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Original Article

New Insights Into Refractory Chronic Cough and Unexplained Chronic Cough: A 6-Year Ambispective Cohort Study

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ABSTRACT

Purpose: Only limited studies have depicted the unique features and management of refractory chronic cough (RCC) and unexplained chronic cough (UCC). These led to the initiation of this study, which reported the demographic characteristics, manifestations, and long-term outcomes on a large series of consecutive RCC/UCC patients, providing a guideline-led real-world clinical experience.
Methods: Retrospective baseline information was obtained from Clinical Research Database (January 2016 to May 2021). At least 6 months after the last clinic visit, included subjects were prospectively followed up.
Results: Three hundred and sixty-nine RCC and UCC patients (199 females, 53.9%) were analyzed. The median cough duration was 24.0 (12.0–72.0) months. Laryngeal symptoms were reported in 95.9% of the patients. The common triggers for coughing were talking (74.9%), pungent odors (47.3%), eating (45.5%), and cold air (42.8%). RCC was considered in 38.2%, and the remainder of 228 patients had UCC, with an equal sex distribution (P = 0.66). Among the 141 RCCs, 90.8% (128) had refractory reflux cough, which was more responsive to current treatments (P < 0.01). Although most features and test results between RCC and UCC were similar, UCC was more commonly inappropriately treated (P < 0.01). Nineteen (7.7–41.1) months after the final clinic visit, 31.2% still coughed persistently, while 68.8% reported cough improvement or remission. RCC reported more favorable treatment outcomes (including cough improvement, control, and spontaneous remission) than UCC (P < 0.01). Coughs with long duration before the initial cough clinic visit (P < 0.01), frequent urinary incontinence (P < 0.01), and being sensitive to "talking" (P < 0.01) or "cold air" (P < 0.01) were less likely to be solved.
Conclusions: The current treatments only improve cough symptoms in two-thirds of patients. Clinical indicators for treatment failure were those coughing for long duration and being sensitive to "talking" or "cold air."

Keywords: Cough; cough hypersensitivity syndrome; population characteristics; treatment outcome

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INTRODUCTION

Chronic cough (CC) in adults is broadly defined as a cough lasting for more than 8 weeks. Based on current cough guidelines,[1,2] its causes can be identified in most patients, and they respond well to subsequent cause-specific treatments that finally lead to cough resolution. However, in 12%–42% of CC patients, etiologically targeted treatments may fail, or no underlying etiology is found after thorough assessments.[3] Refractory chronic cough (RCC) and unexplained chronic cough (UCC) are used to define these conditions, respectively.[4,5] They are more prevalent at specialist cough clinics in countries with a protocoled referral system.[6] These patients self-reported a cough easily triggered by innocuous stimuli which would not be tussive in the healthy population, an exaggerated cough response to noxious stimuli and irritation or itching sensation in the throat., These symptoms leave a severe negative impact on their quality of life (QoL) and stressful socio-economic pressure.[3]

The demographic characteristics of patients with CC appear to differ slightly between China and other countries. The female predominance in CC was commonly reported in some worldwide surveys, especially in older females, who were thought to have higher cough sensitivity.[7] However, the latest national cross-section study on CC reported a male predominance in China.[8] The 2 global randomized placebo-controlled trials (COUGH-1 and COUGH-2) regarding the efficacy of gefapixant (antagonist of P2X3 receptors) on RCC partially provided the preliminary characteristics of the participants, including the common comorbidity such as asthma, gastro-oesophageal reflux disease (GERD) and allergic rhinitis (upper airway cough syndrome, UACS).[9,10] However, specific knowledge about the profile of RCC/UCC in China and the sex differences in this condition are lacking. The reason why patients with abnormal test results failed to respond to the subsequent etiologically targeted treatment also remained unclear. RCC has an underlying cause but does not respond well to currently available treatments; however, there may be treatments that achieve greater efficacy in the future. This makes RCC clinically more amenable to resolution than UCC, which does not yet have a definitive etiological diagnosis and has no therapeutic direction. Defining the etiology and discovering effective therapeutic measures is currently a challenge in the clinical management of UCC. In UCC with at least 1 positive laboratory finding (UCCpos), abnormal findings may not be causally related to cough, making it difficult to effectively predict etiological treatment response, whereas the underlying etiology of UCC without any abnormal laboratory findings (UCCneg) may currently be poorly perceived by clinicians. Therefore, in this study, we retrospectively collected clinical information from RCC and UCC patients attending our cough clinic during the past 6 years and traced the outcomes prospectively to fully reveal the sex specificity of RCC/UCC and to find out differences among RCC, UCCpos, and UCCneg in order to provide clues for early identification of these 3 phenotypes in the clinical setting and to facilitate the search for effective treatment.

MATERIALS AND METHODS

Patients

Consecutive patients with RCC or UCC attending the specialist cough clinic in Tongji Hospital, Shanghai, China, from January 2016 to May 2021 (the initial visit), were included in this ambispective study. RCC and UCC diagnoses were only made after the common causes of CC, including gastro-oesophageal reflux-associated cough (GERC), UACS, and corticosteroid-responsive cough (CRC) like cough variant asthma (CVA), eosinophilic

bronchitis (EB), and atopic cough (AC), were excluded by negative laboratory assessments or failure to etiologically targeted treatments, such as oral corticosteroids, according to the recommendations of Chinese guidelines for cough management with adaptive modifications by our cough research group.[11,12] In this study, the term UCC was used to describe the conditions 1) without any positive findings pointing to an underlying disease after extensive investigations (UCCneg); 2) with at least 1 positive finding pointing to a potential disorder but unresponsive to all the subsequent targeted treatments (UCCpos). The term RCC was only used to define the conditions that patients were responsive to intensified treatment (double dose of treatment aimed against the potential cause or with additional neuromodulators which were prescribed as we reported before, such as gabapentin, baclofen, flupentixol/ melitracen[13,14]), but unresponsive to standard targeted therapy (low dose of treatment aimed against the potential cause) with the specific positive laboratory testing results. For example, the definition of refractory GERC refers to a condition of CC with objective evidence of abnormal reflux as demonstrated by multichannel intraluminal impedance-pH monitoring (MII-pH), which is resistant to low-dose proton-pump inhibitor but responsive to the subsequently intensified therapy.[15] The uniform algorithm for CC management is shown in **Fig. 1**, which has been recommended by the Asthma Group of the Chinese Thoracic Society in 2021.[11] The patients were aged ≥ 18 years with cough duration ≥ 1 year; those with incomplete data, lost to follow-up, or with other concomitant chronic respiratory diseases which can cause cough were excluded.

The ethical approval of this study was gained from the Ethics Committee of Tongji Hospital (K-2020-018). Verbal informed consent was obtained from all the participants at the telephone or instant message follow-ups.

Study procedure

The baseline data were retrospectively collected, including 1) demographic information; 2) cough severity indicated by cough symptom score (CSS)[16]; 3) laboratory assessments, such as blood testing, sinus imaging, spirometry, histamine bronchial provocation, fractional exhaled nitric oxide (FeNO), induced sputum cytology, MII-pH, cough sensitivity to inhaled capsaicin represented with the minimum concentration of capsaicin stimulating ≥ 2 (C2) or ≥ 5 coughs (C5); and 4) the scores of cough-related questionnaires (validated Chinese version) including the Hull airway reflux questionnaire (HARQ),[17] Leicester cough questionnaire (LCQ),[18] Reflux symptom index,[19] Newcastle laryngeal hypersensitivity questionnaire,[20] and Gastro-oesophageal reflux disease questionnaire,[21] by searching the ethics committee approved Clinical Research Database for CC. Patients were screened using inclusion and exclusion criteria. The definite diagnoses were made and classified. At least 6 months after the last clinical review, the participants were prospectively followed up to self-scale the CSS, HARQ and LCQ, and were asked to answer the questions about cough persistence, triggering factors, medication history, and ongoing treatments by telephone and instant messages. The capsaicin challenge test was repeated in the outpatient clinic if consent was given. Another follow-up interview was offered within 1 week if patients missed the initial invitation.
A specific RCC/UCC clinical database was built, and patients were grouped by sex and diagnosis for the subsequent data analysis (**Fig. 2**, **Supplementary Table S1**).

