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Anxiety and depression are associated with reduced quality of life and increased cough severity in chronic cough

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Abstract

Background: Chronic cough has led to a substantial socioeconomic burden globally. Psychiatric comorbidities are reported in many chronic diseases. However, the relationship between mental disorders and chronic cough remains unclear.

Objective: This study aims to explore the relationship between anxiety, depression and chronic cough.

Methods: 238 patients (96 males and 142 females) with chronic cough were enrolled in this study. Responses were collected using the Cough Visual Analog Scale, the Hospital Anxiety and Depression Scale (HADS), and the Leicester Cough Questionnaire.

Results: According to the HADS, 9.2% and 6.3% of patients were identified as having anxiety and depression, respectively. Patients with anxiety and depression were more likely to have a reduced quality of life. Cough duration, cough severity and history of anaphylaxis were found to be positively associated with reduced quality of life in patients with chronic cough. Cough severity was considered as a dependent risk factor for symptoms of anxiety and depression. Also, more severe symptoms of anxiety were observed in patients reported that a history of anaphylaxis. More female patients had a history of anaphylaxis and reduced cough-related quality of life.

Conclusion: Symptoms of anxiety and depression, longer cough duration, more severe cough and a history of anaphylaxis may reduce the quality of life in patients with chronic cough. Cough severity and a history of anaphylaxis are associated with symptoms of anxiety.

Key words: Chronic Cough, Anxiety, Depression, Anaphylaxis, Quality of life

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Introduction

Chronic cough is defined as a cough persisting for 8 weeks or more.[1] A recent meta-analysis has estimated that, the global incidence of chronic cough is approximately 9.6% for general adults.[2] In China, more than one-third of patients seek respiratory specialists support due to chronic cough, contributing to a sizeable socioeconomic burden. Reduced quality of life in patients with chronic cough is the primary reason for the first consultation with a doctor.[3] Quality of life is a clinically meaningful representation of the impact of chronic cough; therefore, it is essential to improve the quality of life in these patients.[4]

Some physical symptoms caused by chronic cough, including urinary incontinence, sleep deprivation and chest pain, have been reported to worsen patients' quality of life.[3,5] However, psychological conditions in chronic cough are often neglected in both scientific studies and clinical treatment. Published evidence has demonstrated that patients with chronic diseases, such as asthma or COPD, are often accompanied

by comorbid anxiety or depression.[6] Nonetheless, the psychological burden of chronic cough remains undefined, especially in China.

Therefore, the present study was performed to investigate the prevalence of anxiety and depression in patients with chronic cough in China, and to explore associations between anxiety, depression and clinical outcomes of chronic cough, including severity of disease and quality of life. In addition, potential risk factors for reduced quality of life in patients with chronic cough were also examined.

Methods

Study Design and Patients

In this retrospective study, 238 adults with chronic cough were recruited from September 2016 to August 2018 in the respiratory department of the Ningbo First Hospital in China. The study protocol was approved by the Ethics Committee of Ningbo First Hospital (2016-R017), and all participants provided written informed consent. The definition of chronic cough is according to the American College of Chest Physician Cough Guidelines.[7] All patients included were aged 18 to 79 years, with cough as the only clinical manifestation, persisting for eight weeks or more. Besides, recruited patients had no obvious abnormality in their chest imaging.

Exclusion criteria are listed as follows:

1) subjects unable to cooperate with the pulmonary function test.
2) patients with interstitial pneumonia, active pulmonary tuberculosis, community-acquired pneumonia, lung cancer, bronchiectasis, pulmonary heart disease, pulmonary embolism or other diseases (coronary heart disease, myocarditis, heart failure, neuromuscular disease) that could influence study outcomes.
3) patients who with a history of alcohol, anesthetics or other drug abuse, a history of mental illness, antagonistic personality, adverse motivation or other concerns that may affect the cognitive competence of participants in this study.
4) subjects who are pregnant.
5) patients with an abnormality in chest high resolution computed tomography.

These criteria are based on existing knowledge from previous studies.[8]

Demographics and clinical observations

The research team designed a questionnaire to collect demographic information and medical history, including age, body mass index (BMI), history of chronic cough, smoking, anaphylaxis and allergic rhinitis. Spirometry was used to measure lung function, including one-second forced expiratory volume (FEV_1), predicted one-second forced expiratory volume (FEV_1%), peak expiratory flow (PEF), predicted peak expiratory flow (PEF%), maximal mid-expiratory flow ($MMEF_{75/25}$), predicted maximal mid-expiratory flow ($MMEF_{75/25}$%), forced vital capacity (FVC), predicted forced vital capacity (FVC%) and forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC).

Assessment of anxiety and depression

The hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression. It has been previously reported as a sensitive and specific instrument for self-rating anxiety and depression.[9-13] There are two subscales in this measurement: anxiety subscale (HADS-A) and depression subscale (HADS-D). Each subscale consists of seven questions related to the current mood, and each is based on a four-point scale: 0, not at all; 1, sometimes; 2, often; 3, all the time. For each subscale, a score of 0 to 7 points was considered normal, a score of 8 to 10 was regarded as borderline anxiety or depression, and > 10 was anxiety or depression. In our study, patients were divided into two groups:

a) non-anxiety/non-depression, in which patients had HADS scores less than 8
b) anxiety/depression, in which patients with HADS scores of 8 or more.

