

Answering Reviewers

First, I would like to thank the two reviewers for taking the time to review the manuscript and providing thoughtful comments that helped me improve the article. The followings are my responses to the issues raised in the peer review report.

Answer to Reviewer #1 (Number ID 05372534):

1. The title is long to be slightly shorter.

My response: Article title has been shortened to 12 words or less.

2. The abstract should be summarized. 400 words is a lot.

My response: Abstract has been streamlined.

Answer to Reviewer #2 (Number ID 01589311):

Major points:

- 1) The text presenting conclusions and future directions is logical, but it lacks a more deep insight into the differences found by this study, compared to findings of other studies, from different regions. What should be the explanation for the higher prevalence of fatigue in Chinese patients? Is it possible that the diagnosis is still done only late in the course of the disease? How adequately are patients currently treated in that region?

My response: Our research is the first to study the fatigue risk factors of IBD in China, which has not been reported in other parts of China, so it is impossible to make a comparison. As for the comparison with foreign-related research, in the discussion part, we not only analyze the same risk factors in detail but also analyze different risk factors. In addition, according to the opinions of the review expert, we conducted a more in-depth analysis of the differences found in the study in the discussion section. Our study found that the prevalence of fatigue in patients with IBD in Eastern China was 60.77%. In a prospective study performed at a high-volume tertiary IBD center in the USA, the prevalence of fatigue in patients with IBD was 62.9%. An observational study in Norway found that 50% of patients newly diagnosed with IBD have fatigue. A multicenter study in Spain found that fatigue occurs in 41% of patients with IBD. One of the explanations for such a high prevalence of fatigue in patients with IBD in Eastern China may be due to psychiatric comorbidity, like depression and anxiety. Further analysis found that psychiatric comorbidity in patients with IBD in Eastern China may be due

to limited therapeutic drug options, which was determined by the special medical conditions in China. In this study, patients with IBD at all stages and course of disease were included, not only those in the later course of the disease. The treatment methods of the patients included in this study followed the consensus on the diagnosis and treatment of inflammatory bowel disease in China (Beijing, 2018), which was the latest and most authoritative guide to IBD in China. As a result, these patients have received regular, correct, and adequate treatment.

- 2) When authors state that fatigue is detected even in patients who are in remission, is it possible that some degree of subclinical activity might be present? Do authors think that this could be related to persistent endoscopic or histological activity? How accurate can be clinical and simple laboratory evaluation regarding the inflammatory activity of IBD?

My response: For some CD patients in remission, it is difficult to determine whether they have subclinical activity by mucosal histology. Some CD patients in remission, whose disease location is in the small intestine, refuse to undergo capsule endoscopy and small intestinal endoscopy because these two examinations are expensive in China and small intestinal endoscopy brings great pain to them. Patient compliance and acceptance are still difficult problems that need to be overcome in the course of our research. In addition, capsule endoscopy has the defect that the mucous membrane cannot be biopsied. Mucosal histology also cannot be evaluated in CD patients whose lesions are located in the small intestine and cannot be biopsied by small intestinal endoscopy. Therefore, these patients can only evaluate their disease activity by their clinical symptoms combined with laboratory examination. In our study, the methods of assessing disease activity are recommended by domestic and foreign guidelines for IBD, which have been verified for more than 60 years. Therefore, they have high credibility and science and are widely used in clinical and scientific research. Moreover, clinical and laboratory evaluation are also important indicators to evaluate disease activity.

- 3) This study presents data on IBD-related surgery and its association as a risk factor for fatigue. Nevertheless, it would be important to show the numbers of surgeries for Crohn's disease (CD) and ulcerative colitis (UC), separately. This could be performed in Table 1, presenting demographics and clinical features. If possible, present all data separately (a column for CD and another one for UC). The Table should continue to be descriptive. There is no point on

comparing CD versus UC, as subgroup analysis with small numbers would render data difficult to interpret.

My response: Table 1 has been modified to show all data separately (a column for CD and another one for UC), including the number of surgeries for CD and UC.

Minor comments:

- 1) In some parts of the manuscript, the authors present abbreviations prior to the definitions (in parenthesis). This occurs even in the abstract.

My response: The abbreviations in the article have been standardized.

- 2) Results: a. 1st paragraph: “Regarding the duration of disease, participants reported a median of 5 (IQR, 2-12).” Did authors mean 5 years? b. Figures 1, 3 and 5: What are the small inserts within the graphs? Please, explain in the Figure and in their respective legends, what are the large and the small graphs. c. Did authors use another software to build the graphs of Figures 1, 3 and 5? In the section regarding statistical analysis, they mention SPSS version 24. Did authors use SPSS to build those graphs, too?

