Dear Editors and Reviewers:
Thanks for your letter and for the reviewers' comments concerning our manuscript entitled "Clinically significant endoscopic findings in patients of dyspepsia with no warning symptoms" (Manuscript NO.: 62352, Observational Study). The 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 revised portion will be listed and explained in the following responses. The main corrections in the paper and the responses to the reviewer's comments are as flowing:
Response to the reviewer's comment:
Reviewer #1:
1. A1) In accordance with the STROBE guideline, please revise the title to indicate the study's design (e.g. cross-sectional study, observational study).
Response: We have changed the title to "Clinically significant endoscopic findings in patients of dyspepsia with no warning symptoms: A cross-sectional study".

2. A5.1) In accordance with item 6 of the STROBE guideline, please explain how and when patients were identified and included in the study.
Response: As the Reviewer suggested that the first sentence of the Methods section has now been revised to "This cross-sectional study included dyspeptic patients with no warning symptoms who met the inclusion and exclusion criteria at the First Affiliated Hospital, Zhejiang Chinese Medical University from April 2018 to February 2019".

3. A5.2) Item 9 of the STROBE guideline specifies: "Describe any efforts to address potential sources of bias". Do the authors have any specific comments in relation to this?
Response: First of all, we developed strict exclusion criteria: for example, we did not exclude patients with reflux and heartburn, which are typical symptoms of reflux esophagitis but not warning symptoms. This brought the percentage of reflux esophagitis we detected closer to the true situation. We also excluded medical histories and drugs that might be associated with important findings on gastroscopy. Secondly, our questionnaire was completed before the gastroscopy, so that no one knew the findings at the time of inclusion. We have collected as many cases as possible, increasing the credibility of the data, such as the detection rate of malignancy. Finally, the researchers who analyzed the data were not aware of the patients' personal information. In summary, we made efforts to address the biases that could be anticipated during the design, execution, and analysis phases of the study.

4. A5.3) Item 12c of the STROBE guideline specifies: "Explain how missing data were addressed"; and item 14b specifies "Indicate number of

participants with missing data for each variable of interest". Do the authors have any specific comments in relation to this?
Response: Among all indicators, there were some missing data for Hp and BMI. We have presented information on the characteristics of these indicators in different subgroups in **Tables 1** and **Table 2**. Based on the Reviewers' suggestions, we have given the specific number of missing Hp and BMI in the flow chart (**Figure 2**).

5. A5.4) Did any patients decline to participate in the study? In accordance with STROBE item 13b and 13c, please specify reasons for non-participation, and consider using a flow-chart to illustrate patient inclusion.
Response: No patients refused the questionnaire during inclusion due to good communication and the efficient filling process by professional physicians. We have informed and prescribed gastroscopy to all included patients, but 6 of them did not show up as scheduled. These patients probably no longer wanted this gastroscopy or went to another hospital for the gastroscopy. Considering the Reviewer's suggestion, we used a flow chart to summarize these situations (**Figure 1**).

6. A5.5) On page 5, lines 6-8, please specify how the Leeds Dyspepsia Questionnaire (LDQ) was adapted to the present study. Were any items of the LDQ removed or added? Did the authors of the present study translate the LDQ into Mandarin, or was a previously translated, adapted, and validated version used? For instance [1].
Response: In the latest version of the manuscript document, on page 6, line 21, we added the description that "We translated LDQ into Mandarin and added two indicators: epigastric burning and postprandial fullness. This version also included demographics (sex and age), general health [weight and height, to calculate body mass index (BMI)], other diseases and family history".

7. A5.6) On page 5, line 12, please elaborate on the following statement: "Patients into three subgroups: EPS, PDS, and EPS-PDS". I understand that the classification was performed according to the Rome IV Criteria for Functional Dyspepsia, as accurately described in the Introduction section, but please clearly state this in the Methods section as well.
Response: We have made corrections according to the Reviewers' comments. The sentence was replaced as "Based on the Rome IV Committee definition, we further divided the patients into three subgroups: EPS, PDS, and EPS-PDS" (Latest manuscript, page 6, line 26).

8. A5.7) On page 5, line 23, please elaborate on "routine mucosal biopsy". Was the biopsy performed according to the Updated Sydney System [2-3]?
Response: We are very sorry for our negligence in using an expression of

unclear meaning. Our biopsy was not based on the Updated Sydney System. In the latest version of the manuscript document (page 7, line 8), we explain in detail how the biopsy was performed in this study: "We took three biopsies from the antrum (the lesser curve), the corpus (the lesser curve) and the incisura angularis, respectively. An additional biopsy was performed from the area if a suspicious lesion was found".

9. A7.1) A more detailed discussion of the study limitations is necessary in order to comply with STROBE item 19. Please consider the limitations of the uncontrolled study design and the possibility of selection bias. On page 13, line 4, please also elaborate on the limitations that a single-center study entails.

Response: In the latest version of the manuscript document (page 11, line 22), we have added a detailed explanation: "First, this was a single-center study, and not all patients were diagnosed with dyspepsia for the first time. In addition, the inclusion process and gastroscopic screening were mainly done by few physicians and therefore selection bias might occur."

