



Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

Ivan Čekerevac^{1,2,†}, Zorica Lazić^{1,2}, Ljiljana Novković^{1,2},
Marina Petrović^{1,2}, Vojislav Ćupurdija^{1,2}, Todorović Željko²,
Predrag Djurdjević^{2,3}, Aleksandra Ilić Dudvarski^{4,5}, Romana Suša^{1,2}

Characteristics of Chronic Obstructive Pulmonary Disease Patients with Depressive Disorder

Карактеристике болесника са хроничном опструктивном болешћу плућа
и депресивним поремећајем

¹Clinical Center of Kragujevac, Clinic for pulmonary diseases, Kragujevac, Serbia;

²University of Kragujevac, Faculty of medical science, Kragujevac, Serbia;

³Clinical Center of Kragujevac, Clinic for Hematology, Kragujevac, Serbia;

⁴University of Belgrade, School of Medicine, Belgrade, Serbia;

⁵Clinical Centre of Serbia, Clinic for Pulmonology, Belgrade, Serbia

Received: May 20, 2016

Revised: September 9, 2016

Accepted: October 11, 2016

Online First: February 28, 2017

DOI: 10.2298/SARH160520039C

* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal.

The date the article was made available online first will be carried over.

† **Correspondence to:**

Ivan Čekerevac

Čiče od Romanije 3/9, 34000 Kragujevac, Serbia

E-mail: icekerevac@gmail.com

Characteristics of Chronic Obstructive Pulmonary Disease Patients with Depressive Disorder

Карактеристике болесника са хроничном опструктивном болешћу плућа и депресивним поремећајем

SUMMARY

Introduction/Objective The origin of depressive disorder in Chronic Obstructive Pulmonary Disease (COPD) patients is still not completely known and probably is caused by various factors.

Objective The aim of this study is to establish the most important characteristics of COPD patients who have depressive disorder.

Methods Eighty nine COPD patients and 65 demographically-matched referents without COPD were included. All patients underwent lung function examination and gas exchange, nutritional status, dyspnoea level by mMRC scale and exercise tolerance were assessed also, as well as evaluation of depressive disorder by Hospital Scale for Anxiety and Depression (HADS) and Geriatrics Scale of Depression (GDS) and quality of life by St. George's Respiratory Questionnaire (SGRQ).

Results Depressive disorder has been found in 30.3% COPD patients evaluated by HADS and 25.3% COPD patients evaluated by GDS. When COPD subjects were stratified by Forced Expiratory Volume in 1 second (FEV_1) categorization, all subgroups were more likely to have depressive disorder, according to HADS and GDS, relative to referents with the OR highest (3.0; 95CI 1.6-4.9) among those with the $FEV_1 < 30\%$. COPD patients with depressive disorder (HADS) compared to non-depressed patients had (differences in mean values): higher intensity of smoking (6.9 (0.5-10.1)), lower body mass index (BMI) (-4.9 (-7.2-5.4)), lower value of $FEV_1\%$ (-8.3(-16.3- 1.2)), higher value of Total Lung Capacity (TLC%) (17.8 (2.3-28.4)), higher mMRC score (1.07 (-1-3.0), and higher SGRQ- total score 32.9 (24.1-40.3).

Conclusion Evaluation of depressive disorder should be considered in every patient with COPD, especially in patients with greater degree of airflow limitation and lung hyperinflation, dyspnoea level and malnourished.

Keywords: COPD; depressive disorder; quality of life

САЖЕТАК

Увод/Циљ Порекло депресивног поремећаја код болесника са хроничном опструктивном болешћу плућа (ХОБП) још увек није потпуно познато и вероватно је узроковано различитим факторима.

Циљ ове студије је да се утврде најважније карактеристике болесника са ХОБП који имају депресивни поремећај.

Метод рада У студију је укључено 89 болесника са ХОБП и 65 особа без ХОБП сличне старосне доби, као контролна група. Код свих са ХОБП урађено је испитивање плућне функције, процењен нутритивни статус, степен диспное помоћу *mMRC* скале, постојање депресивног поремећаја помоћу Болничке Скале за процену анксиозности и депресије (БСАД) и Геријатријске Скале за процену депресије (ГСД). Квалитет живота је процењен помоћу респираторног упитника болнице Свети Ђорђе (УРСЂ).

