List of Responses

Dear Editor, Chief Editor and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "The role of international standardized ratio (INR) in nonpulmonary sepsis screening: a prospective observational study" (World Journal of Clinical Cases Manuscript NO: 67488). **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, tried our best, which we hope meet with approval. Revised portion are **marked in red** in the paper. The main corrections in the paper and the responds to Reviewers and Editorial Formatting Comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

Comment 1: "Authors do not precise if consecutive patients were enrolled. I see that about half of patients were septic according to sepsis-3 criteria, and this is a pretty high number, that could be justified just in Intensive Care Units. As authors well known, the accuracy of a selected test depends greatly from pre-test probability, that is very high in this cohort. Actually in non ICU setting the situation is pretty different, and just a minor percentage of patients result to be septic according to Sepsis 3 criteria. Authors should better elaborate this point."

Response: Thank you professor for your advice. There were not consecutive patients enrolled. We have made this clear in the second paragraph of Study Population, line 2 (line 122).

Thank you, distinguished reviewer, professor. The selection of patients does affect the outcome of clinical studies, especially clinical intervention trials. However, this study was only an observational study of the predictive efficacy of INR in SEPSIS diagnosis according to SEPSIS 3 criteria, and was not involved in a clinical intervention trial. Moreover, we were randomized, and the effect was almost low.

About the "Actually in non ICU setting the situation is pretty different, and just a minor

percentage of patients result to be septic according to Sepsis 3 criteria."

Yes, Professor. Indeed, the patients we enrolled were mainly patients from the ICU, as we explained in the first paragraph of the methodology. In general, this does not affect studies of the efficacy of INR in screening patients with sepsis. Thank you, Professor, for raising this concern.

Comment 2: "Moreover, since many patients do have underlying conditions that affect INR evaluation, many patients could not be evaluated. Authors should better discuss this point and evaluate the overall effect of these exclusion criteria on overall accuracy of INR determination.

Response: Thank you, professor, for this constructive comment. In the inclusion criteria, we excluded patients with underlying diseases that might affect the coagulation function of the patients, and the vast majority of such patients could be identified in the medical history inquiry.

Lines 124-128: The exclusion criteria were the following: age<18 years old; patients with some preexisting diseases which their coagulation function could be notably affected: such as chronic liver diseases, hematologic system diseases, or patients who had previously undergone long-term treatment with immunosuppressants or anticoagulants, and those patients with incomplete data.

Indeed, there are many underlying diseases that can affect INR. Although relevant conclusions in this study were drawn under corresponding exclusion criteria, it is true that in clinical practice, there are still a small number of potentially infected patients with those underlying diseases that cannot be detected at the first time. For this condition, when their INR reach the high-risk value of sepsis, e.g., more than 1.22, they still need to be considered highly suspected of sepsis because they are at higher risk of adverse outcomes when they are missed. (Line 278-284)

Comment 3: "Authors report the overall AUC of INR for sepsis diagnosis. This gives a measure of "Calibration" value. Do they explore in any way the "discrimination" value? in other words, do patients with higher INR have increased risk of sepsis? Is it possible

Response: Thank you again, professor, for your wonderful comment. Yes, it's a very clinical comment.

The diagnostic criteria for Sepsis-3 are based on SOFA score, and SOFA score is also closely related to the prognosis of patients with sepsis. We added correlation analysis between INR and SOFA score, and correlation analysis between INR and APACHE II score, another disease severity score in the ICU. We found that INR had a strong correlation with SOFA score (r=0.660, 95% CI=0.574-0.731, $P<0.001$), but a weak correlation with APACHE II score (r=0.457, 95% CI=0.341-0.560, $P<0.001$). In order to perform risk stratification analysis for INR predicted sepsis, we defined high, medium and low risk (Line 149-152). Finally, when the INR was less than or equal to 1.17, 1.20, and more than 1.22, respectively, it was found to be a low, medium, and high risk of sepsis. These are shown in Figure 3.

Thank you again, professor.

Response to Editor:

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Response: Yes, the language of manuscript was firstly edited and polished by Elsevier Webshop (Elsevier Language Editing), and the rest of the small language issues were again polished up by our native English colleagues.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly. Now we list the abbreviations rules as follows.

Response: We have revised it accordingly and marked it red in the article.

Science editor:

Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions; (2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (4) PMID numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text. 6 Re-

Response: We have revised them one by one.

Dear Editor:

About the Publication fees, "*If an unsolicited manuscript meets any of the following requirements, the publication fees will be reduced by 10%: Supported by a fund of national level or above; Having a corresponding author who is a member of an association of national level or above; Having a first author who is a young scholar under 45 years-old*"; We qualify for a 10% discount because all of our first authors are young scholars under the age of 40.

Thank you for your kind help and best wishes for you!