In this study, cough was considered controlled when cough resolved completely; improved when the CSS (the sum of daytime and night-time scores) decreased by ≥ 50%; persisted when CSS decreased by < 50% or the cough worsened.[22] Spontaneous cough remission was defined as a cough that disappeared without any treatment aimed against it after

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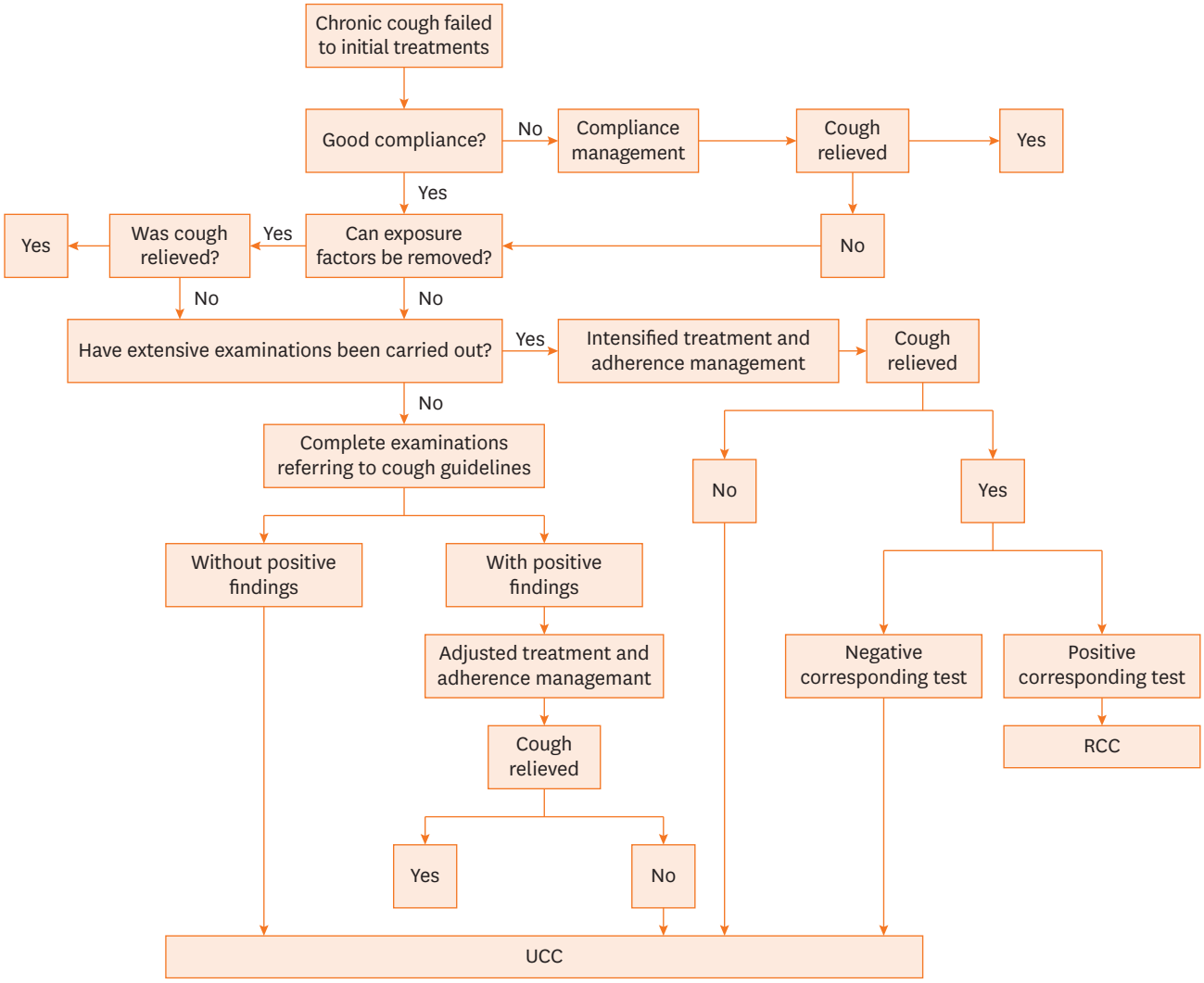

Fig. 1. Diagnostic algorithm for the management of RCC/UCC. A positive laboratory finding refers to blood eosinophils counting > 500/μL, fractional exhaled nitric oxide ≥ 25 ppb, the cumulative provocative dose of histamine causing a 20% fall in forced expiratory volume in one second < 7.8 mol, blood total immunoglobulin E ≥ 100 IU/mL, skin prick test showing allergen, percent eosinophils in induced sputum > 2.5%, computed tomography scan of paranasal sinuses showing inflammation, or multichannel intraluminal impedance-pH monitoring/gastroscopy/saliva pepsin test showing abnormal reflux. If any of these tests are abnormal, then the corresponding targeted treatment will be administered.
RCC, refractory chronic cough; UCC, unexplained chronic cough.

discontinuation of treatment due to lack of efficacy or poor compliance and did not recur by the last follow-up visit. GERC was considered suspicious if there was evidence of reflux, but not confirmed by a good response to anti-reflux treatment.

Statistical analysis

Normally distributed data were expressed as mean ± standard deviations (SDs), while skewed distributed data are expressed as median with a 25%–75% interquartile range. C2 and C5 to inhaled capsaicin were log-transformed and are expressed as geometric mean ± SD. The difference between groups was assessed utilizing the independent-samples *t*-test, Mann-Whitney *U* test, χ^2 test, and Kruskal-Wallis test where applicable. Statistical calculation was performed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, CA, USA). A *P* value < 0.05 was considered statistically significant.

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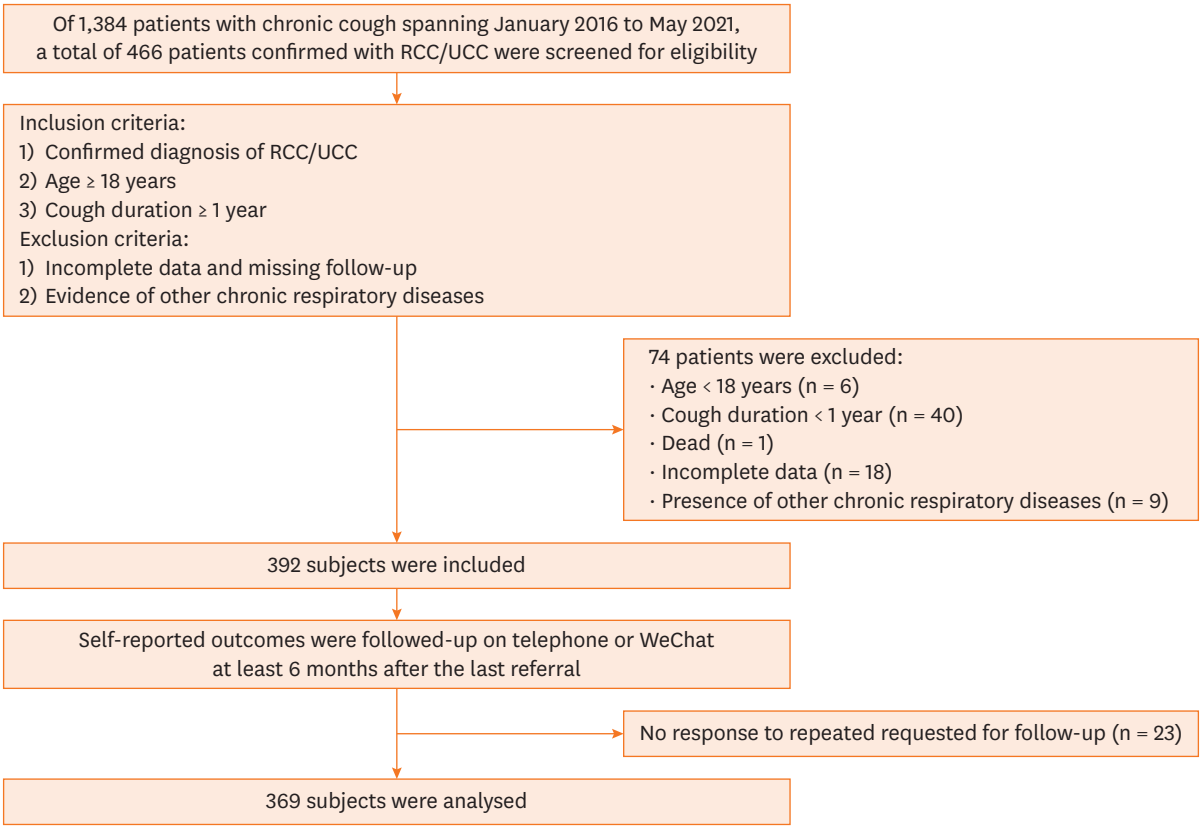

Fig. 2. The flow chart of screening procedures.
RCC, refractory chronic cough; UCC, unexplained chronic cough.

