

Dear Editor,

**Journal title:** World Journal of Psychiatry

**Manuscript NO:** 52321

**Title:** Risk factors for depression in patients with chronic obstructive pulmonary disease

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Thank you for the reviewers' comments concerning our manuscript. These comments are all valuable and have helped us to revise and improve our manuscript. Additionally, these comments have improved the significance of our research. We have made careful modifications to the original manuscript based on these comments and suggestions. All of the changes made to the manuscript are highlighted. In addition, we have consulted native English speakers for revisions before resubmitting. We hope the new manuscript will meet your journal's standard for publication. The manuscript has been improved according to the suggestions of reviewers:

1 The format has been updated.

2 Revisions have been made according to the suggestions of the reviewers.

Responses to the first peer-reviewer (Reviewer ID: 03029582)

(1) **Comment 1:** In Introduction section lines 9-11 "The most common...HADS". This statement is not justified from reference 13. Authors may use other studies to come to this conclusion e.g. Bock et al 2017, Eur Clin Resp J.

**Answer:** Thank you very much for your advice. HADS has been described as "one of the most commonly used instruments for depression in the literature" and the article you mentioned has been cited in revised version.

(1) **Comment 2:** There are some issues regarding patients' selection: did the authors study the files of the patients and then handed the HADS scale to them (after 2018)? Were they inpatients or outpatients? It is important to

clarify the time of the completion of the scale. Were there any participants already diagnosed with depressive disorder or history of such disorder? Was anyone under antidepressants, anxiolytic or other psychiatric medication?

**Answer:** Thank you very much for your advice. We studied the files of the patients carefully to ensure that all factors that might affect the outcome of the assessment were taken into account when the patients were included in this study. Standard treatment was given to each patient. Then the HADS scale was carried out by an experienced psychiatrist when patients were stable. All of patients were inpatients and were recruited from medical hospital wards. For patients already diagnosed with depressive disorder or history of such disorder, Only those with depression associated with COPD could be included in this study and the judgments were made by an experienced psychiatrist. Patients under antidepressants, anxiolytic or other psychiatric medication were excluded in order not to introduce bias as treatment options might have a potential impact on HADS scores.

(1) **Comment 3:** The means of HADs scores in “depressed” and “non-depressed” individuals should be reported (Table 2). If the difference is small then the clinical meaning of the results may be of reduced importance.

**Answer:** Thank you very much for your advice. The means of HADS scores in “depressed” and “non-depressed” individuals ( $9.18 \pm 1.27$  vs.  $3.93 \pm 1.72$ ,  $P < 0.05$ ) have been added in Table 2. The difference was obvious and had statistically significant difference between the 2 groups.

(1) **Comment 4:** The diagnosis of depression was relied mainly on HADS (patients section line 9). Please clarify. Were they examined and interviewed by a psychiatrist? Were they given any medication? HADS is not a tool for establishing diagnosis and this should be stressed in the limitation section. Moreover it has been argued that HADS is not a reliable method of separation between symptoms of anxiety and depression and should be abandoned as measure of depression in patients with somatic diseases (Norton et al 2013, J Psychosom Res; Burns et al 2014, J Psychosom Res) Rather it is proposed as a

measure of general distress. This should be clearly stressed in the limitations section.

**Answer:** Thank you very much for your advice. Patients were examined and interviewed by an experienced psychiatrist and the HADS scales were carried out when they were stable. For recruited patients, whether they needed antidepressant treatment was determined by the psychiatrist. However, for somatic diseases, standard treatment was given to each patient. There were four most common and best validated screening instruments available to assess depressive symptoms in patients with somatic illness, including Beck Depression Inventory (BDI), Geriatric depression scale (GDS), Centre for Epidemiological Studies scale on Depression (CES-D) and HADS. HADS has been validated and was widely used in many different groups of patients. The overall prevalence of clinically relevant depressive symptoms in COPD patients was surprisingly stable with a very low variation among the four different screening tools evaluated in the current review (Bock et al 2017, Eur Clin Resp J). However, some studies indicated that, although tapping into autonomic arousal and anhedonia as originally intended, the HADS was saturated by the presence of a general distress factor, due in part to its narrow focus on anhedonia and autonomic arousal, resulting in problems with distinguishing between anxiety and depression. This explained the finding that the HADS anxiety subscale might act equally as well as the depression subscale as a screening tool for depressive disorder (Mitchell et al 2010, Journal of affective disorders). For research purposes, the use of a summed HADS total score was recommended and appeared to provide an adequate estimate. In clinical practice, where it was important to distinguish between symptoms of anxiety and depression, the use of the HADS was not recommended. Due to its narrow focus the HADS had poor trait coverage and therefore brief tools with a broad coverage of symptoms of anxiety and depression might be more appropriate (Norton et al 2013, J Psychosom Res; Burns et al 2014, J Psychosom Res). The limitations of our study and the

articles you mentioned had been added in revised version.

