Response to reviewer comments

Dear reviewers,

Thank you very much for your warmly feedback on our manuscript entitled *"Development of prediction model for enteral feeding intolerance in intensive care unit patients: a prospective cohort study"* submitted to the *World Journal of Gastrointestinal Surgery* (Manuscript NO.: 79330, Observational Study). Your comments and suggestions are very encouraging, and also helpful for us to improve the quality and readability of our manuscript. We now have made the changes in our current manuscript according to your suggestions and we hope this version will meet the requirements. The modified portions are marked in red in the revised version. Once again, thank you very much for your efforts for improving our manuscript.

The main corrections in the paper and the point-by-point reply are as follows:

Reviewer #1:

Main Comments:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript entitled "Development of prediction model for enteral feeding intolerance in intensive care unit patients: a prospective cohort study" is relevant, has methodology, and the number of cases allows consistent preliminary conclusions. The predictors identified as age, gastrointestinal disease, nutrition, mechanical ventilation and abnormal serum levels before the start of enteral support are easy to identify at the bedside in the ICU. In addition, they can help prevent early complications from artificial nutritional support in intensive care units. I recommend publishing.

Response: On behalf of my co-authors, we thank you very much for your kind work and highly comments of our study. Our study focuses on the risk of enteral feeding intolerance (EFI) in ICU patients, as EFI affects nutritional intake and clinical prognosis. We hope that our research can help screen high-risk patients in advance and give targeted nutritional management. Again, we would like to express our great appreciation reviewer. Thank you and best regards.

Reviewer #2:

Main Comments:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: There are too many old references that must be updated.

Response: Thank you for your comments. Your suggestions have helped us a lot, and I know that updating the references will improve the overall level of this article. We have updated some of the older literature to the latest references and marked them in red in the manuscript. However, due to the need to collect the literature as comprehensively as possible in the process of collecting risk factors, it is not possible to update all the literature. We hope to be able to get your understanding. Again, we would like to express our great appreciation reviewer. Thank you and best regards.

Reviewer #3:

Main Comments:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

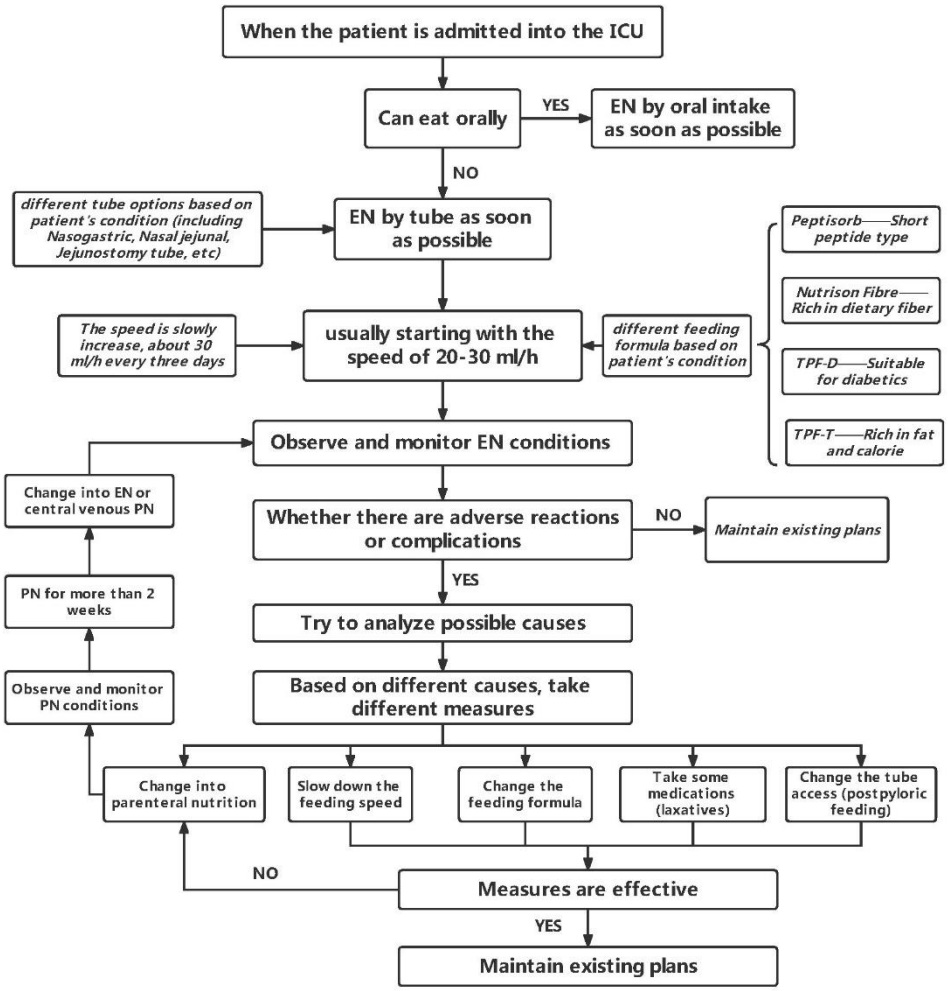
Conclusion: Major revision

Specific Comments to Authors: I read with great interest the manuscript entitled "Development of prediction model for enteral feeding intolerance in intensive care unit patients: a prospective cohort study". The study is well conducted and manuscript is well written. However, I have a few suggestions.

Comments 1: Methods: The feeding practices need to be elaborated. Who prescribed the feed, who decided when the patient is ready for feeding and for how many hours each day the patient was given the feeds? Any routine RT aspiration was performed during the feeds?

Response: Thank you for your comments. In the researching hospital, each patient's chief doctor prescribes the feed to the patient. Doctors will begin to implement enteral nutrition at a time when the patient achieve hemodynamic stability. Doctors will comprehensively consider the patient's current physical condition and nutritional needs, and choose different formulas, intake volume and intake rate, which

determines the intake time of each patient. Usually, a patient would receive 200-500 mL feed at the beginning with an average rate of 20-50 mL/h. So, they receive a 10-hour continuously feeding. In this hospital, on the basis of *"ESPEN guideline on clinical nutrition in the intensive care unit"*, there is no routine RT aspiration during the feeds. Doctors use abdominal ultrasound to monitor if the residual amount of the stomach is too large. The following flow chart is the standard nutrition protocol in this hospital.



Comments 2: Methods: The predictive model was developed on the basis of data collected on only 77 patients with EFI. The impact of several important factors like sepsis (17 pts), trauma (11 pts), dyselectrolytemia (17 pts) was largely missed because of this small sample size.

Response: Thank you for your comments. Your suggestions have helped us a lot, and I know that increasing the sample size will improve the overall level of this article.

There are no generally accepted approaches to estimate the sample size requirements for derivation studies of risk prediction models. Some studies, such as articles in *Annals of Internal Medicine, BMJ Open* have suggested having at least 10 events per candidate variable for the derivation of a model[1,2]. We selected 14 predicting factors and a total of 203 samples were included, which is consistent with basic statistical principles. In clinical, the doctors at the ICU of the hospital where the study was conducted already had some understanding of EFI, and they gave some precautions in advance to reduce the occurrence of EFI, which led to a decline in the incidence rate. For practical considerations, including time and cost, we finally included all patients who received enteral nutrition in the ICU within 7 months. So, the positive sample size was only 77 patients with EFI. To compensate for this shortcoming, we have also adopted other methods to remedy it. For example, after consulting with clinical specialists, the risk factor, sepsis, although not statistically different in univariate analysis, was also included in multivariate analysis because it was clinically generally accepted. In future studies, we plan to conduct cohort studies in more hospitals to expand sample sizes to refine our predictive model.

1 Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. Jan 6 2015;162(1):W1-73. [DOI:10.7326/m14-0698]

2 Puhan MA, Hansel NN, Sobradillo P, Enright P, Lange P, Hickson D, Menezes AM, ter Riet G, Held U, Domingo-Salvany A, Mosenifar Z, Antó JM, Moons KG, Kessels A, Garcia-Aymerich J. Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. BMJ Open. 2012;2(6)[DOI:10.1136/bmjopen-2012-002152]

Comments 3: Methods: “Exclusion criteria included the following: 1) aged ≥18 years; 2) oral intake…” I think it is supposed to be age less than 18 years.

Response: Thank you for your comments. We accidentally reversed the direction of the symbol. In our study, the exclusion criteria for age are less than 18 years and we fixed this error in the manuscript.

Comments 4: Too many feeding formulas were being prescribed. Also, there was a significant difference in the univariate analysis between the 2 groups. Why was this not included in the multivariate analysis?

Response: Thank you for your comments. Because patients in the ICU have a variety

of different problems, doctors prescribe different feeding prescriptions for them. In this study, we included all patients who received enteral nutrition. In future research, we will explore the occurrence of EFI in patients with different diseases, and such studies will have fewer feeding formulas. As written on page 10, line 10 of the manuscript, we included feeding formulas in the multivariate analysis. In the manuscript "**3.3. Selected factors for the model**", we describe all the factors that are selected from the univariate analysis and will be included in the multivariate analysis.

