

Rebuttal Letter

Dear Lian-Sheng Ma,

Dear Reviewers,

Thank you very much for your feedback and thorough reviews.

We would like to answer all comments in detail and describe other changes to the previous version of our manuscript. All changes to the manuscript were highlighted in the manuscript file using the highlighting feature in MS Word.

Reviewers' comments

Reviewer #1:

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The authors aimed to assess the accuracy of laryngopharyngeal pH-monitoring system (Restech) and its correlation with esophageal pH-metry (Eso-pH) in symptomatic patients after esophagectomy.

Major comments 1. The authors stated that there was a 100% correlation between Restech and Eso-pH but in the results section they reported that 29 (88%) patients had an abnormal pH-metry whereas Restech pH-metry was abnormal in 20 (61%) patients, 9 patients had abnormal eso-pH and normal Restech. Therefore a 100% correlation between these two techniques cannot be defined.

Thank you for your comment. Indeed, when looking at our numbers the results of both pH measurement systems were not identical. However, correlation is defined as “a connection or relationship between two or more facts, numbers” and we truly believe that this is the case in 100% of our patients. Reflux episodes that do not reach the oropharynx cannot be measured by laryngopharyngeal pH-monitoring and therefore those patients will show a normal RYAN score. We still defined those patients to have correlating results as we believe that different reflux scenarios exist and that correlation between these two methods is limited by the location of the measurement. We changed the description of correlation in our manuscript to clarify this.

2. The authors define Esophageal pH-metry as the gold standard for the detection of GERD and use this tool in their patients. However, in the last 20 years, esophageal impedance-pH monitoring has demonstrated its superiority in the diagnosis of GERD and has become the real gold standard technique providing many more information and symptom association compared

to the classic pH-metry. Why the authors did not perform esophageal impedance-pH monitoring instead of esophageal pH-metry in their patients?

pH-metry has been the gold standard for the detection of acid reflux. Over the last two decades, impedance-pH monitoring was implemented into clinical routine and therefore the differentiation between acid and non-acid reflux was possible. Still, at the time this study was enrolled, standard pH-metry was widely spread in Germany. According to international data, a positive pH-metry has an important prognostic value in patient selection for antireflux surgery and as we are a surgical clinic, standard pH-metry for detection of acid reflux depicts the current standard in our clinic.

Campos, GM, Peters, JH, DeMeester, TR, Oberg, S, Crookes, PF, Tan, S, DeMeester, SR, Hagen, JA, and Bremner, CG, Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg, May-Jun 1999. 3(3): p. 292-300.

3. Non acid reflux (detectable only with impedance-pH monitoring) has been correlated with esophageal symptoms and esophagitis, but this component cannot be analyzed by the classic pH-metry and Restech.

Thank you for your comment and we agree that this is a limitation of the study. We added a sentence in the limitation section stating this.

4. This sentence in the discussion is confounding: "On the other hand, our collective of patients that undergo 24-hour impedance-pH-monitoring with simultaneous 24-hour Restech pH-monitoring". Did the authors perform impedance-pH monitoring?

Thank you for catching this typing mistake. *This was changed in the manuscript.*

5. How many patients were on other than PPI GERD treatment (i.e. alginate, prokinetics, sucralfate....) ?

We applied our standardized protocol for this study. All patients were off PPIs for at least 7 days prior to our measurements. In addition, any other GERD treatment like alginate, prokinetics and such were paused for at least 48 hours prior to our study to ensure a valid measurement.

6. Relation between the results of Restech and pH-metry with symptoms (reported before and during the investigations) and endoscopy results should be better reported and analyzed (i.e. univariate and multivariate models)

Thank you for your comment and we agree that this would be a very interesting addition to our results of the study. We obtained in-house statistical consulting. Unfortunately, our study group is too small to apply a univariate or multivariate model and get statistically significant results.

7. Information about the diet and beverages during the investigation should also be provided.

Patients were asked to maintain their regular diet. In addition, patients were instructed to eat three meals per day and drink only at mealtimes. Mealtimes were then excluded from the analysis to ensure valid results. We added this information to the manuscript.

8. Data from 10/43 (23%) of recruited patients were missing (not complete data set or not compliant patients). This result should be considered in the limits of the study.

