70353-Answering Reviewers and Editors

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Observational Study

Studying the relationship between clinical features and mental health among late-onset myasthenia gravis patients

We gratefully thank the editor and all reviewers for their time to make their constructive remarks and useful suggestions, which has significantly raised the quality of the manuscript. Each suggested comment brought forward by the reviewers was accurately incorporated and considered. Below the comments of the reviewers are response point by point, and the revisions are indicated.

Reviewer #1:

Specific Comments to Authors:

1. In the core tip, the authors mentioned that "Psychopathological disorders have often been reported in MG patients. In this study, we found that late-onset MG was correlated with more severe impairments to mental state." What are psychopathological disorders that authors intended to describe? These two sentences are poorly written. Please revise the core tip. Please standardize the wording in the manuscript, for example, mental disorders, mental illness, psychopathological disorders. Also, the psychiatry terminology that used in the manuscript are inaccurate, for example, psychopathological disorders, psychiatric abnormalities, mental therapies.

Answer: Thank you for the constructive suggestions. The psychiatry terminology that used in the manuscript has been standardized. The core tip was also revised in the manuscript as follows:

Core Tip: "Mental disorders are the common comorbidities among myasthenia gravis (MG) patients in older age. In this study, we found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher scores on the MG Quality of Life 15 (QOL-15) questionnaire were an independent risk factor for anxiety and depression in patients with late-onset MG, this is the first report detailing the relationship

between clinical features and mental health in the subgroup of MG patients with late disease onset." (Lines 67-73)

2. It would be helpful if the authors could explain a little bit more in detail what the literature suggests concerning protective factors and risk factors for developing mental disorders in persons with myasthenia gravis. The significance of differentiating early-onset and late-onset myasthenia gravis in this study should be described in the Introduction. Why are the authors only seeking to identify this correlation in the group of late-onset patients as the authors mentioned in the last sentence of the Introduction?

Answer: The details about concerning protective factors and risk factors for developing mental disorders in persons with myasthenia gravis, the significance of differentiating early-onset and late-onset myasthenia gravis and related literature were added in the Introduction as follow:

Longer disease duration, severity of disease, and MG-induced respiratory failure may contribute to the increased rates of depression [16, 17]. Compromised swallowing and communication abilities, unpredictable and fluctuating nature of respiratory dysfunction suggests concerning risk factors for developing anxiety among MG patients [7, 16-18]. Fewer work restrictions could be protective factors for developing mental disorders in the limited observational studies [19]. Late-onset MG occurring in older adults is more difficult to manage mainly because of the multiple comorbidities [20, 21] and MG with late disease onset is on the rise in recent years [22]. Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms [23], awareness of the occurrence of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. (Lines 103-113)

References:

7 **Kulaksizoglu IB**. Mood and anxiety disorders in patients with myasthenia gravis: aetiology, diagnosis and treatment. *CNS Drugs* 2007; **21**: 473-481 [PMID: 17521227 DOI: 10.2165/00023210-200721060-00004]

16 **Ybarra MI**, Kummer A, Frota ER, Oliveira JT, Gomez RS, Teixeira AL. Psychiatric disorders in myasthenia gravis. *Arq Neuropsiquiatr* 2011; **69**: 176-179 [PMID: 21537555 DOI: 10.1590/s0004-282x2011000200006]

17 **Paul RH**, Cohen RA, Goldstein JM, Gilchrist JM. Severity of mood, self-evaluative, and vegetative symptoms of depression in myasthenia gravis. *J Neuropsychiatry Clin Neurosci* 2000; **12**: 499-501 [PMID: 11083168 DOI: 10.1176/jnp.12.4.499]