Responses to the second peer-reviewer (Reviewer ID: 02548382)

(2) **Comment 1:** In your abstract, you name risk factors without saying whether high or low (i.e., low BMI, low FEV1, and high CAT). In Introduction, "somatic" hospitals makes no sense, you should put general hospitals.

**Answer:** Thank you very much for reviewing the manuscript carefully. Low BMI, low FEV1, and high CAT were independent risk factors for depression in patients with COPD. This has been added in the "abstract" part. We also replaced "somatic hospitals" with "general hospitals" in the revised version in "Introduction" part.

(2) **Comment 2:** In Materials and Methods, exclusion criteria, did you exclude major depressive disorder comorbidity? You should state this. You should also make clear that you investigate the symptom depression, not the disorder.

**Answer:** Thank you very much for your advice. For patients already diagnosed with depressive disorder or history of such disorder, only those with depression associated with COPD could be included in this study and the judgments were made by an experienced psychiatrist. This study mainly investigated the correlation between clinical parameters and the symptom depression, not the disorder. In the revised version, the description above has been added into "Introduction" and "Patients" part.

(2) **Comment 3:** In describing the CAT scores, you should state that lower scores indicate less severe symptoms, with higher symptoms indicating more severe COPD pictures.

**Answer:** Thank you very much for your advice. The description you mentioned has been added into "Discussion" part.

(2) **Comment 4:** In Results, "Patients' demographics are demonstrated (Table 1)" should read "Patients' demographics are shown in Table 1". Further on, "The results showed that low BMI (OR = 0.893,  $P < 0.05$ ), low FEV1 (OR = 0.325,  $P < 0.05$ ) and CAT score (OR = 1.111,  $P < 0.05$ ) were independent risk

factors for depression" should be "Low BMI (OR = 0.893,  $P < 0.05$ ), low FEV1 (OR = 0.325,  $P < 0.05$ ), and higher CAT score (OR = 1.111,  $P < 0.05$ ) were independent risk factors for depression".

**Answer:** Thank you very much for your advice. In the revised version, a more accurate description about results has been added into "Results" part.

(2) **Comment 5:** In Discussion, you say that depression occurs in 7-42% of persons with COPD, citing [11], a 2005 paper. Yet, you stated both in Abstract and Introduction that it ranges 10-42%, citing [7,8] of 2001 and 2003. You should render this point consistent. In the same sentence, "up to two times often than in persons without COPD" should be "almost twice as often than in persons without COPD".

**Answer:** Thank you for your advice. Actually, the incidence of depression in COPD patients changes over time. We have used a more accurate description in the "Discussion" part according to your advice.

(2) **Comment 6:** In the last paragraph, you state twice that you need larger samples and multicentre studies (which is not true, as it may create other problems with intersite differences) and longitudinal designs; choose just one.

**Answer:** Thank you for your advice. We deleted a duplicate statement in the revised version.

(2) **Comment 7:** In Tables, substitute  $>0.05$  with n.s., specifying below that it means not significant.

**Answer:** Thank you for your advice. We have substituted  $>0.05$  with n.s. in the revised version.

Responses to the third peer-reviewer (Reviewer ID: 03722832)

(3) **Comment 1:** Why does author say the sample size is small?

**Answer:** Thank you for your advice. The reported prevalence of depression in patients with COPD ranges from 10 to 42%. A study aimed to recognize anxiety and depression in persons with COPD recruited 1573 patients to complete the prescreening assessment (Kunik ME, et al 2005, Chest). Our study is a retrospective study with only 293 patients, so a prospective study

with a large sample size and multicenter analysis is needed to validate the results of this study.

Responses to the fourth peer-reviewer (Reviewer ID: 02476743)

(4) **Comment 1:** Please give the power of data collection

**Answer:** Thank you for your advice. The reported prevalence of depression in patients with COPD ranged from 10 to 42%, so the power of data collection was inappropriate to be calculated. However, we strictly adhered to the inclusion and exclusion criterias in order to reduce selection bias.