RESULTS

Clinical characteristics

The final follow-up was completed in November 2021. A total of 369 patients (199 females, 53.9%) were recruited (26.7% of the contemporaneous CC patients) (**Fig. 2**), with a median cough duration of 24.0 (12.0–72.0) months, of whom 79.7% had visited at least 2 different medical facilities before. RCC and UCC diagnoses were usually established within an average of 6 weeks in our cough clinic. Cough was preceded by acute upper respiratory tract infection (URTI) in 17.3% of patients but occurred without any inducers in 78.6%. Two hundred and twenty-five patients (61.0%) coughed predominantly during the daytime, while 95.9% and 57.5% had concomitant laryngeal and epigastric discomforts, respectively. Urinary incontinence was present in 23.6% of females. The common cough triggers included talking (74.9%), irritating or pungent odor (47.3%), eating (45.5%), and cold air (42.8%) (**Table 1**).

The primary abnormalities included sinusitis shown by computed tomography (CT) scan in 20.6% of patients, FeNO ≥ 25 ppb in 13.6%, allergic status as indicated by increased serum total immunoglobulin E level in 9.2%, positive allergen skin prick test in 5.4%, and suspicious GERC as demonstrated by abnormal gastroesophageal parameters in 2.4%–21.4%, and positive histamine bronchial provocation (defined as PD20-FEV1 < 7.8 mmol, also known as bronchial hyperresponsiveness-BHR) in 5.7%—more BHR can be seen in the

Table 1. Differences in clinical characteristics of 369 patients with refractory chronic cough/unexplained chronic cough between sexes

Clinical characteristics	All (n = 369)	Male (n = 170)	Female (n = 199)	*P* value	95% CI of group differences	Size effect value (η^2/Cohen's d)
Age (year)	46.6 (34.3–60.0)	38.4 (31.0–51.5)	55.1 (42.3–63.1)	< 0.01	−13.9, −8.0	0.10
BMI (kg/m^2)	23.8 ± 3.4	24.2 ± 3.2	23.4 ± 3.5	0.09	−0.11, 1.52	0.07
Cough duration (m)	24.0 (12.0–72.0)	24.0 (12.0–60.0)	24.0 (12.0–102.0)	0.75	−21.5, 6.5	0.02
VAS score	60.0 (50.0–70.0)	60.0 (5.00–70.0)	60.0 (50.0–80.0)	0.51	−6.9, 3.5	0.00
Cough symptom score						
Daytime	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	0.53	−0.1, 0.2	0.90
Nighttime	1.0 (1.0–2.0)	1.0 (1.0–1.0)	2.0 (1.0–3.0)	< 0.01	−1.0, −0.5	0.01
Cough phase						
Mainly during the day	225 (61.0)	124 (72.9)	101 (50.8)	< 0.01	12.3, 31.4	0.23
Mainly during the night	36 (9.8)	6 (3.5)	30 (15.1)	< 0.01	5.7, 17.5	0.19
No difference	108 (29.3)	40 (23.5)	68 (34.2)	0.03	1.3, 19.6	0.12
Cough nature						
Dry cough	235 (63.7)	112 (65.9)	123 (61.8)	0.42	−5.8, 13.7	0.04
With sputum	134 (36.3)	58 (34.1)	76 (38.2)	0.42	−5.8, 13.7	0.04
Accompanying symptoms						
Nasal*	133 (36.0)	58 (34.1)	75 (37.7)	0.48	−6.2, 13.2	0.04
Stomach†	212 (57.5)	96 (56.5)	116 (58.3)	0.72	−8.2, 11.8	0.02
Larynx	354 (95.9)	162 (95.3)	192 (96.5)	0.90	−3.1, 5.9	0.01
Hoarseness	135 (36.6)	62 (36.5)	73 (36.7)	0.97	−9.6, 9.9	< 0.01
Clear throat	299 (81.0)	143 (84.1)	156 (78.4)	0.36	−2.4, 13.6	0.05
Itchy or obstructed throat	321 (87.0)	146 (85.9)	175 (87.9)	0.71	−4.8, 9.2	0.02
Chest tightness	167 (45.3)	78 (45.9)	89 (44.7)	0.82	−8.9, 11.2	0.01
Chest pain	54 (14.6)	26 (15.3)	28 (14.1)	0.74	−6.0, 8.7	0.02
Urinary incontinence	47 (12.7)	0 (0)	47 (23.6)	< 0.01	17.8, 30.0	0.35
Syncope	6 (1.6)	4 (2.4)	2 (1.0)	0.42	−1.6, 5.0	0.05
None	73 (19.8)	34 (20.0)	39 (19.6)	0.92	−7.7, 8.7	0.01
Starting causes						
Common cold	64 (17.3)	25 (14.7)	39 (19.6)	0.22	−2.9, 12.5	0.06
Others	15 (4.1)‡	5 (2.9)§	10 (5.0)‖	0.31	−2.3, 6.4	0.05
None	290 (78.6)	140 (82.4)	150 (75.4)	0.10	−1.5, 15.1	0.09
Trigger factors						
Eat or drink	168 (45.5)	88 (51.8)	80 (40.2)	0.03	1.4, 21.5	0.10
Talk	276 (74.9)	130 (76.5)	146 (73.4)	0.49	−5.8, 11.8	0.03
Pungent odors	174 (47.3)	79 (46.5)	95 (47.7)	0.81	−8.9, 11.4	0.01
Cold-air	158 (42.8)	77 (45.3)	81 (40.7)	0.37	−5.5, 14.6	0.01
Others¶	23 (6.2)	12 (7.1)	11 (5.5)	0.54	−3.5, 7.0	0.01
None	72 (19.5)	27 (14.7)	45 (22.6)	0.10	−1.4, 14.6	0.09
Cigarette smoke exposure						
Current smoker	31 (8.4)	30 (17.6)	1 (0.5)	< 0.01	11.7, 23.6	0.31
Ex-smoker	68 (18.4)	58 (34.1)	10 (5.0)	< 0.01	21.3, 36.8	0.37
Never smoker	270 (73.2)	82 (48.2)	188 (94.5)	< 0.01	37.7, 54.0	0.52
Previous medical history						
Hypertension	50 (13.6)	13 (7.6)	37 (18.6)	< 0.01	4.0, 17.7	0.16
Gastrosia	66 (17.9)	34 (20.0)	32 (16.1)	0.33	−3.9, 11.9	0.05
Rhinitis	61 (16.5)	31 (18.2)	30 (15.1)	0.42	−4.4, 10.9	0.04
Pharyngitis	17 (4.6)	8 (4.7)	9 (4.5)	0.93	−4.3, 5.0	< 0.01
Others	57 (15.5)	21 (12.4)	36 (18.1)	0.13	−1.7, 13.0	0.08
None	195 (52.9)	89 (52.4)	106 (53.3)	0.86	−9.2, 11.0	0.01

Values are presented as median with a 25%–75% interquartile range, mean ± standard deviations, or number (%).
n, the number of patients who completed this test; CI, confidence interval; η^2, eta-squared; BMI, body mass index; VAS, visual analogue scale.
*Nasal symptoms include runny nose, sneezing, postnasal drip, *etc*.
†Gastric symptoms include reflux, heartburn, belching, nausea, vomiting, dyspepsia, *etc*.
‡Including pneumonia (n = 4), post lung tumour resection (n = 4), post thyroid surgery (n = 1), post breast cancer chemotherapy bone metastasis (n = 1), asthma attack (n = 1), tonsillitis (n = 1), heat stroke (n = 1), post abortion (n = 1), post house renovation (n = 1).
§Including post lung tumour resection (n = 2), pneumonia (n = 1), heatstroke (n = 1), asthma attack (n = 1).
‖Including pneumonia (n = 3), post lung tumor resection (n = 2), post thyroid surgery (n = 1), post breast cancer chemotherapy bone metastasis (n = 1), tonsillitis (n = 1), post abortion (n = 1), post house renovation (n = 1).
¶Including exertion, exercise, anxiety, stress, *etc*.

