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Original Article

The Predicative Clinical Features Associated with Chronic Cough That Has a Single Underlying Cause

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What is already known about this topic? It is important for successful therapy to identify causes of chronic cough. Few studies have investigated the usefulness of the clinical characteristics of cough, concomitant symptoms, and medical history in the diagnosis of chronic cough.

What does this article add to our knowledge? Some clinical features, including nocturnal cough alone, cough after meals, reflux symptoms, and history of sinusitis, presented high specificities, and mild to moderate sensitivities to indicate causes of chronic cough, suggesting their great “rule in” value for diagnosis of chronic cough.

How does this study impact current management guidelines? The timing of cough, concomitant symptoms associated with gastroesophageal reflux or rhinitis/sinusitis, and history of rhinitis are useful in indicating common causes of chronic cough and guiding empiric therapy.

BACKGROUND: Few studies have investigated the usefulness of the clinical characteristics of cough in the diagnosis of chronic cough.

OBJECTIVE: To evaluate the diagnostic value of clinical characteristics and concomitant symptoms of chronic cough in predicting its cause.

METHODS: We recruited adult patients with chronic cough as a primary presenting symptom and identified those with a single underlying cause. Clinical features of cough were recorded with a custom-designed questionnaire and the relationships between clinical features and cause of cough were analyzed.

RESULTS: A total of 1162 patients with a single underlying cause were enrolled. Nocturnal cough alone was a predictor of cough variant asthma (odds ratio [OR], 2.037; 95% CI, 1.003-4.139) with high specificity (97.6%) and low sensitivity (8.1%). Heartburn (OR, 2.671; 95% CI, 1.544-4.620), belching (OR, 2.536; 95% CI, 1.620-3.971), and acid regurgitation (OR, 2.043; 95% CI, 1.299-3.212) indicated gastroesophageal reflux—related cough with high specificity (85.5%-94.9%) and low sensitivity (22.8%-40.7%). Cough after meals had a high specificity (91.2%) and a low sensitivity (24.8%) for gastroesophageal reflux—related cough. Postnasal dripping (OR, 2.317; 95% CI, 1.425-3.767) and history of sinusitis (OR, 4.137; 95% CI, 2.483-6.892) were indicators for upper airway cough syndrome with high specificity (80.8% and 90.2%, respectively). Rhinitis/sinusitis-related symptoms showed moderate sensitivity (72.9%); however, they showed mild specificity (46.1%) for upper airway cough syndrome.

CONCLUSIONS: Cough timing, several concomitant symptoms associated with gastroesophageal reflux or rhinitis/sinusitis, and medical history are useful to indicate common causes of chronic cough. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:426-32)

Key words: Chronic cough; Clinical features; Diagnostic value

Chronic cough is one of the most common complaints for patients who seek medical attention in primary care and respiratory specialist clinics. Persistent chronic cough not only leads to significant physiological morbidity but also brings a huge psychological burden. Many studies have shown that cough variant asthma (CVA), eosinophilic bronchitis (EB), upper airway cough syndrome (UACS) (previously referred to as postnasal drip syndrome), and gastroesophageal reflux—related...
cough (GERC) are common causes of chronic cough.4,7 Up to about 90% of the underlying causes of chronic cough were identified as single cause.4,8,14 Successful treatment may be achieved if the etiological diagnosis(es) is established in these patients. However, multiple investigations may be required to determine specific causes of chronic cough, such as spirometry, bronchial challenge testing, induced sputum test for differential cells, and 24-hour esophageal pH value monitoring. These investigations are time-consuming and may be unavailable in the primary care setting. In addition, it is inappropriate to conduct these diagnostic tests routinely during the outbreak of some virulent respiratory infectious disease such as coronavirus disease 2019 (COVID-19) transmitted via respiratory droplets and close contact.12-14 Previous empiric therapy for chronic cough emphasized initial treatment directed at one of common causes of chronic cough, regardless of clinical features.15,16 If specific clinical features can be identified to indicate the etiologies of chronic cough, empiric treatments may be more targeted. Studies on whether the clinical characteristics of cough could be useful for the diagnosis of chronic cough are limited.17-19 Hence, we aimed to analyze different cough characteristics, concomitant symptoms, and medical history in diagnosing the causes of chronic cough with a single underlying cause.

METHODS

Based on literature review and authors’ clinical experiences, cough-associated clinical features that may be useful clues for causes of chronic cough were selected to form the fix questionnaire, with the timing of cough, triggers, concomitant symptoms, complications of cough, and medical history included. The variables in the questionnaire are presented in Table 1, and definitions of some clinical features are presented in Table E1 in this article’s Online Repository at www.jacionline.org.

From January 2006 to December 2018, consecutive and unselected patients with chronic cough were prospectively evaluated in our cough clinic. The questionnaire was completed before diagnosis and treatment based on the well-established diagnostic workflow of chronic cough. The inclusion criteria were as follows: (1) age 18 years or more, (2) cough as the sole or predominant symptom lasting for at least 8 weeks, (3) no overt identifiable abnormalities on chest X-ray, and (4) no cigarette smoking history. Patients who were lost to follow-up at the early stages of the diagnosis of chronic cough and patients with multiple causes of chronic cough were excluded.