Evaluation of the severity of chronic cough

The Cough Visual Analog Scale (CVAS) is a linear scale that is 10 cm in length (**Figure 1**). To assess chronic cough severity, patients were required to choose the corresponding tick mark on the scale depending on their subjective feeling. The lowest score is 0 points, representing no cough symptoms, and the highest score is 10 points, meaning the worst cough symptoms the participant has ever suffered. The CVAS has been widely used successfully in previous research.[14]

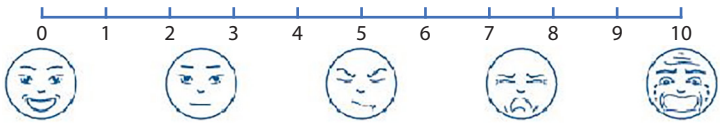

Figure 1. The cough visual analog scale (CVAS) adopted in the study. All participants were asked to pick a tick mark on the horizontal line, according to their severity of chronic cough. The score of the CVAS was the distance in centimeters from the start point.

Measurement of quality of life

The Leicester Cough Questionnaire (LCQ) is a reliable and validated tool for assessing cough-related quality of life (CRQOL). The LCQ is composed of 19 items in three domains (physical, psychological and social). Items are answered on a 7-point scale, from "every time" (1 point) to "never have" (7 points). Each domain is calculated separately and presented as an average score. The total score is the sum of the three domains. Higher scores indicate better quality of life and are also associated with reduced severity of chronic cough. A standard Chinese version of the LCQ was adopted in our study.[15]

Statistical Analysis

To describe different variables, means ± standard (SD) and medians with interquartile ranges were used for continuous data, and categorical data were presented as frequencies. Data were analyzed using the Student *t*-test, Mann-Whitney test, Chi-square test, Spearman correlation or multiple regression analysis. All results were analyzed using SPSS statistical software version 23.0. A double-sided p-value < 0.05 was considered as statistically significant.

Results

Demographics and clinical characteristics of the study population

238 patients (59.7% female) with chronic cough were enrolled in this study, with a mean age of 44.4 ± 14.8 years old (**Table 1**). 8.8% of participants were current smokers, and 10.5% were ex-smokers. In addition, 74 (31.1%) patients in this study had a history of anaphylaxis, 30.7% had a history of allergic rhinitis. According to the Hospital Anxiety and Depression Scale (HADS), 9.2% and 6.3% of patients were established as having anxiety and depression, respectively. Participants with a history of anaphylaxis were more likely to suffer from anxiety or depression than those without (13.5% vs 7.3%; 10.8% vs 4.3%, respectively), but differences between groups did not reach the threshold for statistical significance. No statistical differences between gender, age, BMI, smoking history, allergic rhinitis history or lung function were found between patients with or without anxiety/depression.

Table 1. Characteristics of patients with chronic cough.

Feature	Total (N = 238)
Gender:	
Male	96 (40.3%)
Female	142 (59.7%)
Age (years)	33.5 (196.3)
BMI (kg/m^2)	43.5 (23.0)
Smoking history:	
Never smoker	192 (80.7%)
Ex-smoker	25 (10.5%)
Current smoker	21 (8.8%)
Anaphylaxis history:	
No	164 (68.9%)
Yes	74 (31.1%)
Allergic Rhinitis history:	
No	165 (69.3%)
Yes	73 (30.7%)
FEV_1/L	2.8 (1.1)
FEV_1 (%)	98.9 (17.5)
PEF/L	6.8 (2.7)
PEF (%)	100.2 (23.1)
$MMEF_{75/25}$/L	3.1 (1.9)
$MMEF_{75/25}$ (%)	83.8 (44.0)
FVC/L	3.2 (1.3)
FVC (%)	97.5 (15.5)
FEV_1/FVC	86.2 (12.3)
Cough duration (weeks)	173.6 ± 283.8
Cough VAS	5.0 (3.0)
HADS Score	
HADS-A	3.1 ± 3.1
HADS-D	2.1 ± 2.8
LCQ Score	
The total score	14.9 (4.7)
Physical	4.9 (1.5)
Psychological	4.6 (1.7)
Social	5.5 (1.8)

BMI, body-mass index; FEV_1/L, one-second forced expiratory volume; FEV_1 (%), predicted one-second forced expiratory volume; PEF/L, peak expiratory flow; PEF (%), predicted peak expiratory flow; $MMEF_{75/25}$/L, maximal mid-expiratory flow; $MMEF_{75/25}$ (%), predicted maximal mid-expiratory flow; FVC/L, forced vital capacity; FVC (%), predicted forced vital capacity; FEV_1/FVC, forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio; Cough VAS, the Cough Visual Analog Scale; HADS-A, the anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, the depression subscale of the Hospital Anxiety and Depression Scale; LCQ, the Leicester Cough Questionnaire.

Comparison of cough-related features between patients with or without anxiety/depression

The mean cough duration, mean score of CVAS and LCQ are presented in **Table 1**. A reduced quality of life in patients with anxiety was observed in all LCQ domains (**Table 2**); total score (15.4 (4.5) vs 12.4 (3.5), $P < 0.001$), physical (5.0 (1.4) vs 3.8 (1.3), $P < 0.001$), psychological (4.9 (1.7) vs 3.6 (1.2), $P < 0.001$) and social (5.5 (2.0) vs 5.0 (1.7), $P = 0.034$). Compared with patients without depression, patients with depression had significantly lower scores in the total score of the LCQ

Table 2. Differences between patients with or without significant high anxiety (HADS-A) or depression (HADS-D) score.