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Table 2. Differences in cough-associated assessments of 369 patients with refractory chronic cough/unexplained chronic cough between sexes

Assessments	All (n = 369)	Male (n = 170)	Female (n = 199)	*P* value	95% CI of group differences	Size effect value (η^2/Cohen's d)
Spirometry parameters (n = 313)						
FEV1/predicted (%)	101.0 ± 14.0	98.5 ± 13.5	103.3 ± 14.2	0.01	−8.03, −1.44	0.79
FVC/predicted (%)	102.9 ± 14.9	98.9 ± 13.0	106.8 ± 15.6	< 0.01	−11.32, −4.46	0.29
FEV1/FVC (%)	82.2 ± 7.6	82.9 ± 7.8	81.6 ± 7.3	0.18	−0.56, 3.04	0.63
MMEF/predicted (%)	78.2 ± 25.6	83.6 ± 26.0	73.8 ± 24.5	< 0.01	3.19, 16.40	0.73
FeNO ≥ 25 ppb (n = 247)	50 (13.6)	29 (17.1)	21 (10.6)	0.07	−0.5, 13.8	0.10
PD20-FEV1 < 7.8 mol (n = 260)	21 (5.7)	11 (6.5)	10 (5.0)	0.55	−3.4, 6.7	0.03
Blood total IgE ≥ 100 IU/mL (n = 209)	34 (9.2)	21 (12.4)	13 (6.5)	0.05	−0.2, 12.2	0.10
Positive allergen skin prick test (n = 53)	20 (5.4)	12 (7.1)	8 (4.0)	0.20	−1.7, 8.3	0.07
Blood eosinophils counting (/μL) (n = 238)	50.0 (0.0–100.0)	60.0 (0.0–122.5)	50.0 (0.0–100.0)	0.01	11.4, 61.1	< 0.01
Blood eosinophils % (n = 238)	1.4 (0.9–2.4)	1.6 (1.1–2.5)	1.3 (0.8–2.2)	0.03	−0.03, 0.7	< 0.01
Induced sputum cytology (n = 328)						
Percent eosinophils > 2.5%	33 (8.9)	17 (10.0)	16 (8.0)	0.51	−3.9, 8.2	0.03
Eosinophils counts	1.0 (0.0–1.50)	1.0 (0.1–1.5)	1.0 (0.0–1.5)	0.17	−0.01, 1.0	0.02
CT scan of paranasal sinuses showing inflammation (n = 106)	76 (20.6)	42 (24.7)	34 (17.1)	0.07	−0.7, 16.0	0.09
MII-pH parameters (n = 201)						
AET > 6%	37 (10.0)	20 (11.8)	17 (8.5)	0.30	−3.0, 9.7	0.05
Total reflux episodes in 24-hr > 80	79 (21.4)	45 (26.5)	34 (17.1)	0.03	1.0, 17.8	0.11
SAP ≥ 95%	36 (9.8)	19 (11.2)	17 (8.5)	0.40	−3.5, 9.1	0.04
DeMeester score ≥ 12.7	57 (14.6)	29 (17.1)	28 (14.1)	0.43	−4.4, 10.6	0.04
Esophageal bolus clearance (second)	10.0 (7.0–12.5)	11.0 (8.0–12.6)	10.0 (7.0–12.5)	0.38		0.25
Gastroscopy showing reflux oesophagitis (n = 72)	34 (9.2)	17 (10.0)	17 (8.5)	0.63	−4.5, 7.7	0.03
Positive saliva pepsin test (n = 11)	9 (2.4)	3 (1.8)	6 (3.0)	0.44	−2.4, 4.9	0.04
GerdQ score (n = 273)	6.0 (6.0–7.0)	6.0 (6.0–7.0)	6.0 (6.0–7.0)	0.50	−0.3, 0.5	
RSI (n = 97)	13.6 ± 8.1	13.6 ± 9.0	13.7 ± 7.2	0.99	−3.29, 3.23	0.98
HARQ score (n = 344)	22.5 (17.0–31.3)	23.0 (17.0–32.0)	22.0 (17.0–30.0)	0.73	−2.0, 3.0	0.51
NLHQ score (n = 28)	76.00 ± 11.7	78.5 ± 10.5	74.4 ± 12.5	0.38	−5.27, 13.47	0.32
Total LCQ score (n = 316)	13.4 (11.0–14.8)	12.9 (10.5–14.5)	13.5 (11.4–15.0)	0.20	−1.4, 0.3	0.46
Physical domain	4.5 (3.9–5.1)	4.5 (3.9–5.1)	4.5 (3.9–5.1)	0.56	−0.2, 0.4	0.95
Psycho domain	3.9 (3.1–4.6)	3.6 (2.9–4.4)	4.1 (3.3–4.7)	0.01	−0.8, −0.1	< 0.01
Social domain	4.5 (3.5–5.3)	4.5 (3.5–5.3)	4.8 (3.5–5.5)	0.21	−0.6, 0.1	0.48
Cough threshold (μmol/L) (n = 341)						
C2, geometric mean ± SD	0.6 ± 0.2	0.7 ± 0.3	0.6 ± 0.2	0.17	−0.01, 1.8	0.02
C5, geometric mean ± SD	0.8 ± 0.3	0.9 ± 0.4	0.7 ± 0.3	0.01	1.2, 7.1	0.03

Values are presented as median with a 25%–75% interquartile range, mean ± SDs, or number (%).
N, the number of patients who completed this test; CI, confidence interval; η^2, eta-squared; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FeNO, fractional exhaled nitric oxide; PD20-FEV1, the cumulative provocative dose of histamine causing a 20% fall in forced expiratory volume in one second; IgE, immunoglobulin E; CT, computed tomography; MII-pH, multichannel intraluminal impedance-pH monitoring; AET, acid exposure time; SAP, the symptom association probability; GerdQ, Gastro-esophageal reflux disease questionnaire; RSI: reflux symptom index; HARQ, Hull airway reflux questionnaire; NLHQ, Newcastle laryngeal hypersensitivity questionnaire; LCQ, Leicester cough questionnaire; C2 or C5: the minimum concentration of capsaicin stimulating ≥ 2 or ≥ 5 coughs; SD, standard deviation.

contemporary common CC (12.4%; $P < 0.01$) and decreased by year: 30.1% in 2016, 24.9% in 2017, 23.2% in 2018, 11.6% in 2019, 8.6% in 2020, and 4.8% in 2021 (**Table 2**).

Both sexes coughed predominately during the daytime. Females were significantly older ($P < 0.01$) and had more nocturnal cough ($P < 0.01$) but had less meal-time cough ($P = 0.03$), with fewer smokers ($P < 0.01$), more common history of hypertension ($P < 0.01$), lower C5 ($P = 0.01$), better pulmonary functions, lower rate of abnormal reflux episodes, and higher scores in LCQ psychological domain (**Tables 1** and **2**).