Резултати Депресивни поремећај је имало 30,3% болесника са ХОБП на основу БСАД и 25,3% болесника помоћу ГСД. Када смо болеснике са ХОБП поделили према тежини на основу вредности форсираног експиријумског волумена у првој секунди ($ФЕВ_1$), ризик за развој депресивног поремећаја, на основу БСАД и ГСД, био је значајно већи у свим групама са ХОБП у односу на контролну групу. Највећи ризик је био у групи са $ФЕВ_1 < 30\%$ (OR 3,0; 95CI 1,6-4,9). Пацијенти са ХОБП са депресивним поремећајем (БСАД) су имали у односу на остале пацијенте са ХОБП (разлика у средњим вредностима): значајно већи интензитет пушења 6,9 (0,5-10,1), мањи индекс телесне масе -4,9 (-7,2-5,4), мањи $ФЕВ_1\%$ - 8,3(-16,3- 1,2), већи тотални плућни капацитет (TLC%) 17,8 (2,3-28,4), већи *mMRC* скор 1,07 (-1-3,0) и укупни скор УРСЂ 32,9 (24,1-40,3).

Закључак Процену депресивног поремећаја треба урадити код свих болесника са ХОБП, а посебно код оних са тежом бронхопструкцијом, хиперинфлацијом плућа, већим степеном диспное и потхрањених.

Кључне речи: ХОБП; депресивни поремећај; квалитет живота

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a severe treatment-resistant pulmonary disease with varying impact on the patient's general physical condition, functioning, and quality of life. It is already known that dyspnoea and poor exercise tolerance are frequently observed in patients with COPD [1]. Aside from dyspnoea, mechanisms responsible for depressive disorder in COPD

patients are still not completely known and they are probably multifactorial [2]. Influence of aging, smoking and hypoxemia on brain function, most likely contribute to development of depression. The depressive symptoms in COPD are predominantly irritation, tearfulness, thoughtfulness, anxiety and too much worry. Therefore, it is difficult to recognise depressive disorders in patients with COPD, because symptoms and signs of depression are incorporated in primary pulmonary disease.

Different questionnaires are used to estimate depressive disorder in COPD. However these questionnaires are rather screening than diagnostic tools. In older patients these questionnaires can be less precise, because they contain items exploring somatic state in which patients can answer positive because of aging process, and not for depression existence, which can lead to overestimated prevalence of depression in COPD.

The aim of this study was to analyse characteristics of COPD patients who have depressive disorder and to establish potential influence of depression to quality of life in COPD patients.

METHODS

This study included 89 patients with COPD who were treated at Pulmonary Clinic in Clinical Centre Kragujevac from 2013 to 2015. We aimed to recruit 65 control subjects without COPD, who were matched to COPD subjects by age, gender. Protocol was approved by local Ethical Committee and informed consent was signed by every patient before inclusion into this study. Patients were evaluated in stable phase of disease (respiratory symptoms and therapy which has not been changed at least 4 weeks before examination).

Patients were excluded if they had any of the conditions where suboptimal lung function results are likely (chest or abdominal pain of any cause, dementia or confusion, etc)[3], who can not perform the 6 minute walking test, if they had a myocardial infarction 4 months before beginning of study, have non stabile angina pectoris or congestive heart insufficiency (New York Heart Association (NYHA) Functional Classification, classes III and IV). Evaluation of lung function was performed by spirometry (Master Screen Pneumo Jaeger Germany) and body plethysmography (Master Screen Body Jaeger Germany). Measurements followed criteria European Respiratory Society (ERS) and American Thoracic Society (ATS) for spirometric standardization and procedures [3]. Forced Expiratory Volume in 1 second (FEV_1) was expressed as the percentage of predicted values from European Community for Steel and Coal [4]. Patients were divided according to lung function into 3 groups: I group $FEV_1 \geq 50\%$, II group $30\% \leq FEV_1 < 50\%$, III group $FEV_1 < 30\%$ of predicted values. Evaluation of gas exchange was done by arterial gas analyzer (GEM Premier 3000, Instrumentation Laboratory). Dyspnoea level was determined by Modified Medical Research Council scale (mMRC scale). Exercise tolerance was determined by 6 Minutes Walking Test (6 MWT). Nutritional status was estimated by Body Mass Index (BMI). For evaluation of depressive disorder we used Hospital Scale of Anxiety and Depression (HADS) [5] and Geriatrics Score of Depression (GDS) [6]. HADS contains 7 questions for depression