My response: a. The median course of disease in patients with CD is 5.5 years, and that in patients with UC is 5 years, which are shown in Table 1.

b. The naming of Figures 3 and 5 has been changed to Figures 2 and 4. The small inserts within the graphs in Figures 1 and 4 enlarge the scores of the five subscales of MFI-20 (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) in the IBD patients. The small insert within the graphs in Figure 2 enlarges the scores of the four domains of SIBDQ (bowel symptoms, systemic symptoms, emotional function, and social function) in the IBD patients. The meaning of the small inserts within the graphs in Figures 1, 2 and 4 have been explained in the legend.

c. Figures 1,2 and 4 were created by GraphPad Prism 8, not through SPSS.

- 3) In Article highlights, Research perspectives: a. The investigators recommend “Clinicians and patients should be aware of and prevent the incidence of fatigue.” How do authors think that such action should be performed? Do they think that the treatment of fatigue should be a therapeutic goal itself? Or it should be seen in the context of anemia, depression, anxiety, and etc.? Or perhaps the presence of fatigue, as a somewhat underrated symptom, should be more actively investigated and understood as a reflection of inadequate treatment?

My response: There is a two-way relationship between fatigue and disease symptoms. Fatigue will aggravate the clinical symptoms of IBD patients, conversely, disease activities of patients will also aggravate fatigue. Therefore, early identification of fatigue in patients with IBD is very important for the treatment and prognosis of IBD. For IBD patients with fatigue caused by insufficient treatment, adequate treatment should be given first. If fatigue still occurs, consider whether there are risk factors for fatigue and correct them.

Answer to Reviewer #3 (Number ID 05451950):

1. Introduction may be shorter, brief information is better for not to confuse readers.

My response: The introduction has been streamlined.

2. Prevalence of fatigue and its relationship with quality of life and work productivity in general population would be written briefly.

My response: This study mainly focused on the fatigue of patients with IBD, so there was no study on the prevalence of fatigue of normal people and its relationship with quality of life and work efficiency. However, recent domestic meta-analysis shows that the prevalence of fatigue in the Chinese population is 12.54% [1]. In healthy people, the relationship between fatigue and quality of life and work efficiency has not been reported in China.

[1] WU Qiao, GAO Jing, BAI Dingxi, ZHONG Yizhu, YANG Zhi, JIANG Xiaolin, ZHENG Yuping. Prevalence of chronic fatigue syndrome in China: a Meta-analysis. Youjiang Medical Journal 2020; 48(10): 727-735. [DOI 10.3969/j.issn.1003-1383.2020.10.002]

3. Hypoproteinemia and hypoalbuminemia are different terms, please correct.

My response: Hypoalbuminemia has been corrected.

4. Please determine laboratory cut-offs according to international guidelines, instead of laboratory reference range.

My response: The range of laboratory indicators has been revised in accordance with the guidelines.

5. Please define the criteria of active disease: "A total of 51.45% of IBD patients were in the active phase of the disease".

My response: Disease activity was measured with the Harvey-Bradshaw Activity Index for Crohn's disease (increase to ≥ 5 points) and the partial Mayo Score for UC (increase to ≥ 2 points).

6. Assessing psychopathologic disorders like depression, anxiety etc. with self-report questionnaires provides more subjective data. Assessing the psychiatric disorders with a more objective and standardized method (such as SCID) would increase the quality of the design.

My response: In my future research, I will consider using a more objective and standardized method to assess mental disorders.

7. Absence of a homogeneous control group to compare the variables with IBD patients is decreasing the quality of the study. A control group should be enrolled to assess the results more accurately.

My response: This study mainly focused on the fatigue of patients with IBD, so there was no study on the fatigue of normal people. However, recent domestic meta-analysis shows that the prevalence of fatigue in the Chinese population is 12.54% [1]. In my future research, I will consider recruiting a control group and comparing the variables with IBD patients in order to evaluate the results more accurately.

[1] WU Qiao, GAO Jing, BAI Dingxi, ZHONG Yizhu, YANG Zhi, JIANG Xiaolin, ZHENG Yuping. Prevalence of chronic fatigue syndrome in China: a Meta-analysis. Youjiang Medical Journal 2020; 48(10): 727-735. [DOI 10.3969/j.issn.1003-1383.2020.10.002]