Difference between RCC and UCC

RCC accounted for 38.2% (141 cases), while UCC accounted for 61.8% (228 cases), with similar sex and age distributions between the 2 groups. Males were predominantly 30–39 years, while females were mostly 40–69 (**Fig. 3A-C**). Of 228 UCC patients, 125 (54.8%) with

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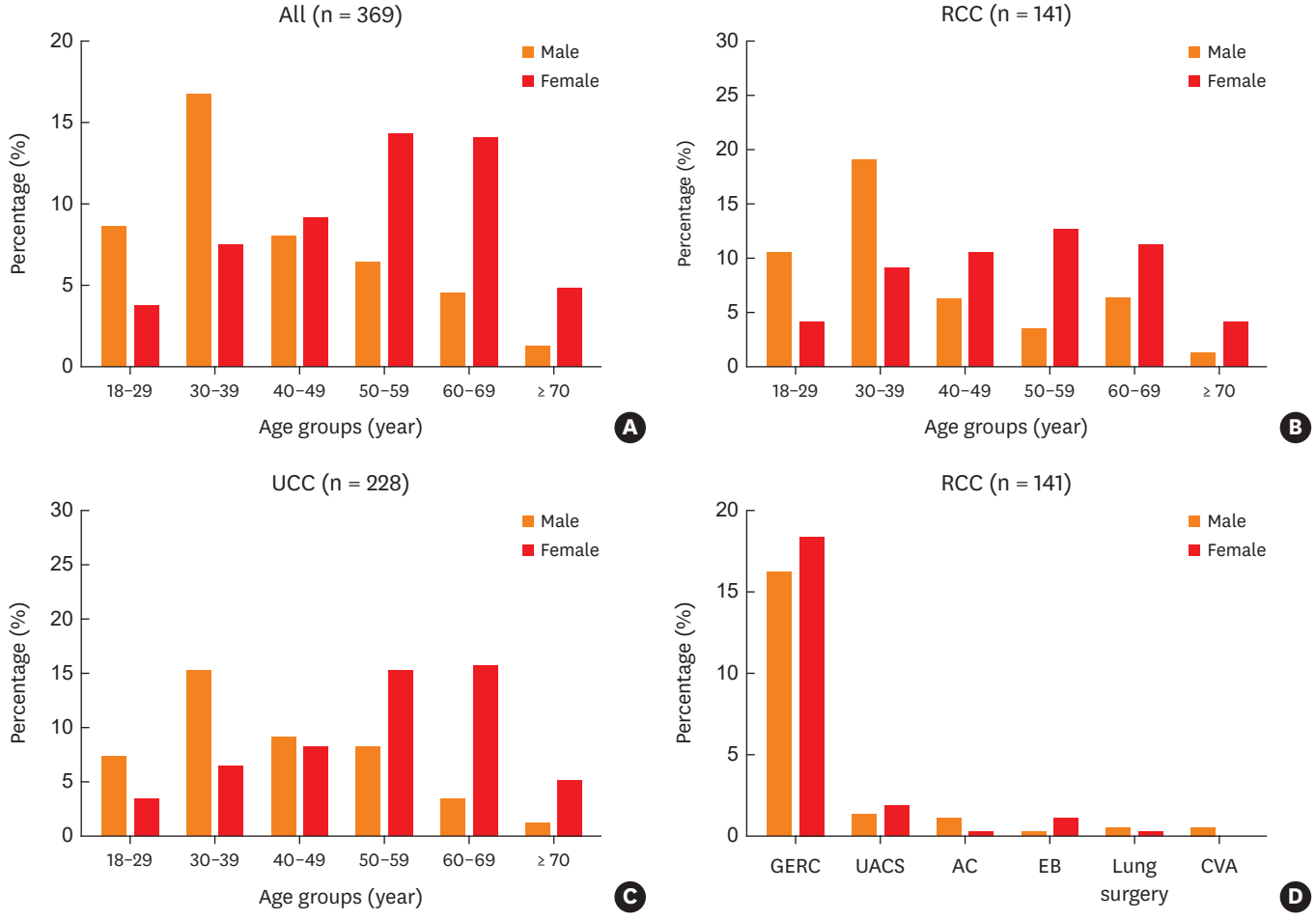

Fig. 3. The sex distribution by age (A-C) or by the diagnostic conditions (D). Percentage (%): ratios of the number of females or males to the total number of the whole cohort (A) or RCC groups (B, D) or UCC group (C).
RCC, refractory chronic cough; UCC, unexplained chronic cough. GERC, gastro-esophageal reflux-induced chronic cough; UACS, upper airway cough syndrome; AC, atopic cough; EB, eosinophilic bronchitis; CVA, cough variant asthma; Lung surgery, cough after lung tumor resection.

positive laboratory findings were defined as UCCpos, while the remaining 45.2% were UCCneg. Cold air aggravated or triggered cough most often in RCC, followed by UCCneg (RCC vs. UCCpos, $P < 0.05$; RCC vs. UCCneg, $P < 0.05$; UCCpos vs. UCCneg, $P < 0.05$). Abnormal MII-pH results were more common in RCC ($P < 0.01$), while more FeNO ≥ 25 ppb and sinusitis (indicated by CT scan) were found in UCCpos ($P = 0.02$ and < 0.01, respectively). UCCneg had a female predominance (RCC vs. UCCpos, $P > 0.05$; RCC vs. UCCneg, $P > 0.05$; UCCpos vs. UCCneg, $P < 0.05$), less current smokers (RCC vs. UCCpos, $P > 0.05$; RCC vs. UCCneg, $P > 0.05$; UCCpos vs. UCCneg, $P < 0.05$), higher scores in LCQ psychological domain (RCC vs. UCCpos, $P = 0.42$; RCC vs. UCCneg, $P = 0.13$; UCCpos vs. UCCneg, $P = 0.03$), and social domain (RCC vs. UCCpos, $P = 0.10$; RCC vs. UCCneg, $P = 0.19$; UCCpos vs. UCCneg, $P = 0.01$) (**Table 3**).

Diagnostic history of RCC/UCC

A hundred and thirty-five (36.6%) patients had been treated as at least one common classification of CC before RCC/UCC diagnosis was made: GERC (80, 21.7%), UACS (45, 12.2%), AC (20, 5.4%), EB (14, 3.8%), CVA (14, 3.8%), and asthma (3, 0.8%). Previous

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Table 3. Comparisons of clinical characteristics and assessment results between RCC and UCC patients

Characteristics	RCC (n = 141)	UCCpos (n = 125)	UCCneg (n = 103)	*P* value
Sex (Male/Female)	67/74	67/58	36/67	0.02
BMI (kg/m^2)	24.15 ± 3.59	23.83 ± 3.42	23.06 ± 2.99	0.11
Starting causes				
Cold	30 (21.3)	20 (16.0)	14 (13.6)	0.26
Others	12 (8.5)*	3 (2.4)†	0 (0.0)	< 0.01
None	99 (70.2)	102 (81.6)	89 (86.4)	0.01
Aggravated by cold-air	85 (60.3)	30 (24.0)	43 (41.7)	< 0.01
Current smoker	12 (8.5)	14 (11.2)	2 (1.9)	0.03
FeNO ≥ 25 ppb	19 (13.5)	31 (24.8)	-	0.02
Sinusitis indicated by CT scan	30 (21.3)	46 (36.8)	-	0.01
MII-pH showing abnormal reflux	89 (63.1)	50 (40.0)	-	< 0.01
Acid/Non-acid	37/52	17/33	-	0.38
Total LCQ score	13.18 (10.45–14.76)	12.45 (10.54–14.34)	14.20 (12.89–15.46)	0.17
Physical domain	4.50 (3.50–5.19)	4.38 (3.88–5.13)	4.63 (4.00–5.25)	0.39
Psycho domain	3.86 (3.14–4.43)	3.79 (2.96–4.43)	4.43 (3.43–5.00)	0.03
Social domain	4.50 (3.50–5.38)	4.25 (3.00–5.00)	5.00 (4.25–5.50)	0.01

Values are presented as median with a 25%–75% interquartile range, mean ± standard deviations, or number (%).
RCC, refractory chronic cough; UCC, unexplained chronic cough; UCCpos, unexplained chronic cough with positive objective test results; UCCneg, unexplained chronic cough without positive objective test results; BMI, body mass index; FeNO, fractional exhaled nitric oxide; CT, computed tomography; MII-pH, multichannel intraluminal impedance-pH monitoring; LCQ, Leicester cough questionnaire.
*Including pneumonia (n = 4), post lung tumour resection (n = 4), asthma attack (n = 1), heat stroke (n = 1), post abortion (n = 1), post house renovation (n = 1).
†Post thyroid surgery (n = 1), post breast cancer chemotherapy bone metastasis (n = 1), tonsillitis (n = 1).

ineffective treatments were more commonly seen in UCC (112, 49.1%) than in RCC (23, 16.3%) ($P < 0.01$). In UCCpos, this reached up to 72%.

Underlying disease of RCC

In 141 RCC patients, refractory GERC was the leading accompanying disease (128, 90.8%), followed by refractory UACS (12, 8.5%), refractory AC (5, 3.6%), refractory EB (5, 3.6%), lung resection induced cough (3, 2.1%), and refractory CVA (2, 1.4%) (**Fig. 3D**). Multiple concomitant diagnoses were presented in 9.9% of RCC, among which, multiple diagnoses, especially refractory GERC plus anyone of other diagnoses, were most common (**Table 4**).