18 **Law C**, Flaherty CV, Bandyopadhyay S. A Review of Psychiatric Comorbidity in Myasthenia Gravis. *Cureus* 2020; **12**: e9184 [PMID: 32802619 DOI: 10.7759/cureus.9184]
19 **Blum S**, Lee D, Gillis D, McEniery DF, Reddel S, McCombe P. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci* 2015; **22**: 1164-1169 [PMID: 26021730 DOI: 10.1016/j.jocn.2015.01.022]
20 **Deymeer F**. Myasthenia gravis: MuSK MG, late-onset MG and ocular MG. *Acta Myol* 2020; **39**: 345-352 [PMID: 33458590 DOI: 10.36185/2532-1900-038]
21 **Aarli JA**. Myasthenia gravis in the elderly: Is it different? *Ann N Y Acad Sci* 2008; **1132**: 238-243 [PMID: 18567874 DOI: 10.1196/annals.1405.040]
22 **Alkhawajah NM**, Oger J. Late-onset myasthenia gravis: a review when incidence in older adults keeps increasing. *Muscle Nerve* 2013; **48**: 705-710 [PMID: 23893883 DOI: 10.1002/mus.23964]
23 **Gilhus NE**, Nacu A, Andersen JB, Owe JF. Myasthenia gravis and risks for comorbidity. *Eur J Neurol* 2015; **22**: 17-23 [PMID: 25354676 DOI: 10.1111/ene.12599]

3. For eligibility for the study, the authors mentioned that patients were excluded if had incomplete data. Please clarify why and what data will drive to this exclusion. The age restriction of this study is above 16 years old. What is the intention of the authors to have an age restriction for inclusion criteria and why the age is set at 16?

Answer: Some patients were reluctant to provide social-demographic data (i.e., marital status, career condition), and absence of quantitative results of serum antibody or other information (detailed in Table1) in the study were excluded as incomplete data. The age is set at 16 because persons above 16 years old shall be deemed to have full capacity for civil conduct in law, and had the greater ability to understand and cooperate during clinical scale-based evaluations independently.

4. In the methodology section, please describe more details about each measure that was applied in this study. The general characteristics of the questionnaires should be presented, such as the number of items, sub-scales (if any), how the items are measured (Type Likert scale), Reliability (i.e. Cronbach's alpha). Please cite the Chinese version right after the original version of the questionnaires.

Answer: The number of items of each measure, how the items are measured and reliability were added in the section of "Clinical data and scales" as follows: (Lines 147-165)

① The MGC scale is composed of 10 items that measure symptoms and signs of MG, with a maximum score of 50 points, the test-retest reliability coefficient

of the MGC was 98%, indicating excellent test-retest reliability. ② MG-ADL scale is composed of 8 questions, aims to assess disability of ocular (2 items), bulbar (3 items), respiratory (1 item), and limb (2 items), with each response graded from 0 (normal) to 3 (most severe), and the total score ranges from 0 to 24, reliability coefficient was 93.7, suggesting excellent test–retest reliability. ③ MG-QOL15 consists of 15 items: mobility (9 items), symptoms (3 items), general contentment (1 item), and emotional well-being (2 items), with each response graded from 0 (not at all) to 4 (very much), and total scores of up to 60 points, the Chinese MG-QOL15 had excellent internal consistency (Cronbach's $\alpha = 0.928$). ④ The HAM-A and HAM-D scales consist of 14 and 17 items, respectively, and were used to measure mental health symptoms. The total scores are 56 (for the HAM-A) and 53 (for the HAM-D), and total HAM-A scores were classified as no (<7), potential (7–13), assured (14–29), and severe (>29) anxiety. Total HAM-D scores were classified as no (<7), potential (7–17), assured (17–24), and severe (>24) depression, the Cronbach' s coefficient of them were larger than 0.8, indicating good internal consistency. The above questionnaires and scales were administered in the Chinese language, and are all reliable, valid, and widely used.

5. Please reconsider the arrangement of paragraphs of the "Groups" and "Clinical data and scales" sections. The information of the measures in the "Groups" section, i.e., cutoff points of questionnaires, should be merged into the "Clinical data and scales" section.

Answer: Considering groups were classified according to the scores of the HAM-A and HAMD scales, the "Clinical data and scales" section was arranged prior to the "Groups". Thanks for your suggestion, the information of cutoff points of questionnaires were merged into the "Clinical data and scales" section.

6. The authors used the median instead of the means for all the measures in the study to test their hypothesis. Did the authors detect severe skewness in their data?

Answer: Yes, we performed normal distribution analysis on the data, we found numerical data didn't conform to a normal distribution in our study, so continuous variables were reported as median and interquartile range (partial distribution) and analyzed by the Mann–Whitney U test, the content was in the "Statistical analysis" section. (Lines 183-184)

7. The authors stated that male patients may have coped better with their openness and resulted in less severe depression and anxiety than female patients. This explanation is quite a stigma. The prevalence of depression and anxiety is higher among females than males. There are many biological,

psychological, and social factors that contributed to this difference, particularly genetic loading.