(4) **Comment 2:** Flow chart of selection of the study population is suggested.

**Answer:** Thank you for your advice. A flow chart including the selection of the study participants has been added in the revised version.

(4) **Comment 3:** A statement including the reference number of the ethics committee where appropriate should appear in the manuscript.

**Answer:** Thank you for your advice. This was a retrospective study with no involvement in clinical or animal research. The requirement for ethical permission was waived according to the statements regarding the application of ethical permission by the Ethical Committee of the First Affiliated Hospital of Nanchang University. The certification has been submitted with the revision.

(4) **Comment 4:** From the epidemiologic viewpoint, there are many confounding factors in the evidenced-based researches. How the authors deal with associated confounding factors in this study?

**Answer:** Thank you for your advice. We studied the files of the patients carefully to ensure that all factors that might affect the outcome of the assessment were taken into account when the patients were included in this study. Standard treatment was given to each patient with somatic diseases. For patients already diagnosed with depressive disorder or history of such disorder, only those with depression associated with COPD could be included in this study and the judgments were made by an experienced psychiatrist. Patients under antidepressants, anxiolytic or other psychiatric medication

were excluded in order not to introduce bias as treatment options might have a potential impact on HADS scores.

(4) **Comment 5:** Please show the exact p-value.

**Answer:** Thank you for your advice. The exact p-value less than 0.05 has been added in the revised manuscript. We substitute  $>0.05$  with n.s. according to another reviewer's comment.

(4) **Comment 6:** More discussion regarding the medical policy implications of their findings would be essential for the use of methodology in medical decision making.

**Answer:** Thank you for your advice. COPD patients are known to have greater disease burden (both physical and mental) than the general population. In addition to a generally high prevalence of depressive symptoms, our data also identified several risk factors for depression including Low BMI, low FEV1, and high CAT. However, Barriers to recognition exist at the provider and system levels. At the provider level, lack of interest/time and stereotypes may be barriers. At the system level, the poor integration of care for mental health into primary care settings may be an obstacle.

(4) **Comment 7:** Please consider the comparison with the other epidemiological studies in other areas using table so make clear the significance of this study.

**Answer:** Thank you for your advice. The purpose of our study is to investigate the correlation between clinical parameters and the symptom depression, and to identify some independent risk factors for definition of patients with COPD at 'high risk' of depression. We think the comparison with the other epidemiological studies in other areas using table is inappropriate. However, we compared the differences between our result and other studies in the discussion part.

(4) **Comment 8:** The authors should add the comments related to selection bias in this study to the perceived limitation subsection.

**Answer:** Thank you for your advice. Selection bias in this study has been clearly stressed in the limitations section.

Responses to the fifth peer-reviewer (Reviewer ID: 02445209)

(5) **Comment 1:** Patient demographics: You write on the household income type of the patients. You use general terms like "low income", "medium income" etc. It would be interesting if you state how much US dollars a low or medium income is, and how much the average income in the country is.

**Answer:** Thank you for your advice. We defined personal monthly income less than 5,000 RMB as low income, 5,000-10,000 RMB as medium income, and greater than 10,000 RMB as high income. According to data from the Chinese government, the average income in China was \$ 9,732 in 2018.

(5) **Comment 2:** Results: You have the title "The cutoff value, sensitivity, and specificity of BMI, FEV1, and CAT score for diagnosing bone metastasis". In my opinion, there should be "depression" and not "bone metastasis".

**Answer:** Thank you for your advice. We have changed "bone metastasis" to "depression".

(5) **Comment 3:** The last part starting with "In conclusion, based on the analysis..." - the information here is duplicate with informations you give in Discussion above. You should change the text "In conclusion..." to a non-duplicate text.

**Answer:** Thank you for your advice. We have modified some descriptions to reduce duplication.

(5) **Comment 4:** Table 1: Why is the number of males so big and the number of females so small? Are there any medical or other reasons?

**Answer:** Thank you for your advice. COPD is a tobacco-related disease. According to 2015 China Adult Tobacco Survey Report released by the Chinese Center for Disease Control and Prevention, more than half of adult men in China are smokers, and women overall have lower smoking rates. This phenomenon may explain why the majority of patients in this study are male.