

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "The predictive value of alarm symptoms in patients with Rome IV dyspepsia: a cross-sectional study" (ID: 56199). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The responds to the reviewers' comments are as following:

Reviewer #1:

We thank Reviewer #1 for the constructive and insightful suggestions. Below is our point-by-point response to the reviewer's comments.

Reviewer's comment: Anemia is treated with one of alarm symptoms in this study. What is the definition of anemia? Is anemia one of subjective symptom or abnormal value of Hb or the numbers of red blood cell? Authors should describe clearly about this point in method.

Response:

We thank the reviewer for pointing this out, and the comments are very helpful for us to improve our paper. Anemia is defined as an abnormal value of hemoglobin (hemoglobin < 130 g/L for men and hemoglobin < 120 g/L for women). We have added this to the methods section of our revised manuscript.

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Reviewer's comment: Sixty-five organic dyspepsia patients are symptoms relieved after HP eradication. How is the rate of HP infection in functional dyspepsia? How many patients include after HP eradication in functional dyspepsia? These points should be shown.

Response:

Thank you very much for the instructive suggestions. Hp-associated dyspepsia was defined as the relief of dyspepsia symptoms after eradication of Hp. And Hp-associated dyspepsia was classified as organic dyspepsia in Rome IV criteria [1]. In the inclusion criteria of this article, Hp test were conducted within the last six months (to ensure that these diagnostic tests were conducted after the onset of dyspeptic symptoms), we counted the number of patients with relief of dyspeptic symptoms after eradication of Hp at the time of data collection. Since our study mainly compared FD with organic dyspepsia and FD with organic upper GI diseases, we only counted the number of patients with relief of dyspeptic symptoms after eradication of Hp (Hp-associated dyspepsia) as a part of organic dyspepsia, but did not further count the number of patients with no relief of dyspeptic symptoms after eradication of Hp and the rate of Hp infection in FD. This is a limitation of our study. Kim et al. showed that the rate of Hp infection in FD was 56.3% based on the Rome III criteria [2], and in the study conducted by Sodhi et al., the rate of Hp infection in FD was 58% based on the Rome II criteria [3]. To our knowledge, no study has been conducted to assess the prevalence of Hp in FD after excluding Hp-associated dyspepsia based on the Rome IV criteria, this is a good research direction. In our next

multicenter and larger sample study, we will further explore this based on the Rome IV criteria. We have added this to the discussion section of our revised manuscript.

See revised manuscript Page 15, Line 1115-1123

- 1 Stanghellini V, Chan Francis KL, Hasler WL et al. Gastrointestinal Disorders. *Gastroenterology* 2016; 150: 1380-1392.
- 2 Kim SE, Park YS, Kim N et al. Effect of Helicobacter pylori Eradication on Functional Dyspepsia. *J Neurogastroenterol Motil* 2013; 19: 233-243.
- 3 Sodhi JS, Javid G, Zargar SA et al. Prevalence of Helicobacter pylori infection and the effect of its eradication on symptoms of functional dyspepsia in Kashmir, India. *J Gastroenterol Hepatol* 2013; 28: 808-813.

Reviewer's comment: What kind of abnormal routine blood tests are there in this study? Are all abnormal routine blood tests associated with dyspeptic symptoms? The authors should explain about this point in discussion.

Response:

Thanks for the reviewer's constructive advice. FD is a type of dyspepsia that has no organic, metabolic, or systemic disease that is likely to explain its symptoms, but only a few studies have rigorously diagnosed functional dyspepsia by laboratory examination, epigastric ultrasound, and upper gastrointestinal endoscopy to exclude related diseases [4, 5]. In this study, FD was diagnosed strictly by laboratory examination, abdominal ultrasound, and upper gastrointestinal endoscopy. In the exclusion criteria of our study, we excluded patients with liver dysfunction, diabetes mellitus, thyroid dysfunction and other organic or metabolic diseases which were treated primarily as non-dyspeptic diseases in clinical practice. In addition, severe abnormalities of white blood cells or platelets were considered as having other serious diseases and were excluded. Mild abnormalities of white blood cells or platelets were considered as normal results without causing any symptoms. Therefore, abnormal routine blood tests refer to anemia in this study.

In this cross-sectional study, we were unable to determine whether dyspeptic symptoms were relieved after treatment for anemia. As anemia is likely to explain dyspeptic symptoms, and FD was diagnosed strictly by laboratory examination, abdominal ultrasound, and upper gastrointestinal endoscopy in this study, so all anemia was considered organic disease regardless of whether it was proven actually associated with dyspeptic symptoms. In this paper, we not only compare FD with organic dyspepsia, but also compare FD with organic upper gastrointestinal diseases to make the results more accurate. We have added this to the discussion section of our revised manuscript.

See revised manuscript Page 13, Line 1018-1032

- 4 Holtmann G, Talley NJ, Liebrechts T et al. A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006; 354(8): 832-840
- 5 Von Arnim U, Peitz U, Vinson B et al. STW 5, a phytopharmakon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007; 102(6): 1268-1275

We also have made some changes in the manuscript according to the editor's requirements, and the modified part can be easily identified because we adopted the Microsoft Word review mode. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. If some contents or formats cannot meet the requirements, we are very willing to revise our manuscript once again.

Thank you very much for your consideration and time.

Yours sincerely,

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