Author’s response to reviews

Title: The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: a diagnostic clinical research

Authors:
Yuling Tong (irenyl@sina.com; 961459033@qq.com)
Yulian Wu (hbtranslation@sina.com)
Zhenya Song (89533384@qq.com)
Yingying Yu (41250433@qq.com)
Xinyan Yu (yuxinyan1214@163.com)

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Response to Reviewers’ comments

Dear Dr. Matteo Fassan

We are very grateful for your feedback regarding our manuscript entitled “The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: a diagnostic clinical research”.

We also thank the reviewers for the sound comments that have helped us markedly improve our study.

Please find below a point by point response to all comments.

We hope that this new very will be suitable for publication in your renowned journal. Please do not hesitate to contact me if you need further information regarding this manuscript.
Best wishes,
Yulian Wu

General Surgery Department, The Second Affiliated Hospital of Zhejiang University, School of Medicine, NO.88 Jiefang Road, Hangzhou, Zhejiang Province, P.R. China
Tel: +86-571-89713988
E-mail: hbtranslation@sina.com

Zhenya Song
International HealthCare Center, The Second Affiliated Hospital of Zhejiang University, School of Medicine, NO.88 Jiefang Road, Hangzhou, Zhejiang Province, P.R. China
Tel: +86-571-89713988
E-mail: 89533384@qq.com

Editor Comments:
The use of a standard gastritis staging (i.e., OLGA, OLGIM,...) should be adopted and implemented in the new version of the manuscript.

Response:
We appreciate very much your constructive comments to our manuscript (BMGE-D-16-00541) entitled "The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: a diagnostic clinical research". We adopted the OLGA system to assess the gastritis staging, and reanalyzed the database. The high risks stage (stage III and IV of the OLGA classification) was defined as severe atrophic gastritis group (SAG), and occupied 1.3% of the population. We highlight the changes by using underlined text. Thank you again for your carefully reviewing and helpful suggestions.

Reviewer reports:
Reviewer 1: The aim of the article is interesting but its topic is too much wide to evaluate realistic the conclusions.
The following points are the main revisions.
- The cut-off of PGI and PGR always show low specificity and low positive predictive value; these values suggest that false positive cases are too many high. And these results seems to be better only for severe atrophy.

- The authors say the serum pepsinogen could be useful to find severe gastric atrophy, dividing Hp-positive and Hp-negative group.

But, it is necessary to underline the small number of cases of this category is absolutely not sufficient to obtain significative conclusions.

The article has a good number of cases from the asymptomatic health population. And the number of discovered severe gastric atrophy (n.13; 1.3%)is quite realist, since this lesion is often symptomatic.

Until now and with these present results, this article shows the serum pepsinogen is not a good and reliable marker to detect atrophy gastritis, because of its statistic analysis.

The authors could extend and screen their health-population, in order the enforce their results, especially in severe atrophy. But it is important to underline that severe atrophy- or gastric atrophy generally- is often symptomatic, so the study could become very expensive and without results.

This article proves one more time the endoscopy and biopsy are the gold standard to "screen", to diagnose and to follow-up, and the serum pespinogen is an useful but not unique marker to screen gastric atrophy.

Response:

We appreciate very much your constructive comments to our manuscript (BMGE-D-16-00541) entitled "The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: a diagnostic clinical research". As your comments mentioned, our objects are asymptomatic health populations, so the number of discovered severe gastric atrophy (n.13; 1.3%)is quite small, but realist. We have highlighted these limitations in our discussion, and recommended further studies should comprise larger number of samples to enrolled more severe atrophy patients. Our next study has begun to take gastric cancer (GC) and precancerous lesions of GC screening in multi-centers throughout the country, and take the follow up by ABC method, using the cutoff value of PG established by this study, to validate these conclusions.

Endoscopy and pathology are the gold standard to diagnose atrophy and GC. But it is invasive and expensive, so it can’t be implemented for population-wide screening. PG is a noninvasive and cost effective method, combining with Helicobacter pylori, have gained great achievement in screening of the risk for GC and precancerous lesions of GC. In the ABC method, different groups have its recommended frequency of endoscopy, thus to early detect the changes of
mucosa. The important thing is which cutoff value should be used for the definition of PG-positive. In Japan, the cutoff value is PGI≤70 ng/ml and PGR≤3. But it varied in different researches. Our study was to discuss the cutoff value, then to discuss who should take endoscopy and how often should be taken. And in our study, we found the cutoff value of PG is quite different in Hp-negative (PGR ≤6.28) and Hp-positive groups (PGR ≤4.28). For ABC method, the PG-positive definition might use different cutoff values of PG in Hp-negative (group A and group D) and Hp-positive (group B and group C) groups, to recommend the frequency of endoscopy.

We have added these discussions in our article. We highlight the changes by using underlined text. Thank you again for your helpful suggestions.

Reviewer 2: Results are interesting.

I only would appreciate some more comments in the conclusion about the possibility to propose this approach as a cost effective screening method and about the possible practical consequences of this approach: who should underwent endoscopy and who not? which could be the economic impact of this approach?

Response:

Sincerest thanks for your comments on our manuscript (BMGE-D-16-00541) entitled "The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: a diagnostic clinical research". In the revised manuscript, we added some comments about this approach. The PG is a cost effective screening method, and combing with Hp, the risk of gastric cancer and precancerous lesions of gastric cancer can be stratified into four groups as follows: group A [Hp(-)PG(-)], group B [Hp(+)PG(-)], group C [Hp(+)PG(+)], and group D [Hp(-)PG(+)]. The important thing is which cutoff value should be used for the definition of PG-positive. In Japan, the cutoff value is PGI≤70 ng/ml and PGR≤3. In our study, we found the cutoff value of PG is quite different in Hp-negative (PGR ≤6.28) and Hp-positive groups (PGR ≤4.28). Thus the four groups can be divided. It is recommended that endoscopic examination be performed at least once every 3 years for group B, at least once every 2 years for group C, and annually for group D, and that group A be excluded from the examination.

We have added these discussions in our article. We highlight the changes by using underlined text. Thank you again for your helpful suggestions.