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Prevalence of and risk factors for depressive symptoms in non-tuberculous mycobacterial pulmonary disease

Y. Matsumura,[1,2] M. Tabusadani,[2] K. Yamane,[1,3] S. Takao,[2] Y. Kuroyama,[1,4] K. Mori,[1,2] K. Ono,[1,2] K. Kawahara,[1,2] S. Omatsu,[1,2] K. Furuuchi,[5,6,] K. Fujiwara,[5,6] K. Morimoto,[5,7] H. Kimura,[1,2,5] H. Senjyu[1,2]

[1]Department of Clinical Mycobacteriology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [2]Respiratory Care and Rehabilitation Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association (JATA), Tokyo, [3]Department of Physical Therapy, Faculty of Social Work Studies, Josai International University, Chiba, [4]Department of Rehabilitation, Showa General Hospital, Kodaira, Tokyo, [5]Respiratory Diseases Center, Fukujuji Hospital, JATA, Tokyo, [6]Department of Basic Mycobacteriology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [7]Division of Clinical Research, Fukujuji Hospital, JATA, Tokyo, Japan

Correspondence to: Hideaki Senjyu, Department of Clinical Mycobacteriology, Nagasaki University, Graduate School of Biomedical Sciences, Fukujuji Hospital, Japan Anti-Tuberculosis Association, 3-1-24 Matsuyama, Kiyose 204-8522, Tokyo, Japan. Email: senjyu@nagasaki-u.ac.jp

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SUMMARY

BACKGROUND: The presence of depressive symptoms in patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD) is an important research topic; however, the prevalence of depressive symptoms and the factors that influence their development are unclear.

OBJECTIVE: To analyse the association between CES-D (Center for Epidemiological Studies Depression Scale) scores and clinical parameters such as age, disease duration, pulmonary function, imaging findings, blood data, physical functions, sleep disturbances, respiratory symptoms and health-related quality of life (HRQOL).

METHODS: We conducted a cross-sectional retrospective study of 114 patients with NTM-PD at a single centre from March 2016 to January 2021 to evaluate the relationship between CES-D scores and clinical parameters.

RESULTS: Participants had a median age of 64 years; 32.5% of them had depressive symptoms. Disease duration, albumin, C-reactive protein, pulmonary function, dyspnoea, exercise capacity, respiratory symptoms, cough-related HRQOL and sleep disturbances were associated with depressive symptoms. Binomial logistic regression analyses indicated that the CES-D score was significantly associated with cough-related HRQOL and sleep disturbances.

CONCLUSION: A high percentage of NTM-PD patients in this study experienced depressive symptoms, and these patients had abnormalities of various clinical parameters. Cough-related HRQOL and sleep disturbance had a strong influence on the development of depressive symptoms.

KEY WORDS: non-tuberculous mycobacterial pulmonary disease; depressive symptoms; health-related quality of life; sleep disturbance

Pulmonary infections caused by non-tuberculous mycobacteria (NTM) have been increasing worldwide in recent years. Japan has one of the highest prevalence rates of non-tuberculous mycobacterial pulmonary disease (NTM-PD) in the world.[1] Although long-term multidrug therapy is the mainstay of treatment for NTM-PD, relapse and/or reinfection following treatment is common, and complete remission is difficult to achieve.[2] Thus, other treatment goals, such as symptom improvement and improvement of health-related quality of life (HRQOL), have been proposed.[3]

The main symptoms of NTM-PD include cough, sputum, fatigue, dyspnoea, fever, haemoptysis, weight loss, anxiety, depression and sleep disturbances,[4] among which depressive symptoms present a serious challenge. Prolonged treatment can result in the development of negative emotions,[5] and psychological problems such as anxiety and depressive symptoms may reduce medication compliance, which raises concerns about the continuity of treatment.[6] Depressive symptoms in chronic pulmonary disease have also been reported in chronic obstructive pulmonary disease (COPD) and pulmonary TB (PTB).[7,8] Moreover, treatment delays and poor compliance to treatment associated with depressive symptoms can lead to increased morbidity and mortality.[9]

It is not uncommon for NTM-PD to be accompanied by bronchiectatic changes. One study in patients with bronchiectasis (BE) reported a relationship between depressive symptoms and sleep disturbances, and the main factors associated with sleep disturbances were depressive symptoms, increased 24-h sputum production, and increased nocturnal cough. Of these, depressive symptoms had the most significant impact.[10] In people with NTM-PD, as in those with BE, there may be a need to prioritise research on depressive symptoms and sleep disturbances.