The diagnostic workflow in our cough clinic was established to identify the causes of chronic cough in 200311 and later slightly modified according to the guidelines by the American College of Chest Physicians20 and the Chinese Medical Association.21 Briefly, detailed medical history was noted, and physical examination was performed as the first step. Chest radiograph, spirometry, assessment of bronchial hyperresponsiveness (bronchial provocation testing or bronchodilator reversibility test), and induced sputum test were conducted in all the patients at entry. Twenty-four-hour esophageal pH-multichannel impedance monitoring, bronchoscopy, chest or sinus computed tomography, or other investigations were selected in some patients if the above investigations failed to indicate the causes of cough, or if the patients failed to respond to treatment based on common causes. The cause of chronic cough was determined if the patient responded to specific treatment. CVA was diagnosed if the patient presented bronchial hyperresponsiveness and well responded to antiasthmatic treatment. Diagnosis of EB was made with normal pulmonary function, a lack of airway hyperresponsiveness, eosinophil count greater than or equal to 2.5% in sputum, and response to corticosteroids. When 24-hour esophageal pH-multichannel impedance monitoring showed a DeMeester score of 12.70 or more and symptom association probability of greater than or equal to 80%, and cough resolved or disappeared after antireflux treatment, GERC was confirmed. UACS was determined on the basis of history and clinical manifestations of nasal and/or throat conditions, results of investigations supporting nasal and/or throat conditions, and improvement in cough after specific therapy directed at UACS. Unexplained chronic cough was considered if the cause could not be found after full investigations and if the cough persisted after treatment directed at potential causes was administered. The patients with chronic cough who entered the diagnostic workflow were followed up by the trained physicians regularly until cough resolved or the final diagnosis was made. The demographic characteristics, clinical features, results of investigations, the response to therapy, and final diagnosis were recorded in our database. The final diagnosis of the included patient was extracted from the database. The relationships between the clinical features in the questionnaire and the cause of cough were analyzed. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (no. 201778). All subjects gave informed consent for their data to be analyzed.

Statistical analyses

Data were expressed as frequency (percentage), mean ± SD, or median (interquartile range). Statistical comparisons between groups were performed with 1-way ANOVA for normally distributed data, Kruskal-Wallis tests for skewed data, and χ² tests or Fisher exact test for proportions data, followed by post hoc tests with Bonferroni correction for multiple comparisons. A logistic regression test was used to identify the variables that were independent predictors of the cause of chronic cough. Multiple logistic regression analysis was conducted with the method of forward stepwise (likelihood ratio). As the variables age and sex were adjusted to intrinsic individual variables, they were selected to enter all the multiple logistic regression analysis. For those clinical features that showed some overall value for diagnosing the common cause of chronic cough (P < .05), sensitivities, specificities, and positive and negative predictive values were calculated. Data were analyzed using SPSS Statistics version 25.0 (IBM Corp, Armonk, NY).

RESULTS

Clinical feature of patients

A total of 1567 patients with chronic cough as a primary presenting symptom were recruited from January 2006 through December 2018. There were 405 (25.8%) excluded because of the following: loss of follow-up, 259 (16.5%); incomplete questionnaire data, 21 (1.3%); and multifactorial cough, 125 (8.0%). A total of 1162 patients with a primary complaint of chronic cough with a single identified cause were entered into the
| Variable | CVA (N = 222) | EB (N = 259) | GERC (N = 145) | UACS (N = 85) | OC (N = 451) | P value |
|----------|---------------|--------------|----------------|--------------|--------------|---------|
| Sex: female | 165 (74.3)* | 133 (51.4)† | 66 (45.5)* | 38 (44.7)* | 242 (53.7)† | <.0001 |
| Age (y) | 42.0 ± 14.0,† | 42.3 ± 14.9,† | 40.8 ± 12.3,† | 39.2 ± 11.8† | 44.3 ± 14.5* | .0074 |
| Duration (mo) | 18.0 (6.0-55.5)* | 22 (6.0-84.0),† | 24.0 (12.0-84.0),† | 24.0 (6.0-72.0),*,†,‡ | 36.0 (12.0-96.0),* | <.0001 |
| Nonproductive cough, n (%) | 139 (62.6)* | 142 (55.3)* | 114 (79.2)* | 51 (60.0)* | 268 (59.4)* | <.0001 |
| Timing of cough | | | | | | |
| Daily cough alone | 74 (33.3)* | 128 (49.4)† | 101 (70.1) | 52 (61.2),† | 267 (59.6)† | <.0001 |
| Nocturnal cough alone | 18 (8.1)* | 12 (4.6),† | 0 (0)† | 2 (2.4),†,‡ | 8 (1.8)† | .0001 |
| Total nocturnal cough | 147 (66.2)* | 128 (49.4)† | 43 (29.9),† | 31 (36.5),†,‡ | 176 (39.4),†,‡ | <.0001 |
| Triggers | | | | | | |
| Dust | 85 (38.3)* | 91 (35.1)* | 61 (42.1)* | 38 (44.7),*,‡ | 260 (57.6)* | <.0001 |
| Cooking smell | 103 (46.4) | 115 (44.4) | 75 (51.7) | 40 (47.1) | 218 (48.3) | .6856 |
| Cold air | 123 (55.4) | 134 (51.7) | 75 (51.7) | 49 (57.6) | 227 (50.3) | .6297 |
| Common cold | 144 (62.3) | 130 (50.2) | 75 (51.7) | 47 (55.3) | 246 (54.7) | .0886 |
| Lying down | 58 (26.1)* | 40 (15.4)* | 23 (15.9),*,‡ | 18 (21.2),*,‡ | 73 (16.2)† | .0116 |
| Cigarettes smoke | 96 (43.2) | 119 (45.9) | 73 (50.3) | 39 (45.9) | 232 (51.4) | .2816 |
| Exercise | 39 (17.6) | 40 (15.4) | 31 (21.4) | 9 (10.6) | 85 (18.8) | 2.283 |
| Talking | 52 (23.4)* | 71 (27.5),*,‡ | 65 (44.8),* | 31 (36.5),*,†,‡ | 166 (37.0),* | <.0001 |
| Eating | 9 (4.1)† | 15 (5.8),*,‡ | 22 (15.2) | 10 (11.8),*,†,‡ | 37 (8.2)†,‡ | .0011 |
| After meals | 8 (3.6)* | 15 (5.8)† | 36 (24.8),* | 11 (12.9),*,‡ | 55 (12.2)† | <.0001 |
| Other | 28 (12.6) | 26 (10.0) | 17 (11.7) | 7 (8.2) | 49 (10.9) | .8111 |
| Concomitant symptoms | | | | | | |
| Runny nose | 77 (34.7),* | 63 (24.4),* | 33 (22.8),* | 36 (42.4)* | 94 (20.8)† | <.0001 |
| Postnasal dripping | 46 (20.7)* | 57 (22.0)* | 25 (17.2)* | 37 (43.5)* | 79 (17.5)* | <.0001 |
| Sneezing | 104 (46.8)* | 98 (37.5),* | 38 (25.5)* | 37 (42.4)* | 131 (28.8)* | <.0001 |
| Nasal itching | 94 (42.3)* | 63 (23.6)* | 31 (21.4),*,‡ | 30 (35.3),*,‡ | 79 (17.5)* | <.0001 |
| Nasal congestion | 76 (34.2),*,‡ | 74 (28.6)* | 37 (25.5)* | 40 (47.1)* | 128 (28.4)* | .0038 |
| Itchy throat | 136 (61.3) | 137 (52.9) | 86 (59.3) | 52 (61.2) | 265 (58.8) | .3681 |
| Itching below the throat | 74 (33.3) | 87 (33.6) | 41 (28.3) | 34 (40.0) | 137 (30.4) | .3497 |
| Pharyngeal foreign body sensation | 30 (24.0),*,‡ | 40 (17.5)* | 41 (28.9)* | 31 (37.8),*,‡ | 169 (39.3)* | <.0001 |
| Frequent throat clearing | 79 (35.6),* | 78 (30.1)† | 69 (47.6),* | 53 (62.4)† | 160 (35.5),*,‡ | <.0001 |
| Chest tightness | 70 (31.5) | 55 (21.2) | 46 (31.7) | 20 (23.5) | 117 (25.9) | .0597 |
| Shortness of breath | 55 (24.8) | 43 (16.6) | 28 (19.3) | 16 (18.8) | 84 (18.6) | .2333 |
| Acid regurgitation | 24 (10.8)* | 30 (11.6)* | 59 (40.7)† | 14 (16.5)* | 79 (17.5)* | <.0001 |
| Heartburn | 4 (1.8)* | 8 (3.1),*,‡ | 33 (22.8),* | 3 (3.5),* | 37 (8.2)† | <.0001 |
| Belching | 25 (11.3),* | 26 (10.0) | 59 (40.7)* | 11 (12.9)* | 84 (18.6)* | <.0001 |
| Medical history | | | | | | |
| Rhinitis | 104 (47.1)* | 88 (34.0)† | 33 (22.8),* | 33 (39.3),*,‡ | 70 (15.9)† | <.0001 |
| Sinusitis | 21 (9.5)* | 22 (8.5)* | 19 (13.1)* | 30 (35.7)* | 43 (9.8)* | <.0001 |
| Gastrointestinal disorders | 39 (17.6)* | 44 (17.0)* | 53 (38.6)* | 20 (23.8),*,‡ | 94 (21.4)* | <.0001 |
| Hypertension | 28 (12.7) | 26 (10.0) | 11 (7.6) | 4 (4.8) | 50 (11.4) | .2136 |