and anxiety, where borderline disorder exists if the score is 8-10, and depressive disorder if probable if the score is ≥ 11 . The GDS scores 10-19 are graded as mild and 20-30 as serious. For evaluation of quality of life we used St. George's Respiratory Questionnaire (SGRQ).

In this study we used descriptive statistics - arithmetic means, standard deviations, percentages. For comparison of arithmetic's means in two independent groups of patients we used independent t-test, and ANOVA, as appropriate. To compare differences of measured variables in same patients at the beginning and the end of the study paired T-test was used. Correlation between two numeric features was tested by Pearson's coefficient of correlation. We used multivariate logistic regression to determine the adjusted odds ratio (OR).

RESULTS

A total of 89 COPD patients and 65 control subjects without COPD, who were analyzed between 2013 and 2015, satisfied the eligibility criteria for inclusion in the study. By design, patients with and without COPD were similar in age, gender, BMI (table 1). Among the 89 patients, 27

Table 1. Characteristics of COPD patients and referents.

	COPD patients (n= 89)	Referents (n=65)	<i>P</i>
Age, (yr) mean \pm SD	62.6 \pm 9.1	64.5 \pm 8.4	0.46
Male sex, n (%)	62 (69.6)	46 (70.7)	0.68
Never smoker, n (%)	9 (10.1)	38 (58.4)	
Ex-smoker n (%)	38 (42.7)	11 (17.0)	
Current smokers, n (%)	42 (47.2)	16 (24.6)	
BMI (mean \pm SD, kg/m ²)	27.6 \pm 7.8	26.4 \pm 6.9	0.59
Depressive symptoms (HADS-D), n(%)	27 (30.3)	8 (12.3)	<0.001
Depressive symptoms (GDS), n(%)	23 (25.8)	6 (9.2)	<0.001

Table 2. Airflow limitation and depression scores in COPD patients.

Depression score	FEV ₁ \geq 50% n=27	30% \leq FEV ₁ <50% n=35	FEV ₁ <30% n=27	<i>P</i>
GDS (mean \pm SD)	9.16 \pm 6.27	14.0 \pm 8.08	15.33 \pm 4.86	0.048
HADS-D (mean \pm SD)	5.58 \pm 4.05	9.75 \pm 5.01	10.26 \pm 4.63	0.028

Table 3. Prevalence and odds of depression (HADS) in patients with COPD compared to referents.

COPD patients	n	Depressive symptoms (HADS-D \geq 11)	OR (95% CI)
Referents	65	8 (12.3%)	1.0 (referent)

Table 4. Prevalence and odds of depression (GDS) in patients with COPD compared to referents.

COPD patients	n	Depressive symptoms (HADS-D \geq 11)	OR (95% CI)
Referents	65	6 (9.2%)	1.0 (referent)

patients (30.3%) were found to be depressed according to HADS score and 23 patients (25.8%) by GDS (Table 1). Compared with referents, patients with COPD had a greater prevalence of depressive disorder ($p < 0.001$ for all).

We analyzed the presence of depressive disorder using GDS and HADS in patients with different airflow limitation. The values of both scores differed significantly among the groups. (Table 2). In the group with FEV₁<30% we observed the highest average values for both scores. In this group the mean HADS depression score was 10.2 (SD 4.6) and score GDS was 15.3 (SD 4.8).

In addition, when COPD subjects were stratified by

FEV₁ categorization, all subgroups were more likely to have depressive disorder, according to HADS, relative to referents, with the OR highest (3.0, 95% CI 1.6–4.9) among those with the FEV₁<30% (table 3). Similar results were obtained in the group with the FEV₁<30% using GDS (OR 2.8, 95CI 1.5–6.0) (table 4). Results are from multivariate logistic regression adjusted for age, gender, body-mass index and smoking status (table 3,4).