The purpose of the present study was to determine the prevalence of depressive symptoms in NTM-PD patients and to identify the factors that influence the development of depressive symptoms.

METHODS

Study populations (check—remove shading from all sub-headings)

From March 2016 to January 2021, we recruited 297 patients who met American Thoracic Society/American Infectious Diseases Society diagnostic criteria for NTM-PD,[2] who were referred to the Center for Respiratory Care and Rehabilitation, Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan, and consented to the study. Patients whose pulmonary

rehabilitation interventions were interrupted because of COVID-19 were excluded, which resulted in a total of 114 patients being included in the study (Figure 1). The study was approved by the Ethics Committee of Fukujuji Hospital, Tokyo, Japan (approval numbers: 19011, 19020).

Clinical and laboratory data

Clinical characteristics and the most recent laboratory data, such as age, sex, disease duration, body mass index (BMI) and blood data (total protein [TP], albumin [Alb], C-reactive protein [CRP], white blood cells [WBC], haemoglobin [Hb]) were collected from medical records.

Evaluation of spirometry data and imaging findings

Pulmonary function test (PFT) data were examined for percent predicted vital capacity (%VC), percent predicted forced vital capacity (%FVC), percent predicted forced expiratory volume in 1 sec (%FEV_1) and FEV_1/FVC. Imaging findings were classified into non-cavitary nodular bronchiectatic type, cavitary nodular bronchiectatic type, and fibrocavitary type based on high-resolution chest computed tomography findings.[11]

Depressive symptoms

We used the Center for Epidemiological Studies Depression (CES-D) Scale, which is a screening tool for depressive symptoms. The CES-D is a 20-item self-administered rating scale that was developed by the National Institute of Mental Health (Bethesda, MD, USA) to investigate the prevalence of depressive symptoms in the general population.[12] The maximum score is 60, and a score of ≥16 indicates the presence of clinical depressive symptoms. Similar to previous studies, we classified participants with a score of ≥16 as having depressive symptoms.

Dyspnoea

The severity of dyspnoea in daily life was assessed using the modified Medical Research Council (mMRC) dyspnoea scale. This scale ranges from 0 to 4, with a higher score indicating greater functional limitations due to dyspnoea.[13] We classified participants into three groups: 0, 1 and ≥2.[14]

Respiratory symptoms

We used the Japanese version of the COPD Assessment Test (CAT) to evaluate patients' cough symptoms. The CAT consists of eight items: cough, phlegm, chest tightness, breathlessness, activities, confidence, sleep and energy level. Each item is rated on a six-point scale from 0 to 5, yielding a total score ranging from 0 (best possible health status) to 40 (worst possible health status).[15] We used a cut-off score of 7 for the respiratory symptom items, and participants with a score of ≥7 were classified as the group with respiratory symptoms.[16]

HRQOL

The Leicester Cough Questionnaire (LCQ) was used to evaluate HRQOL. Permission to use the Japanese version of the LCQ was obtained from A Niimi and H Ogawa. The LCQ is a cough-specific HRQOL questionnaire that is easy to administer and has shown high validity for use in NTM-PD patients.[17] A higher LCQ score indicates better health status. Participants were classified into four groups based on the quartiles of the LCQ total score, which ranged from a low score, indicating poor health due to cough symptoms, to a high score, indicating good health (LCQ1, LCQ2, LCQ3 and LCQ4).[14]

Exercise capacity

Functional exercise capacity was assessed using the incremental shuttle walk test (ISWT), which was performed according to a standardised protocol.[18] The test is a threshold symptom field test conducted over a 10-m course with a voice signal indicating the walking speed. The test is performed continuously and in stages, with speed increasing every minute. The distance walked (ISWD) was recorded in meters and expressed as a percentage of the predicted data for Japanese people.[19] Participants with a percent predicted ISWD (%ISWD) value of <80% were classified as the decreased exercise capacity group.

