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Joo Young Cho, Bing Hu, Anastasios Koulaouzidis, Sang Chul Lee

Editors-in-chief

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Dear Editors-in Chief:

We appreciate you and your reviewers for your valuable time in reviewing our work and providing important feedback. Your corrections and comments help us to improve the current version of our study. We considered each comment carefully and tried our best to address them. Below we provide a point-by-point response.

We hope our work meet your standards for publication in your Journal. If you require any further information, please do not hesitate to contact us.

Sincerely,

Carlos Robles-Medranda, MD

Head of the Endoscopy Division

Instituto Ecuatoriano de Enfermedades Digestivas

Guayaquil, Ecuador

POINT-BY-POINT Letter

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

Manuscript entitled "Endoscopic ultrasound elastography in the diagnosis of malignant pancreatic masses and associated lymph nodes: a critical evaluation of the strain ratio cut-off value" is an interesting study that scientifically demonstrates the value of EUS-elastography in the diagnosis of solid PMs and associated LNs. Authors demonstrated that the SR cut-off values proposed have a high sensitivity and specificity for the detection of malignancy. The language of the article is fluent, and the logic is smooth. Several points should pay attention and be improved.

1. There are several grammatical mistakes, and the writing should be improved.

Answer: Dear Reviewer. Thank you for the suggestion. We have checked the manuscript and made the respective grammatical corrections. Additionally, to further address the grammatical mistakes and writing improvement, the document was reviewed by Nature Research Editing Services.

2. The discussion of conclusion and perspectives part in this field is insufficient.

Answer: Dear Reviewer, thank you for the suggestion. We have rewritten the conclusion as follows: *"We found that EUS combined with qualitative and quantitative elastography analysis via SR is a helpful resource when assessing PMs and associated LNs. This approach is more effective and convenient than limiting the evaluation to only conventional EUS-fine needle aspiration for the detection of malignancy. Although histological analysis is mandatory for a final diagnosis, elastography should be included in the diagnostic workup of PMs and their associated LNs. However, validating this recommendation through a prospective, multi-center, controlled trial is preferable."*

3. For the novelty of this review, more recent references should be cited.

Answer: We thank Reviewer 1 for this suggestion. Accordingly, we performed an update of the references and include them in our work. The following new references were included:

Xie Juan, Liu H, Liu W, Li J. Quantitative shear wave elastography for noninvasive assessment of solid pancreatic masses. *Clin Hemorheol Microcirc.* 2020; 72 (2); 179-187. [PMID: 31476148 DOI: 10.3233/CH-190665].

Tanaka M, Fernandez-del Castillo C, Kamisawa T, Young Jang J, et al. Revisions of International consensus Fukuoka guidelines for the management

of IPMN of the pancreas. *Pancreatology*. 2017; 17 (5):738-753. [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007].

Chacaltana A, et al., Usefulness of endoscopic ultrasound guided elastography in the assessment of solid pancreatic lesions. *Rev Gastroenterol Peru*. 2019; 39 (1): 38-44. [PMID:31042235]

Kongkam P, Lakananurak N, Navicharen P. Combination of EUS-FNA and elastography (strain ratio) to exclude malignant solid pancreatic lesions: A prospective single-blinded study. *J Gastroenterol Hepatol*. 2015; 30 (11); 1683-9. [PMID:26238152 DOI: 10.1111/jgh.13067]

4. Figures of EUS-elastography should be added in order to make the study more convinced.

Answer: Dear Reviewer, thank you for the suggestion, we have added two figures of EUS-elastography as figure 3. Figure 3 is a quantitative and qualitative EUS elastography assessment. Figure 3A represents case 84: a 26-year-old woman with a pancreatic mass. A plain B-mode image (left) and color-code strain image (right) are shown, SR= 2,66, Giovannini elastic score of 2 (green). Biopsy confirmed chronic pancreatitis; figure 3B) represents case no. 73: a 46-year-old man with a pancreatic mass. A plain B-mode image (left) and a color-coded strain image (right) are shown, SR= 23.8, Giovannini elastic score of 4 (dark blue). Biopsy confirmed a pancreatic adenocarcinoma.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Please make the following modifications:

1. Rewrite the title of the manuscript.

Answer: Dear Reviewer, thank you for the suggestion. We have shortened the manuscript title. In the previous submission, the title was "Endoscopic ultrasound elastography in the diagnosis of malignant pancreatic masses and associated lymph nodes: a critical evaluation of the strain ratio cut-off value". As suggested, we reduce the number of words according to the journal guidelines and reviewer suggestion. The current title is "Endoscopic ultrasound elastography for malignant pancreatic masses and associated lymph nodes: critical evaluation of strain ratio cutoff value". This new title contains 18 words as suggested.

