Author’s response to reviews

Title: Associations of mood symptoms with NYHA functional classes in angina pectoris patients: A cross-sectional study

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Author’s response to reviews:

Dear Editor,

Thank you very much for your letter and the comments from the reviewers concerning our manuscript entitled “Associations of mood symptoms with NYHA functional classes in angina pectoris patients: A cross-sectional study” (ID: BPSY-D-18-00909). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper and the trace of the revision in retained. We truly hope that our manuscript could be reconsidered for publication on “BMC Psychiatry”.

The responses to the comments are as following:

Replies to Editor Comments:

1. Provide a revision with continuous line numbers.

Answer: We have added the line numbers in the revised version.
2. Figure 2 is missing.
Answer: We have re-uploaded Figure 2.

3. It is difficult to understand the use of a cardiomyopathy measure in CHD patients. Please justify the use of NYHA class for coronary patients when persons with cardiomyopathy were excluded.
Answer: We have added the inclusion and exclusion criteria in the Methods. Patient selection section. To make sure CHD to be the main diagnosis of patients, subjects with severe valvular heart disease, or severe cardiomyopathy unlikely caused by coronary stenosis, or other complications that might interfere the mechanism that symptoms were primarily resulted from the narrowed coronary were excluded,

4. Language revision required for “to be with bad mood” and “there are hardly two researches in which the outcomes”
Answer: The sentences are revised to ”... to be in a bad state of mind..” and “... there are hardly any researches adjusting with same variables to eliminate the influence of disease severity on outcomes” (Background, line 40 and line 45).

5. Methods – change “stands for” to “represents” when describing PHQ scores.
Answer: The sentence has been rewritten (Methods. Patient Health Questionnaire-9, line 112).

6. Clarify and justify your position that somatic and cognitive subscales were used as raw scores rather than converted to z-scores. It appears that after CFA the authors have summed items into factors based on fit indices, and the median of PHQ somatic items are likely to be higher than somatic items. In the total sample, the SD for the factors are nearly as large as the mean.
Answer: Yes, the somatic and cognitive subscale scores were used as raw scores. They were skewed and Wilcoxon rank-sum test was used for the comparisons. In the analysis with binary logistic model, somatic and cognitive were converted to dichotomous variables depending on whether the upper quartile was reached.
7. The analyses begs the question what is the GAD-7 comprised of? Is it possible to perform a CFA on its structure?

Answer: The 7 item of GAD-7 evaluate the severity of symptoms of (1) feeling nervous, (2) being unable to stop worrying, (3) worrying to much, (4) trouble relaxing, (5) being restless, (6) being irritable and (7) feeling afraid. It measures the severity of generalized anxiety disorders and also exhibits good convergent validity when compared with other commonly-used anxiety scales (Methods.Generalized anxiety disorder-7, line 147). Previous studies have shown the underlying structure of GAD-7 to be unidimension.

8. I don’t agree with the use of the term strict and lax, as the PHQ measures symptoms along a gradient of severity. Please use appropriate terms as mild and moderate depression symptoms.

Answer: We have modified this sentence (Methods.Statistical analysis.Part 1 line 187).

9. Table 2 and 3 require use of footnotes to help clarify to readers the terms clinical vs not clinical and dep v non-depressed or anx v non-anxious.

Answer: Corrections have been made in the revised version (Table 1 line 633, and Table sup2 line 696).

10. Please clarify the variable in Table 5 which produces OR but it is unclear from reading the table whether NYHA was used as a continuous or dichotomised variable.

Answer: We have added footnote in Table sup3 (Table sup3 line 713).
Replies to Silvia Cocchio (Reviewer 1):

Background

1. The sentence "We therefore postulated NYHA class to be a simple but comprehensive and efficient indicator of disease severity which can independently be utilized in analysis." should be shifted in the discussion section.

Answer: The sentence has been rewritten (Background line 55). In the discussion section, we have also stressed MYHA classes to be an integrated index reflecting patients’ physical status (Discussion line 297).

2. The sentence "Through all these analyses, we hoped to deepen the understanding of emotional symptoms in CHD patients" should be rewritten to explain the aim of the study better.

Answer: The sentence has been rewritten: "Through all these analyses, we hoped to reach a better understanding of mood symptoms in CHD patients and its change pattern along with worsening of physical condition. This may be of guiding significance for the timing of intervention and the selection of treatment” (Background line 63).

Methods

3. -Page 4, line 25: Please explain the modality of choosing of patient (inclusion and exclusion criteria) better. How do the authors define the first diagnosis of CHD? I understand that there are 443 people in the study only after seeing the Figure lecture but in the text it is very difficult to understand why. Please clarify the design of the study. Moreover, are the questionnaires administered validated in the Chinese language?