Thank you for your comment and we agree that this is unfortunately a limitation to the study. We added this aspect to our discussion.

9. The usefulness of Restech technique is currently controversial and some references (reporting negative results) are missing (i.e. Yadlapati R, Pandolfino JE, Lidder AK, Shabeeb N, Jaiyeola DM, Adkins C, Agrawal N, Cooper A, Price CP, Ciolino JD, Gawron AJ, Smith SS, Bove M, Tan BK. Oropharyngeal pH Testing Does Not Predict Response to Proton Pump Inhibitor Therapy in Patients with Laryngeal Symptoms. Am J Gastroenterol. 2016 Nov;111(11):1517-1524)(Yadlapati R, Adkins C, Jaiyeola DM, Lidder AK, Gawron AJ, Tan BK, Shabeeb N, Price CP, Agrawal N, Ellenbogen M, Smith SS, Bove M, Pandolfino JE. Abilities of Oropharyngeal pH Tests and Salivary Pepsin Analysis to Discriminate Between Asymptomatic Volunteers and Subjects With Symptoms of Laryngeal Irritation. Clin Gastroenterol Hepatol. 2016 Apr;14(4):535-542.)(Ummarino D, Vandermeulen L, Roosens B, Urbain D, Hauser B, Vandenplas Y. Gastroesophageal reflux evaluation in patients affected by chronic cough: Restech versus multichannel intraluminal impedance/pH metry. Laryngoscope. 2013 Apr;123(4):980-4)(Plocek A, Gębora-Kowalska B, Białek J, Fendler W, Toporowska-Kowalska E. Esophageal Impedance-pH Monitoring and Pharyngeal pH Monitoring in the Diagnosis of Extraesophageal Reflux in Children. Gastroenterol Res Pract. 2019)(Chiou E, Rosen R, Jiang H, Nurko S. Diagnosis of supra-esophageal gastric reflux: correlation of oropharyngeal pH with esophageal impedance monitoring for gastro-esophageal reflux. Neurogastroenterol Motil. 2011 Aug;23(8):717-e326).

Thank you for your comment. We are well aware of the controversial literature on oropharyngeal pH testing and added some studies to our discussion to emphasize this. Unfortunately, many studies did not perform simultaneous or any esophageal pH testing so that no reference or validation of the results is possible. Moreover, this shows the importance of our study and the implementation of a standardized protocol to evaluate patients with atypical symptoms and suspected LPR. Patients with atypical symptoms are a very inhomogeneous group and the

diagnostic pathway can be particularly challenging. We believe that every diagnostic tool should be utilized, especially to help support the decision for or against antireflux surgery.

Minor comments In the first line of the introduction the term “benign” for GERD is questionable because many patients had long-life impaired quality of life and because of an increased risk for aspiration pneumonia, esophageal adenocarcinoma and Barrett’s esophagus.

Thank you for your comment. We deleted the term “benign” in this context.

Science Editor:

(1) 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);

Thank you for your comment. We uploaded an approval document.

(2) 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;

Thank you for your comment. The original pictures will be provided.

(3) PMID numbers are missing in the reference list. Please provide the PubMed numbers to the reference list and list all authors of the references. Please revise throughout;

Thank you for your comment. The reference list was reformatted.

(4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text;

Thank you for your comment. We added “article highlights” to our manuscript.

(5) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The

Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable;

Thank you for your comment. We removed Figure 1 as the Figure has been meanwhile published elsewhere. Figure 2 and 3 are original figures that have not been published before.

(6) Authors should cite no more than 3 their own published articles. Please check and remove the inessential self-citations.

Thank you for your comment. We kept only 4 self-citations and replaced our studies other with evidence-based references. As we are the biggest centers of excellence of the upper gastrointestinal tract, we conducted many studies and multicenter projects with other key opinion leaders around the world in the last years especially focusing on esophageal cancer and GI function testing including the Restech device.

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 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 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).

Thank you for your comment. We shortened the title to: “Gastrointestinal Function Testing Model using a new laryngopharyngeal PH Probe (Restech) in patients after Ivor-Lewis esophagectomy”

We would like to thank you in advance for considering our manuscript for publication with the included changes.