Long-term outcomes

Patients were followed up with a median of 19.1 (7.7–41.8) months after the last clinic visit. At the last interview, 82.1% of patients stopped any antitussive treatments for a median of 14.0 (4.0–32.5) months. The ongoing treatments are presented in **Table 5**. Favorable outcomes were reported in 68.8% of patients (cough improved in 24.9%, controlled in 40.1%, and

Table 4. Underlying diseases of 141 refractory chronic cough patients

Underlying disease composition	Frequency	Percentage (%)
GERC	114	80.9
GERC + UACS	7	5
UACS	5	3.5
GERC + EB	4	2.8
GERC + AC	3	2.1
Cough after lung tumor resection	3	2.1
AC	2	1.4
CVA	2	1.4
EB	1	0.7

GERC, gastro-esophageal reflux-induced chronic cough; UACS, upper airway cough syndrome; AC, atopic cough; EB, eosinophilic bronchitis; CVA, cough variant asthma.

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Table 5. Ongoing treatments at the last follow-up interview

Treatments	Dosing	Frequency, n (%)
PPIs	Double-dose, BID	3 (0.8)
Gabapentin	0.4g, TID	2 (0.5)
	0.3g, TID	12 (3.3)
	0.2g, TID	6 (1.6)
	0.1g, TID	8 (2.2)
	0.1g, PRN	1 (0.3)
Deanxit (Flupentixol + Melitracen)	1s, BID	13 (3.5)
	1s, QD	11 (3.0)
	1/3s, TID	1 (0.3)
	1s, PRN	2 (0.5)
Baclofen	20mg, TID	1 (0.3)
	20mg, BID	2 (0.5)
	10mg, TID	1 (0.3)
Pregabalin	150mg, BID	2 (0.5)
Codeine	15mg, TID	1 (0.3)

PPI, proton-pump inhibitor; TID, 3 times daily; BID, twice daily; QD, once a day; PRN, as needed.

Table 6. Outcomes of follow-up at a median of 19.1 (7.7–41.8) months after the last treatment (n = 369)

Results	Total	Groups			
		Refractory GERC (n = 128)	Other RCC (n = 13)	UCCpos (n = 125)	UCCneg (n = 103)
Cough controlled	148 (40.1)	68 (53.1)*	3 (23.1)	37 (29.6)†	40 (38.8)‡
Cough improved	92 (24.9)	40 (31.3)§	4 (30.8)	25 (20.0)	23 (22.3)‖
Cough persisted	115 (31.2)	18 (14.1)	6 (46.2)	55 (44.0)	36 (35.0)
Spontaneous remission	14 (3.8)	2 (1.6)	0	8 (6.4)	4 (3.9)

Values are presented as numbers (%).
RCC, refractory chronic cough; UCCpos: unexplained chronic cough with positive findings; UCCneg, unexplained chronic cough without positive findings; GERC, gastro-esophageal reflux-induced chronic cough.
*Two patients controlled cough by taking Chinese medicine, one by radiofrequency ablation and one by losing weight simultaneously during treatment.
†Eight patients controlled cough by taking Chinese medicine.
‡Four patients controlled cough by taking Chinese medicine, one by otitis media surgery, and one benefitted from mint tablets.
§Two patients benefitted from taking Chinese medicine, 2 from radiofrequency ablation, and one from losing weight simultaneously during treatment.
‖One patient's cough subsided after starting to exercise more.

spontaneously remitted in 3.8%), while 31.2% still coughed vigorously. In parallel to cough improvement, HARQ scores were dramatically reduced ($P < 0.01$; mean difference: −6.8 ± 11.6); however, LCQ scores markedly improved ($P < 0.01$; mean difference: 2.4 ± 4.0), even though cough thresholds C2 and C5 did not change obviously (n = 45; C2: $P = 0.39$; C5: $P = 0.98$). RCC reported more favorable treatment outcomes than UCC ($P < 0.01$). Only 14.1% of refractory GERC had a persistent cough, and this was much higher in other classifications ($P < 0.01$), but there was no significant difference between the UCC (+) and UCC (−) groups ($P = 0.35$) (**Table 6**). Shorter-duration cough (14.5 [12.0–60.0] vs. 36.0 [22.5–120.0], $P < 0.01$), less frequent urinary incontinence (9.1% vs. 20.9%, $P < 0.01$), and more insensitive to "talking" (70.5% vs. 81.7%, $P < 0.01$) or "cold-air" (37.8% vs. 53.9%, $P < 0.01$) tended to have favorable outcomes (**Supplementary Table S2**).

DISCUSSION

This is the first cohort study that reports the clinical nature and long-term outcomes of RCC and UCC in a large series of consecutive patients. Most of these patients were referred from primary care or other healthcare facilities and had previously undergone repeated laboratory

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investigations and ineffective treatments. In addition to additional examinations, such as induced sputum cytology, histamine bronchial provocation, and MII-pH, the failed empirical trials also helped efficiently rule out suspected causes such as CRC. The diagnosis of RCC or UCC can therefore be established within an average of 6 weeks in our clinic.

This cohort had a self-reported long duration of severe cough. The onset of cough was often ascribed to presumed acute URTI, but most coughs do not have recognizable causes (especially UCC). The prominent clinical feature was a paroxysmal dry cough, which was more severe during the daytime, and triggered or aggravated by talking, irritating, or pungent odor, eating, and cold air. Up to 95.9% of patients reported laryngeal discomfort. Other concomitant manifestations included epigastric discomfort, chest tightness, nasal symptoms, chest pain, and urinary incontinence (only females). These characteristics are comparable with those described in previous studies.[23-25]

The sex distribution of CC and RCC/UCC is skewed toward females in some worldwide studies,[7,9,26,27] whereas in China, this tends to be even with variability between studies.[7,28,29] The fact that patients can be free to visit reputable specialist clinics in China may lead to a bias in the proportion of patients among healthcare institutions, but promote patients to visit clinics. This may explain why RCC/UCC patients in this study were approximately 20 years younger than those in a large epidemiological survey.[7] This cohort had a marginal predominance of older females. The particular prevalence in menopausal females is due in part to the increased $CD4^+$ T-cells in the respiratory tract and the hormone-induced anatomical brain changes.[7,30] Exposure to occupational and environmental cough triggers (male smokers are more common) may be responsible for the considerable number of younger male coughers in China.[31] In this study, women reported more nocturnal cough with better results in lung function. Over half of the males coughed during meal-times and were more likely to have GERC and higher eosinophil levels in the blood. Currently, it is difficult to assume a definite association between eosinophils and sex, given the impact of several intrinsic, extrinsic, and technical factors.[32] The total LCQ scores between sexes were comparable, in line with the result of our previous study[18]; however, psychological domain scores in women were significantly higher with QoL better, which was contradictory with the traditional thinking.[18] The predominance of elderly women might be postulated, as higher scores in psychological and social dimensions associated with aging have previously been described.[33] Further confirmation work is needed. Persistent troublesome cough seems to have a greater negative psychological impact on predominantly young and middle-aged men (the main working and social networking population), which could, to some extent, explain why UCCneg, with up to 65% female prevalence, had fewer current smokers and scored higher in LCQ psychological and social domains than UCCpos. Consistent with most studies, cough sensitivity was higher in females.[31,34,35] Since angiotensin-converting enzyme inhibitor-related cough has been excluded, more prevalent hypertension in females may be associated with aging and not likely to be related to enhanced cough sensitivity. There was no sex difference in HARQ scores, whereas previous data by Morice *et al.*[36] demonstrated that females had higher scores in a Caucasian population. In addition, the HARQ scores were lower compared to those of the previous report[9] (mean of approximately 23 vs 40, respectively), and 90% of patients were above the upper limit of normal. The shorter duration of the cough history in this study was likely to be a contributor to the lower score, since higher HARQ scores are associated with a longer duration of cough.

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RCC patients in this study were more likely to display sensitivity to cold air or have abnormal reflux than UCC. Stimulation of a thermosensor of noxious cold, Transient Receptor Potential Cation Channel A1 (TRPA1), has been demonstrated to be enhanced in CC patients[37] and may be associated with cold-air-induced cough.[38,39] We speculate that the more frequent abnormal reflux seen in RCC may sensitize TRPA1 and thus enhance the sensitivity to cold air. Although airway reflux was observed in over one-fifth of UCC patients, as demonstrated by MII-pH measurements, intensive treatment failure excluded GERC from the consideration. The greater FeNO results and a higher proportion of sinusitis in UCC may indicate a potential association between intractable airway reflux and upper/lower airway inflammation.

