

December 2, 2016

Damian Garcia-Olmo, MD, PhD, Stephen Strom, PhD, and Andrzej Tarnawski, DSc, MD, PhD
Editors-in-Chief, World Journal of Gastroenterology

Re: Revision of Systematic Review for World Journal of Gastroenterology Manuscript NO. 30557

Dear professors Garcia-Olmo, Strom, Tarnawski, and Editors of the World Journal of Gastroenterology,

We greatly appreciate the Editors' and the Reviewers' thoughtful comments of our manuscript entitled "Esophagogastric Junction Distensibility Assessed using the Functional Lumen Imaging Probe – A Systematic Review. We have revised our manuscript in accordance to the reviewers' comments. Please find also our point-by-point response to specific comments below.

We would like to thank the editors for the opportunity to revise our manuscript. We look forward to hearing from you regarding our resubmission and to respond to any further questions and comments you may have.

Sincerely,

Joan Chen, MD MS

Department of Gastroenterology

University of Michigan

Authors' reply to Reviewers' comments

Reviewer 00033010

Chen and Rubenstein wrote a systematic review of literature concerning the use of FLIP system to evaluate esophagogastric junction (EGJ) in achalasia, GERD patients undergoing surgical procedure and healthy controls. The review is well written and it addresses a novel field with possible evolution in the future. The research strategy is adequate and adherent to the standard of quality.

Main comments:

1) Some typos should be corrected.

We thank the reviewer for pointing out some typos. These have been checked and corrected.

2) Authors should precise why they considered studies which adopted the specific range of 7-10 cm for balloon size and 30-40 mL for volume distension (in Methods, possibly reporting references).

Balloon length and distention volume varied in the literature. Based on our experience and in reviewing the literature, distensibility and CSA data are affected by distention volume and, to a lesser degree, balloon length. Thus, we have limited our review to including the most common balloon size and volume distention. This was explained in the methods section: "Due to the variability of study protocol in terms of balloon length and volume distension at the time of distensibility measurement, which can affect measurement values, we focused our report on the most commonly used balloon sizes and distension volumes in our analysis: EndoFLIP balloon sizes between 7 and 10cm, and volume distension of 30 and 40mL."

3) Since Newcastle-Ottawa scale is used for non randomized trials, Authors should report the nature of included studies in the table. Were they all non randomized?

As EndoFLIP is mostly used as a diagnostic tool, all studies included were non-randomized. They were observational/cross-sectional studies. The following statement was included in the results section: "Due to the nature of EndoFLIP as a diagnostic tool currently, studies included were non-randomized observational/cross-sectional studies."

To specify the NOS for each studies, the following statement has also been made in the Results section, "The Newcastle-Ottawa Scale (NOS) score for each study is included in Table 1. All included studies had NOS score between 6 and 8."

4) Was FLIP procedure compared to a standard of care (such as manometry) in included studies?

The majority of studies using FLIP to date have been using it as a tool for assessment of EGJ distensibility. No direct correlation between manometry and FLIP has been made. More recently, researchers have begun comparing FLIP *topography* with high-resolution manometry EPT plots in the body of the esophagus. This is beyond the scope of this review.

Reviewer 03254126

I read with interest your manuscript on EGJ distensibility addressed by FLIP. I have the following comments:

1. Can you correct aim of the “study,” end of page 5?

We thank you for the correction. The aim has been modified to “To assess reference values in the literature for esophageal distensibility and cross-sectional area (CSA) in healthy and diseased subjects measured by the Functional Lumen Imaging Probe (FLIP).”

2. In the result section, you have excluded EoE patients, can you comment on that?

Studies involving EoE subjects were excluded as these 3 studies used FLIP balloon in the esophageal body. In addition, it was unclear if FLIP was used in distal esophageal body, proximal, or both. As our review focused on esophagogastric junction distensibility measured by FLIP, we excluded studies on EoE. The following statement was added to the results section: “FLIP studies including EoE subjects were also excluded as these 3 studies measured FLIP parameters in the esophageal body; in addition, it was unclear if FLIP measurements were taken in the distal, proximal esophagus, or both.”

3. For readability, can you add subtitles in the result section for healthy, GERD and achalasia patients?

Thank you for this suggestion. We have added the subtitles prior to each section.

4. Please, can you edit table legend #1.

Thank you for the suggestion. Table 1 legend has been modified to the following:

“List of all eligible studies including healthy, achalasia, and GERD subjects based on inclusion/exclusion criteria. The NOS quality score for each study, number of subjects (N) for pre- and post-intervention, bag length (cm) and volumes (ml) are as listed.”

5. Can you edit figure #2 legend to better mix mean/SD and median/range?

We thank you for the recommendation. We have edited the figure legends (2A-C) to clarify mean/SD and median/range. For example, Figure 2A legend has been modified to the following: “Mean values (open circles) with standard deviations (vertical boxes around means) and median values (closed circles) with 5th to 95th percentile (vertical boxes around medians), and ranges (vertical lines) for distensibility (mm²/mmHg) at FLIP bag volume of 30, 40, and 50mL in healthy volunteers are shown in this plot.”

Reviewer 02839995

I've read with interest this systematic review. It is well written, aims are clear, as well as results and discussion. Good readability with interesting messages for readers.

Reviewer 02542060

I think this article is well written. In this paper, chen et al summarizes the published literature before 2014 on the FLIP used in healthy volunteers, gastroesophageal reflux disease and achalasia patients to assess EGJ distensibility, and found that FLIP may especially have a role in assessment of treatment response in patients with achalasia or GERD patients undergoing intervention. Chen et al also suggested that use of an 8cm balloon at 40mL volume is the most likely clinically relevant protocol for distinguishing achalasia from normal esophagus, and assessing response to therapy. This paper provides an important reference for clinical practice to understand the function of EGJ by measuring the expansion of EGJ. But there are some typing errors in the text.

1、 p6: line 4, “EndoFLIPimpedance planimetry” should be “EndoFLIP impedance planimetry”.

Regarding comments 1-9, these typos were likely due to formatting changes during the review process as these were not found in the original Word document . We thank the reviewer for reading our manuscript carefully and pointing these out nonetheless.

2、 P:6 line14, “post-antirefluxprocedures” should be “post-antireflux procedures”

3、 P:6 line18, “thesedone” should be “these done”

4、 P:10 line1, “TransoralIncisionless Fundoplication” should be “Transoral Incisionless Fundoplication”

5、 P:11 line7, “offersinformation ondistensibility” should be “offers information on distensibility”

- 6、 P:11 line7, “canpotentially” should be “can potentially”
- 7、 P:12 line15, “antireflux proceduressuggests” should be “antireflux procedure ssuggests”
- 8、 P:12 line16, “fromdate” should be “from date”
- 9、 P:12 line16, “surgerypatients” should be “surgery patients” And the meaning of “Of the 19 included studies, 8 studies were in patients with achalasia, 5 in GERD patients, 3 in eosinophilic esophagitis patients, and 11 included FLIP measurements in healthy controls.”(p:8 line16-18) is difficult to understand. As 8 and 5 and 3 is not equal to 19, what the remaining 3 studies about?

Thank you for pointing out the confusion. The reason for the numbers not adding up is because some of the studies included more than one subject types (healthy controls + a diseased population). The 19 studies included 8 studies with achalasia subjects +/- controls, 5 with GERD subjects +/- controls, 3 that included EoE subjects +/- controls, and the 3 remaining studies, as you pointed out, were studies that included only normal controls. This adds up to 11 studies that included normal controls.