

Dear editors and reviewer:

Thank you for your letter and for the reviewer's comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our manuscript.

Now, we would like to contribute the revised manuscript (Manuscript NO.: 89523, Editorial) entitled "Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions: Clinical significance" for consideration for publication in World Journal of Gastrointestinal Endoscopy.

You have informed us that our article is not acceptable for publication without revisions that address each of the following comments:

We have carefully studied comments and made corrections accordingly in the revised version of the manuscript. The revision address each of the following comments with our responses to each comment in parentheses

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions: Clinical significance. Thank you for inviting me to review the above-titled manuscript. The topic may be interesting.

However, the manuscript needs to be revised.

(We feel great thanks for your professional review work on our article. As you are concerned, there are several problems that need to be addressed. According to your nice suggestions, we made extensive corrections to our previous draft. We added necessary data to supplement our article and edited our manuscript extensively. The detailed corrections are listed below.)

Abstract-

1) Third line: Please state the four variables.

(Thanks for your careful checks. We have added these four variables in the abstract section. "We focus specifically on the research actuality and clinical significance of four-variable nomogram, namely diabetes, lesion origin, surgical resection method, and surgical duration for predicting gas-related complications in transoral endoscopic resections")

2) Line 6 from the bottom: "Based on the author's results in ...and additions to the relevant content" sentence needs to be clearly written.

(Thank you very much for pointing this out, we have rewritten this sentence more clearly. "Based on the authors' results in the prepublication of the article "Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions", and in conjunction with our evaluation and additions to the relevant

content, radiographs may help screen patients at high risk for gas-related complications”)

3) Last line: "high-risk patients." Who are these? The editing of the abstract and manuscript is needed.

(Thanks for your suggestions, it is really a giant mistake to the whole quality of our article. For this purpose, we have explained the high-risk patients and made relevant edits to the abstract, as detailed in our revised manuscript.)

Introduction-

1) The first paragraph needs references.

(Thanks for your suggestions, we have added the necessary references in the first paragraph.)

2) The introduction flow needs organisation,

(Thanks for your suggestions, we apologize for the neglect of the flow in the introduction section, and after some revisions we have tried to improve the flow, see the revised version of the manuscript for details of the changes.)

3) Last paragraph, same page - What is the mechanism underlying gas-related complications?

(Thank you for pointing out this important issue. Firstly, we feel sorry for our carelessness and supplemented the relevant contents according to your suggestion. “The main influencing factors leading to gas-related complications are (1) depth of intrinsic myotomy, (2) intra-tunnel pressure. They are mainly caused by gas entering the lumen outside the esophageal wall, entering the mediastinum to form mediastinal emphysema, infiltrating into the subcutaneous tissues to form subcutaneous emphysema, and entering the abdominal and thoracic cavities to form pneumomediastinum and pneumothorax. Usually, mild symptoms do not require treatment, but severe cases can lead to rapid changes in respiratory circulation for a short period of time, which can be life-threatening. At present, some progress has been made in domestic and international research on the mechanism and factors affecting the occurrence of gas-related complications during endoscopic operations, which may be related to the duration of the disease, previous treatment history, Eckardt's score, S-type esophagus, Ling's staging, the way of establishing the tunnel entrance, the width of the tunnel, the length of the tunnel, the duration of the operation, and the use of the hybrid knife. Many of these factors are still in disagreement.)

4) Page 4, top paragraph- Needs references and explains the scientific basis connecting these four variables concerning gas-related complications.

(Thank you for the reminder, concerning the scientific basis connecting these four variables concerning gas-related complications. Because of the limitation of the introduction, this part of the content is placed in the subsequent chapter "Clinical significance of four-variable nomogram for predicting gas-related complications in transoral endoscopic resections", in which we explain and discuss in detail the scientific basis connecting these four variables concerning gas-related complications, including the respective significance of the four-variable nomograms for predicting gas-related complications. complications, including a best-effort search of the literature and discussion of the associations between Diabetes, lesion origin, surgical resection method,

and surgical duration, respectively, and gas complications, and thank you again for your suggestions.)

Page 4- Line 5 from the bottom- "All studies...", but no citations or references.

(Thank you for pointing out this important issue. We are very sorry for our oversight. As you are concerned, we have refined "All studies" to "Most of studies" and added reference citation.)