Sleep disturbances

Sleep disturbances were assessed using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI), which is a questionnaire that assesses subjective sleep quality and symptoms of sleep disturbances over the past month. The PSQI consists of 18 questions and the total score ranges from 0 to 21 points, with higher scores indicating more disturbed sleep.[20] Similar to previous studies, we used a cut-off value of 5.5 points, and participants who scored above 5.5 points were classified into the group with sleep disturbances.

Statistical analysis

Statistical analysis was performed using SPSS software v25 (IBM Corp, Armonk, NY, USA). Data were expressed as means or medians for continuous variables and numbers (%) for categorical variables. The distribution of the data was assessed using the Shapiro-Wilk test. Comparisons of clinical variables (age, BMI, disease duration, TP, Alb, CRP, WBC, Hb, %VC, %FVC, %FEV_1, FEV_1/FVC, mMRC, %ISWD, CAT respiratory question score, LCQ score [physical, psychological, social and total scores] and PSQI score) between those with and without depressive symptoms classified by the CES-D score were performed using the Mann-Whitney *U*-test or unpaired *t*-test.

Pearson's χ^2 test was used to examine the associations among HRQOL, presence of sleep disturbances, presence of respiratory symptoms, dyspnoea severity, presence of decreased exercise capacity, radiological pattern, disease duration and presence of depressive symptoms. For disease duration, we compared two groups (≤3 years vs. >3 years of median disease duration). Stepwise binominal logistic regression analysis was performed to examine the predictors of depressive symptoms as determined using the CES-D. Variables that showed significant differences between those with presence or absence of depressive symptoms (i.e., disease duration, Alb, CRP, %VC, %FVC, presence of decreased exercise capacity, presence of sleep disturbances, presence of respiratory symptoms, dyspnoea severity and LCQ severity classification) were used in the model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and $P < 0.05$ was considered statistically significant.

RESULTS

Participant characteristics

The clinical characteristics and the most recent laboratory data of the participants obtained from the clinical records are shown in Table 1. Among all participants, 51% had restrictive impairment in pulmonary function based on %VC. Depressive symptoms were present in 37 patients (prevalence 33%). Mild to severe dyspnoea was present in 54 (47%) patients, 66 (58%) patients had respiratory symptoms, 39 (34%) patients had decreased exercise capacity and 62 (54%) patients had sleep disturbances (Table 2).

Correlation between CES-D score and clinical parameters

When clinical variables were compared between the two groups according to the presence of depressive symptoms, disease duration, Alb, CRP, %VC, %FVC, mMRC score, %ISWD, CAT respiratory question score, LCQ score and PSQI score were significantly poorer in the group with depressive symptoms (Table 3).

We also examined the relationship between sleep disturbances, dyspnoea, respiratory symptoms, HRQOL, exercise capacity, disease duration, imaging findings, and depressive symptoms (Tables 4). We found that the group with sleep disturbances (P = 0.018, adjusted residuals 2.4), the group with respiratory symptoms (P = 0.024, adjusted residuals 2.3), the group with moderate-to-severe breathlessness (P = 0.038, adjusted residuals 2.0), the group with decreased exercise capacity (P = 0.007, adjusted residuals 2.7), and those with disease duration exceeding 3 years (P = 0.028, adjusted residuals 2.2) had significantly higher proportions of patients with depressive symptoms. For HRQOL, the proportion of patients with depressive symptoms was significantly higher in the LCQ1 group ($P < 0.01$, adjusted residuals 3.8). There were no significant associations between the presence of depressive symptoms and imaging findings (P = 0.756).

Factors determining the onset of depressive symptoms in patients with NTM-PD

Stepwise binomial logistic regression analyses of the clinical parameters to analyse the independent factors affecting the presence of depressive symptoms (Table 5) showed that the LCQ1 group was identified as an independent variable for depressive symptoms by a factor of 6.8, followed by sleep disorder by a factor of 3.1.

DISCUSSION

This was a cross-sectional study aimed at determining the prevalence of depressive symptoms and identifying the factors influencing the presence or absence of depressive symptoms in NTM-PD patients for whom pulmonary rehabilitation was indicated at our hospital. In this study, disease duration, Alb, CRP, pulmonary function, dyspnoea, exercise capacity, respiratory symptoms, cough-related HRQOL and sleep disturbances were associated with depressive symptoms. The most influential factor for depressive symptoms was cough-related HRQOL deterioration. Moreover, we found that the worse the HRQOL, the higher the likelihood of depressive symptoms. After cough-related HRQOL, the presence of sleep disturbances revealed as the second most influential factor for the development of depressive symptoms. To the best

of our knowledge, this study is the first to evaluate the impact of HRQOL and sleep disturbances on depressive symptoms using the CES-D in NTM-PD patients.

