

Psychological morbidity and chronic cough: which is predominant? A comparison of clinical characteristics

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Abstract

Background: The clinical characteristics of chronic cough with pre-existing psychological co-morbidity (PCC) and chronic cough with secondary anxiety and depression (SCC) were compared to provide a basis for diagnosing and treating psychological co-morbidities in people with chronic cough.

Methods: A prospective study was conducted to analyze the general clinical data between the PCC, SCC, and the chronic cough without anxiety and depression (CC) groups. A total of 203 patients with chronic cough were enrolled in the study. The final diagnosis was made in all cases using a combination of psychosomatic and respiratory diagnoses. The three groups' general clinical data, capsaicin cough sensitivity, cough symptom score, Leicester cough questionnaire (LCQ), and psychosomatic scale scores were compared among the three groups. The diagnostic value of the patient health questionnaire (PHQ)-9 and general anxiety disorder (GAD)-7 in patients with PCC and the follow-up information were analyzed.

Results: Compared with the SCC group, the duration of cough in the PCC group was shorter ($H = -3.54, p = 0.001$), the night cough symptoms were milder ($H = -4.60, p < 0.001$), the total LCQ score was lower ($H = -2.97, p = 0.009$), and the PHQ-9 ($H = 2.90, p = 0.011$) and GAD-7 scores ($H = 2.71, p = 0.002$) were higher. When using PHQ-9 and GAD-7 scores for the combined prediction and diagnosis of PCC, the area under the curve (AUC) was 0.88, and the sensitivity and specificity were 90.0% and 73.85%, respectively. After 8 weeks of psychosomatic treatment, cough symptoms improved in the PCC group, but the psychological improvement was not significant. The psychological status of the SCC group improved after cough symptoms were ameliorated by etiologic or empirical treatment.

Conclusion: The clinical characteristics of patients with PCC and SCC are different. The evaluation of psychosomatic scales is of value to distinguish between the two groups. Chronic cough patients with psychological co-morbidity benefit from the combined diagnosis of psychosomatic medicine in a timely fashion. PCC requires more attention in psychological therapy, but for SCC, targeting etiological treatment of the cough is preferred.

Trial registration: The protocol was registered in the Chinese Clinical Trials Register (<http://www.chictr.org.cn/>) [ChiCTR2000037429].

Keywords: anxiety, clinical characteristics, cough, depression, psychological co-morbidity

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Introduction

Chronic cough is a common and intractable symptom that significantly reduces patient quality

of life and causes psychological problems.^{1,2} Chronic cough and psychological issues that occur simultaneously in the clinical setting are

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common. Psychological issues may be an underlying pathogenic factor for some chronic cough patients. Initially, we use terms, such as ‘psychogenic cough’ or ‘habitual cough’, to describe cough with no obvious etiology, difficult to cure, and thought to have a psychiatric or psychological basis.³ Many studies have confirmed that if chronic cough patients with co-morbid psychiatric diagnoses are offered psychiatric intervention as soon as possible, good results can be achieved, and unnecessary examinations and treatments can be avoided.⁴⁻⁶ Psychological symptoms may be the result of chronic cough. Studies have also shown that in some patients with chronic cough, the incidence of anxiety and depression is increased, and the psychological symptoms of such patients are often improved after effective treatment targeting the cause of cough.^{7,8} Thus, the priority approach to psychological co-morbidity with cough may differ depending on whether the co-morbidity is considered primary or secondary to the cough.

The previously used term, ‘psychogenic cough’, is usually an exclusive diagnosis with no characteristic clinical or laboratory evidence to support the diagnosis; thus, establishing a diagnosis can be a challenge.⁹ If the diagnosis and targeted treatment are not initiated, long-term social distress and economic burden are likely to occur. Therefore, the latest American College of Chest Physicians (ACCP) guideline suggested using the term, ‘somatic cough syndrome’, instead of psychogenic cough, which puts more emphasis on the co-morbidity of cough and psychological issues.¹⁰ Currently, the evidence on chronic cough patients with psychological co-morbidities is limited. Previous studies regarding psychogenic cough lack uniform diagnostic criteria, validated cough evaluation methods and a control group comparison.³ In addition, there is insufficient evidence regarding the new term, ‘somatic cough syndrome’, at present. It is still worth exploring the relationship between chronic cough and psychological issues.

A prospective study was conducted to analyze the basic clinical characteristics of adult chronic cough patients with pre-existing psychological co-morbidity (PCC) and chronic cough with secondary anxiety and depression (SCC), to evaluate the cough symptoms, cough-related quality of life, and psychological status-related scales of

affected patients. In addition, the impact of cough and psychological status after different treatment methods were compared between the two groups to provide a basis for the clinical management of chronic cough patients with psychological co-morbidities.

Materials and methods

Participants

This was a prospective observational study. A total of 203 patients with chronic cough from our respiratory clinic were enrolled in this study between January 2016 and March 2023. All patients completed a cough symptom score, Leicester cough questionnaire (LCQ), and psychosomatic scales evaluation, including a depression-related scale patient health questionnaire (PHQ)-9 and the general anxiety disorder (GAD)-7. A complete medical history, physical examination, capsaicin cough sensitivity test, chest computed tomography (CT) or X-ray, lung function testing, histamine bronchial stimulation test, induced sputum cytology, and combined multichannel intraluminal impedance-pH monitoring (MII-pH) data were collected.

The inclusion criteria were as follows: (1) age ≥ 18 ; (2) the diagnosis of chronic cough was by the Chinese Guidelines for the Diagnosis and Treatment of Cough in 2015¹¹ issued by the Asthma Group of the Respiratory Society of Chinese Medical Association; and (3) the cough symptom score, LCQ questionnaire, and psychosomatic scale assessment (PHQ-9 and GAD-7) were completed at the first visit. The exclusion criteria were as follows: (1) smoking history or smoking cessation < 2 years; (2) patients with incomplete clinical data; (3) the scales were not completed by the patients at the time of the initial diagnosis; and (4) lack of psychosomatic joint diagnosis.