OC. Other causes.

Data are presented as frequency (percentage), mean ± SD, or median (interquartile range). P values for post hoc test was adjusted with Bonferroni method.

*A subset of different causes of chronic cough categories whose column data do not differ significantly from each other at the .05 level.

†A subset of different causes of chronic cough categories whose column data do not differ significantly from each other at the .05 level.

Analysis, including 259 (22.3%) with EB, 222 (19.1%) with CVA, 145 (12.5%) with GERC, 85 (7.3%) with UACS, 155 (13.3%) with unexplained cough, and 296 (25.5%) with other identified unique causes of chronic coughing. The top 10 identified other unique causes of chronic cough included 65 (5.6%) with atopic cough, 60 (5.3%) with chronic bronchitis, 32 (2.8%) with bronchietasis, 27 (2.3%) with postinfectious cough, 25 (2.2%) with protracted bacterial bronchitis, 25 (2.2%) with psychogenic cough, 20 (1.7%) with interstitial lung disease, 5 (0.4%) with angiotensin-converting enzyme inhibitor–induced cough, 4 (0.3%) with obstructive sleep apnea syndrome, and 4 (0.3%) with bronchial tuberculosis. Those patients with unexplained cough and with other identified causes were placed into an “other cough” group. The number of subjects with a single cause in each group enrolled annually is presented in Table E2 in this article’s Online Repository at www.
The increased proportion of patients with unexplained cough or other causes were found in our cough clinic from 2012 through 2018.

The proportion of total nocturnal cough (66.2%) was significantly higher in patients with CVA when compared with other patients (Table I). There was no significant difference among different causes of chronic cough in terms of cough triggers, the proportion of dust, cooking odor, cold air, common cold, lying down, cigarette smoke, talking, exercise, itchy throat, eating, after a meal, or other. With regard to concomitant symptoms of cough, the incidence of postnasal dripping in patients with UACS (43.5%) was significantly higher than that in other patients. The incidence of acid regurgitation (40.7%), heartburn (22.8%), and belching (40.7%) in the GERC group was significantly higher than that in other groups. However, the remaining concomitant symptoms of cough did not show a significantly higher incidence in any specific group of chronic coughs. The prevalence of a history of sinusitis (35.7%) was significantly higher in the UACS group.

### The diagnostic value of common causes of chronic cough

The individual clinical features related to common causes of chronic cough are presented in Tables II to IV. The number of clinical features serving as positive predictors on univariate logistic analysis was 9 in CVA, 10 in GERC, 7 in UACS, and 1 in EB.