2. Try to incorporate the primary numerical values in the results portion of the abstract.

Answer: Dear Reviewer, thank you for the suggestion. At the abstract, we have added median SR for malignant and non-malignant PMs/LNs, as follows: "A sample of 121 patients was included, 45.4% of whom were female. 69 (57.0%) PMs were histologically malignant, with a median SR of 50.4 vs 33.0 for malignant vs. nonmalignant masses ($P<.001$). EUS evaluation identified associated LNs in 43/121 patients (35.5%), in whom 22/43 (51.2%) patients had histologically confirmed malignant diagnosis, with a median SR of 30 vs 40 for malignant vs. nonmalignant LNs ($P=.7182$). In detecting malignancy in PMs, an SR cutoff value of >21.5 yielded a sensitivity of 94.2%, while a cutoff value of >121 yielded a specificity of 96.2.2%. There were significant differences in the Giovannini scores, a previously established elastic score system, between the patients grouped by their final histology results ($p<0.001$). For LNs, SR cutoff values of >14.0 and >155 yielded a sensitivity of 90.9% and a specificity of 95.2%, respectively, in detecting malignancy."

3. Summarize the background portion of the manuscript with additional recent references.

Answer: Dear reviewer, thank you for your suggestion. We included new updated references in the background section. Additionally, these references were included in the reference section, accordingly. The following new references were included:

Xie Juan, Liu H, Liu W, Li J. Quantitative shear wave elastography for noninvasive assessment of solid pancreatic masses. Clin Hemorheol Microcirc. 2020; 72 (2); 179-187. [PMID: 31476148 DOI: 10.3233/CH-190665].

Tanaka M, Fernandez-del Castillo C, Kamisawa T, Young Jang J, et al. Revisions of International consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017; 17 (5):738-753. [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007].

Chacaltana A, et al., Usefulness of endoscopic ultrasound guided elastography in the assessment of solid pancreatic lesions. Rev Gastroenterol Peru. 2019; 39 (1): 38-44. [PMID:31042235]

Kongkam P, Lakananurak N, Navicharen P. Combination of EUS-FNA and elastography (strain ratio) to exclude malignant solid pancreatic lesions: A prospective single-blinded study. J Gastroenterol Hepatol. 2015; 30 (11); 1683-9. [PMID:26238152 DOI: 10.1111/jgh.13067]

4. The methods section is well-written and does not require any additional revisions.

Answer: Dear Reviewer, thank you for the compliment.

5. Remove the subheadings from the results section.

Answer: Dear Reviewer, thank you for the suggestion. We have removed the subheadings from the results section.

6. The limitation, recommendation, and future prospects must be included in the manuscript's discussion section.

Answer: Dear Reviewer, thank you for the suggestion. In accordance with it, we have modified the following paragraph at the manuscript's discussion section: *"The present study has several limitations, including its retrospective design and single-center nature, leading to a limited number of operators. A few patients from the malignant case group underwent surgery, limiting the histological description of this research. The nonmalignant control group was defined as patients with nonmalignant masses instead of a healthy population. However, this study has the advantage of using the qualitative elastic score proposed by Giovannini et al. for the interpretation of PMs and their associated LNs, instead of the 4-score by Furukawa [16], and may be one of the first studies to evaluate the utility of EUS elastography in Hispanic patients. Future research on this topic will be designed as diagnostic trials, considering the Giovannini score for PMs and associated LN descriptions."*

7. Try to expand upon your conclusion.

Answer: Dear Reviewer. Thank you for the suggestion. We have rewritten and expanded the conclusion as following: *"We found that EUS combined with qualitative and quantitative elastography analysis via SR is a helpful resource when assessing PMs and associated LNs. This approach is more effective and convenient than limiting the evaluation to only conventional EUS-fine needle aspiration for the detection of malignancy. Although histological analysis is mandatory for a final diagnosis, elastography should be included in the diagnostic workup of PMs and their associated LNs. However, validating this recommendation through a prospective, multi-center, controlled trial is preferable."*

8. Several typographical errors were detected when reviewing.

Answer: Dear reviewer, thank you for your comment. We have checked the manuscript taking into consideration the typographical corrections. Additionally, the received manuscript was edited by Nature Editing Services after reviewing the entire document following the journal's recommendations, to address any grammatical error and writing improvements. In the new submission, Nature Editing Services certificate will be included.