We divided COPD patients into 2 groups based on HADS- depression score. Table 5 shows that depressed patients with depressive disorder had lower FEV₁, higher TLC expressed in % of predicted values, lower BMI, had more severe dyspnea and a shorter 6MWD as compared with non-

Table 5. HADS scores and COPD patients characteristics.

Subject Characteristics	Nondepressive disorder (HADS ≤10) n=62	Depressive disorder (HADS ≥11) n=27	Difference* in Means or Proportions (95% CI)
Age, yr, (mean ± SD)	64.1±8.1	63.2±9.2	-0.8 (-0.5-4.1)
BMI (kg/m ²), (mean± SD)	26.2±4.3	21.3±3.8	-4.9 (-7.2-5.4) [†]
Cumulative smoking, pack-years (mean±SD),	30.2±8.4	37.1 ± 9.6	6.9 (0.5-10.1)
FEV ₁ ,% of predicted value (mean±SD)	42.5±10.1	34.2±7.4	-8.3 (-16.3- 1.2) [†]
TLC, % of predicted value (mean ± SD)	101.2±15.4	118.1±19.6	17.8 (2.3-28.4) [†]
PaO ₂ (Kpa),(mean±SD)	8.5±2.2	8.1±1.9	-0.4 (-0.8- 1.2)
mMRC, (mean±SD)	1.0±1.0	2.07±0.75	1.07 (-1-3.0) [†]
6MWT (m), (mean±SD)	402.0±40.1	346.2±59.6	-56 (-124-26) [†]
SGRQ total and subscore, (mean±SD)			
SGRQ total score	43.3±16.7	76.6±10.5	32.9 (24.1-40.3) [†]
SGRQ symptom	36.2±9.4	69.4± 7.3	33.2 (25.3-38.9) [†]
SGRQ acitivity	49.8±11.5	81.7±8.4	32.4 (23.9-39.6) [†]
SGRQ impact	38.3±18.9	78.9±10.4	40.6 (21.7- 47.3) [†]
Long term oxygen therapy, n(%)	8 (12.9%)	6 (22.2%)	9.3% (2.1-11.5) [†]

*-Differences (95% CI) in mean values (for continuous variables) and in proportions (for categorical variables) between patients with and without psychological disorders

[†]-p-value < 0.05. Unpaired two-tailed t test was used for continuous variable (compare two means); x2 test was used for categorical variables (compare percentages).

depressed patients. Finally, they had worse HRQL (higher SGRQ total score and all subscores) compared to COPD patients without depressive disorder.

DISCUSSION

The main finding of this study is that depressive disorder identified in patients with stable COPD was significantly associated with lower FEV₁, higher TLC expressed in % of predicted values, lower BMI, more severe dyspnea, shorter 6MWD and worse HRQL. Compared with referents, patients with COPD had greater prevalence of depressive disorder. In the group with FEV₁ <30% we observed the highest average values for both scores for assessment of depression. When COPD

subjects were stratified by FEV₁ categorization, all subgroups were more likely to have depression relative to referents adjusted for age, gender, body-mass index and smoking status.

In our study, the incidence of depressive disorder in COPD patients was 30.3 % according to HADS. Data from clinical research show that in clinically stable patients with COPD prevalence of depression which requires medical treatment varies from 10-57% [7,8]. Such large difference between depression frequencies in patients with COPD can be explained by differences in size of examined population, especially difference between methodology and instruments and border line scores used for depression evaluation. We showed a higher prevalence of depressive disorder in COPD patients, according to HADS, compared to the control group, although there were no significant differences in age between the groups. The questionnaires for the assessment of depression in older people may be less accurate because they contain somatic compartments which can exist as part of the aging process, which may overestimate the prevalence of depression. Geriatric Depression Scale is specifically designed to overcome these limitations. Using this score, we have also found a higher frequency of depressive disorder (25.8%) compared to the control group, which could indicate that depression is not a consequence of age but of COPD itself.