Significant positive univariate predictors of CVA were nocturnal cough alone, total nocturnal cough, trigger-common cold, trigger-lying down, nasal itching, sneezing, runny nose, shortness of breath, and history of rhinitis. On multivariate analysis, nocturnal cough alone (odds ratio [OR], 2.037; 95% CI, 1.003-4.139), total nocturnal cough (OR, 2.412; 95% CI, 1.711-3.402), trigger-common cold (OR, 1.369; 95% CI, 0.988-1.898), nasal itching (OR, 2.408; 95% CI, 1.664-3.485) remained independent predictors (Table II).

On univariate analysis, nonproductive cough, daily cough alone, trigger-after meals, trigger-eating, trigger-talking, heartburn, belching, acid regurgitation, frequent throat clearing, and history of gastrointestinal disorders were significant positive predictors of GERC. On multivariate analysis, nonproductive cough (OR, 2.508; 95% CI, 1.587-3.965), daily cough alone (OR, 1.989; 95% CI, 1.295-3.053), trigger-after meals (OR, 2.312; 95% CI, 1.398-3.822), heartburn (OR, 2.671; 95% CI, 1.544-4.620), belching (OR, 2.536; 95% CI, 1.620-3.971), acid regurgitation (OR, 2.043; 95% CI, 1.299-3.212), and frequent throat clearing (OR, 1.467; 95% CI, 0.992-2.170) remained independent predictors (Table III).

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**Table II. Univariate and multiple logistic regression of predictors of CVA**

| Characteristic                  | Univariate analysis | Multiple analysis |
|--------------------------------|---------------------|------------------|
|                                | OR  | 95% CI   | P value | OR  | 95% CI   | P value |
| Age                            | 0.997 | 0.986-1.007 | .5407 | 0.989 | 0.978-1.001 | .0644 |
| Sex: female                    | 2.818 | 2.028-3.917 | <.0001 | 2.527 | 1.764-3.619 | <.0001 |
| Nocturnal cough alone          | 3.666 | 1.931-6.960 | <.0001 | 2.037 | 1.003-4.139 | .0491 |
| Total nocturnal cough          | 2.888 | 2.174-3.927 | <.0001 | 2.412 | 1.711-3.402 | <.0001 |
| Trigger-common cold           | 1.483 | 1.098-2.003 | .0102 | 1.369 | 0.988-1.898 | .0592 |
| Nasal itching                  | 2.700 | 1.983-3.676 | <.0001 | 1.626 | 1.122-2.356 | .0102 |
| History of rhinitis            | 2.794 | 2.601-3.786 | <.0001 | 2.408 | 1.664-3.485 | <.0001 |
| Sneezing                       | 1.880 | 1.397-2.531 | <.0001 | 1.675 | 1.224-2.294 | .0013 |
| Runny nose                     | 1.481 | 1.047-2.095 | .0265 | 1.278-2.550 | <.0001 |
| Shortness of breath            | 1.805 | 1.278-2.253 | <.0001 | 1.278-2.550 | <.0001 |

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**Table III. Univariate and multiple logistic regression of predictors of GERC**

| Characteristic                  | Univariate analysis | Multiple analysis |
|--------------------------------|---------------------|------------------|
|                                | OR  | 95% CI   | P value | OR  | 95% CI   | P value |
| Age                            | 0.989 | 0.977-1.002 | .1001 | 0.999 | 0.984-1.014 | .8620 |
| Sex: female                    | 0.634 | 0.447-0.899 | .0106 | 0.860 | 0.573-1.291 | .4658 |
| Nonproductive cough            | 2.628 | 1.725-4.005 | <.0001 | 2.508 | 1.587-3.965 | <.0001 |
| Daily cough alone              | 2.223 | 1.524-3.242 | <.0001 | 1.989 | 1.295-3.053 | .0017 |
| Trigger-after meals            | 3.444 | 2.229-5.321 | <.0001 | 2.312 | 1.398-3.822 | .0011 |
| Heartburn                      | 5.468 | 3.390-8.820 | <.0001 | 2.671 | 1.544-4.620 | .0004 |
| Belching                       | 4.093 | 2.813-5.954 | <.0001 | 2.536 | 1.620-3.971 | <.0001 |
| Acid regurgitation             | 4.060 | 2.792-5.905 | <.0001 | 2.043 | 1.299-3.212 | .0020 |
| Frequent throat clearing        | 1.558 | 1.119-2.253 | .0097 | 1.467 | 0.992-2.170 | .0551 |
| History of gastrointestinal disorders | 2.360 | 1.627-3.424 | <.0001 |
| Trigger-eating                 | 2.383 | 1.426-3.984 | <.0001 | 1.759 | 1.236-2.504 | <.0001 |
| Trigger-talking                | 1.558 | 1.119-2.253 | .0097 | 1.759 | 1.236-2.504 | <.0001 |
TABLE IV. Univariate and multiple logistic regression of predictors of UACS

| Characteristic       | Univariate analysis | Multiple analysis |
|----------------------|---------------------|-------------------|
|                      | OR                  | 95% CI            | P value | OR                  | 95% CI            | P value |
| Age                  | 0.980               | 0.964-0.997       | .0215   | 0.986               | 0.969-1.004       | .1193   |
| Sex: female          | 0.628               | 0.403-0.980       | .0404   | 0.723               | 0.450-1.161       | .1789   |
| Postnasal dripping   | 3.240               | 2.056-5.105       | <.0001  | 2.317               | 1.425-3.767       | .0007   |
| Frequent throat clearing | 2.965               | 1.879-4.678       | <.0001  | 2.228               | 1.378-3.601       | .0011   |
| History of sinusitis | 5.079               | 3.113-8.288       | <.0001  | 4.137               | 2.483-6.892       | <.0001  |
| Nasal itching        | 1.671               | 1.049-2.663       | .0307   |                    |                   |         |
| Nasal congestion     | 2.147               | 1.375-3.353       | .0008   |                    |                   |         |
| Runny nose           | 2.226               | 1.417-3.498       | .0005   |                    |                   |         |
| History of rhinitis  | 1.689               | 1.068-2.670       | .0249   |                    |                   |         |