According to the psychosomatic scale results, if the patient was at risk of psychological problems on the psychosomatic scales (a PHQ-9 and GAD-7 scores ≥ 5 points), then a joint diagnosis was established in the Psychosomatic Outpatient Clinic. According to the combined diagnosis results, the patients were divided into the chronic cough with pre-existing psychological co-morbidity (PCC), the SCC, and the chronic cough

without anxiety and depression (CC) groups; the latter group was designated as the control group.

The CC group was defined as follows: (1) patients with chronic cough who met the inclusion criteria; and (2) no risk of anxiety and depression on the psychosomatic scales (both PHQ-9 and GAD-7 scores <5 points).

The PCC group was defined as follows: (1) there were no abnormalities detected on imaging examinations (chest CT or radiographs), lung function testing, induced sputum cytology examination, and MII-pH. After empirical treatment, other possible causes of chronic cough were excluded; (2) there was a risk of psychological problems on the psychosomatic scales (PHQ-9 and GAD-7 scores ≥ 5 points); (3) the diagnosis or symptoms of mental illness precede the onset of cough; and (4) the final diagnosis was made in all cases *via* a combination of the psychosomatic outpatient clinic and respiratory clinic diagnoses.

The SCC group was defined as follows: (1) the risk of psychological problems on the psychosomatic scales of the initial diagnosis assessment (PHQ-9 and GAD-7 scores ≥ 5 points); (2) the diagnosis or symptoms of mental illness after the onset of cough; and (3) the final diagnosis was made in all cases based on a combination of the psychosomatic outpatient clinic and respiratory clinic diagnoses.

We have a multidisciplinary outpatient clinic. Every Thursday morning, we open an outpatient clinic especially for chronic cough patients. In the afternoon, patients with abnormal psychosomatic scales went to the psychosomatic outpatient clinic for further assessment and diagnosis. Detailed information about patients will be collected in the Psychosomatic Outpatient Clinic. All procedures were performed by one experienced chief or associate chief physician in the psychosomatic department. The diagnosis of mental illness was based on the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).¹² Patients diagnosed with psychosomatic disorders in the past were diagnosed based on their medical history, with diagnostic criteria based on the tenth revision of International Classification of Diseases (ICD-10) classification of mental and behavioral disorders.¹³ Patients who had not been diagnosed with psychosomatic diseases were diagnosed through standard diagnostic interviews conducted

according to the Structured Clinical Interview for DSM-IV (SCID), a semistructured clinical interview for making psychiatric diagnoses based on DSM-IV criteria, and one of the most widely accepted methods for making psychiatric diagnoses. We used the Chinese translation version of the SCID, which has been confirmed to have good reliability and validity.¹⁴ Electing relevant diagnostic modules included the following: major depressive disorder, minor depressive disorder, generalized anxiety disorder, mixed anxiety and depressive disorder, and conversion disorder. We administered and scored each SCID item using standard SCID response categories. The final diagnosis was made by obtaining consistent scores and diagnoses from more than two psychiatrists.

Laboratory investigation

Pulmonary function and bronchial provocation tests: These procedures were conducted by professional technicians and were performed according to the guidelines established by the Respiratory Society of the Chinese Medical Association.¹¹ A Master Screen Diffusion Lung Function instrument and Acute Pain Service (APS) nebulizer were used (Jaeger Company, Germany). Using histamine as a stimulant, when the cumulative histamine dose (PD20-FEV1) reduced FEV1 by 20%, increased airway reactivity was considered. The above tests were repeated to obtain conclusive results.

Induced sputum cytology examination: The analysis was conducted according to a method established by the Department of Pulmonary and Critical Care Medicine at Tongji Hospital.¹⁵ Finally, the differential cell count was performed manually by counting 400 nucleated cells.

Capsaicin cough sensitivity test: This test was evaluated according to the European Respiratory Society (ERS) guidelines.¹⁶ The modified method was initially described by Fujimura *et al.*¹⁷ with the lowest capsaicin inhalation concentration required to induce ≥ 2 (C2) or ≥ 5 (C5) coughs as the subject's cough threshold.

Cough symptom score: This was performed with the scale developed by Hsu *et al.*¹⁸ The scale had two parts: daytime and nighttime cough symptom scores, ranging from 0 to 5, with 0 being the best (no cough) and 5 being the worst (characterized by a distressing cough).

LCQ: The cough-related quality of life was assessed using the Chinese version of the LCQ, which is a 19-item questionnaire that assesses the physical, psychological, and social impacts of chronic cough.^{19,20}

PHQ-9: This is a nine-item validated questionnaire for evaluating the severity of depressive symptoms over the past 2 weeks. The total score ranges from 0 to 27; a score >5 suggests that the individual has abnormalities.²¹

GAD-7: This is a multipurpose seven-item instrument to describe the severity of the patient's anxiety symptoms in the past 2 weeks. The total score ranges from 0 to 21; a score >5 suggests that the individual has abnormalities.²²

Treatment and follow-up

The PCC group only received psychosomatic drug therapy or nonpharmacologic psychotherapy, while the SCC group was only treated based on etiology or empirically of cough. Changes in questionnaire scores (including the cough symptom score, PHQ-9, and GAD-7) at the 8-week follow-up evaluation between the PCC and SCC groups were collected and analyzed.

Statistical analysis

Normal distribution data are expressed as a mean \pm standard deviation (*SD*), while data with a skewed distribution are expressed as a median (interquartile range). Furthermore, cough threshold values C2 and C5 were log-transformed to normalize the data. A chi-square test was used to analyze the constituent ratio of gender and etiologies. Data among the three groups were analyzed using a one-way analysis of variance (ANOVA) or a nonparametric test (Kruskal–Wallis H test), followed by post hoc Bonferroni correction to detect differences between groups.

