Dear Sir,

Thank you for your kind letter of December 30, 2016. We sincerely appreciate the constructive criticism of our paper entitled, “Factors Associated with Residual Gastroesophageal Reflux Disease Symptoms in Patients Receiving Proton Pump Inhibitor Maintenance Therapy”.

We have revised the manuscript according to the comments from the reviewers and yourself. We showed the sentences that we changed or added by highlighting the text (the highlighting in yellow indicates responses to reviewers and editor, and the highlighting in blue indicates revisions by a professional English language editing company; AMERICAN JORNAL EXPERTS).

Reviewer #1 (Reviewer’s code 00069819)

Comment

＞My only suggestion is that in the conclusion section the Authors should state their suggestions and perspectives for future research. They should also expand on further (practical) recommendations for the treating physician.

→Based on the reviewer's comment, we revised and added the description in the conclusion section of the DISCUSSION as follows.

In conclusion, approximately half of the GERD patients receiving maintenance PPI therapy had residual symptoms associated with a lower quality of life. Although CYP2C19 genetic polymorphisms appeared to be associated with these residual symptoms, the impact of the genetic polymorphisms differed significantly between the EE and NERD patients. NERD patients with the CYP2C19 IM or PM genotype might require additional treatment other than PPIs. Further studies on the usefulness of the treatment strategy tailored to the CYP2C19 genotype are required for PPI-refractory GERD patients.

(from lines 1 to line 8 of page 17)

Reviewer #2 (Reviewer's code 02999941)

Comment 1

＞1. why were 39 patients used? Was there a power calculation based on previous studies? The small number of patients makes logistic regression with a large of variables difficult.

→In this study, we prospectively enrolled as many eligible patients as possible within a one-year period to investigate the actual situation of GERD symptoms in patients in clinical practice receiving maintenance PPI therapy. As a result, as

the reviewer commented, the number of study subjects was small. Although we did not perform a strict power calculation because this study was a preliminary study, we believed that we could analyze the factors associated with residual GERD symptoms using the FSSG score, which characterized GERD symptoms quantitatively. However, we did not feel it appropriate to conduct a multivariate analysis due to the small number of subjects.

Comment 2

＞2. Perhaps a note on how CYP2C19 genotyping was carried out would be reasonable.

→Based on the reviewer's comment, we revised and added the description in the *subjects* section in the MATERIALS AND METHODS as follows.

The CYP2C19 genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism technique with allele-specific primers using a DNA sample extracted from each patient's peripheral blood leukocytes. Based on the finding of the wild-type allele or the two mutated alleles (*2 and *3), the patients were classified as rapid metabolizers (RM: homozygous for the wild-type allele), intermediate

metabolizers (IM: carrier of only one mutated allele), or poor metabolizers (PM: homozygous for the mutated allele) [24-27].

(from lines 4 to line 10 of page 9)

Comment 3

＞3. Based on the author's experience, does the type of PPI and response make a difference? Were there enough patients using different PPIs to address this?

→As the reviewer commented, we did not include a sufficient number of patients to examine differences in the types of PPI in this study. However, in the statistical sub-analyses with the rabeprazole users (who represented the majority of the study subjects), a similar correlation was observed between the CYP2C19 genotype and the FSSG-RS or FSSG-DS score. Further studies with a larger number of subjects are needed to clarify the relationship between the CYP2C19 genotype and the residual GERD symptoms in patients receiving maintenance PPI therapy.

Comment 4

＞4. In Table 2, what does "half-dose" PPI mean?

→The data on the use of a half dose of PPI in Table 2 show no difference in the residual GERD symptoms between the EE patients receiving the half-dose PPI and the EE patients receiving the full-dose or double-dose PPI. This result indicates that the residual GERD symptom in the EE patients are not due to an insufficient PPI dose.

Comment 5

＞5. Figures 4a and 4b may be better served as text +/- supplementary tables.

→Based on the reviewer's comment, we deleted Figures 4a and 4b. We revised and added the description in the *Correlation between the CYP2C19 genotype and FSSG score in the EE and NERD patients* of the RESULTS as follows.

We also examined the correlation between the CYP2C19 genotypes and the FSSG-RS or FSSG-DS scores in the EE and NERD patients. In the EE patients, the FSSG-RS scores of the subjects with the CYP2C19 RM genotype were significantly higher than the scores of the subjects with the other CYP2C19 genotypes (11±1.9 vs. 3.8±0.8, P = 0.0044). In contrast, the FSSG-DS scores of the NERD patients with the CYP2C19 RM genotype were significantly lower than the scores of the NERD subjects with the other CYP2C19 genotypes (1.3±0.4 vs.

5.2±0.8, *P* = 0.0069).

Significant differences in the FSSG-RS scores in the EE patients (RM: 11.0±1.9, IM: 3.6±0.9, PM: 4.5±1.5, *P* = 0.0147) and the FSSG-DS scores in the NERD patients (RM: 1.3±0.4, IM: 4.7±0.8, PM: 7.0±2.3, *P* = 0.0177) were also observed in the bivariate analyses among the three CYP2C19 genotypes.

(from lines 11 of page 12 to line 4 of page 13)

Reviewer #3 (Reviewer's code 02440510)

→We appreciate your kind comments.

Additionally, according to the Editor's suggestions, we revised the corresponding author's address and the format of the quotation numbers in the text.

To correct the inappropriate description, we deleted the word "GERD" in the text of the *Statistical analysis* section of the MATERIALS AND METHODS as follows.

A bivariate analysis (Mann-Whitney U test, Pearson's correlation coefficient, or Kruskal-Wallis test) was performed to assess differences in the FSSG scores

(total score, RS score or DS score) and background factors in the EE and NERD patients. (from lines 8 to line 11 of page 10)

I hope that these revisions to the text and figures satisfactorily address the referees' concerns and that the revised version will now be considered acceptable for publication in *World Journal of Gastroenterology*.

Sincerely yours,

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