TABLE V. Predictive clinical features for common causes of chronic cough

| Cause         | Clinical feature                                      | Sensitivity | Specificity |
|---------------|-------------------------------------------------------|-------------|-------------|
| CVA           | Total nocturnal cough                                  | 66.2%       | 59.6%       |
|               | Nocturnal cough alone†                                 | 8.1%        | 97.6%       |
| GERC          | Cough after meals                                      | 24.8%       | 91.2%       |
|               | Heartburn                                              | 22.8%       | 94.9%       |
|               | Belching                                               | 40.7%       | 85.6%       |
|               | Acid regurgitation                                     | 40.7%       | 85.5%       |
|               | Combined reflux symptoms§                              | 10.3%       | 99.3%       |
| UACS          | History of sinusitis                                   | 35.7%       | 90.2%       |
|               | Postnasal dripping                                     | 43.5%       | 80.8%       |
|               | Rhinitis/sinusitis-related symptoms§                   | 72.9%       | 46.1%       |

*Cough occurs at night, with or without daily cough.
†Cough mainly occurs after falling asleep.
§Presence of all of the following symptoms: regurgitation, heartburn, and belching.
§Presence of 1 or more symptoms of sneezing, nasal itching, runny nose, and nasal congestion.

Regarding UACS, we found that postnasal dripping (OR, 2.317; 95% CI, 1.425-3.767), frequent throat clearing (OR, 2.228; 95% CI, 1.378-3.601), and history of sinusitis (OR, 4.137; 95% CI, 2.483-6.892) remained independent predictors on a multivariate model (Table IV). On multivariate analysis, history of rhinitis (OR, 1.381; 95% CI, 1.024-1.861) is the only positive predictor of EB.

The sensitivities, specificities, and positive and negative predictive values of the above significant predictors and some composite features are reported in Table E3 in this article’s Online Repository at www.jacionline.org and some promising predictive clinical features are presented in Table V. Nocturnal cough alone had a specificity of 97.6%, but low sensitivity of 8.1% for diagnosing CVA. Total nocturnal cough showed a moderate sensitivity (66.2%) and specificity (59.6%) and a high negative predictive value (88.1%) for CVA. Specificities of acid regurgitation, heartburn, and belching for diagnosing GERC are 85.5%, 94.9%, and 85.6%, respectively, and their sensitivities are 22.8% to 40.7%. Combined reflux symptoms, a composite symptom with heartburn, belching, and acid regurgitation, had the highest specificity (99.3%), a poor sensitivity (10.3%), and a moderate positive predictive value (68.2%) for diagnosing GERC. Also, trigger-after meals and heartburn may serve as promising “rule in” tests for GERC, with a specificity of 91.2% and 94.9%, respectively, despite a weak sensitivity. Rhinitis/sinusitis-related symptoms were the most sensitive (72.9%), and a history of sinusitis had the highest specificity (90.2%) for UACS.

DISCUSSION

To our knowledge, this is the first study with large sample size to investigate the diagnostic value of cough features in patients with chronic cough. In this study, we found that some features of cough, concomitant symptoms, and medical history were useful in determining the causes of chronic cough.

Patients with CVA often presented with nocturnal cough.22,23 Although the cough frequency of patients with asthma was low during night time,24 we found that nocturnal cough was an important clinical feature of CVA, and the incidence (66.2%) was significantly higher than that in other patients. The total nocturnal cough had moderate sensitivity and specificity, and nocturnal cough alone had the highest diagnostic specificity for CVA. Therefore, the diagnosis of CVA is most likely in patients with nocturnal cough. Rhinitis is frequently associated with asthma.25 Tajiri et al.26 reported that the prevalence of rhinitis in patients with CVA was around 49.4%, which is close to our data. However, rhinitis is also generally related to UACS.27 Besides, about one-third of EB was accompanied by rhinitis as well.28 Because a history of rhinitis was a positive predictor of CVA and EB on logistic regression analysis, it seems to be likely a clinical feature for diagnosing eosinophilia-related cough due to similar eosinophilic inflammation.

Previous studies reported that even up to 75% of patients with GERC lacked typical reflux symptoms.29,30 However, we found that up to 57.2% of patients with GERC reported at least a reflux-related symptom in this study. The reasons for these differences in results between our study and previous studies remain
unclear. Heartburn had the lowest sensitivity but the highest specificity among single reflux symptoms, indicating its “rule in” value for GERC. When using combined reflux symptoms for diagnosing GERC, the specificity was up to 99.3%, whereas the sensitivity was only 10.3%, suggesting that the value of composite symptoms in diagnosing GERC may be limited. Foods could increase reflux and patients often reported that meals worsen their symptoms of gastroesophageal reflux.\(^9,32\) Our study showed that cough after meals was a predictor of GERC with high specificity, indicating that cough after meals was a good “rule in” symptom of GERC.

The UACS was previously termed as postnasal drip syndrome, which was largely based on the patient reporting a sensation of postnasal dripping, nasal discharge, or throat clearing.\(^33\) Our data showed that postnasal dripping was a unique positive predictor for UACS among common causes of chronic cough. On univariate logistic regression analysis, frequent throat clearing, runny nose, nasal itching, and nasal congestion were also found to be predictive factors for UACS. However, these symptoms are also found in patients with cough due to other causes.\(^\) The study showed that rhinitis/sinusitis-related symptoms have a higher sensitivity, moderate specificity, and a high negative predictive value for UACS. Therefore, UACS is unlikely if an adult patient with chronic cough does not have rhinitis/sinusitis-related symptoms.