Depression is a common disease and affects more than 264 million people worldwide.[21] In this study, 32.5% of patients were found to have depressive symptoms. This result is similar to that found in patients with chronic pulmonary diseases, such as PTB and COPD, which also have a high prevalence of depression. This study also showed that prolonged morbidity was associated with depressive symptoms, suggesting the need for early action to prevent the onset of these symptoms.

In this study, CRP and pulmonary function were associated with depressive symptoms. High serum CRP and low FEV_1 have been reported to be risk factors for the development of depressive symptoms in patients with COPD.[22]

In addition, 34.2% of participants had %ISWD <80%, and there was significantly lower exercise capacity in participants with depressive symptoms. Moreover, there was a significant relationship between HRQOL and depressive symptoms associated with respiratory symptoms and cough, and the most determining factor for depressive symptoms was low HRQOL related to cough. Furthermore, the lower the HRQOL, the greater the likelihood of depressive symptoms. An association between exercise capacity and HRQOL in patients with pulmonary *Mycobacterium avium* complex disease has been reported previously.[23] Cough symptoms have also been reported to be associated with both HRQOL[24] and depressive symptoms.[25] Similarly, we suggest that decreased mobility and cough symptoms in our participants may have contributed to decreased HRQOL, and this, in turn, may have resulted in the development of depressive symptoms.

We observed that sleep disturbances were associated with depressive symptoms. After cough-related HRQOL, the presence of sleep disturbances was the second greatest risk factor for the development of depressive symptoms. The review reported that sleep disturbance in COPD patients results from a combination of impaired ventilation and gas exchange, and respiratory symptoms, including cough and various systemic symptoms, and that sleep disturbance is associated with HRQOL, depressive and anxiety symptoms.[26] A meta-analysis showed that sleep disturbance is a risk factor for depression with an OR of 2.6.[27] Although the causal relationship between depressive symptoms and sleep disturbances cannot be determined because of the cross-sectional nature of this study, our findings suggest that interventions to improve sleep quality could help NTM-PD patients to control their symptoms of depression.

NTM-PD generally occurs in patients with pre-existing structural lung disease; in our study, more than half of patients had cavitary lesions and approximately 80% of patients had bronchiectatic lesions. Furthermore, several patients had both cavitary and bronchiectatic lesions.

Currently, chemotherapy is the primary treatment for NTM-PD;[2] however, previous studies have reported that chest physiotherapy is effective for reducing cough and sputum symptoms.[28] In addition, recent studies have demonstrated therapeutic effects of pulmonary rehabilitation in diseases similar to NTM-PD, such as BE and PTB. Exercise training for BE is associated with short-term improvements in exercise capacity, dyspnoea and fatigue, as well as fewer exacerbations over 12 months,[29] and air clearance techniques reduce respiratory symptoms related to coughing, which, in turn, improve HRQOL.[30] Similarly, in PTB, pulmonary rehabilitation plays an important role in the treatment of the sequelae of PTB,[31] and the effects of pulmonary rehabilitation intervention on depressive and anxiety symptoms have been shown in COPD patients.[32] Furthermore, previous studies have reported the effects of exercise therapy on sleep disturbances in middle-aged and older adults.[33]

Like COPD, NTM-PD is a chronic pulmonary disease and requires long-term treatment. We found that almost one third of patients with NTM-PD experienced depressive symptoms, and disease duration, cough symptoms, sleep disturbances and cough-related HRQOL were shown to be associated with these symptoms.

Taken together, our findings indicate that there is a clear need for pulmonary rehabilitation and pulmonary physiotherapy interventions for NTM-PD patients.

There are several limitations to our study. First, our study was a single-centre study, which may limit the generalisability of the results. In addition, we did not consider the differences in patient background and bacterial species. Due to the cross-sectional nature of this investigation, we were unable to assess the effect of pulmonary rehabilitation on depressed symptoms; further research is therefore required.