Feature	Anxiety (HADS-A Score)			Depression (HADS-D Score)		
	0-7 (N = 216)	≥ 8 (N = 22)	p value	0-7 (N = 223)	≥ 8 (N = 15)	*p* value
Gender:			0.821			0.111
Male	88 (91.7%)	8 (8.3%)		93 (96.9%)	3 (3.1%)	
Female	128 (90.1%)	14 (9.9%)		130 (91.5%)	12 (8.5%)	
Age (years)	43.0 (22.8)	46.5 (23.8)	0.502	43.0 (22.0)	49.0 (24.0)	0.205
BMI (kg/m^2)	23.1 (5.4)	21.7 (4.9)	0.067	23.1 (5.4)	21.0 (4.8)	0.077
Smoking history:			0.877			0.346
Never smoker	175 (91.1%)	17 (8.9%)		179 (93.2%)	13 (6.8%)	
Ex-smoker	22 (88.0%)	3 (12.0%)		25 (100.0%)	0 (0.0%)	
Current smoker	19 (90.5%)	2 (9.5%)		19 (90.5%)	2 (9.5%)	
Anaphylaxis history:			0.148			0.080
No	152 (92.7%)	12 (7.3%)		157 (95.7%)	7 (4.3%)	
Yes	64 (86.5%)	10 (13.5%)		66 (89.2%)	8 (10.8%)	
Allergic Rhinitis history:			0.145			0.799
No	153 (92.7%)	12 (7.3%)		155 (93.9%)	10 (6.1%)	
Yes	63 (86.3%)	10 (13.7%)		68 (93.2%)	5 (6.8%)	
FEV_1/L	2.8 (1.1)	2.8 (1.0)	0.771	2.8 (1.2)	2.7 (0.9)	0.427
FEV_1 (%)	100.3 (17.3)	97.1 (13.5)	0.547	100.0 (17.8)	97.5 (19.3)	0.655
PEF/L	6.8 (2.8)	6.4 (1.9)	0.312	6.8 (2.8)	6.4 (2.2)	0.179
PEF (%)	100.7 (22.6)	94.1 (27.5)	0.192	100.5 (23.1)	95.6 (22.7)	0.568
$MMEF_{75/25}$/L	3.0 (1.9)	3.3 (2.2)	0.640	3.0 (1.9)	3.5 (2.6)	0.533
$MMEF_{75/25}$ (%)	83.2 (41.8)	96.1 (53.4)	0.352	83.0 (42.2)	106.0 (60.9)	0.097
FVC/L	3.2 (1.4)	3.0 (1.0)	0.426	3.2 (1.3)	3.1 (0.8)	0.269
FVC (%)	98.0 (15.4)	96.0 (17.0)	0.278	97.6 (15.3)	94.7 (18.8)	0.906
FEV_1/FVC	86.1 (12.2)	90.1 (12.3)	0.330	86.1 (12.2)	90.3 (14.1)	0.267
Cough duration (weeks)	174.2 ± 289.4	167.6 ± 226.3	0.918	173.9 ± 288.7	169.4 ± 202.5	0.937
Cough VAS	5.0 (3.0)	5.0 (4.0)	0.988	5.0 (3.0)	5.0 (4.0)	0.931
LCQ Score						
The total score	15.4 (4.5)	12.4 (3.4)	< 0.001	15.4 (4.5)	10.9 (4.7)	< 0.001
Physical	5.0 (1.4)	3.8 (1.3)	< 0.001	5.0 (1.4)	3.8 (1.0)	< 0.001
Psychological	4.9 (1.7)	3.6 (1.2)	< 0.001	4.7 (1.9)	3.4 (1.3)	< 0.001
Social	5.5 (2.0)	5.0 (1.7)	0.039	5.5 (2.0)	4.0 (1.8)	< 0.001

BMI, body-mass index; FEV_1/L, one-second forced expiratory volume; FEV_1 (%), predicted one-second forced expiratory volume; PEF/L, peak expiratory flow; PEF (%), predicted peak expiratory flow; $MMEF_{75/25}$/L, maximal mid-expiratory flow; $MMEF_{75/25}$ (%), predicted maximal mid-expiratory flow; FVC/L, forced vital capacity; FVC (%), predicted forced vital capacity; FEV_1/FVC, forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio; Cough VAS, the Cough Visual Analog Scale; LCQ, the Leicester Cough Questionnaire; HADS-A, the anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, the depression subscale of the Hospital Anxiety and Depression Scale.

(15.4 (4.5) vs 10.9 (4.7), $P < 0.001$) and each domain; physical (5.0 (1.4) vs 3.8 (1.0), $P < 0.001$), psychological (4.7 (1.8) vs 3.4 (1.3), $P < 0.001$) and social (5.5 (2.0) vs 4.0 (1.8), $P < 0.001$). No significant difference in cough duration and cough severity (using CVAS) was demonstrated between patients with or without anxiety/depression. These results indicate that higher anxiety or depression symptoms may be associated with reduced quality of life in patients with chronic cough.

Correlations among cough, anxiety, depression and other related features

Spearman correlation was carried out to found features that were correlated with cough, anxiety and depression furtherly (**Table 3**). Consistent with the above results, the score of anxiety subscale in HADS (HADS-A) was inversely correlated with the total score of the LCQ (r = -0.054, $P < 0.0001$) and each domain; physical (r = -0.339, $P < 0.0001$), psychological (r = -0.547, $P < 0.0001$) and social (r = -0.452, $P < 0.0001$). A significant inverse correlation was also found between the HADS-D and the total score of the LCQ (r = -0.510, $P < 0.0001$) and each domain; physical (r = -0.362, $P < 0.0001$), psychological (r = -0.536, $P < 0.0001$) and social (r = -0.441, $P < 0.0001$). Notably, results suggested that increased cough duration and increased severity of cough was positively correlated with reduced quality of life in the domains of psychological (r = 0.173, P = 0.008; r = 0.283, $P < 0.0001$) and social (r = 0.135, P = 0.038; r = 0.338, $P < 0.0001$). History of anaphylaxis was also found to be a related factor of reduced quality of life in patients with chronic cough: the total score of the LCQ (r = -0.163, P = 0.012) and each domain; physical (r = -0.158, P = 0.015), psychological (r = -0.131, P = 0.043) and social (r = -0.147, P = 0.023). Cough duration (r =0.173, P = 0.008) and history of anaphylaxis (r =0.145, P = 0.026) showed positive correlations with HASD scores.

