

Dear Editor,

Thank you very much for your decision letter and advice on our manuscript (Manuscript 87319) entitled “Prognostic significance and relationship of SMAD3 phospho-isoforms and VEGFR-1 in gastric cancer: A clinicopathological study”. We also thank the reviewers for the constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are indicated by yellow color in the revised manuscript. In addition, our point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by *Medjaden, Inc.*

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely,

De-Qiang Huang

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In this clinicopathological study, authors investigated the prognostic value and relationship of SMAD3 phospho-isoforms and VEGFR-1 in gastric cancer. They showed that high expression of pSMAD3L and VEGFR-1 was associated with poor prognosis in gastric cancer patients. Based on the results, moreover, co-upregulation of pSMAD3L and VEGFR-1 was considered as a predictive marker for poor gastric cancer prognosis. Although this study was conducted as an observational, single center study, the main research findings of this paper will be important for predicting prognosis of postoperative gastric cancer cases. I have no practical criticisms in terms of methods, results and interpretation.

Response: We greatly appreciate receiving their input through the peer review process. The reviewer's confirmation that our findings and interpretations are sufficiently sound is valuable as we work to strengthen our paper prior to publication. We are grateful for the effort they have put into reviewing our manuscript.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear Authors, Thank you for your submitting the manuscript titled, "Prognostic significance and relationship of SMAD3 phospho-isoforms and VEGFR-1 in gastric cancer: A clinicopathological study" in WJGO. The manuscript is well written, however one major criticism should be addressed as below. Major) The most serious problem is the methodology of scoring

the amount of protein expressed in the target gene using only immunostaining and dividing the degree of staining into four categories. Recently, immunostaining, quantification by labeling with fluorescent antibodies, quantification of gene expression by quantitative RT-PCR, and quantification of protein levels by the Western blot method are commonly used to determine whether there are significant differences, and these methods are highly evaluated in terms of priority. Please add Figures as shown in the figure of the following paper. Min Peng, et al. J Gastroenterol 2023;58:908-924

Response: Thank you for pointing out that our study could be improved in this way and providing the reference paper. We agree that evaluating the expression of the protein of interest using approaches other than immunohistochemical staining would add a layer of solidity to our findings. We have carefully considered the reviewer's recommendations to validate our IHC results with fluorescent antibody staining, RT-PCR, and Western blot analysis. Our study primarily focuses on analyzing protein expression in tissues, thus RT-PCR is not applicable to our work. Additionally, to explore the clinical significance of these biomarkers, we want to use detection methods that are clinically relevant and feasible. Currently, IHC is one of the most commonly used techniques to assess protein expression in tissues in clinical laboratories. We did attempt fluorescent antibody staining of tissue sections, but were unable to identify suitable antibodies for the phosphorylated proteins we studied. Therefore, we had to abandon plans to use fluorescent antibodies.

Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>. Before

final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response: Thank you for your feedback on the English language quality of our manuscript. We utilized the professional editing service of Medjaden Inc. to polish our language. We have included the English Language Editing Certificate issued by Medjaden Inc with this revision. We hope that our manuscript is now acceptable for publication in your journal. Thank you again for your guidance.