

## Answer to Reviewer

Thank you for your important comments, which were extremely helpful for improving the quality of our manuscript.

### Comments:

*Toyoshima et al. aimed to investigate the association between Kyoto classification and the topographic distribution of neutrophil activity and suggest that Kyoto classification score is associated with the topographic distribution of neutrophil activity. This is a very interesting study and clinical and endoscopy based criteria for atrophic gastritis/cancer risk assessment is encouraged. The study has a number of weaknesses as mentioned by authors themselves and these would reduce the strength of the study conclusion. The presence of neutrophils might be a risk factor for gastric cancer and based on Kyoto classification. However, the neutrophils are a non-specific inflammatory reaction that would require more quantitative specification like a cut off to signify these arguments and statements. In discussion authors mention after the atrophic gastritis progression, intestinal metaplasia occurs, especially in the antrum. I would suggest the authors define clearly what they mean by atrophic gastritis? In my opinion intestinal metaplasia and fibrosis are the main component of atrophic gastritis. The presence of neutrophil might be associated with atrophic gastritis but this could be present also without atrophic gastritis. Discussion should be more focused on authors finding.*

In our study, the histological estimation was conducted based on the updated Sydney System. Neutrophil infiltration was graded on a scale of 0-3 (none, 0; mild, 1; moderate, 2; severe, 3).

Based on the topographic distribution of neutrophil infiltration, the patients were divided into four categories: “inactive stomach,” “antrum-predominant gastritis,” “pangastritis,” and “corpus-predominant gastritis.” When neutrophil activity was null for the antrum and the corpus, the diagnosis was “inactive stomach.” When the antrum score was larger than that of the corpus, the diagnosis was “antrum-predominant gastritis.” When neutrophil activity was positive, and the antrum score was equal to that of the corpus, the diagnosis was “pangastritis.” When the corpus score was larger than that of the antrum, the diagnosis was “corpus-predominant gastritis.”

Atrophy is defined as the loss of normal glandular tissue of the gastric mucosa. The loss of glands may be followed by fibrosis of the lamina propria. Intestinal metaplasia is defined as a phenotypic change from the normal epithelial cell of gastric mucosa to an intestinal phenotype. Intestinal metaplasia is considered to be an advanced stage of atrophy. During the process, neutrophil infiltration leads to destruction of gastric glands.

Correa et al. proposed the following consecutive steps in *H. pylori*-associated gastritis as Correa’s cascade: normal gastric mucosa → atrophic gastritis → intestinal metaplasia → dysplasia → adenocarcinoma [Correa P et al. *Gastroenterology* 2007]. Atrophic gastritis progresses from the antrum to the corpus. Intestinal metaplasia mainly occurs in the antrum.

In early phase of atrophic gastritis, neutrophils are mainly infiltrated in the antrum. This condition could correspond to “antrum-predominant active gastritis”. When atrophic gastritis progresses from

the antrum to the corpus, neutrophil infiltration in antrum and corpus would be similar. This condition could correspond to “pangastritis”. When intestinal metaplasia occurs in the antrum, neutrophil infiltration in the antrum decreases. This condition could correspond to “corpus-predominant gastritis”. Namely, pathologically active gastritis could progress in the order of “antrum-predominant gastritis”, “pangastritis”, and “corpus-predominant gastritis”.

In our study, age, endoscopic atrophy score, and endoscopic intestinal metaplasia score and Kyoto classification score showed the same stepwise increase as the order of pathologically active gastritis topography. These comments were added into the revised manuscript.

*1 Scientific quality: The manuscript describes a retrospective study of the Kyoto score for neutrophil activity topography. The topic is within the scope of the WJG. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: This is a very interesting study and clinical and endoscopy-based criteria for atrophic gastritis/cancer risk assessment is encouraged. The study has a number of weaknesses as mentioned by authors themselves and these would reduce the strength of the study conclusion. The presence of neutrophil might be associated with atrophic gastritis, but this could be present also without atrophic gastritis. Discussion should be more focused on authors finding. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 2 figures. A total of 39 references are cited, including 18 references published in the last 3 years. There are 12 self-citations. 2 Language evaluation: Classification: Grade A. A language editing certificate issued by Editage was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Ministry of Education, Culture, Sports, Science and Technology of Japan; and the Tailor-Made Medical Treatment with the BBJ Project from Japan Agency for Medical Research and Development, AMED. The topic has not previously been published in the WJG. The corresponding author has published 2 articles in the BPG. 5 Issues raised: (1) I found 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); (2) I found the authors did not provide the original figures. 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; and (3) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.*

(1) We uploaded the approved grant application forms.

(2) We uploaded the original figures on a Power Point file.

(3) We added the “article highlight” as following.

## Research background

The pathological topographic distribution of neutrophil activity in the gastric mucosa correlates to gastric cancer development. Endoscopy-based Kyoto classification of gastritis has also been reported to be associated with gastric cancer risk.

## Research motivation

The consistency of the Kyoto classification score with the topographic distribution of neutrophil activity was not clear.

## Research objectives

To investigate the association between endoscopic findings of gastritis based on the Kyoto classification and pathological topography of neutrophil activity.

## Research methods

This study consisted of participants who underwent esophagogastroduodenoscopy at the Toyoshima Endoscopy Clinic from December 2013 to January 2016. We obtained two-points biopsy samples from the greater curvature of corpus and antrum. Based on the pathological topographic distribution of neutrophil activity, the subjects were divided into four categories: inactive stomach, antrum-predominant gastritis, pangastritis, and corpus-predominant gastritis. We tested the association between the Kyoto classification score, including atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness score, and the four categories of topographic distribution of neutrophil activity.

## Research results

We enrolled 327 patients. The Kyoto scores were significantly higher in the order of inactive stomach, antrum-predominant gastritis, pangastritis, and corpus-predominant gastritis (3.05, 4.57, 5.21, and 5.96, respectively). Especially, atrophy score and intestinal metaplasia score were correlated with the topographic distribution of neutrophil activity. On multivariate analysis, the Kyoto score, age, and serum *H. pylori* antibody were independently associated with the topographical distribution of neutrophil activity.

## Research conclusions

Endoscopic findings of gastritis based on the Kyoto classification were associated with the pathological topographic distribution of neutrophil activity and showed the stepwise increase in the order of inactive stomach, antrum-predominant gastritis, pangastritis, and corpus-predominant gastritis.

## Research perspectives

Our study supports the hypothesis that endoscopic findings based on the Kyoto score are useful for the assessment of gastric cancer risk. However, further studies are warranted to clarify the association between the Kyoto classification of gastritis and gastric cancer risk.

*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 Gastroenterology, 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 author(s) must include the keyword "gastritis" in the manuscript title.*

According to your comment, the title was modified to "Endoscopy-based Kyoto classification score of gastritis related to pathological topography of neutrophil activity".

Thank you again for your helpful reviews.