A receiver operating characteristic (ROC) curve was used to evaluate the diagnostic efficacy of the PHQ-9 and GAD-7 scores of PCC, and the area under the curve (AUC), sensitivity (%), specificity (%), positive predictive value (%), negative predictive value (%), and Youden index were calculated. A logistic regression model was used to fit the PHQ-9 and GAD-7 scores to generate a joint predictor. The statistical significance of the improvement in AUC was calculated by DeLong's test.

A prospective statistical power calculation based on the results of the published data²³ indicated that the LCQ scores were 15.4 ± 4.5 and 12.4 ± 3.4 in patients with and without anxiety, respectively. Therefore, a minimum of 47 patients per group (chronic cough with anxiety and depression risk group and chronic cough without anxiety and depression risk group) would be required to provide 80% power between the two groups using a 5% two-sided test.

SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A *p* value < 0.05 was accepted as statistically significant.

Results

General clinical information

The medical records of 288 chronic cough patients who were evaluated with both cough-related scales (including the cough symptom score and LCQ) and psychological-related scales (including the PHQ-9 and GAD-7 scales) at the first visit were enrolled. A total of 30 patients were excluded because they had incomplete laboratory test results, and 48 patients who did not complete the psychosomatic assessment scale at the time of the initial diagnosis were excluded. In addition, seven patients lacking the combined diagnosis of psychosomatics were excluded. A total of 203 patients, consisting of 20 patients with PCC, 65 patients with SCC, and 118 patients with CC, were selected for analysis. A flow chart of the enrolled patients is shown in Figure 1. Among the 20 PCC patients, 13 had previously been diagnosed and treated in the psychosomatic department, three patients were referred to the psychosomatic department for evaluation of sleep disturbances, and the other four patients described symptoms related to psychological problems prior to the onset of the cough. Of these 20 patients, 10 described factors that predisposed them to psychological problems before the onset of cough including six who had experienced family changes (one mother died, two family members died of lung cancer, one was divorced, one was widowed, and one in trouble with her daughter-in-law), two with an unpleasant job transfer, and two who underwent major surgeries. The psychosomatic etiology distribution of the PCC group is shown in Table 1, and the etiology distribution of chronic cough in the SCC group is shown in Table 2.

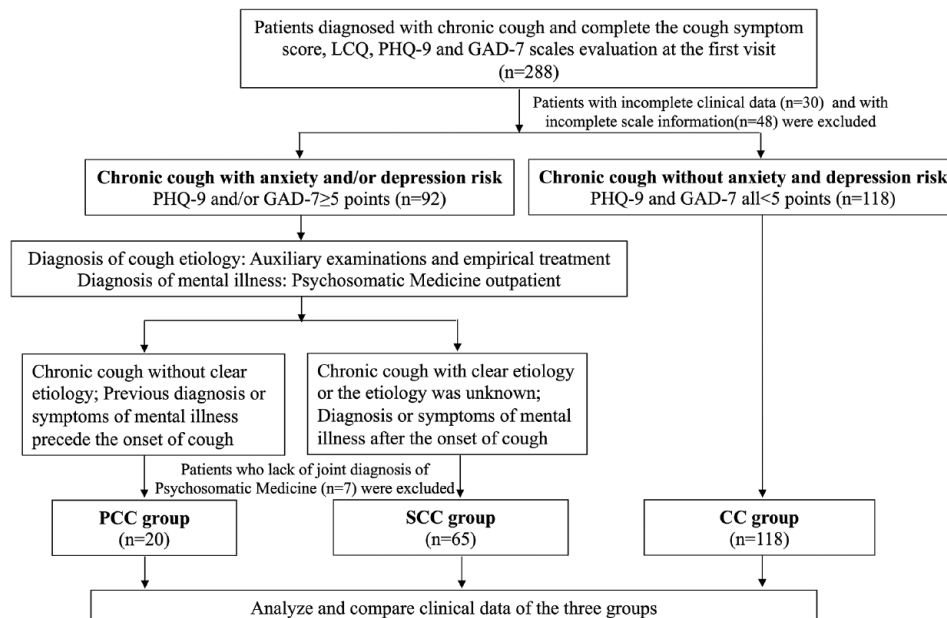


Figure 1. Flow of patients through the study.

There were no significant differences in age, gender distribution, body mass index, capsaicin cough sensitivity, and lung function parameters among the three groups. The duration of cough was significantly lower in the PCC and CC groups than in the SCC group ($H = -3.54$, $p = 0.001$; $H = 2.98$, $p = 0.009$). The eosinophil count in induced sputum was significantly lower in the PCC group than in the SCC and CC groups ($H = -3.28$, $p = 0.003$; $H = 3.62$, $p = 0.001$; Table 3).

Comparison of cough-related and psychological-related assessment between the three groups

The daytime cough symptom score was comparable among the PCC and CC groups but was significantly higher in the SCC group than in the CC group, while the nighttime cough symptom score was significantly lower in the PCC group than in the SCC and CC groups and was significantly higher in the SCC group than the CC group (Figure 2 and Table 4).

When compared with the SCC and CC groups, the PCC group had lower total LCQ, LCQ physical domain, LCQ psychological domain, and LCQ social domain scores. Moreover, the SCC group had lower total LCQ, LCQ physical domain, LCQ psychological domain, and LCQ

Table 1. Psychosomatic etiology distribution of 20 PCC group patients.

Cause of mental diseases	n	%
Conversion disorder	2	10.0
Depressive disorder	3	15.0
Generalized anxiety disorder	4	20.0
Mixed anxiety and depressive disorder	11	55.0
PCC, chronic cough with pre-existing psychological co-morbidity.		

social domain scores than the CC group (Figure 3 and Table 4).

