

To The Editor, World Journal of Clinical Cases
Response to Reviewers' and Editors' comments

We thank the reviewers and editors for their comments and provide our responses below. Where necessary, changes have been made to the manuscript according to the remarks of the editors.

Reviewer #1: This is a valuable study where the Authors explored the expression of inflammatory cytokines' genes in esophageal mucosa in patients with erosive esophagitis (EE) and non-erosive (NERD) forms of gastroesophageal reflux disease and its association with the data of esophageal multichannel intraluminal pH-impedance measurements, with a control group of non-symptomatic subjects with normal endoscopy and pH-impedance results. The study has been carried out well in all respects and contains findings not previously reported in the literature. However in the Discussion the Authors should discuss more widely and deeply the impact of these results on clinical research. For example, what is the impact of different profile of local expression of cytokines genes in subgroups of patients with EE and NERD?

Authors' response: *We are grateful to the reviewer for the favorable comments and thoughtful approach to our results. According to the comments, the discussion section was revised.*

The absence of an association of IL-10 expression with acid exposure and the fact that the mean esophageal pH values of the EE group did not differ from those of NERD group could have also another possible explanation. The weakly acidic refluxes could contain deoxycholic acid, that impairs integrity of the esophageal mucosa (Am J Physiol Gastrointest Liver Physiol. 2016;310:G487-96 and Neurogastroenterol Motil. 2020 Dec;32(12):e13919.), being arrived in the esophagus through a duodeno-gastroesophageal reflux, which is a not uncommon event and must be taken into account in pathophysiology of esophagitis.

Authors' response: *Thank you for this valuable comment! We fully agree that bile acids may play an important role in pathogenesis of GERD. In the present study, it was not possible for us to assess this factor and its association with local expression of cytokines' genes. However, this is an interesting idea that requires further research in specially planned studies. **According to your comment, we made appropriate correction to the discussion (page 11).** In addition, the lack of association of IL-10 gene expression with esophageal acidity and number of gastroesophageal refluxes may be explained by anti-inflammatory nature of this cytokine [FASEB J. 2000 Sep;14(12):1666-8. DOI: 10.1096/fj.99-0874fje] and that it inhibits the induction of the pro-inflammatory cytokines TNF α , IL-1 β , IL-12, and IFN γ secretion.*

In our study, we failed to establish any association of the studied genes' expression with weak-acid and non-acid refluxes. Probably, this was caused by the fact that number of refluxes of these types was significantly lower than acid ones (however, the amounts correspond to what we see in a real-life practice). Evidently, larger studies to make an association much clear.

We agree with the Authors that the relatively small number of patients is a limitation of the study which prevents further subdivision of subgroups for more in-depth analysis of correlations. I hope the sample size can be expanded in the future, possibly with bile reflux monitoring.

Authors' response: Thank you for this comment. We also hope that it would be possible to continue this work at new methodological level.

Reviewer #2: Authors should strongly justify the necessity to conduct the described research. This part of the introduction is insufficient.

Authors' response: The Introduction section was revised (page 5).

Case-control, study design diagram should be given

Authors' response: Thank you for this comment. We added figure 1 "Study design and subjects' flow and allocation chart" to address your suggestion and fulfill the requirements of International Committee of Medical Journal Editors.

(1) Science editor:

The manuscript describes the expression of inflammatory cytokine gene in esophageal mucosa of patients with erosive esophagitis and non erosive gastroesophageal reflux disease and its correlation with pH impedance measurement data in esophageal multi-channel cavity. This is a single center study with good experimental design, but it is only a descriptive study. For me, it is not a very valuable topic.

Authors' response: We regret that the topic of the article is not valuable to the Science Editor. However, we hope that the results of the study can serve as a basis for further systematization of knowledge in this area.

It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Authors' response: We made necessary correction in accordance to your comment. Thank you.

After revision the paper was proofread by the professional linguist to ensure quality of English.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Clinical Cases.

Authors' response: We are grateful to the Company Editor-in-Chief for the kind invitation and the opportunity to publish our data.

On behalf of the authors
Sergey Morozov, MD, PhD