Table 3. Spearman correlations between variables.

		The score of CVAS	LCQ domains				HADS score	
			Total score	Physical domain	Psychological domain	Social domain	Anxiety subscale	Depression subscale
Gender	*r*	0.042	-0.138*	-0.073	-0.123	-0.148*	0.107	0.064
	p value	0.517	0.033	0.264	0.057	0.022	0.100	0.329
Age (years)	*r*	-0.031	0.019	-0.014	-0.001	0.045	0.083	0.078
	p value	0.632	0.766	0.830	0.987	0.494	0.200	0.229
BMI	*r*	-0.002	0.124	0.022	0.130*	0.168**	-0.159*	-0.094
	p value	0.979	0.057	0.740	0.045	0.009	0.014	0.149
Cough duration (weeks)	*r*	0.038	-0.143*	-0.087	-0.173**	-0.135*	0.173**	0.119
	p value	0.562	0.028	0.183	0.008	0.038	0.008	0.066
Smoking history	*r*	-0.072	-0.065	-0.010	-0.055	-0.082	0.044	0.007
	p value	0.270	0.320	0.873	0.400	0.207	0.499	0.918
Anaphylaxis history	*r*	0.111	-0.163*	-0.158*	-0.131*	-0.147*	0.145*	0.133*
	p value	0.088	0.012	0.015	0.043	0.023	0.026	0.040
Allergic Rhinitis history	*r*	0.001	-0.034	-0.053	0.018	-0.021	0.040	0.014
	p value	0.986	0.605	0.412	0.777	0.753	0.536	0.832
FEV_1/L	*r*	-0.032	0.084	0.068	0.109	0.046	-0.155*	-0.135*
	p value	0.627	0.196	0.293	0.092	0.478	0.017	0.037
FEV_1%	*r*	-0.083	0.090	0.103	0.104	0.042	-0.084	-0.102
	p value	0.205	0.166	0.113	0.111	0.521	0.198	0.116
PEF/L	*r*	-0.099	0.159*	0.164*	0.140*	0.119	-0.158*	-0.129*
	p value	0.127	0.014	0.011	0.031	0.066	0.015	0.047
PEF%	*r*	-0.180**	0.133*	0.216**	0.089	0.073	-0.079	-0.077
	p value	0.005	0.041	0.001	0.169	0.263	0.224	0.234
$MMEF_{75/25}$/L	*r*	-0.006	0.057	0.109	0.046	0.015	-0.083	-0.089
	p value	0.923	0.379	0.095	0.482	0.822	0.200	0.174

Table 3. (Continued)

		The score of CVAS	LCQ domains				HADS score	
			Total score	Physical domain	Psychological domain	Social domain	Anxiety subscale	Depression subscale
$MMEF_{75/25}$%	*r*	-0.031	0.039	0.120	0.007	-0.004	-0.011	-0.035
	p value	0.638	0.554	0.065	0.911	0.950	0.869	0.587
FVC/L	*r*	-0.059	0.119	0.068	0.143*	0.086	-0.171**	-0.135*
	p value	0.368	0.068	0.293	0.027	0.186	0.008	0.037
FVC%	*r*	-0.150*	0.125	0.063	0.148*	0.113	-0.096	-0.084
	p value	0.021	0.054	0.333	0.023	0.083	0.140	0.199
FEV_1/FVC	*r*	0.037	-0.054	0.006	-0.052	-0.068	0.081	0.023
	p value	0.568	0.405	0.924	0.427	0.296	0.213	0.728
CVAS	*r*	1.000	-0.381**	-0.428**	-0.283**	-0.338**	0.108	0.105
	p value		< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.096	0.105
HADS-A	*r*	0.108	-0.514**	-0.339**	-0.547**	-0.452**	1.000	0.772**
	p value	0.096	< 0.0001	< 0.0001	< 0.0001	< 0.0001		< 0.0001
HADS-D	*r*	0.105	-0.510**	-0.362**	-0.536**	-0.441**	0.772**	1.000
	p value	0.105	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	
LCQ Score (the total score)	*r*	-0.381**	1.000	0.788**	0.889**	0.907**	-0.514**	-0.510**
	p value	< 0.0001		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
The physical domain	*r*	-0.428**	0.788**	1.000	0.544**	0.590**	-0.339**	-0.362**
	p value	< 0.0001	< 0.0001		< 0.0001	< 0.0001	< 0.0001	< 0.0001
The psychological domain	*r*	-0.283**	0.889**	0.544**	1.000	0.740**	-0.547**	-0.536**
	p value	< 0.0001	< 0.0001	< 0.0001		< 0.0001	< 0.0001	< 0.0001
The social domain	*r*	-0.338**	0.907**	0.590**	0.740**	1.000	-0.452**	-0.441**
	p value	< 0.0001	< 0.0001	< 0.0001	< 0.0001		< 0.0001	< 0.0001

*$P < 0.05$; **$P < 0.01$; BMI, body-mass index; FEV_1/L, one-second forced expiratory volume; FEV_1 (%), predicted one-second forced expiratory volume; PEF/L, peak expiratory flow; PEF (%), predicted peak expiratory flow; $MMEF_{75/25}$/L, maximal mid-expiratory flow; $MMEF_{75/25}$ (%), predicted maximal mid-expiratory flow; FVC/L, forced vital capacity; FVC (%), predicted forced vital capacity; FEV_1/FVC, forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio; Cough VAS, the Cough Visual Analog Scale; LCQ, the Leicester Cough Questionnaire; HADS-A, the anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, the depression subscale of the Hospital Anxiety and Depression Scale.