The PHQ-9 and GAD-7 scale scores were significantly lower in the CC group than the PCC and SCC groups. In addition, the PHQ-9 and GAD-7 scale scores of the PCC group were significantly higher than the SCC group (Figure 2 and Table 4).

Predictive value of the PHQ-9 and GAD-7 scores for the PCC group

When the PHQ-9 scale was used to predict the diagnosis of PCC, the AUC was 0.80, and the sensitivity and specificity were 65.00% and 87.68%, respectively. When the GAD-7 scale was used in the predictive diagnosis of PCC, the AUC

Table 2. Etiology distribution of 65 SCC group patients.

Cause of cough	n	%
Single etiology		
GERC	28	43.1
CVA	12	18.5
EB	6	9.2
Post-infectious cough	2	3.1
ACEI-related chronic cough	2	3.1
AC	2	3.1
Dual etiologies		
GERC + UACS	6	9.2
GERC + CVA	2	3.1
GERC + ACEI-related chronic cough	1	1.5
Unexplained cough	4	6.2

AC, atopic cough; ACEI, angiotensin-converting enzyme inhibitor; CVA, cough variant asthma; EB, eosinophilic bronchitis; GERC, gastroesophageal reflux-induced chronic cough; SCC, chronic cough with secondary anxiety and depression; UACS, upper airway cough syndrome.

was 0.83, and the sensitivity and specificity were 75.00% and 83.00%, respectively. When the PHQ-9 scale was combined with GAD-7 in the predictive diagnosis of PCC, a binary logistic regression analysis was performed. When the linear model was used in the predictive diagnosis of PCC, the AUC was improved to 0.88, and the sensitivity and specificity were 90.00% and 73.85%, respectively; however, DeLong's test showed no statistical significance (PHQ-9 *versus* combined: $Z = 1.71$, $p = 0.087$; GAD *versus* combined: $Z = 1.64$, $p = 0.102$; Figure 4 and Table 5).

Outcomes at 8 weeks of follow-up in the PCC and SCC groups

The 8-week follow-up evaluation was completed in the PCC group, and four patients in the SCC group were lost to follow-up. After 8 weeks of treatment, the PCC and SCC groups had decreased cough symptom scores compared with pretreatment and an increased total LCQ score (PCC group: $Z = 3.54$, $p < 0.001$; SCC group: $Z = 2.91$, $p = 0.003$) compared with pretreatment. The PHQ-9 and GAD-7 scale scores showed a

downward trend, but no statistical difference in the PCC group after treatment. The PHQ-9 and GAD-7 scale scores decreased significantly in the SCC group from baseline over the 8-week treatment period (Figure 5). The treatment of patients in the PCC group is shown in Table 6.

Discussion

It is often found that psychological problems and chronic cough co-exist clinically. However, the relationship between the two remains unclear. Currently, the definition and diagnostic criteria for such patients in different regions are inconsistent. We conducted a prospective study in conjunction with psychosomatic diagnosis, and for the first time made a comparison between PCC and with secondary anxiety and depression. Compared with chronic cough patients with secondary anxiety and depression patients, patients with pre-existing psychological co-morbidity had a shorter duration, lighter nighttime cough symptoms, lower LCQ scores, and higher anxiety and depression scale scores. After treatment in the psychosomatic department, the cough symptoms and related quality of life of patients with PCC were significantly improved, but the improvement in psychological status was not significant. Cough symptoms, cough-related quality of life, and psychological problems in patients with SCC were significantly improved after etiologic or empiric treatment.

According to some studies, the median duration of psychogenic cough in children is 3 months,²⁴ while a retrospective study used the term 'somatic cough syndrome' with a median course of 48 months in adults.⁶ In this study, the median duration of PCC was 6 months, which was shorter than the SCC group. This may be because PCC patients have a basis of psychological disease before the occurrence of cough, as well as sensitivity to their cough symptoms. When the cough symptoms persist, their tolerance of symptoms may be lower than patients without psychological problems; thus, they will seek hospital evaluation earlier. In addition, in this study, we adopted the psychosomatic joint diagnosis, so that patients could be diagnosed based on a psychosomatic evaluation in time. The psychological problems of the SCC patients were more likely due to persistent cough symptoms; thus, the cough duration of the SCC group was longer than the other

Table 3. General clinical characteristics for enrolled chronic cough patients.

Variables	PCC (n=20)	SCC (n=65)	CC (n=118)	Test results
Age (y)	49.15 ± 15.54	47.74 ± 14.68	45.66 ± 14.71	$F=1.289, p=0.278$
Gender (F/M)	12/8	43/22	64/54	$\chi^2=2.471, p=0.291$
Body mass index (kg/m ²)	22.87 ± 3.02	23.85 ± 4.01	24.63 ± 4.62	$F=1.919, p=0.150$
Duration (m)	6.00 (3.50)	12.00 (30.00)*	10.00 (20.00)**	$H=15.874, p<0.001$
Capsaicin cough sensitivity				
C2	0.87 ± 0.12	0.89 ± 0.21	0.88 ± 0.18	$F=0.071, p=0.932$
C5	0.87 ± 0.12	0.98 ± 0.41	0.93 ± 0.33	$F=2.772, p=0.065$
Lung function				
FEV1 predicted (%)	101.06 ± 7.43	101.97 ± 12.18	98.72 ± 13.26	$F=1.133, p=0.326$
FVC predicted (%)	102.27 ± 9.11	101.22 ± 13.94	103.15 ± 15.24	$F=1.430, p=0.244$
FEV1/FVC%	83.60 ± 7.14	83.87 ± 7.29	84.66 ± 7.91	$F=0.269, p=0.764$
Total cell count and cell differentials in induced sputum				
Total cells (× 10 ⁶ /ml)	4.08 ± 1.25	4.00 ± 1.37	3.95 ± 1.31	$F=0.070, p=0.933$
Neutrophils (%)	20.38 ± 12.45	20.20 ± 10.87	19.57 ± 10.65	$F=0.061, p=0.941$
Lymphocytes (%)	9.15 ± 6.32	8.29 ± 5.66	8.61 ± 5.59	$F=0.110, p=0.896$
Macrophages (%)	70.35 ± 8.84	69.18 ± 10.14	69.32 ± 9.70	$F=0.162, p=0.850$
Eosinophils (%)	0 (0)	1 (4.50)*	1 (4.88)*	$H=13.988, p=0.001$
<p>C2, capsaicin solution concentration with ≥2 coughs; C5, capsaicin solution concentration for ≥5 coughs; CC, chronic cough without anxiety and depression; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PCC, chronic cough with pre-existing psychological co-morbidity; SCC, chronic cough with secondary anxiety and depression; SD, standard deviation.</p> <p>Data are presented as mean ± SD, median (interquartile range), or number (%) unless otherwise indicated.</p> <p>*Compared with PCC group, $p<0.05$; **Compared with SCC group, $p<0.05$.</p>				