Whether the characteristic of cough and concomitant symptoms are useful in diagnosing the causes of chronic cough remains controversial. Mello et al\(^17\) reported that the characteristics, timing, and complications of chronic cough were unlikely to be useful in diagnosing chronic cough. In contrast, Otoshi et al\(^19\) found that cough with seasonal variation was useful for diagnosing asthma and cough without daily or seasonal variation indicated gastroesophageal reflux disease. Everett and Morice\(^34\) showed that a symptom complex that is characteristic of reflux cough can be identified. In addition, our previous study showed that empiric therapy based on history and clinical characteristics is a more targeted approach, leading to a quicker improvement in chronic cough.\(^35\) This discrepancy may be due to the different clinical features selected, different populations, sample size, and patients with single or multiple conditions. In Mello et al’s study,\(^17\) 88 patients with both single causes and multiple causes of cough were enrolled. In this study, we enrolled a large sample of patients with chronic cough with a single cause, and included detailed clinical features, as much as possible, to explore a potential diagnostic value. The specificities of promising diagnostic clinical features were high in our study, suggesting their great “rule in” value for diagnosis, which may be helpful to guide empiric treatment of chronic cough.

Many investigations for chronic cough are unavailable in the primary care setting, especially in developing countries, and some investigations are time-consuming or expensive. Empiric treatments are widely used in clinical practice. It was usually suggested that initial empirical treatment could be directed to one of the most common causes such as CVA and GERC.\(^15,16\) According to our results, we think that the empirical treatment based on clinical features of chronic cough may be more targeted and may result in better outcomes. Because COVID-19 is transmitted via respiratory droplets and close contact,\(^13\) procedures of diagnostic tools of chronic cough including pulmonary function testing, induced sputum test, and bronchoscopy can increase the risk of COVID-19 transmission among patients and medical staffs. It will be more important to identify diagnostic clues or treatable traits from clinical features to guide empirical treatment in patients with chronic cough when those valuable diagnostic tools are not available routinely during the COVID-19 pandemic. On the basis of results of this study and our previous report,\(^35\) we suggest that corticosteroids or other antiasthmatic drugs could be administered first if patients present with nocturnal cough; antireflux treatment (proton pump inhibitor plus prokinetic agents) could be prescribed if patients present with reflux symptoms or cough after meals or exclude other common cause of chronic cough; and therapy directed to UACS should be considered if patients present with postnasal dripping, history of sinusitis, and/or rhinitis/sinusitis-related symptoms.

Although the first Chinese Guidelines for Diagnosis and Management of Cough was released in 2005,\(^1\) the cough guideline was generalized relatively late and the level of diagnosis and treatment of chronic cough differed much in different regions in China. Our previous survey showed that up to 80% of the patients with chronic cough were misdiagnosed as bronchitis, chronic bronchitis or chronic pharyngitis.\(^36\) The patients usually spent times on multiple medical visits (20 times on average) before visiting our clinic,\(^36\) a well-known cough clinic in China. That may explain the relatively long duration of cough in our data. With popularization of Chinese cough guideline in recent years, patients with the common causes of chronic cough could be identified and treated in other hospitals, and an increasing number of patients with other causes and unexplained chronic cough visited our clinic, which resulted in the decreased proportion of patients with chronic cough with a common cause and the increased proportion of patients with unexplained cough or other causes in our data.

There were some limitations to our study. The clinical features based on medical history taking, especially the history of gastrointestinal disorders or rhinitis, may not be accurate. However, the way to attain that information reflects the reality of clinical practice. Considering that it is difficult to separate the exact clinical feature responsible for chronic cough in an individual with multiple causes, this study only included patients with chronic cough with a single cause; thus, its application in patients with multiple causes may be limited. Nevertheless, the findings could still be applied to the general clinic population because most cases of chronic cough are caused by a single condition.\(^6,9,11\) The diagnostic value of the clinical features should be identified further in the different populations.

CONCLUSIONS

We investigated the diagnostic value of cough timing, concomitant symptoms, and clinical history in common causes of chronic cough. Nocturnal cough indicates CVA. If a patient has reflux symptoms or cough after meals, gastroesophageal reflux–related cough should be considered. If a patient presents with postnasal dripping and/or rhinitis/sinusitis-related symptoms, the diagnosis of UACS should be high on the differentials. These clinical features can be useful in indicating common causes of chronic cough and guiding empiric therapy.