Answer: We have added the inclusion and exclusion criteria in the Methods. Patient selection section to better explain the modality of choosing patients. The term first diagnosis was misused and have been replaced by primary diagnosis in revised manuscript. All questionnaires administered have been validated in the Chinese and this has been stated in the revised version (Methods. Patient Health Questionnaire-9 line 118).
4. Page 5, line 1, Braunwald criteria: a citation must be included.

Answer: Corrections have been made in the revised version (Methods.Generalized Anxiety Disorder-7 line 118).

5. Page 5, line 11 (… in the definition of NYHA classes[23] sound a little vague, it does offer convenience for physicians the first time to get the whole picture..) The limits of this classification, if necessary, should be indicated in discussion section.

Answer: The section of Method.New York Heart Association classification has been simplified and this part has been deleted.

6. Page 5, line 15 New York Heart Association classification: please simplify the paragraph, it not necessary to indicate the researcher's names, but only the way it was classified.

Answer: Corrections have been made in the revised version (Method.New York Heart Association classification).

7. Page 6. "Somatic and cognitive depressive symptoms" paragraph should be simplified. Is not necessary to report all the results in the text, they are already in the Table (is clearer.).

Answer: Corrections have been made in the revised version (Method.Somatic and cognitive depressive symptoms).

8. Page 6, line 59. Re-define the anxiety severity score as reported in Table 4 better (I think that a non anxious person is 0-4, is correct?). Again, the categories used should be uniform within the text.

Answer: Yes, a non-anxious person has GAD-7 score 0-4. Throughout the study, patients were divided into both 4 categories for depression (normal, mild, moderate, moderately severe to severe) and for anxiety (normal, mild, moderate, severe). However, due to the small sample size, in univariate analyses, we has incorporated the latter two categories and the name was changed to “moderate to severe”. Corrections have been made in Table 2 and in Method.Patient Health Questionnaire-9 section in the revised version.
Results

Answer: The first sentence in page 7 of original manuscript explained how the coronary stenosis score was acquired. The score reflected the severity of coronary stenosis and was compared between groups. As a result, we think it may be inappropriate to shift it to the start of the method. The sentence on page 4 line 51 (original manuscript) has been modified into inclusion criteria. The rest has all been corrected in the revised version (Methods.Statistical analysis).

10.-Page 9, line 6 Please verify the percentage (i.e I think is 3.4% instead 4.5%)

The classification of depressed and anxiety subjects are not uniform throughout the paper. It should be better explained in the Methods section).

Answer: Yes, 3.4% is correct. We have corrected the mistake and unified the classification of depressed and anxious subjects (Methods.Patient Health Questionnaire-9).

10.-Page 10, line 1. This sentence is not clear. The authors are reporting the comparison of anxious people vs non-anxious people but the conclusions are refer to elevated anxiety. Could the authors explain better?

Answer: That mistake is caused by imprecise word use. The sentence have been rewritten (Results.Predictors of elevated depression and anxiety symptoms line 240).
Discussion

12. The discussion must be shorter and the grammar needs to revised to a better readability and intelligibility.

Answer: We have re-written the initial part of discussion and refined the content. Corrections have been made in the revised version (Discussion.).

13. Page 12, line 45. More details about similar studies should be provided to support the initial part of discussion. Another problem in this manuscript includes improper use of terminology. First, the term "clinical characteristics" in discussion must been better defined. What are the clinical variables used? After, "cognitive factor such as gender, education…" Should the authors explain why education and gender are considered as cognitive factors?

Answer: We have refined the content of the discussion. Clinical characteristics referred to Pro-BNP, EF, creatinine and so on, the indices associated with heart failure. Corrections have been make in Discussion section line 314. The term cognitive factor has been abandoned in the revision. The influence of education background on mood symptoms has been discussed.

14. Page 12, line 47. The sentence is not clear. Please rewrite it.

Answer: We have refined the content of the discussion and this part has been deleted.

Replies to Serdar Sever, MSc (Reviewer 2):

1 - How somatic and cognitive depressive symptoms scores are calculated and used in the analyses needs to be more explicit in the methods section.

Answer: To make the methods more explicit, we have modified the content in Methods.somatic and cognitive depressive symptoms section (line 143) and Methods.Statistical analysis.Part 3 (line 207) in the revised version.
2 - Why the cut-off point of 5 has been chosen for depressed and non-depressed categorization needs a rationale and should be supported with the literature. Besides, why there was a difference in the results between using the cut-off point of 10 and 5 in terms of statistical significance may need an explanation.

Answer: The rationale of why the cut-off point of 5 has been chosen has been explained in Methods.Patient Health Questionnaire-9 section (line 116) and Methods, Generalized Anxiety Disorder Scale-7 section (line 152) in the revised version. Why there was a difference in the results between using the cut-off point of 10 and 5 has been discussed in discussion section (paragraph 2).