Comments 5: Methods: "….ultrasonographic data were recorded by doctors", which doctors, ICU physicians trained in performing USG or trained Ultrasonologists?

Response: Thanks for your comments. In our study, the ultrasonographic data were recorded by ICU physicians trained in performing USG. The ultrasonologists at the hospital where the study was conducted is not responsible for bedside ultrasound, which is often the responsibility of the ICU doctor. We also describe this situation more clearly in the manuscript.

Comments 6: Methods: In discussion the authors mention "When we performed univariable analysis, we included predictors whose P-values were smaller than 0.15 with the aim that no possible significant factors were omitted." Why was the p value of less than 0.15 taken?

Response: Thanks for your comments. Recently, researchers have discussed the reliability of using hypothesis testing to determine the effects of experimental results. A comment piece published in the journal *Nature* said that we should never conclude there is 'no difference' or 'no association' just because a *P* value is larger than a threshold such as 0.05 or, equivalently, because a confidence interval includes zero[3]. Researchers need to consider not only the *P* value, but also statistical values such as risk ratio and effect size. Many common practices show how reliance on thresholds of statistical significance can mislead us. This does not mean calling for a ban on *P* values, but whether a *P* value is small or large, caution is warranted. Therefore, after consultation with statisticians and following their advice and literature support, we considered the sample size that might be collected in our study and expanded the *P* values to 0.15 so as not to miss out those factors that were clinically different but not statistically different between the two groups. This is a choice based on our small sample size study. In future studies, we will expand the sample size to increase the

statistical effect.

3 Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. Mar 2019;567(7748):305-307. [DOI:10.1038/d41586-019-00857-9]

Comments 7: Results: the nomograph itself is confusing. It should be clearly stated under the figure what 1 and 2 stand for. The lower part of the figure, ie. Total points and predictive value should be clearly demarcated and separated from the above portion.

Response: Thanks for your clear suggestions about nomogram. We've added descriptions of the nomogram to the document and adjusted the nomogram content to make it easier to read.

Comments 8: Discussion: "Similarly, we found that ICU patients with GI disease (e.g., pancreatitis, post-gastrectomy, or upper GI hemorrhage) were less likely to experience EFI." Even though they were given significantly reduced feed but as the number of patients were small, such findings may be misleading.

Response: Thanks for your comments. Our study found that the incidence of EFI was lower in ICU patients with gastrointestinal disorders. In health and critical illness, small-intestinal nutrients increase blood flow through the superior mesenteric artery. Recently, it has been found that EFI may be an adaptive symptom of the intestine to reduce mesenteric blood flow distribution and preserve autophagy (or 'self-eating')[4]. Because of the already existing mesenteric blood flow distribution problems, patients with a history of gastrointestinal disorders may not be prone to EFI. In our study population, we found that ICU patients with gastrointestinal disorders, possibly due to reduced feeding, were less likely to develop EFI. Further basic research is needed on whether the probability decreases due to a certain pathophysiological mechanism. Of course, our study does have the problem of small sample sizes, and we will set up control experiments and expand the sample size in future studies to explore the relationship between gastrointestinal diseases and EFI more clearly. Again, we would like to express our great appreciation reviewer. Thank you and best regards.

4 Reintam Blaser A, Deane AM, Preiser JC, Arabi YM, Jakob SM. Enteral Feeding Intolerance: Updates in Definitions and Pathophysiology. Nutr Clin Pract. Feb 2021;36(1):40-49. [DOI:10.1002/ncp.10599]

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The main corrections in the paper and the point-by-point reply are as follows:

Reviewer #1:

Main Comments:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Thank you for addressing all the concerns. I believe the manuscript has significantly improved after incorporating these changes. However, I would suggest to add the following limitations: The effect of sepsis, trauma, dyselectrolytemia could not be properly addressed because of the small size size. The effect of various formula feeds could not be ascertained because of use of several feeding formulas.

Response: On behalf of my co-authors, we thank you very much for your kind work and comments of our study. We have added these limitations which marked in red in the DISCUSSION part of our manuscript. Your comments are very meaningful, and it is indeed possible that these factors may be ignored due to the small sample size. Due to the actual situation, the specific effect differences between various nutritional formulas cannot be accurately analyzed. In the future, we hope to be able to analyze the effect of individual factors on EFI on the basis of expanding the sample size. Again, we would like to express our great appreciation reviewer. Thank you and best regards.