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REFERENCES

1. French CT, Fletcher KE, Irwin RS. Gender differences in health-related quality of life in patients complaining of chronic cough. Chest 2004;125:482-8.
2. Ma W, Yu L, Wang Y, Li X, Lu H, Qiu Z. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough 2009;5:7.
3. Li B, Lai K, Wang F, Zhong N. Quality-of-life questionnaire in patients with chronic cough. Int J Respir 2011;31:326-8.
4. Lai K, Chen R, Lin J, Huang K, Shen H, Kong L, et al. A prospective, multicenter survey on causes of chronic cough in China. Chest 2013;143:613-20.
5. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981;123:413-7.
6. Lai K, Pan J, Chen R, Liu B, Luo W, Zhong N. Epidemiology of cough in relation to China. Cough 2013;9:18.
7. ChungKF, Favord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2000;356:1364-74.
8. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. Am J Respir Crit Care Med 1999;160:406-10.
9. Irwin RS, Curley FJ, French CL. Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 1990;141:640-7.
10. Fujinura M, Abo M, Ogawa H, Nishi K, Kibe Y, Hirose T, et al. Importance of atopic cough, cough variant asthma and sinusobronchial syndrome as causes of chronic cough in the Hokuriku area of Japan. Respir Med 2005;10:201-7.
11. Lai K, Chen R, Liu C, Luo W, Zhong S, He M, et al. Etiology and a diagnostic protocol for patients with chronic cough [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:96-9.
12. Wahidi MM, Shojaee S, Lamb CR, Osi D, Maldonado F, Eapen G, et al. The use of bronchoscopy during the COVID-19 pandemic: CHEST/AABIP Guideline and Expert Panel Report. Chest 2020;158:1268-81.
13. Task Force of Pulmonary Function Testing and Clinical Respiratory Physiology, Chinese Association of Chest Physicians; Pulmonary Function Testing Group, Respiratory Therapeutics Group, Chinese Thoracic Society. Expert consensus on pulmonary function testing during the epidemic of coronavirus disease 2019 [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:302-7.
14. WHO-China Joint Mission. Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19). Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed March 6, 2020.
15. Pratter MR, Brightling CE, Boulet LP, Irwin RS. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:2225-31S.
16. Yu L, Qiu Z, Lu H, Wei W, Shi C. Clinical benefit of sequential three-step empirical therapy in the management of chronic cough. Respirology 2008;13:353-8.
17. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 1996;156:997.
18. Lai K, Chen R, Lin L, Shen L, Zheng Y, Wang F, et al. Diagnostic values of the clinical characteristics of chronic cough [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi 2009;32:418-21.
19. Otoosi T, Nagano T, Funada Y, Takenaka K, Nakata H, Ohnishi H, et al. A cross-sectional survey of the clinical manifestations and underlying illness of cough. Vivo 2019;33:543-9.
20. Irwin RS, Baumann MH, Bobser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006;129:1S-23S.
21. Asthma Workgroup of Chinese Society of Respiratory Diseases (CSRD), Chinese Medical Association. Guidelines for diagnosis and management of cough (draft). Zhonghua Jie He He Hu Xi Za Zhi 2005;28:738-44.
22. Shirahata K, Fujimoto K, Arioka H, Shouda R, Kido K, Ikeda SI. Prevalence and clinical features of cough variant asthma in a general internal medicine outpatient clinic in Japan. Respir Med 2005;10:354-8.
23. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2019. Available from: www.ginasthma.com. Accessed July 30, 2019.
24. Lodhi S, Smith JA, Satia I, Holt KJ, Maidstone RJ, Durrington HJ. Cough rhythms in asthma: potential implication for management. J Allergy Clin Immunol Pract 2019;7:2024-7.
25. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. J Allergy Clin Immunol 2017;140:950-8.
26. Tajiri T, Niimi A, Matsumoto H, Ito I, Oguma T, Otsuka K, et al. Prevalence and clinical relevance of allergic rhinitis in patients with classic asthma and cough variant asthma. Respiration 2014;87:211-8.
27. Lai K, Shen H, Zhou X, Qiu Z, Cai S, Huang K, et al. Clinical practice guidelines for diagnosis and management of cough-Chinese Thoracic Society (CTS) Asthma Consortium. J Thorac Dis 2018;10:6314-51.
28. Lai K, Chen R, Peng W, Zhan W, Peng C. Non-asthmatic eosinophilic bronchitis and its relationship with asthma. Pulmon Pharmacol Therapeut 2017;47:66-71.
29. Fontana GA, Pistolesi M. Cough : chronic cough and gastro-oesophageal reflux. Thorax 2003;58:1092-5.
30. Pratter MR, Bartter T, Akers S, DuBois J. An algorithmic approach to chronic cough. Ann Intern Med 1993;119:977-83.
31. Ing AJ, Ng MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160.
32. Nebel OT, FORNES MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am J Dig Dis 1976;21:953-6.
33. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest 2006;129:638-71S.
34. Everett CF, Morice AH. Clinical history in gastroesophageal reflux. Respir Med 2007;101:345-8.
35. Deng H, Luo W, Zhang M, Xie J, Fang Z, Lai K. Initial empirical treatment based on clinical feature of chronic cough. Clin Respir J 2016;10:622-30.
36. Lai K, Li B, Wang F, Chen R, Liu X, Zhong N. Survey on the diagnosis and management of the patients with chronic cough. Int J Respir 2011;31:645-7.
### TABLE E1. Definition of clinical features

| Clinical feature                  | Definition                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| Nonproductive cough              | Cough was nonproductive or minimally so                                   |
| Daily cough alone                | Cough mainly occurs at daytime and before bedtime                         |
| Nocturnal cough alone            | Cough mainly occurs after falling asleep                                  |
| Total nocturnal cough            | Cough occurs at night, with or without daily cough                        |
| Trigger-eating                   | Cough when eating                                                         |
| Trigger-after meals              | Cough after meals                                                         |
| Reflux-related symptoms          | Experienced 1 or more symptoms of acid regurgitation, heartburn, and belching |
| Combined reflux symptoms         | Presence of all of the following symptoms: regurgitation, heartburn, and belching |
| Rhinitis/sinusitis-related       | Experienced 1 or more symptoms of sneezing, nasal itching, runny nose, and nasal congestion |
| History of gastrointestinal      | Previously diagnosed as chronic gastritis, stomach ulcer, or gastroesophageal reflux disease, etc |
| History of rhinitis              | Previously diagnosed as allergic rhinitis or nonallergic rhinitis         |
| History of sinusitis             | Previously diagnosed as acute sinusitis or chronic sinusitis              |
### TABLE E2. Number of subjects with a single cause enrolled annually