Smoking increases the risk and severity of COPD, makes daily activities effortful and stressful, and increases the risk of depression in patients with COPD [9]. Smoking and depression have a bidirectional interaction. Depressed individuals are more likely to smoke, display higher risk to commence smoking, and find smoking cessation more difficult. Conversely, smokers are more likely to be depressed, which could be caused by activation of nicotinic acetylcholine receptors, or direct inflammatory effects of smoking [10]. When COPD subjects in our study were stratified by FEV₁ categorization, all subgroups of COPD patients were more likely to have depressive disorder relative to referents adjusted for smoking status. In study of Negi et al, there is no statistically significant relationship between the occurrence of depression and smoking status in COPD patients [11].

We found the highest frequency and scores for depression evaluation in COPD patients who had severe airflow limitation. Explanation for significant depressive disorder in more advanced stages in COPD can be expressive dyspnoea, decreased physical activity, worse exercise tolerance, frequent exacerbations which can lead to further physical activity decrease, social isolation, fear and depression[12]. In study of Tse et al, only the exacerbation frequencies in prior year and dyspnea level remained significant independent predictors for depression in COPD patients[13]. This study has shown that the COPD phenotype of frequent exacerbator represents significant independent predictor for depression in COPD patients.

In COPD patients with advanced stage, respiratory failure is common and treated with long-term oxygen therapy (LTOT). The influence of LTOT on depression symptoms in patients with COPD is less known. Verim et al. found that LTOT can decrease movements and social communications in patients with COPD, which can aggravate depression [14]. In our study the

percentage of patients who have used LTOT was significantly higher in the group with depressive disorder (22.2%).

In our study, group of COPD patients with depressive disorder had lower average value of BMI compared to non-depressed COPD patients. Malnutrition shows to be connected with muscle mass loss, leads to worse exercise tolerance, and possible social isolation and depressive disorders. Study by Negi et al. [11] showed that the incidence of depressive disorder is associated with lower BMI. On the other hand, Ghoddusi et al, had shown that higher depression score according to HADS is connected with higher BMI in patients with COPD[15]. It is considered that several factors contribute to psychiatric disorders in obese patients, such as social status, degree of obesity and negative perception about own body.

We found that depressed COPD patients had more severe dyspnea compared to non-depressed patients. The cause and relationship between psychological factors and dyspnea is, however, unclear. There are indications that dyspnea may induce psychiatric disorders while other studies indicate that psychological illnesses intensify with the subjective sensation of dyspnea [16].

Depressed COPD patients, according to HADS, in our study significantly worse tolerated physical effort compared to non-depressed. Kim et al.[17] found that depression had greater prognostic significance than FEV₁ value on level of decrease of physical activity in patients with COPD.

It is considered that depressive symptoms are correlated with psychical, physical and social functioning which determines quality of life [18]. We have found significant worsening in every area of quality of life in depressed COPD patients and the highest score was noted in area connected with physical activities (SGRQ-subscore activity). Depressive symptoms, controlling for COPD severity as well as sociodemographics and comorbidities, were strongly associated with worse respiratory-specific quality of life and worse overall physical quality of life, as reported by Omachi et al. [18]. In study of Blakemore et al. depression predicts quality of life in COPD patients, but this longitudinal analysis did not show the cause and effective relationships between depression and future quality of life [19].

There is evidence that treating depression in COPD patients improves quality of life [20]. Although this might include antidepressive pharmacotherapy, interventions such as pulmonary rehabilitation, which often includes psychosocial support, may also improve mood and reduce depressive symptoms. Because of the strong association between depressive symptoms and quality of life, further study regarding effective methods of treating depression in COPD appears clearly warranted.

Several study limitations must be considered. There were significantly more smokers in the group with COPD compared to control group. The study did not consider the impact of comorbidity in patients with COPD in the development of depressive disorder.

CONCLUSION

Depressive disorder is very common in COPD patients. It is not easy to diagnose depressive disorder in COPD patients because of the overlapping symptoms between COPD and depression. However, the seven-item HADS – depression subscale and GDS appear to be useful screening tools. Although the respiratory disorder is dominant somatic problem, emotional response on COPD significantly correlates to poor quality of life. Evaluation of depressive disorder should be considered in every patient with COPD, especially in patients with greater degree of airflow limitation and lung hyperinflation, dyspnoea level and malnourished.