The influence factors for anxiety, depression and quality of life in chronic cough

Multiple regression analysis was employed to find determinants that could best predict anxiety, depression and quality of life in chronic cough (**Table 4**). The psychological and physical domains of LCQ, cough severity and FVC were considered dependent variables of the HADS-A score. The psychological and physical domains of LCQ and cough severity were considered dependent variables of the HADS-D score. The HADS score (both the anxiety subscale and the depression subscale), cough severity and cough duration were considered dependent variables of the LCQ score (the total).

In addition, a history of anaphylaxis was also found as a risk factor for increased symptoms of anxiety and reduced quality of life in patients with chronic cough (**Table 5**). Patients with a history of anaphylaxis scored significantly higher in HADS-A (2.0 (4.0) vs 3.0 (5.0), $P = 0.026$) than those without a history. Compared patients without a history of anaphylaxis, reduced quality of life in the domains of physical (5.0 (1.5) vs 4.6 (1.5), $P = 0.015$), psychological (4.9 (2.0) vs 4.3 (1.8), $P = 0.043$) and social (5.5 (1.8) vs 5.1 (2.0), $P = 0.024$) were found in patients with a history of anaphylaxis. It should also be noted that in patients with chronic cough, female patients were more likely to have a history of anaphylaxis.

Table 4. Linear regression models for scores of HADS-A, HADS-D and LCQ (the total).

Variables	R2	*p* value
HADS-A		
LCQ Score (the psychological domain)	0.278	< 0.001
LCQ Score (the physical domain)	0.292	< 0.001
Cough VAS	0.306	< 0.001
FVC/L	0.319	< 0.001
HADS-D		
LCQ Score (the psychological domain)	0.248	< 0.001
LCQ Score (the physical domain)	0.265	< 0.001
Cough VAS	0.293	< 0.001
LCQ Score (the total)		
HADS Score (the anxiety subscale)	0.268	< 0.001
Cough VAS	0.419	< 0.001
HADS Score (the depression subscale)	0.445	< 0.001
Cough duration (weeks)	0.458	< 0.001

LCQ, the Leicester Cough Questionnaire; Cough VAS, the Cough Visual Analog Scale; HADS, the Hospital Anxiety and Depression Scale; HADS-A, the anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, the depression subscale of the Hospital Anxiety and Depression Scale.

Table 5. Differences between patients with or without history of anaphylaxis.

Feature	Non-anaphylaxis history (N = 164)	Anaphylaxis history (N = 74)	*p* value
Gender:			< 0.001
Male	79 (82.3%)	17 (17.7%)	
Female	85 (59.9%)	57 (40.1%)	
Age (years)	44.0 (20.8)	40.5 (27.0)	0.944
BMI (kg/m²)	23.2 (5.0)	21.7 (5.5)	0.070
HADS-A score	2.0 (4.0)	3.0 (5.0)	0.026
HADS-D score	1.0 (3.0)	1.0 (4.0)	0.040
Cough VAS	5.0 (3.8)	5.0 (3.0)	0.088
LCQ Score			
The total score	15.5 (4.6)	14.2 (4.2)	0.012
Physical	5.0 (1.5)	4.6 (1.5)	0.015
Psychological	4.9 (2.0)	4.3 (1.8)	0.043
Social	5.5 (1.8)	5.1 (2.0)	0.024

BMI, body-mass index; Cough VAS, the Cough Visual Analog Scale; LCQ, the Leicester Cough Questionnaire; HADS-A, the anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, the depression subscale of the Hospital Anxiety and Depression Scale.

Discussion

238 adult patients with chronic cough were recruited into this study; their clinical observations and scores of CVAS, HADS, LCQ were collected. This study demonstrated that patients with chronic cough would have a reduced quality of life if also considered to have comorbid anxiety or depression. Cough severity and cough duration were also positively associated with reduced quality of life. Patients with a history of anaphylaxis were more likely to report a reduced quality of life. Cough severity and history of anaphylaxis were also related to increased symptoms of anxiety in this study.

In our study, the prevalence of anxiety and depression in patients with chronic cough was 9.2% and 6.3%, respectively. Lorcan and colleagues reported an anxiety prevalence of 33% and a depression prevalence of 16% among chronic cough patients.[16] This difference in the prevalence of anxiety and depression may be attributable to the proportion of females and the duration of cough. In Lorcan's study, 72.7% of participants were female and the mean cough duration was approximately 277 weeks.[16] These data were much higher than those found in our study (the proportion of females: 59.7% vs 72.7%, mean cough duration: 173 weeks vs 277 weeks). A previous study in the USA reported 24.2% of anxiety in chronic cough patients, with a higher proportion of females (73.4%).[17] Besides, patients of chronic cough in Australia were found higher scores of HADS than our study (HADS-A score: 6.3 ± 4.6 vs 3.1 ± 3.1, HADS-D score: 4.8 ± 4.1 vs 2.1 ± 2.8).[18] The proportion of females in the study was 81.8%, and the mean cough duration was about 367 weeks.[18] Because of the different studied populations, the prevalence of anxiety and depression in Asian patients with chronic cough is likely lower than that in Western populations. In the UK, 43.3% of patients with chronic cough were diagnosed with anxiety, 25.4% with depression.[8] In the USA, the prevalence of depression in patients with chronic cough was about 53%.[19] Another study in Korea identified only 4.4% of patients with depression in chronic cough, which is similar to our results.[20] Published evidence reported that cough-variant asthma was one of the most common causes of chronic cough in China (32.6%).[21] Our previous study demonstrated that the prevalence of anxiety and depression was associated with asthma.[22] 13.7% of patients were found to have anxiety symptoms and 10.2% to have depression symptoms in the previous study.[22] The different causes of chronic cough between countries may lead to various prevalence of anxiety and depression. Studies demonstrated that cigarette smoking is positively associated with increased levels of anxiety.[23] Yun's findings suggested that smoking was strongly associated with depression, particularly among females.[24] In Edelstein's study, young adults reported higher symptoms of anxiety than older adults.[25] But there is no proof yet that the prevalence of anxiety and depression could be differed by smoking history or mean age in patients with chronic cough. All those above characteristics of the current study and previous studies are presented in the **Table S1**.