10. A7.2) Could you speculate what additional insight a controlled trial might provide?

Response: Yes. In future large prospective cohort studies of dyspeptic patients, the presence or absence of warning symptoms as a grouping criterion will allow comparison of the detection rates of two local dyspeptic populations. Long-term benefits can be assessed through further follow-up. Moreover, controlled studies could be used to comprehensively assess the benefits of gastroscopy and guide local health authorities in developing an aggressive gastroscopy strategy for dyspeptic patients. In the latest manuscript, we expressed similar opinions. On page 11, line 26: "Therefore, future large controlled studies with more indicators are needed to assess the long-term benefits of gastroscopy, such as setting up another cohort with warning symptoms to compare the value of gastroscopy in patients with these two types of dyspepsia". On page 13, line 11, "Gastroscopy should be the initial management strategy for dyspeptic Chinese patients even in the absence of warning features. In the future, more controlled studies from multicenter samples will be needed to confirm this".

11. A7.3) Please give a more clear description of the possible clinical implications of the findings of the present study. This is necessary to comply with STROBE item 20

Response: An additional paragraph (page 11, line 17) was added before the last paragraph of the Discussion section: "Many studies have shown that warning symptoms can hardly predict positive endoscopic findings. They concluded that gastroscopy should not be based solely on warning symptoms. Our study supports this from a different perspective. Overall, Chinese

patients with dyspepsia should undergo gastroscopy regardless of the presence or absence of warning symptoms".

12. A8.1) Please place all figures and tables at the end of the document in compliance with the journal guidelines.
Response: The latest manuscript files are automatically generated, with only the literal parts. We have uploaded all figures and tables as required by the journal.

13. A8.2) In Table 3, please elaborate on "Other esophageal lesions".
Response: We have added a descriptive sentence under **Table 3**: "Other esophageal lesions: esophageal ulcer, esophageal hiatus hernia, and mycotic esophagitis".

14. A8.3) Please consider using a flow-chart to illustrate patient inclusion.
Response: As Reviewer suggested that we have added a flow chart (**Figure 2**).

15. A8.4) Is it possible to add illustrative photos? Either endoscopic or histological?
Response: Yes. We have selected 6 pictures of endoscopy in **Figure 1**, which were general findings: (A) chronic superficial gastritis and (B) chronic atrophic gastritis; and clinically significant findings: (C) reflux esophagitis, (D) Barrett's esophagus, (E) peptic ulcer, (F) malignancy.

16. A9.1) Was Bonferroni correction used?
Response: Yes. We are sorry for inadvertently writing: "$^{a}p < 0.05$" in **Table 5**. It has now been corrected to "$^{a}p < 0.017$".

17. A9.2) According to the attached biostatistics certificate, a statistical review of the study was performed by a biomedical statistician. Please comply with the journal guidelines and state this clearly in the Methods section.
Response: It is now explicitly stated in the Methods section. On page 7, line 15: "All statistical analyses were performed using SPSS version 25.0 and were statistically reviewed by a biomedical statistician".

18. A12.1) The journal guidelines specify that a separate Conclusion section is necessary. Please add a clear and accurate conclusion after the Discussion section.
Response: This section has been added as required on page 12, line 2: "Our study showed a high detection rate of CSFs in dyspeptic patients with no warning symptoms under the Rome IV criteria. Gastroscopy has significant implications in dyspeptic patients, especially for those with independent risk factors. Therefore, gastroscopy should not be performed based on warning

symptoms exclusively. Taken together, our study provided a basis for the development and progression of the initial treatment strategy for these patients."

Special thanks to you for your good comments.

Reviewer #2:

1. Any reason to exclude (a), (c) and (d) in the exclusion criteria?, it is because in the title its only exclude the warning signs, not others: (a) predominant symptoms of gastroesophageal reflux disease, such as reflux and heartburn; (c) a previous history of gastrointestinal surgery, malignancy, liver failure, gallbladder stones, and cholecystitis; or (d) use of NSAIDs and PPIs or H2 blockers before the study.

Response: Yes. (a) Reflux and heartburn are typical symptoms of reflux esophagitis, and the inclusion of these patients may result in a significantly higher detection rate of reflux esophagitis. (c) Referring to similar studies, these populations were not included even if warning symptoms were present. We believe the reason is that such patients are likely to have a higher detection rate of positive results, typical examples being patients with malignancy metastatic to the upper gastrointestinal tract. (d) NSAIDs drugs are likely to increase the detection rate of positive results, especially for peptic ulcer, and acid suppressants such as PPIs and H2 blockers are likely to mask positive results, mainly also for peptic ulcer.

2. What/where is the statistical analysis of other subgroup - female patient, other BMI groups etc.

Response: We are very sorry we don't have a standard expression in **Table 4**. We did include all subgroups (including age, gender, BMI, epigastric pain, epigastric burning, bloating, belching, early satiety, nausea, and *H. pylori* status) in the statistical analysis. We have filtered out the statistically significant indicators and displayed them in the table, but it is not clearly expressed. We have modified the names of the risk factors in **Table 4** and made additional comments to remove this ambiguity.

3. How's the patient managed if the author exclude the patient with PPIs or H2 blockers before the study.

Response: For these patients, we will give recommendations for further examination and treatment based on their conditions. If necessary, we will also perform gastroscopy on them. However, these patients are not the subjects of this study.

Special thanks to you for your good comments.