9. In the references section, revise your list of references to reflect the necessary changes.

Answer: Dear reviewer, thank you for your suggestion. We made the necessary changes in the references section so that all bibliographic references maintain a uniform structure. Additionally, we updated our references. The following new references were included:

Xie Juan, Liu H, Liu W, Li J. Quantitative shear wave elastography for noninvasive assessment of solid pancreatic masses. *Clin Hemorheol Microcirc.* 2020; 72 (2); 179-187. [PMID: 31476148 DOI: 10.3233/CH-190665].

Tanaka M, Fernandez-del Castillo C, Kamisawa T, Young Jang J, et al. Revisions of International consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology.* 2017; 17 (5):738-753. [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007].

Chacaltana A, et al., Usefulness of endoscopic ultrasound guided elastography in the assessment of solid pancreatic lesions. *Rev Gastroenterol Peru.* 2019; 39 (1): 38-44. [PMID:31042235]

Kongkam P, Lakananurak N, Navicharen P. Combination of EUS-FNA and elastography (strain ratio) to exclude malignant solid pancreatic lesions: A prospective single-blinded study. *J Gastroenterol Hepatol.* 2015; 30 (11); 1683-9. [PMID:26238152 DOI: 10.1111/jgh.13067]

10. Best of luck.

Answer: Dear Reviewer, thank you for the compliment.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is a retrospective case-control study about endoscopic ultrasound elastography in the diagnosis of malignant pancreatic masses and associated lymph nodes: a critical evaluation of the strain ratio cut-off value.

1. A correlation analysis between PM/LN diameter and Strain Ratio value is suggested.

Answer: Dear Reviewer, thank you for the suggestion. We have performed the suggested statistical sub analysis among PM/LN diameter vs Strain Ratio value. We have added the necessary information in the statistical analysis of the method section and results. The following sentences were included in the respective sections:

- § METHODS, Statistical analysis: *“Association among PMs and LNs SR vs. diameter was demonstrated through Spearman's rank correlation (ρ)”.*
- § RESULTS, Pancreatic masses: *“A proportionally significant association was demonstrated between a higher PM SR vs. a larger PM diameter ($\rho=0.251$, 95% CI 0 – 0.481; $P=0.05$)”.*
- § RESULTS, Lymph nodes: *“There was not demonstrated an association among LN SR vs diameter ($\rho=-0.017$, 95% CI -0.503 – 0.421; $P= 0.937$)”.*

Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Endoscopy, 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 title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Answer: Dear Company editor-in-chief, thank you for the suggestion. We have shortened the manuscript title. In the previous submission, the title was "Endoscopic ultrasound elastography in the diagnosis of malignant pancreatic masses and associated lymph nodes: a critical evaluation of the strain ratio cut-off value". As suggested, we reduce the number of words according to the journal guidelines and reviewer suggestion. The current title is "Endoscopic ultrasound

elastography for malignant pancreatic masses and associated lymph nodes: critical evaluation of strain ratio cutoff value". This new title contains 18 words as suggested.

§ Before final acceptance, 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: ...".

Answer: Dear Company editor-in-chief, thank you for your suggestion. In our manuscript, **Figure 2** represents areas under the receiver operating characteristic curve (AUROCs) of the strain ratio in the detection of malignancy. **Figure 2A** represents the AUROC in pancreatic masses; **Figure 2B** represents AUROC in only solid pancreatic masses; and **Figure 2C** represents AUROC in associated lymph nodes.

§ Please provide the original figure documents.

Answer: Dear Company editor-in-chief, the original figure documents will be provided in the new submission in a separated file as suggested.

§ Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Answer: Dear Company editor-in-chief, a PowerPoint document containing all the figures of the manuscript will be provided in the new submission to be reprocessed by as suggested.

§ In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights.

Answer: Dear Company editor-in-chief, in the PowerPoint document we included the author's copyright "Copyright © Puga-Tejada M et al. 2022" for the original figures included in the final version of the manuscript as suggested.

§ 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) 2022.

Answer: Dear Company editor-in-chief, in the PowerPoint document we included the author's copyright "Copyright © Puga-Tejada M et al. 2022" for the original figures included in the final version of the manuscript as suggested.

§ Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden.

Answer: Dear Company editor-in-chief, we provided the standard three-line tables in the submission.

§ The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned.

Answer: Dear Company editor-in-chief, the contents of each cell in the table are conform to the editing specifications, and the lines of each row or column of the table are aligned.

§ Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Answer: Dear Company editor-in-chief, no carriage returns or spaces are used to replace lines, and we do not segment cell content as suggested.

§ 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 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/>.

Answer: Dear Company editor-in-chief, according to your suggestion, references have been updated and included in our work.