Results showed that symptoms of anxiety or depression were related to reduced quality of life in patients with chronic cough. These results suggest that anxious or depressive individuals are more sensitive to or concerned about their physical symptoms, impacting the poor quality of life. Several studies have reported that anxiety could regulate the emotive and motor parts of cough.[26-28] Amitriptyline, a medicine indicated for depression, has also demonstrated some effect in the therapy of chronic cough, which may be due to the co-mechanism or interaction between chronic cough and psychological comorbidities.[29,30] Moreover, psychological disorders are related to the inflammatory status, which has also been observed in other researches in chronic cough.[31,32] Therefore, the association between psychological disorders and chronic cough may be bidirectional, but there is still a need for further investigated.

Furthermore, increased severity and longer duration of cough were associated with reduced quality of life. Patients with longer durations of cough will have reduced quality of life in psychological and social domains. The severity of cough was considered as a dependent risk factor for symptoms of anxiety and depression. Chronic cough is highly bothersome to the patient affected and people around them. A long-term and serious cough could contribute to many inconveniences for patients, such as exhaustion, embarrassment in public places, difficulty speaking on the telephone, urinary incontinence and complaints from family, friends and colleagues.[33] These frustrations may result in worsening mood and reduced quality of life in the psychological and social domains.

We also evaluated the influence of self-reported allergies on chronic cough. It has been reported that allergic irritants might lead to the sensitization of cough reflex by triggering inflammatory reactive and damaging autonomic nerves.[34] Results suggested that individuals without anaphylaxis history tended to have a better quality of life. Besides, participants without anaphylaxis history usually had fewer symptoms of anxiety or depression. Similar to these findings, one prior study reported a positive relationship between anxiety and self-reported allergies, but not objectively verified allergies.[35] Compared with children without food allergy, higher anxiety symptoms and decreased quality of life were demonstrated in children with a history of food allergy.[36] This could indicate that mental health status plays a critical role in individuals with a history of atopic disease. The expected changes of the hypothalamic-pituitary-adrenocortical (HPA) axis and vegetative nerves might account for the correlation between mental health and atopic disease.[37,38] Taken together, anxiety, depression, anaphylaxis history and chronic cough appear to share common key elements of pathogenesis. The possible mechanisms may be explained partially by the dysfunction of the inflammatory reaction, autonomic damage and cough hypersensitivity.

Consistent with other studies, our study had a higher proportion of female patients with chronic cough (female vs male: 59.7% vs 40.3%). Our results revealed that gender was also one of the independent determinants in quality of life; females tended to score lower in cough related quality of life in the social domain. In addition, more females than males presented with a history of anaphylaxis. This might be the cause of the increased proportion of females with chronic cough.[39] Other literature has reported loose associations between quality of life, age and BMI.[40,41] The effects of these factors require further exploration.

To the best of our knowledge, this research was one of the few studies that simultaneously measured the association between psychiatric morbidity, anaphylaxis history and chronic cough. However, there are still some limitations in our study. Firstly, the cross-sectional study design hindered us from investigating interactions with more in-depth understanding. A longitudinal study may provide more effective and reliable results for patients with chronic cough. Secondly, the sample size of this study was not large enough, which was a major limitation. Further studies with larger sample sizes are needed to verify our conclusions. Thirdly, it should be noted that this study didn't compare symptoms of anxiety and depression among different causes of chronic cough patients. We recognize this is a limitation, as we cannot identify the causes of chronic cough in included participants. It would be helpful for future research to distinguish between those with idiopathic cough and those with an explained cough.

In conclusion, to improve the therapeutic effect and quality of life in patients with chronic cough, psychiatric status should be considered, especially in female patients, those with serious severity of cough or with a history of anaphylaxis. Further and longitudinal studies are required to confirm our findings.

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Authors' contributions

- **Yiting Li:** Conceptualization; Formal analysis; Investigation; Methodology; Data curation; Software; Writing-original draft.
- **Chao Cao:** Conceptualization; Formal analysis; Data curation; Funding acquisition; Investigation; Supervision; Writing–review & editing.
- **Yunxin Ji:** Conceptualization; Investigation; Methodology; Supervision; Writing–review & editing.
- **Suling Xu:** Conceptualization; Formal analysis; Methodology; Funding acquisition; Supervision; Writing–review & editing.

Declaration of Conflicting Interests

The authors have no conflicts of interest to declare.

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Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Ningbo First Hospital (2016-R017), and all participants provided written informed consent.

Availability of data and materials

Participant data without names and identifiers will be made available after approval from the corresponding author.