| Year | Total  | EB     | CVA     | UACS     | GERC     | UC     | Other causes |
|------|--------|--------|---------|----------|----------|--------|--------------|
| 2006 | 69 (100)| 29 (42.0) | 11 (15.9) | 3 (4.3)  | 10 (14.5) | 10 (14.5) | 6 (8.7)      |
| 2007 | 50 (100)| 19 (38.0) | 13 (26.0) | 2 (4.0)  | 11 (22.0) | 2 (4.0)  | 3 (6.0)      |
| 2008 | 66 (100)| 27 (40.9) | 20 (30.3) | 3 (4.5)  | 8 (12.1)  | 3 (4.5)  | 5 (7.6)      |
| 2009 | 75 (100)| 28 (37.3) | 20 (26.7) | 9 (12.0) | 7 (9.3)   | 2 (2.7)  | 9 (12.0)     |
| 2010 | 118 (100)| 40 (33.9)| 26 (22.0)| 11 (9.3) | 14 (11.9) | 6 (8.7)  | 16 (13.6)    |
| 2011 | 115 (100)| 33 (28.7)| 19 (16.7)| 11 (10.4)| 9 (7.8)   | 12 (10.4)| 24 (20.9)    |
| 2012 | 96 (100)| 14 (14.6)| 19 (19.8)| 11 (11.5)| 6 (6.3)   | 14 (14.6)| 32 (33.3)    |
| 2013 | 87 (100)| 12 (13.8)| 17 (19.5)| 3 (4.5)  | 8 (12.1)  | 14 (14.6)| 27 (27.8)    |
| 2014 | 94 (100)| 13 (13.8)| 16 (17.0)| 5 (5.3)  | 6 (6.4)   | 12 (13.8)| 27 (27.8)    |
| 2015 | 115 (100)| 21 (18.3)| 14 (12.2)| 5 (5.3)  | 6 (6.4)   | 12 (10.4)| 27 (27.8)    |
| 2016 | 71 (100)| 7 (9.9)  | 17 (23.9)| 2 (2.8)  | 7 (9.9)   | 6 (8.5)  | 32 (45.1)    |
| 2017 | 94 (100)| 9 (9.6)  | 16 (17.0)| 7 (7.4)  | 13 (13.8)| 20 (21.3)| 29 (30.9)    |
| 2018 | 112 (100)| 7 (6.3)  | 11 (9.8) | 6 (5.4)  | 23 (20.5)| 25 (22.3)| 40 (35.7)    |

UC, Unexplained cough.
Data were presented as frequency (percentage).

### TABLE E3. Characteristics of each predictive clinical feature as a diagnostic test for common causes of chronic cough

| Diagnosis     | Clinical feature                        | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---------------|-----------------------------------------|-------------------------|-------------------------|-----------------|-----------------|
| CVA           | Nocturnal cough alone                    | 8.1 (5.0-12.7)          | 97.6 (96.4-98.5)        | 45.0 (29.6-61.3) | 81.8 (79.3-83.9) |
|               | Total nocturnal cough                    | 66.2 (59.5-72.3)        | 59.6 (56.3-62.7)        | 28.0 (24.2-57.5) | 88.1 (85.3-90.5) |
|               | Triggers-common cold                     | 62.6 (55.9-68.9)        | 47.0 (43.7-50.2)        | 21.8 (18.7-25.3) | 84.2 (80.7-87.1) |
|               | Nasal itching                            | 42.3 (35.8-49.1)        | 78.6 (75.8-81.2)        | 31.9 (26.6-37.6) | 85.2 (82.7-87.5) |
|               | History of rhinitis                      | 47.1 (40.4-53.9)        | 75.9 (73.0-78.6)        | 31.7 (26.8-37.1) | 85.7 (83.1-88.0) |
| GERC          | Nonproductive cough                      | 79.2 (71.4-85.3)        | 40.9 (37.9-44.0)        | 16.0 (13.4-18.9) | 93.3 (90.4-95.3) |
|               | Daily cough alone                        | 70.1 (61.9-77.3)        | 48.6 (45.5-51.7)        | 16.2 (13.5-19.4) | 92.0 (89.3-94.1) |
|               | Triggers-after meals                     | 24.8 (18.2-32.8)        | 91.2 (89.3-92.8)        | 28.8 (21.2-37.7) | 89.5 (87.4-91.3) |
|               | Frequent throat clearing                 | 47.6 (39.3-56.0)        | 63.6 (60.6-66.6)        | 15.7 (12.5-19.5) | 89.5 (87.9-91.6) |
|               | Acid regurgitation                       | 40.7 (32.7-49.2)        | 85.5 (83.2-87.6)        | 28.6 (22.7-35.4) | 91.0 (89.0-92.7) |
|               | Heartburn                                | 22.8 (16.4-30.6)        | 94.9 (93.3-96.1)        | 38.8 (28.6-50.0) | 89.6 (87.6-91.3) |
|               | Belching                                 | 40.7 (32.7-49.2)        | 85.6 (83.3-87.7)        | 28.8 (22.8-35.6) | 91.0 (89.0-92.7) |
|               | Reflux-related symptoms                  | 57.2 (48.8-65.3)        | 75.0 (72.2-77.6)        | 24.6 (20.2-29.7) | 92.5 (90.4-94.1) |
|               | Combined reflux symptoms                 | 10.3 (6.1-16.8)         | 99.3 (98.5-99.7)        | 68.2 (45.1-85.3) | 88.6 (86.6-90.4) |
| UACS          | Postnasal dripping                       | 43.5 (32.9-54.7)        | 80.8 (78.3-83.1)        | 15.2 (11.0-20.4) | 94.8 (93.1-96.1) |
|               | Frequent throat clearing                 | 62.4 (51.1-72.4)        | 64.2 (61.2-67.0)        | 12.1 (9.2-15.6)  | 95.6 (93.7-96.9) |
|               | History of sinusitis                     | 35.7 (25.8-47.0)        | 90.2 (88.2-91.8)        | 22.2 (15.7-30.3) | 94.7 (93.1-95.9) |
|               | Rhinitis/sinusitis-related symptoms      | 72.9 (62.0-81.7)        | 46.1 (43.1-49.1)        | 9.6 (7.5-12.3)   | 95.6 (93.3-97.1) |
| EB            | History of rhinitis                      | 34.0 (28.3-40.1)        | 73.0 (70.0-75.9)        | 26.8 (22.2-32.0) | 79.2 (76.2-81.9) |

NPV, negative predictive value; PPV, positive predictive value.