chronic cough patients. Regarding the nocturnal symptoms, we found PCC patients were typically minor in this study. Studies have shown that although 54% of psychogenic cough patients who are awake at night have the most serious cough symptoms, 93% of the coughing disappears completely when sleeping,²⁴ and somatic cough syndrome patients had a lower proportion of nocturnal cough.⁶ Our study also showed that although PCC patients had persistent night cough symptoms, the symptoms were milder than the

other two groups, which suggests that cough symptoms in this group may be more psychologically related. In addition, in the SCC group, gastroesophageal reflux-induced chronic cough (GERC) was the most common etiology. A Korean study has suggested that gastroesophageal reflux disease is a risk factor for psychological disorders, especially depression.^{25,26} Our previous studies confirmed that the treatment of GERC is difficult, with poor drug efficacy and a long course of treatment, and some antireflux treatments are

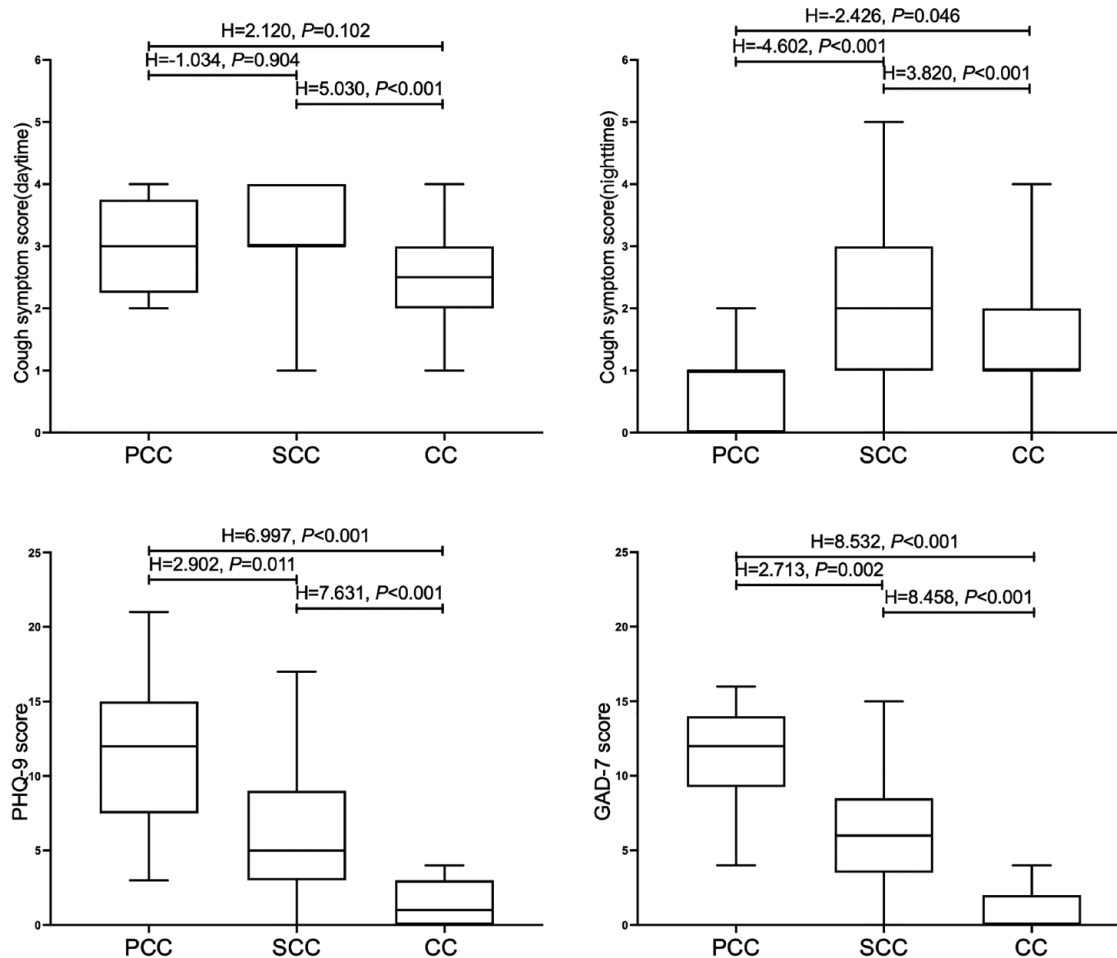


Figure 2. Comparison of cough symptom scores, PHQ-9 and GAD-7 scores between the three groups.

ineffective for some patients, which may be the reason why patients with GERC are more likely to develop psychological problems.^{27,28}

