest CT scans were performed in 23.2% of the study population; among 7833 patients with normal chest X-rays at baseline, chest CT scans were done in 19.3%.

H1-antihistamines were the most common medications prescribed to subacute cough (39.5%) and chronic cough patients (50.9%; Table 3). They were followed by pseudoephedrine (27.4%), antibiotics (23.7%), PPIs (21.0%), codeine-containing drugs (20.4%), ICS (16.9%), and antileukotrienes (15.8%). Most medications were significantly prescribed more to chronic cough patients, except for antibiotics and inhaled short-acting beta2-agonists. OCS were given to 6.6% of subacute cough and 9.9% of chronic cough patients. One-year cumulative OCS doses were median 35 mg (IQR: 25–70 mg, prednisolone equivalent) in chronic cough and 35 mg (25–40 mg) in subacute cough patients, respectively (p < 0.001; Fig. 5). The number of subsequent outpatient visits was significantly higher in chronic cough patients, but hospitalization did not differ. Long-term
16.0% of chronic cough and 8.2% of subacute cough patients ($p < 0.001$; Table 3).

### Discussion

Using a large academic institutional EHR collected for 8 years, this study described the clinical characteristics and
healthcare utilization of newly referred patients with subacute and chronic cough to the tertiary allergy and asthma clinics in Seoul, Korea. Cough was a common chief complaint, comprising a large proportion of all referrals to the clinics (46.7% of 28,312 referrals). Cough was frequently accompanied by anterior nasal (about 50%), lower airway (30%), or acid reflux symptoms (20%), as well as by test abnormalities in chest X-rays, spirometry, or T2 inflammation markers, indicating the heterogeneity of the clinical presentation of subacute and chronic cough patients visiting allergy and asthma clinics.

It has been reported that cough is one of the most common reasons why patients seek medical care [11]. However, comprehensive large-scale data are scarce. In the US National Ambulatory Medical Care Survey, acute cough was a common reason for seeking outpatient consultation [12]. In the Asia–Pacific multicenter questionnaire survey of 5250 allergic or respiratory patients, cough or coughing up phlegm was frequently reported as the main reason for the outpatient visit (23%) [13]. However, the Asia–Pacific study [13] focused only on patients with an established diagnosis of allergic rhinitis, rhinosinusitis, asthma, or COPD. Both surveys [12, 13] lacked specific information on cough characteristics and cough-related healthcare utilization. In this regard, our findings are a valuable addition to the literature, providing specific data on cough presentation and subsequent healthcare utilization in the real world.

Recent real-world studies from the US reported the disease burden in patients with chronic cough (vs. those without chronic cough), including increased healthcare resource utilization, outpatient visits, diagnostic tests, and treatment needs [14–16]. Our findings are generally in line with these [14–16]. We found a substantial proportion of patients who required additional diagnostic tests, drug treatments, and outpatient visits, among the new referrals. Codeine-containing drugs were given to 21.5% of patients with chronic cough, and oral antibiotics to 23.7% and OCS to 9.9%; these drugs have potential concerns with overuse, side effects, complications, or antimicrobial resistance in the long term [10, 11]. Given their potential health risks, the medication uses and health consequences should be the outcomes of long-term follow-up studies of cough patients.

Subacute cough was the chief complaint in 34.8% of this tertiary care population, which was much higher than expected. This high proportion is likely attributed to the national healthcare systems in South Korea, which allow easy and rapid access to tertiary care hospitals even with a simple referral letter from a primary clinic [17], and the findings are presumably distinct from some countries with strict referral systems like the UK. Although lower than that of chronic cough patients, the proportion of subacute cough patients who required additional diagnostic tests (e.g., chest CT in 21.6%) and drug treatments (codeine-containing drugs in 18.3%, and OCS in 6.6%) was considerable. These findings suggested large unmet clinical needs in subacute cough patients as well.

In comparison with previous small studies of Korean patients visiting specialist cough clinics [18, 19] and a recent global clinical trial on refractory chronic cough patients [20], our study population were relatively younger.
(mean age 52.9 years), had less women (63.6%), and had a shorter cough duration (median 6 months). A major reason for the differences among these study populations is that the population evaluated in the present study was derived from allergy and asthma clinics, whereas the populations investigated in previous studies were from specialist cough clinics. In this regard, the information presented here may represent the characteristics of chronic cough patients at allergist and pulmonologist clinics.

This study has several limitations. First, since it is a tertiary institution-based analysis, it has limited external validity. Second, there is a risk of misclassification as the information on cough characteristics and history relied on patient reports collected during routine clinical practice. Also, cough-associated symptoms were recorded in a dichotomous manner. Third, tools to evaluate cough severity or its impact on life were not included in the routine EHR data collection. Their inclusion would help increase the utility of institutional RCD analyses. Fourth, this study did not evaluate unstructured, free-text data at follow-up visits, and thus could not determine treatment responses and clinical outcomes such as the proportion of chronic refractory cough patients. Fifth, we acknowledge the lack of gastrointestinal evaluation as a limitation in the analysis of healthcare utilization. Finally, since our analyses were limited to an academic institutional EHR database, healthcare utilization outside the institution could not be evaluated. In this study, we observed relatively low proportions of patients who underwent routine diagnostic tests, such as chest X-rays (83.6%) and spirometry (51.7%). The present data did not include the information on previous diagnostic testing before the referral, which might be a reason for the findings. Most limitations are intrinsic due to the nature of institutional RCD analysis. Although this study has several limitations, it also has few strengths. This study had a large sample size. Moreover, detailed longitudinal data collection including cough-related prescriptions, diagnostic tests, and healthcare utilization was performed.

In conclusion, cough was a common chief complaint among new referrals to tertiary allergy and asthma clinics. Patients with either subacute or chronic cough had frequent comorbidities and different accompanying symptoms, indicating the heterogeneity of clinical presentations. They frequently required additional diagnostic tests, drug treatments (including OCS and codeine), and outpatient visits, suggesting the disease burden and future health risk. Further studies are needed to understand long-term health outcomes and reduce the disease burden of cough.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00408-022-00555-w.

**Acknowledgements** None.

**Author Contributions** Each of the authors confirms that this manuscript has not been previously published and is not currently under consideration by any other journal. Additionally, all authors have approved the contents of this paper and have agreed to the journal submission policies. WJS contributed to the design of the study. JA performed the main analysis and wrote the original draft. JHL, HKW, and YK assisted in the analysis and interpretation of the data. HSK, JSL, SWL, TBK, YMO, YSC, SDL, and HBM collected the data. All authors reviewed the manuscript.

**Funding** This study was supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp.

**Declarations**

**Competing interest** The authors declare that they have no competing interest.

**Ethical Approval** This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the hospital institutional review board (IRB No. 2019–0511).

**Consent to Participate** Individual subject informed consent was waived due to the retrospective nature of the study and no prospective engagement with subjects or their legal guardians.

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