REFERENCES:

1. Pumar M, Gray C, Walsh J, Yang I, Rolls T, Ward D. Anxiety and depression-Important psychological comorbidities of COPD. *Thorac Dis* 2014; 6(11): 1615–31.
2. Marsh S, Guck T. Anxiety and depression: Easing the burden in COPD patients. *J Fam Pract*. 2016; 65(4): 246–56
3. Miller M, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J* 2005; 26: 153–161;
4. Quanjer PH, Tammeling GJ, Cotes JE, et al. Symbols, abbreviations and units. Working Part Standardization of Lung Function Tests, European Community for Steel and Coal. *Eur Respir J* 1993; 6 (16): 85–100.
5. Zigmond A, Snaith R. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* 1983; 67(6): 361–70.
6. Yesavage J, Brink T, Rose T, Lum O, Huang V, Adey M, Leirer V. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982–83; 17(1): 37–49.
7. Zhang M, Ho R, Cheung M, Fu E, Mak A. Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. *Gen Hosp Psychiatry* 2011; 33(3): 217–23.
8. Schneider C, Jick S, Bothner U, Meier C. COPD and the risk of depression. *Chest* 2010; 137(4): 341–7.
9. Goodwin R, Lavoie K, Lemeshow A, Jenkins E, Brown S, Fedoronko D. Depression, anxiety, and COPD: The unexamined role of nicotine dependence. *Nicotine & Tobacco Research*. 2012; 14: 176–183.
10. Sinden N, Stockley R.. Systemic inflammation and comorbidity in COPD: a result of ‘overspill’ of inflammatory mediators from the lungs? Review of the evidence. *Thorax* 2010; 65: 930-6.
11. Negi H, Sarkar M, Raval A, Pandey K, Das P. Presence of depression & its risk factors in patients with chronic obstructive pulmonary disease. *Indian J Med Res* 2014; 139(3): 402–8.
12. van Manen J, Bindels P, Dekker F, IJzermans C, van der Zee J, Schadé E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax* 2002; 57: 412–6.
13. Tse H, Tseng C, Wong K, Ng L, Lai T, Yee K. Frequent Exacerbator: The Phenotype at Risk of Depressive Symptoms in Geriatric COPD Patients. *Lung*. 2016; 194(4): 665–73.
14. Balbo NA, Acosta MA, Kevorkof GV. Quality of life in patients with COPD and long term oxygen therapy. *Rev Fac Cien Med Univ Nac Cordoba* 2012; 69(2): 83–9.
15. Ghodduzi K, Aslani J, Farahani M, Assari S, Tavallaii S. Association of Depression with Body Mass Index in Patients with Chronic Obstructive Pulmonary Disease. *Tanaffos* 2007; 6(3): 47–53.
16. Neumana A, Gunnbjörnsdottira M, Tunsäterb A, Nyströmc L, Franklind K, Eva Norrmand, et al. Dyspnea in relation to symptoms of anxiety and depression: A prospective population study. *Respiratory Medicine* 2006; 100(10):1843–9.

17. Kim HF, Kunik ME, Molinari VA, Hillman SL, Lalani S, Orengo CA, et al. Functional impairment in COPD patients: the impact of anxiety and depression. *Psychosomatics* 2000; 41: 465–71.
18. Omachi T, Katz P, Yelin E, Gregorich S, Iribarren C, Blanc P, et al. Depression and Health-Related Quality of Life in Chronic Obstructive Pulmonary Disease. *Am J Med* 2009; 122(8): 778.e9–778.15.
19. Blakemore A, Dickens C, Guthrie E, Bower P, Kontopantelis E, Afzal C, et al. Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2014; 9: 501–512.
20. Simon G, Von Korff M, Lin E. Clinical and functional outcomes of depression treatment in patients with and without chronic medical illness. *Psychol Med*. 2005; 35(2): 271–9.

Paper accepted