This study showed that the LCQ scores were lower in the PCC and SCC patients, which is consistent with the results of a recently published study that concluded anxiety and depression symptoms reduce the quality of life of patients with chronic cough.²³ In our study, both the PCC and SCC groups were patients with psychological problems. However, in the two groups, not only were the psychological range score on the LCQ scale low, but the physiologic and social ranges were low, which indicates that psychological states, such as anxiety or depression, also affect patients' physical feelings and social emotions. Previous studies have demonstrated an increased incidence of psychological problems in patients

with chronic cough.^{8,29} On one hand, this may be due to the long time required for a definite diagnosis of chronic cough, which can be psychologically stressful for some patients. On the other hand, many physical, social, and emotional side effects of chronic cough such as avoidance of daily activities, interpersonal difficulties, stress urinary incontinence, and avoidance of conversation may affect patients' mental health.^{30,31}

This study explored the predictive diagnostic value of the psychosomatic scale for PCC and showed that a GAD-7 and PHQ-9 could be meaningful, but the sensitivity was low, which may be related to the scales we used. In addition to the scales used in this study, there are other scales related to psychological problems. According to the results of this study, the evaluation of depression and anxiety is meaningful in

Table 4. Comparison of cough symptom scores, LCQ scores, PHQ-9 and GAD-7 scores between the three groups.

Variables	PCC (n = 20)	SCC (n = 65)	CC (n = 118)	Test results
Cough symptom score				
Daytime	3.00 (1.50)	3.00 (1.00)*	2.50 (1.00)	H = 26.308, p < 0.001
Nighttime	1.00 (1.00)*, **	2.00 (2.00)*	1.00 (1.00)	H = 26.023, p < 0.001
LCQ score				
Total score	9.87 (3.00)*, **	12.16 (2.75)*	15.36 (1.91)	H = 89.521, p < 0.001
Physical domain	3.31 (1.19)*, **	4.38 (1.06)*	5.27 (1.00)	H = 56.716, p < 0.001
Psychological domain	2.93 (0.43)*, **	3.72 (0.86)*	4.71 (1.15)	H = 78.765, p < 0.001
Social domain	3.75 (1.13)*, **	4.25 (1.25)*	5.53 (0.72)	H = 75.113, p < 0.001
Psychosomatic scale				
PHQ-9	12.00 (7.50)*, **	5.00 (6.00)*	1.00 (3.00)	H = 82.102, p < 0.001
GAD-7	12.00 (4.75)*, **	6.00 (5.00)*	0.00 (2.00)	H = 111.715, p < 0.001
CC, chronic cough without anxiety and depression; GAD-7, general anxiety disorder; LCQ, Leicester cough questionnaire; PCC, chronic cough with pre-existing psychological co-morbidity; PHQ-9, patient health questionnaire-9; SCC, chronic cough with secondary anxiety and depression. Data are presented as median (interquartile range). *Compared with CC group, p < 0.05; **Compared with SCC group, p < 0.05.				

patients with chronic cough. Psychosomatic scale evaluation could be used as an initial method to screen for whether psychological problems are primary or secondary to the cough. If the results could be further combined with a psychosomatic diagnosis, the diagnosis can be confirmed earlier to reduce unnecessary examination and treatment for patients.

It has been reported that patients with psychogenic cough show significant improvement in cough symptoms within a few weeks after psychosomatic treatment^{7,32,33} which is consistent with our results in the PCC group. Besides, we also found that the psychological problems of patients with PCC were improved, but not significantly after the relief of cough symptoms, which may be

because the psychological problems of these patients are more serious and require longer psychosomatic professional treatment to improve their psychological status. For SCC patients, as the cough symptoms improved after treatment, anxiety and depression also improved significantly. This finding is consistent with previous studies. Dicipinigitis *et al.*⁷ reported that 53% of patients with chronic cough have abnormal depression scale scores. The patients did not take antidepressant medications, and the depression symptoms improved after the successful treatment of chronic cough. French *et al.*³⁰ reported that anxiety symptoms and depression scores of patients with chronic cough improved after treatment of the cough symptoms. This evidence also showed that the anxiety and depression of such