Answer: Thank you for your important point. This viewpoint was cited from the below literature, Bogdan et.al [1] found the high score of depression and stress associated with openness, but this group of mostly men had the lowest relapse rate. An explanation may be that they had better coping mechanisms using a more problem-focused method of handling stressful experiences, and having more emotional inhibition (original article). According to your comment, the paragraph was revised in the manuscript as follows:

"The prevalence of depression and anxiety is higher among females than males, this difference in mental disorders is the result of a complex interplay between genetic, hormonal, and psychosocial factors. Some studies have shown females rather than males carrying the SS genotype of serotonin transporter gene-linked promoter region (5-HTTLPR) are easier to develop depressive symptoms under negative environment." (Lines 273-278)

Reference: [1] **Bogdan A**, Barnett C, Ali A, AlQwaifly M, Abraham A, Mannan S, et al. Prospective study of stress, depression and personality in myasthenia gravis relapses. Bmc Neurol 2020; 20: 261 [PMID: 32600271 DOI: 10.1186/s12883-020-01802-4]

8. Also, late-onset patients had higher BMI than early-onset. The correlation between obesity and depression is widely described. Please consider revising this paragraph.

Answer: Late-onset patients had higher BMI than early-onset. This could be related to older age, which contributes to reductions in physical activity and possibly susceptibility to the adverse effects of glucocorticoids. However, BMI was not statistically significantly associated with the incidence of depression or anxiety in MG patients after unadjusting or adjusting for possible confounds in our study. Above were be described in the Result and Discussion Section. (Lines 231-234 and lines 312-315)

9. Any contribution of the serum anti-AChR antibodies to depression and anxiety?

Answer: This is a great point. The serum anti-AChR antibodies were not statistically significantly associated with the incidence of depression or anxiety in MG patients in our study by the multivariate logistic regression analyses (Table 3). Whether the very autoimmune process such as the anti-AChR antibodies has any direct action on the central nervous system, leading to

psychological maladies, may be an interesting proposition to be pursued scientifically.

10. The authors mentioned that the sampling method restricted the conclusion of this study and healthy control is needed for future study. Why the healthy controls are needed if the authors only aimed to assess the correlation of clinical features and mental health among patients with late-onset myasthenia gravis? What is the limitation of the sampling method?

Answer: Late-onset MG patients had higher BMI, and were more prone to dyspnea than early-onset group in our study, this is a clear example of the need of a healthy control group: healthy people (irrespective of diseases) may get fatter getting older. Age maybe a risk factor on its own for breathing problems. So healthy control is needed for future study. (Lines 326-328)

11. "Our research showed that female patients with late-onset MG were more susceptible to mental health issues than their male counterparts" This statement is sweeping.

Answer: Thank you for the point. The sentence was revised as follow (Lines 335-336):

"Our research showed that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts."

12. In the attachment file, the name of the participants is not masked or blinded in the informed consent form. The authors should be more careful when providing this document.

Answer: You are right. We appreciate and accept the suggestion, we will be more careful when providing this document.

13. What is the significance of this study? As already known, the more severe impairment in daily function, regardless of the disease type, the more depressed or anxious a person will be. The novelty of this study is questionable.

Answer: Actually **in the Introduction section** (Lines 85-89 and lines 109-113), we clarified the significance of this study, "myasthenic symptoms of MG may overlap with somatic symptoms of depression and anxiety, comorbidities accompanied by mental and myasthenic symptoms may lead to misdiagnosis", "Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms, awareness of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome".

And MG patients were seldom assessed mental state by mental scales routinely, so little is known about the exact relationship between MG and mental disorders that often accompany it. More importantly, QOL-15 Scale is widely used in managing MG patients (including evaluating efficacy and prognosis) by neurologists. Our study showed that QOL-15 scores were independently associated with an increased risk of anxiety and depression when gender, age at onset, BMI, and anti-AChR antibody levels were adjusted for in a multivariate analysis. **How severe in daily function is required to cause anxiety or depression, we need a threshold to recognize it earlier.** Our data revealed that a QOL-15 score cut-off of 14.5 could be a good indicator for poor mental health in need of attention amongst late-onset MG patients **(In the Discussion section).** (Lines 299-306)

Reviewer #2:

Specific Comments to Authors: CRITERIA CHECKLIST FOR NEW MANUSCRIPT PEER-REVIEW 1. Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes, the title reflects the main subject/hypothesis of the manuscript. 2. Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes, the abstract summarizes and reflects the work described in the manuscript. 3. Key words. Do the key words reflect the focus of the manuscript? Yes, the key words reflect the focus of the manuscript. 4. Background. Does the manuscript adequately describe the background, present status and significance of the study? Yes, the manuscript adequately describe the background, present status and significance of the study. 5. Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes, the manuscript describe methods in adequate detail. 6. Results. Are the research objectives achieved by the experiments used in this study? Yes, the research objectives achieved by the experiments. What are the contributions that the study has made for research progress in this field? The study found that late-onset MG patients were more prone to dyspnea, had higher levels of serum anti-acetylcholine receptor antibodies, and had higher total scores on the MG Quality of Life 15 (QOL-15), HAM-D, and HAM-A questionnaires, than early-onset MG patients. The study revealed that QOL-15 score cut-off of 14.5 could be a good indicator for poor mental health in need of attention amongst late-onset MG patients. 7. Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Yes, the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Yes, the findings and their applicability/relevance to the literature stated in a clear and definite manner. Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical

practice sufficiently? Yes, the discussion is accurate. 8. Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Yes the figures, diagrams and tables are sufficient, good quality and appropriately illustrative of the paper contents. Do figures require labeling with arrows, asterisks etc., better legends? Yes, the figures require labeling with arrows, asterisks etc. 9. Biostatistics. Does the manuscript meet the requirements of biostatistics? Yes, the manuscript meet the requirements of biostatistics, because this research is a quantitative research. 10 Units. Does the manuscript meet the requirements of use of SI units? Yes, the manuscript meet the requirements of use of SI units. 11. References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? No, most of the references are above the last 5 years. Does the author self-cite, omit, incorrectly cite and/or over-cite references? Yes, the author self-cite. 12. Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Yes, the manuscript well, concisely and coherently organized and presented. Is the style, language and grammar accurate and appropriate? Yes, the style, language and grammar accurate and appropriate. 13. Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? Yes, the author prepares the manuscript according to the appropriate research methods and reporting. 14. Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? No, the manuscript didn't meet the requirements of ethics.

Answer: Thank you for your important point. This study was approved by the ethics committee of the First Affiliated Hospital of the Sun Yat-sen University. **(In the attachment files)**

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This manuscript explored for the relationship between clinical features and the mental health symptoms within late-onset MG patients, and concluded that higher QOL-15 scores were a risk factor for anxiety and depression in patients with late-onset MG, and female patients with late -onset MG were more likely to have anxiety and depression than their male counterparts. Please revise the core tip, standardize the wording in the manuscript, for example, mental disorders, mental illness, psychopathological disorders and psychiatry terminology, and explain more in detail what the literature suggests concerning protective factors and risk factors for developing mental disorders in persons with The general information selected for myasthenia gravis. needs to be further clarified.

Answer: Thank you for these constructive suggestions. The psychiatry terminology that used in the manuscript has been standardized. What the literature suggests concerning protective factors and risk factors for developing mental disorders in persons with myasthenia gravis were added in the revised manuscript. The details above and related literature were added in the Introduction and Reference as follows: (Lines 103-108)

Longer disease duration, severity of disease, and MG-induced respiratory failure may contribute to the increased rates of depression [16, 17]. Compromised swallowing and communication abilities, unpredictable and fluctuating nature of respiratory dysfunction suggests concerning risk factors for developing anxiety among MG patients [7, 16-18]. Fewer work restrictions could be protective factors for developing mental disorders in the limited observational studies [19].

References:

7 **Kulaksizoglu IB**. Mood and anxiety disorders in patients with myasthenia gravis: aetiology, diagnosis and treatment. *CNS Drugs* 2007; **21**: 473-481 [PMID: 17521227 DOI: 10.2165/00023210-200721060-00004]

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18 **Law C**, Flaherty CV, Bandyopadhyay S. A Review of Psychiatric Comorbidity in Myasthenia Gravis. *Cureus* 2020; **12**: e9184 [PMID: 32802619 DOI: 10.7759/cureus.9184]

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(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Answer: Thank you for your important points. The figures were organized into a single PowerPoint file and we provide standard three-line tables in the article. **(In the attachment files)**