CONCLUSION

A high percentage of NTM-PD patients in this study had depressive symptoms; patients with depressive symptoms were found to have abnormalities across various clinical parameters. Cough symptoms, cough-related HRQOL and poor sleep quality were significantly associated with depressive symptoms, which suggests that pulmonary rehabilitation interventions aimed

at controlling cough and sputum and improving sleep quality are necessary to improve depressive symptoms.

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Table 1 Clinical characteristics of participants with NTM-PD (*n* = 114)

Variables	*n* (%)
Sex	
Female	106 (93.0)
Male	8 (7.0)
Age, years, median [IQR] (range)	64 [58–70] (28–80)
Disease duration,* years, median [IQR]	3 [1–9] (0–23)
Disease duration >3 years	51 (44.7)
Mycobacterium species	
M. avium	62 (54.4)
M. intracellurare	13 (11.4)
M. abscessus subsp. *abscessus*	14 (12.3)
M. abscessus subsp. *massiliense*	17 (14.9)
M. lentiflavum	2 (1.8)
M. avium + other NTM	6 (5.3)
Radiological pattern	
NC	50 (43.9)
C-NB	39 (34.2)
NB/FC	25 (21.9)
Comorbidity	
Bronchiectasis	33 (28.9)
COPD	1 (0.9)
BROS	1 (0.9)
Bronchial asthma	7 (6.1)
Interstitial pneumonia	2 (1.8)
Sequelae of PTB	4 (3.5)
Pulmonary aspergillosis	6 (5.3)

* Interval between disease diagnosis and time of pulmonary rehabilitation evaluation.

NTM-PD = non-tuberculous mycobacterial pulmonary disease; IQR = interquartile range; NC-NB = non-cavitary nodular bronchiectatic type; C-NB = cavitary nodular bronchiectatic type; FC = fibrocavitary type; COPD = chronic obstructive pulmonary disease; BROS = bronchiectasis rheumatoid overlap syndrome; PTB = pulmonary TB.

Table 2 Clinical data and questionnaire scores in participants with NTM-PD (*n* = 114)

Variables	Median [IQR] (range)
BMI, kg/m^2	18.3 [16.5–20.6] (12.8–25.3)
Laboratory data	
Total protein, g/dl	7.10 [6.74–7.43] (3.61–8.77)
Albumin, g/dl	3.96 [3.66–4.25] (2.82–4.79)
CRP, mg/dl	0.15 [0.06–0.85] (0.01–8.11)
WBC, 10^3/μl	54.4 [44.6–62.4] (23.3–115.2)
Haemoglobin, g/dl	12.70 [11.80–13.30] (6.40–15.80)
Pulmonary function test	
%VC, %	79.4 [62.3–90.7] (33.9–118.6)
%FVC, %	81.8 [65.4–95.7] (35.0–125.5)
%FEV_1, %	80.3 [63.4–94.9] (34.6–127.7)
FEV_1/FVC, %	80.0 [73.6–84.5] (53.5–100.0)
mMRC, *n* (%)	
0	60 (52.6)
1	42 (36.9)
≥2	12 (10.5)
CAT Respiratory Question score	8 [4.3–12.0] (0–18)
CAT Respiratory Question ≥7, *n* (%)	66 (57.9)
LCQ scores	
LCQ physical score	5.8 [4.8–6.5] (2.4–7.0)
LCQ psychological score	5.6 [4.3–6.4] (1.0–7.0)
LCQ social score	6.0 [4.8–7.0] (1.8–7.0)
LCQ total score	17.8 [13.3–19.6] (5.8–21.0)
LCQ1 score	25
LCQ2 score	27
LCQ3 score	29
LCQ4 score	33
%ISWD, %	87.5 [74.2–101.0] (28.6–142.9)
%ISWD < 80%, *n* (%)	39 (34.2)
CES-D score	12 [8–17] (0–50)
CES-D ≥ 16, *n* (%)	37 (32.5)
PSQI score	6 [4–8.8] (0–16)
PSQI > 5.5, *n* (%)	62 (54.4)

NTM-PD = non-tuberculous mycobacterial pulmonary disease; IQR = interquartile range; BMI = body mass index; CRP = C-reactive protein; WBC = white blood cell; VC = vital capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 sec; mMRC = modified Medical Research Council (dyspnoea scale); CAT = Chronic Obstructive Pulmonary Disease Assessment Test; LCQ = Leicester Cough Questionnaire; ISWD = incremental shuttle walk test

distance; CES-D = Center for Epidemiological Studies Depression Scale; PSQI = (Japanese version) Pittsburgh Sleep Quality Index.