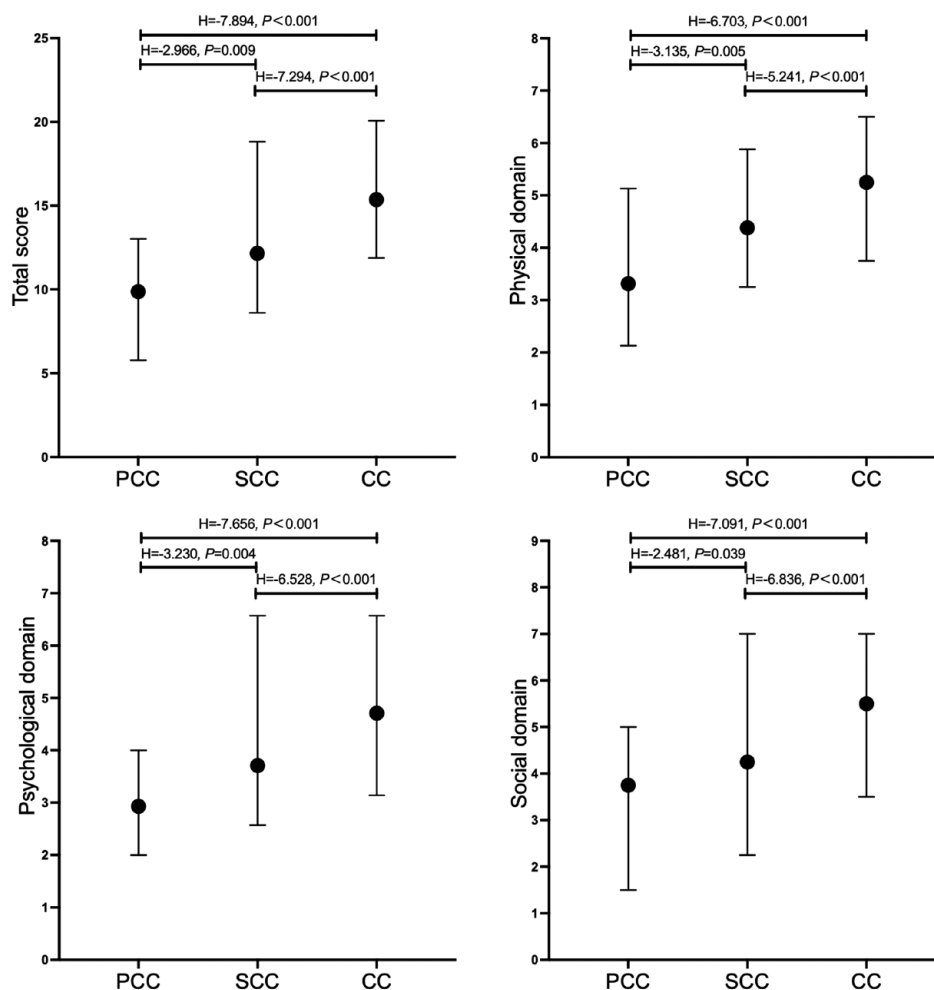


Figure 3. Comparison of LCQ scores between the three groups.

patients are closely related to the occurrence of cough symptoms.

The relationship between psychological problems and chronic cough is complex. Vertigan proposed three different possible relationships between psycho-morbidity and chronic cough.⁹ Previous terminology such as ‘psychogenic cough’ may emphasize more on the dominance of psychological issues, more similar to the PCC group in this study, which seems cough is the result of mental illness. In the SCC group, mental illness is more like the result of cough. Although mental illness may be the result of chronic cough, other studies have confirmed that cough and respiratory symptoms are more common in patients with mental illness.^{34,35} The new term ‘somatic cough syndrome’ refers to the transformation of psychological

distress into a somatic disorder, which emphasizes more on the co-morbidity of psychological issues and cough. Thus, compared with psychogenic cough, the incidence of somatic cough syndrome may be higher because chronic cough patients with different cough etiologies may be included. It is noteworthy, however, that a subset of patients with chronic cough associated with anxiety and depression may not be included in this new definition due to the diagnosis of somatic symptom disorder, according to the fifth edition of the *Diagnostic Statistical Manual of Mental Disorders (DSM-V)*, which is inconsistent with the diagnosis of anxiety and depression (which has been found in our ongoing research). Perhaps, more evidence is needed to explore the relationship between psychological problems and chronic cough and related definitions. This study initially explored the

Table 5. Prediction of PCC by PHQ-9 or GAD-7.

Items	PHQ-9	GAD-7	PHQ-9 and GAD-7
ROC	0.800	0.830	0.882
Cutoff value	11	9	0.1468
<i>p</i>	<0.001	0.001	<0.001
Youden index	0.527	0.581	0.639
Sensitivity (%)	65.00 (40.80–84.60)	75.00 (50.90–91.30)	90.00 (68.30–98.80)
Specificity (%)	87.69 (77.20–94.50)	83.08 (71.70–91.20)	73.85 (61.50–84.00)
Positive predictive value (%) (95% CI)	61.90 (44.10–77.00)	57.70 (42.90–71.20)	51.40 (40.70–62.00)
Negative predictive value (%) (95% CI)	89.1 (81.7–93.7)	91.5 (83.4–95.9)	96.0 (86.5–98.9)
chi-square	19.327	14.997	15.739
<i>P</i> in chi-square test	<0.001	<0.001	<0.001
κ value	0.541	0.477	0.403
<i>P</i> in κ test	<0.001	<0.001	<0.001

CI, confidence interval; GAD-7, general anxiety disorder; PHQ-9, patient health questionnaire; ROC, receiver operating characteristic.
PHQ-9 and GAD-7: $\text{PHQ-9} \times 0.18 + \text{GAD-7} \times 0.285 - 5.22$.

relationship between PCC and SCC by comparing their clinical differences. Although mental illness and cough symptoms may likely co-exist alone or in combination in a given patient over time. Distinguishing which is dominant can help us to determine whether it is necessary to offer psychotherapeutic intervention in a timely fashion. Links between changes in mental state and physical sensations of symptoms are common and do not only exist in cough patients. But the question of whether psychological emotions drive somatic symptoms or vice versa has long vexed researchers because it is hard to control either factor independently. Research in other fields has suggested that higher central nervous system mechanisms could be involved.³⁶ Chronic cough is related to increased central sensitivity, and a study has found that functional magnetic resonance imaging (MRI) of patients with refractory cough shows changes in structural and functional alterations in the left frontal brain regions, which are also related to psychological factors.³⁷ Thus, much remains to be investigated between psychological problems and chronic cough in the future.

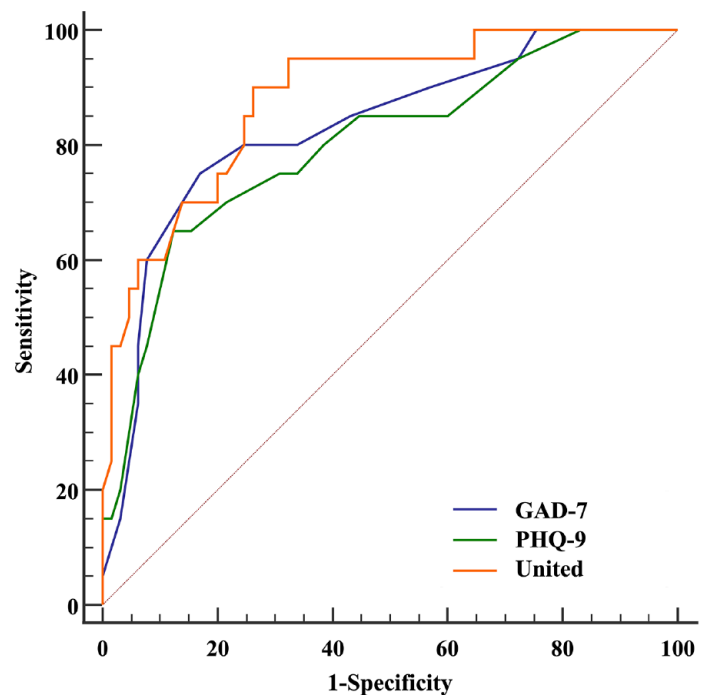
**Figure 4.** Diagnostic value of PHQ-9 and GAD-7 scores in PCC.