Unlike previous reports which had a predominance of RCC (62%),[10] our cohort was mostly UCC, accounting for over 60%. This might stem from the difference in diagnostic criteria. Patients with positive clinical examinations pointing to a possible etiology, but who subsequently were unresponsive to targeted treatment have been termed as RCC by some investigators.[40,41] In contrast, we suggest that the diagnosis should be made based on clinical history associated with abnormal laboratory findings and effective targeted treatment; positive findings in patients refractory to targeted treatment may be a bystander rather than the confirmative relevance to the etiology of cough. We have therefore developed a clear classification of RCC and UCC in this study. The majority of RCC had GERC with non-acid reflux shown by impedance. These patients had abnormal reflux-associated findings and poor response to low doses of omeprazole + domperidone but benefited from double doses of omeprazole or a combination of neuromodulators such as baclofen and gabapentin.[15] The fact that this study was conducted at a single and specialized center may also contribute to the high proportion of refractory GERC. UACS associated with chronic sinusitis constituted the second leading cause of RCC. Due to the lack of effective treatments for GERD or sinusitis,[42,43] GERC, and UACS are more likely to be refractory. In general, CVA, EB, and AC are sensitive to steroids and less likely to be refractory. The reason for refractory cough in 5 patients of AC and 5 of EB may be unavoidable exposure to allergens or non-allergic mechanisms.

RCC and UCC are exclusive diagnoses with frequent mismanagement. Nearly two-fifths of patients in this cohort had received ineffective targeted treatments before. UCC patients were less likely to be responsive to the targeted treatment, particularly those with positive tests (only a 28% response rate). Thus, the test results failed to predict treatment response in most patients. Most patients had been empirically treated as CVA, AC, and EB before the first visit to our clinic. CVA has clear diagnostic criteria and usually responds well to anti-asthmatic treatment. This is supported by the fact that only 5.7% of our patients had BHR, significantly less than that in the contemporary common CC patients in our clinic (12.4% overall but dropped from 30.1% in 2016 to 4.8% in 2021 since the 3-step empirical therapy protocol was recommended[44]) and that reported in a Dutch CC cohort (54.2%; $P < 0.01$).[45] Some patients with CVA later proved unresponsive to asthma treatment, possibly indicating a change in the evolution of cough etiology. After ruling out CRC, GERC needed to be considered. The MII-pH is sensitive in detecting reflux, and the results are often abnormal, explaining why 22% of patients evolved to a GERC diagnosis. Therefore, the tentative exploratory work-up before confirming RCC/UCC is inevitable, and we suggest a formalized protocol needs to be followed to effectively manage this process. Recently, Morice[46] has suggested that the term UCC might be removed as a diagnosis, given the similarity between UCC and RCC. The paradigm of cough hypersensitivity syndrome has defined them as a distinct physiological entity.[47] In this study, the equivalent HARQ score also supported this idea. We do agree that the current evidence points to a single underlying entity and that with improved diagnostic

techniques, rare phenotypes are easy to identify, which will lead to fewer UCC diagnoses. However, considering the issue that nearly half of the current UCC might be treated with inappropriate intervention, we prefer to keep this diagnosis.

For over 40% of patients, the cough was completely controlled or spontaneously relieved in approximately 1.5 years after the last clinical review. Markedly reduced HARQ scores at the last follow-up suggested remission of cough hypersensitivity in a quarter of patients, although we failed to demonstrate the change in capsaicin sensitivity. This may be because this study was based on real-world data and factors such as smoking may confound the objective findings. Nearly a third of patients still had a persistent cough. Only coughs in patients with refractory GERC were more likely to be solved. Several clinical characteristics, such as "long cough duration," "urinary incontinence," "cough when talking," and "cold-air sensitive cough," were likely to be associated with cough persistence. Cold-air hypersensitivity was found to be associated with cough persistence in CC before, and CC patients were reported with an incidence of cough persistence at about 20% and 47%.[48,49] These patients are likely to be the major portion of the RCC/UCC population. Yousaf *et al.*[50] described the 7-year outcomes of UCC, of which 60% had an unchanged or worse cough. The large discrepancy from this study can best be explained by our shorter follow-up period and the administration of neuromodulators.[5] All evidence indicates that the cough may continue or recur after systematic management at specialist clinics. Further study is needed to understand the variation in treatment outcomes. Future clinical management of RCC with a definite etiology should involve all etiologically specific therapeutic measures to achieve cough relief, while available nonspecific antitussive therapies such as neuromodulators should be considered for UCC.

There are some limitations in our study. First, this is a single-center study, and selection bias is unavoidable. Although, as one of the few specialist cough clinics in China, there is a high proportion of referrals from across the country which makes our patients quite representative of Chinese patients, the external validity and applicability still need to be further investigated. Furthermore, some findings, such as the sex-age distribution, do not differ that much from previous multicentre studies of CC in China. This validates the results of this study. Secondly, the follow-up outcomes were self-reported by patients rather than via objective assessment, thus being subject to a recall bias. There is a high rate of non-response bias as well. Thirdly, further details of medication adherence and combination medication proved difficult to obtain. However, this is a non-randomized observational study and represents guideline-led clinical practice, which may reflect a real-world experience.

In conclusion, most features between RCC and UCC were similar, but UCC was more commonly treated inappropriately and ineffectively. The current management of RCC and UCC only improve cough symptom in two-thirds of patients. Nearly one-third of patients still had a persistent or recurrent cough after systematic treatment attempts, especially for those with long cough duration and being sensitive to "talking" or "cold air." Novel agents for RCC and UCC are in urgent clinical need, and the promising results of recent trials give hope for the future.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Prospective follow-up updates

Click here to view

Supplementary Table S2

Comparisons of clinical characteristics and assessment results between patients with good outcomes and those with severe cough (n = 369)

Click here to view

REFERENCES

1. Spanevello A, Beghé B, Visca D, Fabbri LM, Papi A. Chronic cough in adults. Eur J Intern Med 2020;78:8-16.
PUBMED | CROSSREF
2. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020;55:1901136.
PUBMED | CROSSREF
3. Song WJ, Morice AH. Cough hypersensitivity syndrome: a few more steps forward. Allergy Asthma Immunol Res 2017;9:394-402.
PUBMED | CROSSREF
4. Morice A, Dicpinigaitis P, McGarvey L, Birring SS. Chronic cough: new insights and future prospects. Eur Respir Rev 2021;30:210127.
PUBMED | CROSSREF
5. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. Chest 2016;149:27-44.
PUBMED | CROSSREF
6. Al-Shekly B, Satia I, Badri H, Khalid S, Haines J, Woodcock A, et al. P5. Prevalence of refractory chronic cough in a tertiary cough clinic. Thorax 2018;73:A98-98.

7. Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. Eur Respir J 2014;44:1149-55.
PUBMED | CROSSREF

8. Huang K, Gu X, Yang T, Xu J, Yang L, Zhao J, et al. Prevalence and burden of chronic cough in China: a national cross-sectional study. ERJ Open Res 2022;8:00075-2022.
PUBMED | CROSSREF

9. McGarvey LP, Birring SS, Morice AH, Dicpinigaitis PV, Pavord ID, Schelfhout J, et al. Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. Lancet 2022;399:909-23.
PUBMED | CROSSREF

10. Muccino DR, Morice AH, Birring SS, Dicpinigaitis PV, Pavord ID, Assaid C, et al. Design and rationale of two phase 3 randomised controlled trials (COUGH-1 and COUGH-2) of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough. ERJ Open Res 2020;6:00284-2020.
PUBMED | CROSSREF

11. Asthma Group of Chinese Throacic Society. Chinese expert consensus on the diagnosis and treatment of chronic refractory cough. Zhonghua Jie He He Hu Xi Za Zhi 2021;44:689-98.
PUBMED | CROSSREF

12. Wei W, Yu L, Lu H, Wang L, Shi C, Ma W, et al. Comparison of cause distribution between elderly and non-elderly patients with chronic cough. Respiration 2009;77:259-64.
PUBMED | CROSSREF

13. Dong R, Xu X, Yu L, Ding H, Pan J, Yu Y, et al. Randomised clinical trial: gabapentin vs baclofen in the treatment of suspected refractory gastro-oesophageal reflux-induced chronic cough. Aliment Pharmacol Ther 2019;49:714-22.
PUBMED | CROSSREF

14. Chen Q, Zhang M, Si F, Wang S, Xu X, Yu L, et al. Flupentixol/melitracen for chronic refractory cough after treatment failure with other neuromodulators. Int J Tuberc Lung Dis 2021;25:648-54.
PUBMED | CROSSREF

15. Lv HJ, Qiu ZM. Refractory chronic cough due to gastroesophageal reflux: Definition, mechanism and management. World J Methodol 2015;5:149-56.
PUBMED | CROSSREF

16. Hsu JY, Stone RA, Logan-Sinclair RB, Worsdell M, Busst CM, Chung KF. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J 1994;7:1246-53.
PUBMED | CROSSREF

17. Huang Y, Yu L, Xu XH, Chen Q, Lyu HJ, Jin XY, et al. Validation of the Chinese version of Hull airway reflux questionnaire and its application in the evaluation of chronic cough. Zhonghua Jie He He Hu Xi Za Zhi 2016;39:355-61.
PUBMED | CROSSREF

18. Ma W, Yu L, Wang Y, Li X, Lü H, Qiu Z. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough 2009;5:7.
PUBMED | CROSSREF

19. Zheng JY, Zhang LH, Li JJ, Li JR, Cheng CF. Chinese version of the reflux symptom index was evaluated for reliability and validity. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012;47:894-8.
PUBMED

20. Vertigan AE, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. Cough 2014;10:1.
PUBMED | CROSSREF

21. Wong WM, Lam KF, Lai KC, Hui WM, Hu WH, Lam CL, et al. A validated symptoms questionnaire (Chinese GERDQ) for the diagnosis of gastro-oesophageal reflux disease in the Chinese population. Aliment Pharmacol Ther 2003;17:1407-13.
PUBMED | CROSSREF

22. Zhang M, Chen Q, Dong R, Yu L, Ai Z, Xu X, et al. Prediction of therapeutic efficacy of gabapentin by Hull Airway Reflux Questionnaire in chronic refractory cough. Ther Adv Chronic Dis 2020;11:2040622320982463.
PUBMED | CROSSREF

23. Vertigan AE, Gibson PG. Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers. J Voice 2011;25:596-601.
PUBMED | CROSSREF

24. Morice AH, Birring SS, Smith JA, McGarvey LP, Schelfhout J, Martin Nguyen A, et al. Characterization of patients with refractory or unexplained chronic cough participating in a phase 2 clinical trial of the P2X3-receptor antagonist gefapixant. Lung 2021;199:121-9.
PUBMED | CROSSREF

25. Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical features of the urge-to-cough in patients with chronic cough. Respir Med 2015;109:701-7.
PUBMED | CROSSREF

26. Dicpinigaitis PV. Thoughts on one thousand chronic cough patients. Lung 2012;190:593-6.
PUBMED | CROSSREF

27. 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.
PUBMED | CROSSREF

28. Lai K, Long L. Current Status and future directions of chronic cough in China. Lung 2020;198:23-9.
PUBMED | CROSSREF

29. 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.
PUBMED | CROSSREF

30. Mund E, Christensson B, Larsson K, Grönneberg R. Sex dependent differences in physiological ageing in the immune system of lower airways in healthy non-smoking volunteers: study of lymphocyte subsets in bronchoalveolar lavage fluid and blood. Thorax 2001;56:450-5.
PUBMED | CROSSREF

31. Lai K, Long L, Yi F, Tang J, Chen Z, Chen F, et al. Age and sex distribution of Chinese chronic cough patients and their relationship with capsaicin cough sensitivity. Allergy Asthma Immunol Res 2019;11:871-84.
PUBMED | CROSSREF

32. Chipps BE, Jarjour N, Calhoun WJ, Iqbal A, Haselkorn T, Yang M, et al. A comprehensive analysis of the stability of blood eosinophil levels. Ann Am Thorac Soc 2021;18:1978-87.
PUBMED | CROSSREF

33. Koo HK, Bae W, Moon JY, Lee H, Kim JW, Jang SH, et al. Differential features of chronic cough according to etiology and the simple decision tree for predicting causes. Sci Rep 2021;11:10326.
PUBMED | CROSSREF

34. Song WJ, Kim JY, Jo EJ, Lee SE, Kim MH, Yang MS, et al. Capsaicin cough sensitivity is related to the older female predominant feature in chronic cough patients. Allergy Asthma Immunol Res 2014;6:401-8.
PUBMED | CROSSREF

35. Kastelik JA, Thompson RH, Aziz I, Ojoo JC, Redington AE, Morice AH. Sex-related differences in cough reflex sensitivity in patients with chronic cough. Am J Respir Crit Care Med 2002;166:961-4.
PUBMED | CROSSREF

36. Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM. Cough hypersensitivity syndrome: a distinct clinical entity. Lung 2011;189:73-9.
PUBMED | CROSSREF

37. Long L, Yao H, Tian J, Luo W, Yu X, Yi F, et al. Heterogeneity of cough hypersensitivity mediated by TRPV1 and TRPA1 in patients with chronic refractory cough. Respir Res 2019;20:112.
PUBMED | CROSSREF

38. Dong R, Zhang T, Wei W, Zhang M, Chen Q, Xu X, et al. A cold environment aggravates cough hyperreactivity in guinea pigs with cough by activating the TRPA1 signaling pathway in skin. Front Physiol 2020;11:833.
PUBMED | CROSSREF

39. Matsumoto H, Tabuena RP, Niimi A, Inoue H, Ito I, Yamaguchi M, et al. Cough triggers and their pathophysiology in patients with prolonged or chronic cough. Allergol Int 2012;61:123-32.
PUBMED | CROSSREF

40. Wright ML, Sundar KM, Herrick JS, Barkmeier-Kraemer JM. Long-term treatment outcomes after behavioral speech therapy for chronic refractory cough. Lung 2021;199:517-25.
PUBMED | CROSSREF

41. Slovarp LJ, Jetté ME, Gillespie AI, Reynolds JE, Barkmeier-Kraemer JM. Evaluation and management outcomes and burdens in patients with refractory chronic cough referred for behavioral cough suppression therapy. Lung 2021;199:263-71.
PUBMED | CROSSREF

42. Katzka DA, Kahrilas PJ. Advances in the diagnosis and management of gastroesophageal reflux disease. BMJ 2020;371:m3786.
PUBMED | CROSSREF

43. Ghogomu N, Kern R. Chronic rhinosinusitis: the rationale for current treatments. Expert Rev Clin Immunol 2017;13:259-70.
PUBMED | CROSSREF

44. Wei W, Yu L, Wang Y, Li X, Qiu Z, Wang L, et al. Efficacy and safety of modified sequential three-step empirical therapy for chronic cough. Respirology 2010;15:830-6.
PUBMED | CROSSREF

45. van den Berg J, Baxter C, Edens M, Patberg N, van der Velden H, Weijerse A, et al. The demographics, clinical characteristics and quality of life of chronic cough in patients from the Isala Cough Clinic in the Netherlands. ERJ Open Research 2022;8:00232-2022.
PUBMED | CROSSREF

46. Morice AH. On chronic cough diagnosis, classification, and treatment. Lung 2021;199:433-4.
PUBMED | CROSSREF

47. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J 2014;44:1132-48.
PUBMED | CROSSREF

48. Kang SY, Song WJ, Won HK, Chung SJ, Kim JY, Park HW, et al. Cough persistence in adults with chronic cough: a 4-year retrospective cohort study. Allergol Int 2020;69:588-93.
PUBMED | CROSSREF

49. Koskela HO, Lätti AM, Purokivi MK. Long-term prognosis of chronic cough: a prospective, observational cohort study. BMC Pulm Med 2017;17:146.
PUBMED | CROSSREF

50. Yousaf N, Montinero W, Birring SS, Pavord ID. The long term outcome of patients with unexplained chronic cough. Respir Med 2013;107:408-12.
PUBMED | CROSSREF