References

1. Kang SY, Kim GW, Song WJ, Chang YS, Cho SH. Chronic cough in Korean adults: a literature review on common comorbidity. Asia Pac Allergy. 2016;6(4):198-206.
2. Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J. 2015;45 (5):1479-81.
3. Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. Lung. 2008;186 Suppl 1:S55-8.
4. Dicpinigaitis PV. Clinical perspective - cough: an unmet need. Curr Opin Pharmacol. 2015;22:24-8.
5. Shariat SF, Zimmern PE, Hilton K, Gruchalla RS. Prospective Questionnaire-Based Evaluation of the Prevalence of Urinary Incontinence in Women with Chronic Cough. Urol Int. 2009;83(2):181-6.
6. Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR. Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. Chest. 2019;156(1):80-91.
7. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary - ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl): 1S-23S.
8. Hulme K, Deary V, Dogan S, Parker SM. Psychological profile of individuals presenting with chronic cough. ERJ Open Res. 2017;3(1): 00099-2016.
9. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale - An updated literature review. J Psychosom Res. 2002;52(2):69-77.
10. Leung CM, Wing YK, Kwong PK, Lo A, Shum K. Validation of the Chinese-Cantonese version of the hospital anxiety and depression scale and comparison with the Hamilton Rating Scale of Depression. Acta Psychiatr Scand. 1999;100(6):456-61.
11. Martin CR, Thompson DR, Chan DS. An examination of the psychometric properties of the Hospital Anxiety and Depression Scale in Chinese patients with acute coronary syndrome. Psychiatry Res. 2004;129(3): 279-88.
12. Li Q, Lin Y, Hu C, Xu Y, Zhou H, Yang L, et al. The Chinese version of hospital anxiety and depression scale: Psychometric properties in Chinese cancer patients and their family caregivers. Eur J Oncol Nurs. 2016;25: 16-23.
13. Yang Y, Ding R, Hu D, Zhang F, Sheng L. Reliability and validity of a Chinese version of the HADS for screening depression and anxiety in psycho-cardiological outpatients. Compr Psychiatry. 2014;55(1):215-20.
14. Schmit KM, Coeytaux RR, Goode AP, McCrory DC, Yancy WS Jr, Kemper AR, et al. Evaluating cough assessment tools: a systematic review. Chest. 2013;144(6):1819-26.
15. Ma W, Yu L, Wang Y, Li X, Lu H, Qiu Z. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough (London, England). 2009;5:7.
16. McGarvey LP, Carton C, Gamble LA, Heaney LG, Shepherd R, Ennis M, et al. Prevalence of psychomorbidity among patients with chronic cough. Cough (London, England). 2006;2:4.
17. Hartley NA, Petty BE, Johnson B, Thibeault SL. Comparative analysis of clinical profile: Chronic cough vs paradoxical vocal fold motion. Respir Med. 2015;109(12):1516-20.
18. Vertigan AE, Bone SL, Gibson PG. Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. Respirology. 2013;18(6):948-56.
19. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43.
20. Won HK, Lee JH, An J, Sohn KH, Kang MG, Kang SY, et al. Impact of Chronic Cough on Health-Related Quality of Life in the Korean Adult General Population: The Korean National Health and Nutrition Examination Survey 2010-2016. Allergy Asthma Immunol Res. 2020;12(6): 964-79.
21. 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(3):613-20.
22. Li Y, Jiang Q, Ji Y, Cao C. Anxiety and depression may associate with poorer control and quality of life in adults with asthma. Allergy. 2020; 75(7):1759-62.
23. Garey L, Olofsson H, Garza T, Shepherd JM, Smit T, Zvolensky MJ. The Role of Anxiety in Smoking Onset, Severity, and Cessation-Related Outcomes: a Review of Recent Literature. Curr Psychiatry Rep. 2020; 22(8):38.
24. Yun WJ, Shin MH, Kweon SS, Ryu SY, Rhee JA. Association of smoking status, cumulative smoking, duration of smoking cessation, age of starting smoking, and depression in Korean adults. BMC Public Health. 2012;12: 724.
25. Gerolimatos LA, Edelstein BA. Anxiety-related constructs mediate the relation between age and health anxiety. Aging Ment Health. 2012;16(8): 975-82.
26. von Leupoldt A, Chan YS, Bradley MM, Lang PJ, Davenport PW. The impact of anxiety on the neural processing of respiratory sensations. Neuroimage. 2011;55(1):247-52.
27. Davenport PW, Vovk A, Duke RK, Bolser DC, Robertson E. The urge-to -cough and cough motor response modulation by the central effects of nicotine. Pulm Pharmacol Ther. 2009;22(2):82-9.
28. Van den Bergh O, Van Diest I, Dupont L, Davenport PW. On the psychology of cough. Lung. 2012;190(1):55-61.
29. Ryan MA, Cohen SM. Long-term follow-up of amitriptyline treatment for idiopathic cough. Laryngoscope. 2016;126(12):2758-63.
30. Ryan NM, Vertigan AE, Birring SS. An update and systematic review on drug therapies for the treatment of refractory chronic cough. Expert Opin Pharmacother. 2018;19(7):687-711.
31. Raison CL, Miller AH. Do cytokines really sing the blues? Cerebrum. 2013;2013:10.
32. Chung KF, McGarvey L, Mazzone S. Chronic cough and cough hypersensitivity syndrome. Lancet Respir Med. 2016;4(12):934-5.
33. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Ribas CD, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020;55: (1):1901136.
34. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med. 2013;1(5):414-22.
35. Gregory AM, Caspi A, Moffitt TE, Milne BJ, Poulton R, Sears MR. Links between anxiety and allergies: psychobiological reality or possible methodological bias? J Pers. 2009;77(2):347-62.
36. Goodwin RD, Rodgin S, Goldman R, Rodriguez J, deVos G, Serebrisky D, et al. Food Allergy and Anxiety and Depression among Ethnic Minority Children and Their Caregivers. J Pediatr. 2017;187:258-64.e1.
37. Hlavacova N, Solarikova P, Marko M, Brezina I, Jezova D. Blunted cortisol response to psychosocial stress in atopic patients is associated with decrease in salivary alpha-amylase and aldosterone: Focus on sex and menstrual cycle phase. Psychoneuroendocrinology. 2017;78:31-8.
38. Choi HG, Kim JH, Park JY, Hwang YI, Jang SH, Jung KS. Association Between Asthma and Depression: A National Cohort Study. J Allergy Clin Immunol Pract. 2019;7(4):1239-45.e1.
39. French CT, Fletcher KE, Irwin RS. A comparison of gender differences in health-related quality of life in acute and chronic coughers. Chest. 2005;127(6):1991-8.
40. Song WJ, Morice AH, Kim MH, Lee SE, Jo EJ, Lee SM, et al. Cough in the elderly population: relationships with multiple comorbidity. PLoS One. 2013;8(10):e78081.
41. Judson MA, Chopra A, Conuel E, Koutroumpakis E, Schafer C, Austin A, et al. The Assessment of Cough in a Sarcoidosis Clinic Using a Validated instrument and a Visual Analog Scale. Lung. 2017;195(5):587-94.

