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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 complains 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.[1-3] 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

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Abbreviations used
COVID-19- Coronavirus disease 2019
CVA- Cough variant asthma
EB- Eosinophilic bronchitis
GERC- Gastroesophageal reflux–related cough
OR- Odds ratio
UACS- Upper airway cough syndrome

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.[4,8-11] 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 vicious 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 I, 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 2003[11] and later slightly modified according to the guidelines by the American College of Chest Physicians[20] 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 χ^2 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

TABLE I. Clinical feature among different causes of chronic cough

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)	42.07 ± 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)	.2283
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)*	61 (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.

‡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 bronchiectasis, 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.

TABLE II. Univariate and multiple logistic regression of predictors of CVA

	Univariate analysis			Multiple analysis		
Characteristic	**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			
Runny nose	1.675	1.224-2.294	.0013			
Shortness of breath	1.481	1.047-2.095	.0265			
Trigger-lying down	1.805	1.278-2.550	.0008			

TABLE III. Univariate and multiple logistic regression of predictors of GREC

	Univariate analysis			Multiple analysis		
Characteristic	**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	.0009			
Trigger-talking	1.759	1.236-2.504	.0017			

jacionline.org. 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, 1.626; 95% CI, 1.122-2.356), and history of rhinitis (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).

TABLE IV. Univariate and multiple logistic regression of predictors of UACS

	Univariate analysis			Multiple analysis		
Characteristic	**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 predicative 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.[29-31] 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 reux 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.[29,32] 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.[9] 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,[14] 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,[21] 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.[4,8-11] 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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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 reux symptoms	Presence of all of the following symptoms: regurgitation, heartburn, and belching
Rhinitis/sinusitis-related symptoms	Experienced 1 or more symptoms of sneezing, nasal itching, runny nose, and nasal congestion
History of gastrointestinal disorders	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)	11 (9.3)	16 (13.6)
2011	115 (100)	33 (28.7)	22 (19.1)	15 (13.0)	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)	5 (5.7)	19 (21.8)	12 (13.8)	22 (25.3)
2014	94 (100)	13 (13.8)	16 (17.0)	5 (5.3)	6 (6.4)	27 (28.7)	27 (28.7)
2015	115 (100)	21 (18.3)	14 (12.2)	6 (5.2)	12 (10.4)	11 (9.6)	51 (44.3)
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 (87.0-91.6)
	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.