Table 6. Treatment of patients in the PCC group.

Treatment	n	%
Pharmacological therapy		
Escitalopram, 20 mg QD	1	5.0
Sertraline hydrochloride tablets, 50 mg QD	2	10.0
Zolpidem tartrate granules, 10 mg QN	2	10.0
Duloxetine, 20 mg BID	6	30.0
Diazepam, 2.5 mg QN	7	35.0
Nonpharmacological psychotherapy		
Hypnosis	5	25.0
Suggestion therapy	6	30.0
Reassurance and counseling	15	75.0

BID, bis in die; PCC, chronic cough with pre-existing psychological co-morbidity; QD, quaque die; QN, quaque nocte.

This study had some limitations. First, because the earliest sample included in this study was diagnosed in 2016, the diagnostic criteria for

chronic cough followed the 2015 Chinese cough guidelines at that time, and the combined diagnosis of psychosomatics also followed the diagnostic criteria of DSM-IV. Therefore, there is a lack of data on the assessment of patients' somatization symptoms. Second, the sample size of the PCC group in this study was small, mainly because the proportion of these chronic cough patients was very low, and more relevant studies with a large sample size are needed to support the results.

Conclusion

This study showed that psychological co-morbidity is common in chronic cough and a significant minority have mental illness, which may be present before the onset of chronic cough. Anxiety, depression, and cough-related quality of life are worse in this group. The evaluation of psychosomatic scales is of value, and psychosomatic joint diagnosis and treatment are necessary. The approach to chronic cough patients with psychological co-morbidity may differ depending on whether it is considered primary or secondary to the cough. In the pre-existing psychological co-morbidity group, psychological treatments alone

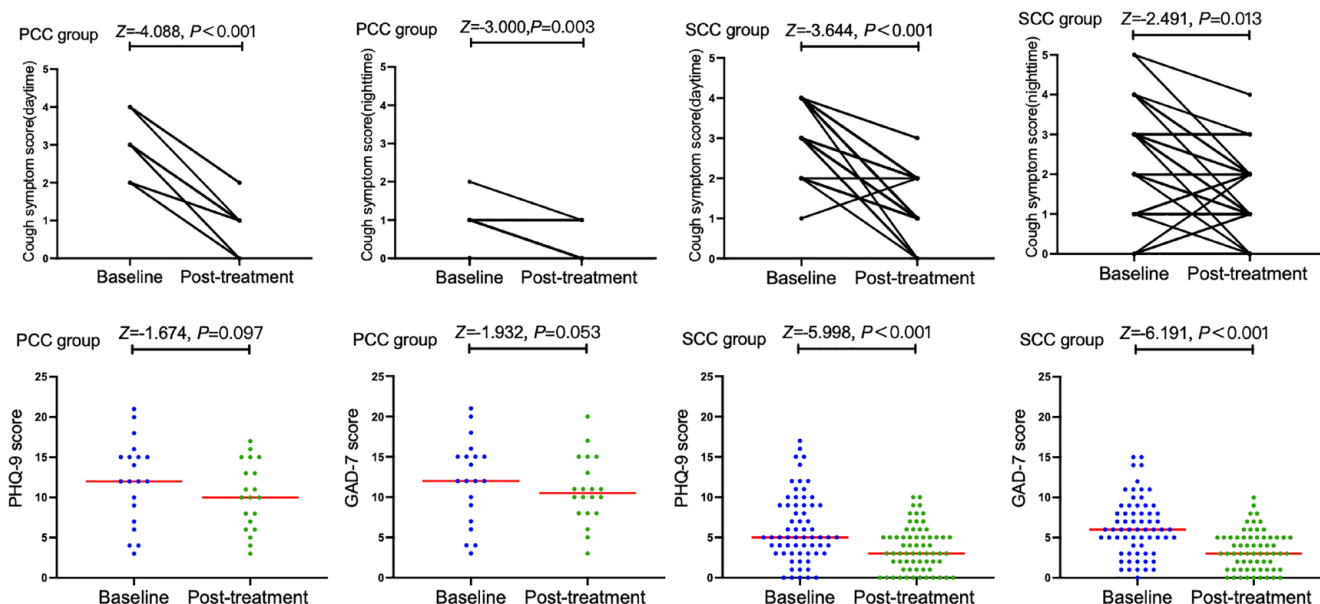


Figure 5. Follow-up of the cough symptom scores and the psychosomatic scale scores (PHQ-9 and GAD-7) between the PCC and SCC groups.

help the cough; in those with secondary anxiety and depression, the psychological morbidity improves with specific treatments for cough.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tongji Hospital (The ethics approval number is 2016-KYSB-160). The protocol was registered in the Chinese Clinical Trials Register (<http://www.chictr.org.cn/>) (ChiCTR2000037429). Written informed consent was obtained from all participants before enrollment.

Consent for publication

Written informed consent for publication was obtained from all participants.

Author contributions

Tongyangzi Zhang: Conceptualization; Data curation; Methodology; Software; Writing – original draft; Writing – review & editing.

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Wanzhen Li: Data curation; Formal analysis; Methodology; Writing – original draft.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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