Page 5 and 6- 1) Please add possible scientific basis or underlying mechanisms for these 4 variables;

(Thank you very much for the reminder, and we apologize that we may not have been clear in the manuscript, and we really did not describe in detail the potential mechanisms for each of these four variables, whose associations with gas-related complications we described separately in the previous sections "Clinical significance of four-variable nomogram for predicting gas-related complications in transoral endoscopic resections". For the supplement, we have added in their respective scientific basis and mechanisms of occurrence, as detailed in the highlighted section of the returned manuscript.

For diabetes mellitus, after searching a large number of literatures, there are very few studies on diabetes mellitus and as-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions, and we analyzed diabetes mellitus and gas-related complications mainly from the perspective of neuropathy. Previous studies have shown that the morphology and biomechanical properties of the gastrointestinal tract change during diabetes, such as increased wall thickness and hardness of the gastrointestinal tract. The changes in stress distribution and wall stiffness likely alter the stress in the vicinity of the mechanosensitive afferents. Consequently, the perception and motility of the intestinal tract will change as well. Therefore, the morphological changes and biomechanical remodeling are likely to affect the function of mechanosensitive afferents in the gastrointestinal wall and further affect the motor and sensory function[29]. Some studies confirms that type 2 diabetes is an independent risk factor for esophageal foreign body perforation[30]. The underlying mechanism of diabetes-induced esophageal foreign body perforation may lie in impaired wound healing and neuropathy in DM patients. Neuropathy can cause abnormal esophageal movement in most people with diabetes, sometimes similar to diffuse esophageal spasm. As the course of the disease prolongs, some small injuries caused by foreign bodies tend to be repaired in nondiabetic patients, whereas diabetic patients are more prone to worsening injuries and a tendency to persistent stagnation, which may lead to serious complications such as gas-related complications or perforation and exacerbation of the disease. In part, this is the result of neuropathy. Therefore, future studies target neuropathy associated with diabetes. For example, we may be able to obtain data on the patient's glycosylated hemoglobin before the procedure, which could help determine whether poor glycemic control in diabetic patients increases the risk of gas-related complications or perforation

For lesion origin, we focus primarily on endoscopic sites. Endoscopic procedure-related morbidity (i.e., pneumomediastinum and subcutaneous emphysema) is the main reason for the differences shown, which may be related to anatomical features such as lack of serosa in

the esophagus and thin intestinal wall. The development of extended subcutaneous emphysema has been reported to be an enhancing factor for CO₂ retention during laparoscopic surgery and requires immediate attention to determine the presence of pneumothorax or pneumomediastinum, especially when the endoscopic procedure involves the chest[31]. In this case, patients with Endoscopic submucosal dissection require more careful attention. Some studies have shown that increases in PaCO₂ and prevalence of adverse events were greater in patients undergoing esophagoscopy than in those undergoing gastroduodenoscopy[32] As things stand, it is uncertain whether the degree of CO₂ retention may be different with different targeted organs for endoscopy

For surgical resection method. The incidence of gas-related complications during transoral endoscopic resection varies significantly depending on the surgical method. The main influencing factors leading to gas-related complications are the depth of myometrium propria incision

For surgical duration. The duration of transoral endoscopic resections may be affected by various resection devices, traction techniques, and even submucosal injection of materials, which may further affect the results)

2) Many statements made need citations/references.

(Thanks for your suggestions, it is really a giant mistake to the whole quality of our article. For this purpose, We have done our best to insert citations where references are needed in the text, and some of the specific corrections can be found in the yellow highlights of the revised manuscript)

Page 7 before conclusions- Please add a section about clinical significance, the validity of these variables, the limitations and areas that need further research for other possible variables, and future research in this area.

(Thank you for your careful inspection. It is really a giant mistake to the whole quality of our article. We added a new section called "Limitations of four-variable nomogram for predicting gas-related complications in transoral endoscopic resections." It is important to note that the clinical significance and validity of these four variables we have already described in the previous section " Clinical significance of four-variable nomogram for predicting gas-related complications in transoral endoscopic resections", and in order to better improve the quality of our article, we have added to it accordingly, to the point of making it more convincing.)

Based on the above additions and modifications to the manuscript, we believe that the research is of interest to the scientific community and thank you again for your review and comments!