Supplemental material

Table S1. Characteristics of patients with chronic cough in the current study and previous studies

Source	Countries	Assessment scale	No. patient	Age, years (Mean ± SD)	Female (%)	Cough duration, weeks	Ex smoking (%) / Current smoking (%)	Anxiety (%)	Depression (%)
Current study	China	HADS	238	44.4 ± 14.8	59.7%	173	10.5% / 8.8%	9.2%	6.3%
McGarvey LP, et al[1]	UK	HADS	57	47.5 ± 14.3	72.7%	277	/	33.0%	16%
Hulme K, et al[2]	UK	HADS	67	/	64.2%	/	/	43.3%	25.4%
Everett CF, et al[3]	UK	Likert scale	373	65.3 ± 12.0	73.0%	339	41.0% / 2.0%	69.0%	55.0%
Hartley NA, et al[4]	USA	GAD-7	128	55.4 ± 13.5	73.4%	/	31.5% / 3.2%	24.2%	/
Dicpinigaitis PV, et al[5]	USA	CES-D	100	59.5 ± 12.6	79.0%	454	/	/	53.0%
Meltzer EO, et al[6]	USA	GAD-7 and PHQ-9	3654	50.1 ± 17.4	60.4%	/	27.3% / 30.8%	54.7%	65.5%
Vertigan AE, et al[7]	Australia	HADS	33	58.7 ± 14.9	81.8%	369	/	6.3 ± 4.6	4.8 ± 4.1
Koskela HO, et al[8]	Finland	PHQ-2	421	/	/	/	/	/	4.8%
Heo IR, et al[9]	Korean	PHQ-9	226	59.9 ± 11.1	44.2%	/	18.6% /35.8%	/	4.4%
Won HK, et al[10]	Korean	/	/	57.3 ± 0.6	39.2%	405	17.6% / 43.0%		4.9%

Please note: Vertigan AE and his colleagues (ref 7) only show the mean score of the HADS in their studies. "6.3 ± 4.6" (mean ± SD) was the score of the anxiety subscale in the HADS, "4.8 ± 4.1" (mean ± SD) was the score of the depression subscale in the HADS.
Abbreviations: HADS, the Hospital Anxiety and Depression Scale; GAD-7, the Generalized Anxiety Disorder 7-item Scale; CES-D, the Center for Epidemiologic Studies Depression Scale; PHQ-9, the Patient Health Questionnaire-9; PHQ-2, the Patient Health Questionnaire-9.

References

1. McGarvey LP, Carton C, Gamble LA, Heaney LG, Shepherd R, Ennis M, et al. Prevalence of psychomorbidity among patients with chronic cough. Cough (London, England). 2006;2:4.
2. Hulme K, Deary V, Dogan S, Parker SM. Psychological profile of individuals presenting with chronic cough. ERJ Open Res. 2017;3(1): 00099-2016
3. Everett CF, Kastelik JA, Thompson RH, Morice AH. Chronic persistent cough in the community: a questionnaire survey. Cough (London, England). 2007;3:5.
4. Hartley NA, Petty BE, Johnson B, Thibeault SL. Comparative analysis of clinical profile: Chronic cough vs paradoxical vocal fold motion. Respir Med. 2015;109(12):1516-20.
5. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43.
6. Meltzer EO, Zeiger RS, Dicpinigaitis P, Bernstein JA, Oppenheimer JJ, Way NA, et al. Prevalence and Burden of Chronic Cough in the United States. J Allergy Clin Immunol Pract. 2021;9(11):4037-44.e2.
7. Vertigan AE, Bone SL, Gibson PG. Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. Respirology. 2013;18(6):948-56.
8. Koskela HO, Lätti AM, Pekkanen J. The impacts of cough: a cross-sectional study in a Finnish adult employee population. ERJ Open Res. 2018;4(4): 00113-2018.
9. Heo IR, Kim JY, Go SI, Kim TH, Ju S, Yoo JW, et al. Chronic cough is associated with depressive mood in women regardless of smoking status and lung function. Clin Respir J. 2021;15:753-60.
10. Won HK, Lee JH, An J, Sohn KH, Kang MG, Kang SY, et al. Impact of Chronic Cough on Health-Related Quality of Life in the Korean Adult General Population: The Korean National Health and Nutrition Examination Survey 2010-2016. Allergy Asthma Immunol Res. 2020; 12(6):964-79.