3 - NYHA class was not associated with the levels of anxiety this needs to be emphasized in the results section.

Answer: Corrections have been made in the revised version (Results.NYHA classes and clinical characteristics line 248 and Results.Associations of NYHA classes with depression and anxiety line 284).

4 - Some results were overly stated, "... when comparing those not depressed with depressed patients, features that marked worse physical status became extraordinarily outstanding".

Answer: Corrections have been made in the revised version (Results.Predictors of elevated depression and anxiety symptoms line 233).

5 - Can the authors provide a rationale in the text for why they have separated the analyses for different AP types such as SAP and UAP? In the preliminary analyses, the type of angina pectoris was not significantly associated with anxiety and depression levels.

Answer: Actually, it was not until we finished analyzing the internal relationship of depression and anxiety in patients in different NYHA classes and found a difference between SAP and UAP (Figure 2), that we realized it may be meaningful to separately run logistic analyses for different AP types. As a result, we chose to exhibit the results of Figure 2 prior the result of logistic analyses.
Adjustments were only made for gender, age, BMI and education, other variables included in the preliminary analysis such as EF and creatinine clearance perhaps could also have an influence on the outcome.

Answer: Yes, other variables could have an influence on the outcome. In the preliminary analysis, we have also confirmed the EF, creatinine clearance to be associated with NYHA classes. To avoid the collinearity of independent variables, we thought that it may be better not to take EF and creatinine clearance into adjustment.

In the binary regression analysis in table 6 which cut-off point used for the dichotomous outcome variable whether it is 5 or 10 needs to be clear in the methods section.

Answer: Corrections have been made in the revised version (Methods. Statistical Analysis. Part 3 line 199)

In table 1 "TIL" needs to be changed to "TLI" please correct.

Answer: Corrections have been made in the revised version (Table sup1)

Please also indicate that GAD7 is 7 item scale scored between 0-21.

Answer: Corrections have been made in the revised version (Methods. Generalized Anxiety Disorder-7 line 149).

In the discussion section, the contribution of the findings was overstated " This study may help partly explain … why left ventricular assist device can help heart failure patients reduce anxiety and depression, why antidepressant is hardly to be efficient to improve prognosis in CHD patients…" which this study did not aim to assess for.

Answer: This part has been rewritten. Corrections have been made in the revised version (Discussion line 342)
11 - In the limitations, it can be mentioned that only some of the variables could have been adjusted for due to small sample size. Other variables such as EF and creatinine clearance perhaps could have an impact on the depression outcome as an association found in preliminary analyses.

Answer: Corrections have been made in the revised version (Discussion line 349). Similar to question 6, in consideration for avoid the collinearity of independent variables, we thought that it may be better not to take EF and creatinine clearance into adjustment.

12 - At the end of the paper, the authors concluded that the study findings "...lead to a better understanding of the mechanism of psychosomatic diseases..." Looking at the study results and what this study tested, this assumption is hard to be made.

Answer: This sentence has been rewritten: “... deeper rethink of the associations of mood symptoms with CHD and with the prognosis, lead to a better understanding of the mechanism of mood disorder in CHD patients and help to make the intervention more timely and efficient” (Conclusions line 388).

13 - There is a great inconsistency in the results for NYHA class II vs I comparison both for SAP and UAP patients this has not been mentioned in the results section. Again for NYHA class II vs I, there was not a significant association with somatic and cognitive depressive symptoms in all AP types.

Answer: We have added a description of this result in Results. Associations of NYHA classes with depression and anxiety section line 278 in the revised manuscript.

14 - Education has been adjusted and shown in table 6 but not in table 7. In the statistical analysis section, it has been stated that "All models were adjusted for age, sex, body mass index (BMI) and education background". If education has not been adjusted for in table 7 this should be noted.

Answer: Education has been adjusted for in table 7, but that part of results has not been exhibited in original manuscript in consideration for being concise. We has attached a new table 7 with complete data in the revised manuscript.
15 - One limitation is NYHA class IV group of patients could not be investigated separately due to small sample size. Perhaps this study may be unable to represent the seriously ill classification of NYHA IV. Another limitation is that this is a single centered study, therefore, generalisability of the study results needs careful consideration.

Answer: Corrections have been made in the revised version (Discussion paragraph 7).

Other revisions,

1 Table 1, 3 and 5 in original manuscript are regarded as supplementary material in the revised version. As a result, the number of tables has changed from Table 1, 3, 5 to Table sup1, 2, 3, and from Table 2, 4, 6, 7 to Table 1 ,2 ,3 ,4.

2 Guangdong General Hospital has been renamed to Guangdong Provincial People’s Hospital, as a result the name of affiliations need to be changed. Corrections have been made in the revised manuscript.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the framework of the paper. Changes we did not list here are marked in red in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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