Table 3 Relationships between participant characteristics and depressive symptoms*

	CES-D score		
	Depression (n = 37) Median or Mean	No depression (n = 77)	P value
Age, years**	63.0	64.0	0.559
BMI, kg/m^2***	18.0	18.8	0.165
Disease duration, years**	6.0	3.0	0.029
Total protein, g/dl**	7.12	7.09	0.892
Albumin, g/dl**	3.79	3.98	0.030
CRP, mg/dl**	0.43	0.13	0.028
WBC, 10^3/μl**	53.8	54.7	0.453
Haemoglobin, g/dl**	12.70	12.80	0.093
Pulmonary function test			
%VC, %***	70.0	79.5	0.014
%FVC, %***	74.6	83.4	0.034
%FEV_1, %***	74.6	82.2	0.078
FEV_1/FVC, %***	80.1	79.4	0.673
mMRC grade	1.00	0.00	0.013
%ISWD, %***	80.1	91.5	0.009
CAT Respiratory Question score**	9.0	7.0	0.022
LCQ score			
LCQ physical score**	5.0	6.1	0.000
LCQ psychological score**	4.3	5.9	0.000
LCQ social score**	5.3	6.5	0.001
LCQ total score**	14.8	18.4	0.000
PSQI score**	7	5	0.038

*Relationships were analysed using the Mann-Whitney U test or unpaired t-test, $P < 0.05$.

**Data are reported as the median.

***Data are reported as the mean.

CES-D = Center for Epidemiological Studies Depression Scale; BMI = body mass index; CRP = C-reactive protein; WBC = white blood cell; VC = vital capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 sec; mMRC = modified Medical Research Council (dyspnoea scale); ISWD = incremental shuttle walk test distance; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; LCQ = Leicester Cough Questionnaire; PSQI = (Japanese version) Pittsburgh Sleep Quality Index.

Table 4 Relationships between clinical parameters and depressive symptoms*

	Depressive symptoms in CES-D			
	Depression	No depression	Total	*P* value
PSQI				
Low sleep quality	26	36	62	
Normal	11	41	52	0.018
CAT Respiratory Question ≥7				
High respiratory symptom	27	39	66	
Low respiratory symptom	10	38	48	0.024
LCQ Severity Classification				
LCQ1	16	9	25	
LCQ2	8	19	27	
LCQ3	8	21	29	
LCQ4	5	28	33	0.001
mMRC				
0	14	46	60	
1	16	26	42	
≥ 2	7	5	12	0.038
Exercise capacity				
Decreased	19	20	39	
Normal	18	57	75	0.007
Disease duration, years				
≤3	15	48	63	
>3	22	29	51	0.028

*Relationships were assessed using Pearson's χ^2 test, adjusted residuals > 1.96, $P < 0.05$.

CES-D = Center for Epidemiological Studies Depression Scale; PSQI = (Japanese version) Pittsburgh Sleep Quality Index; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; LCQ = Leicester Cough Questionnaire; mMRC = modified Medical Research Council (dyspnoea scale).

Table 5 Clinical parameters influencing the presence of depressive symptoms in binomial logistic regression analysis*

Model	B†	SE	Wald	OR	95% CI	*P* value
Constant	−2.460	0.598	16.937	0.085		0.000
LCQ severity			8.041			0.045
LCQ1	1.916	0.708	7.322	6.792	1.696–27.204	0.007
LCQ2	0.762	0.672	1.286	2.143	0.574–8.005	0.257
LCQ3	0.518	0.659	0.618	1.679	0.461–6.113	0.432
CRP	0.246	0.149	2.713	1.278	0.954–1.712	0.100
PSQI > 5.5	1.147	0.482	5.654	3.147	1.223–8.098	0.017

*Results were calculated using stepwise binomial logistic regression analysis. $P < 0.05$.

†Partial regression coefficient.

SE = standard error; OR = odds ratio; CI = confidence interval; LCQ = Leicester Cough Questionnaire; CRP = C-reactive protein; PSQI = (Japanese version) Pittsburgh Sleep Quality Index.

FIGURE LEGEND

Figure Study flow diagram.