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Title: Helicobacter pylori infection in subjects negative for high titer serum antibody

Answers to Reviewers

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

Reviewer 1

Minor comments 1. In the "Results" section, does "No patient was excluded" mean that the healthy individuals with normal gastric mucosa were excluded?

No, that is not what we meant. Healthy individuals with normal gastric mucosa were also included. Therefore, we have deleted the particular sentence to avoid confusion.

2. As described in the "Discussion" section, further study is strongly necessary to analyze the association between the presence of CagA positive H. pylori and Kyoto classification.

We strongly agree with you and as you indicated, this is an important point. We have added the following comment in the revised manuscript: "Further studies should be performed to analyze the association between the presence of CagA positive *H. pylori* infection and Kyoto classification"

Reviewer 2

Major points

1. A table with multivariate analysis is missing.

We have added the table (Table 4) with multivariate analysis in the revised

version.

2. Abstract should include data only from multivariate analysis.

In accordance with your comment, we have deleted the data derived from univariate analyses from the abstract.

3. The lack of central reading for evaluating endoscopic findings is a major limitation of the study.

In this study, the EGD images were retrospectively reviewed by the chief investigator (OT). Any disagreements were resolved by consulting a third reviewer (TN). These comments have been added to the revised manuscript.

4. Long-term outcome of the 17% of the patients with negative-high titer serum anti-H. pylori antibodies without history of eradication therapy who had H. pylori infection, would be of great clinical value.

In this study, we did not analyze the long-term outcomes of the 17% of the patients who had negative-high titer serum anti-H. pylori antibodies without history of eradication therapy and who had H. pylori infection. Further studies should be performed to analyze the long-term outcomes. A comment in this regard has been added to the revised manuscript.

Minor points

1. How was the cut-off from ROC analysis identified? (Based on the Youden index?).

In our study, the cut-off values were based on the Youden index. This has been added to the revised manuscript.

2. Continuous variables should be better presented as median (IQR).

In accordance with your comment, continuous variables are now presented as median (IQR).

Reviewer 3

Previously, Sugimoto et al., investigated a total of 1,200 patients with H. pylori-positive gastritis alone (n=932), early-stage H. pylori-positive gastric cancer (n=189), and successfully treated H. pylori-negative cancer (n=79) were endoscopically graded according to the Kyoto gastritis classification for atrophy, intestinal metaplasia, fold hypertrophy, nodularity, and diffuse redness (Sugimoto M1, Ban H, Ichikawa H, Sahara S, Otsuka T, Inatomi O, Bamba S, Furuta T, Andoh A. Efficacy of the Kyoto Classification of Gastritis in Identifying Patients at High Risk for Gastric Cancer. Intern Med. 2017;56(6):579-586. doi: 10.2169/internalmedicine.56.7775. Epub 2017 Mar 17). In the present study the small number of cases is a big limitation compared to the similar studies in the literature. In order to categorize the patients according to the Kyoto gastritis classification, endoscopy should be applied. On the other hand, UBT is less irritating compared to the endoscopy. UBT is indicated to confirm H. pylori colonization and to monitor its eradication. Positive UBT indicates and active H. pylori infection (Ferwana M, Abdulmajeed I, Alhajiahmed A, Madani W, Firwana B, Hasan R, Altayar O, Limburg PJ, Murad MH, Knawy B. Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis. World J Gastroenterol. 2015 Jan 28;21(4):1305-14. doi: 10.3748/wjg.v21.i4.1305). As UBT is accepted as gold standard, the authors should clearly discuss why Kyoto gastritis classification should be considered in H pylori infection (high antibody titer, negative cases, as well). Kyoto gastritis classification and association with cancer development should also be discussed.

Kyoto classification score is believed to provide an estimate of the risk of gastric cancer. In the study by Sugimoto *et al.*, they observed that the mean Kyoto classification score in the cancer group was 4.6 ± 1.2 , which was significantly higher than that in the control group (3.8 ± 1.1 ; $p < 0.001$). In subgroup analysis within the cancer group, the mean Kyoto classification score in the *H. pylori*-uneradicated subgroup was 4.8 ± 1.1 , which was significantly higher than that in the eradicated subgroup (4.2 ± 1.2 ; $p < 0.001$). These comments have been

added to the revised manuscript.

Serum anti-*H. pylori* antibodies are routinely evaluated during medical checkups or in clinical practice because the test is inexpensive and easy. Similarly, EGD is also popular because it can accurately diagnose upper gastrointestinal malignancies. Although UBT is accepted as the gold standard, the procedure is more cumbersome for the medical staff than the testing the serum antibodies. Therefore, clinical evaluation is often made based on combined results of EGD and serum antibody. Although Kyoto classification score was developed to estimate the risk of gastric cancer, our study showed that Kyoto classification score could predict *H. pylori* infection in negative-high titer patients as well. These comments have been added to the revised manuscript.

As a reference, the paper by Ferwana M, *et al.* (*Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis. World J Gastroenterol. 2015; 28;21(4): 1305-14*) has been added to the revised manuscript.