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Dr. Murakami et al reply

To the Editor:

We sincerely appreciate the thoughtful comments and constructive feedback by Dr. Zhuo[1] regarding our article on the association between proton pump inhibitor (PPI) use and the incidence of intestinal Behçet disease (BD).[2] We are grateful for the opportunity to clarify several points and to discuss the limitations and future directions of our research.

First, Dr. Zhuo noted that the risk of intestinal BD appeared higher after 1-2 years of PPI use than after more than 2 years. As we also discussed in our article,[2] this observation may be due to the relatively small number of cases in each subgroup, which limited the statistical power to confirm this trend. We agree with Dr. Zhuo's hypothesis that changes in the gut microbiota might underlie this phenomenon, and we consider this an important area for further prospective investigation.

Second, regarding disease severity, comorbidities, and inter-individual variability, we fully acknowledge that these factors may influence both the incidence of intestinal BD and the effect of PPIs. Unfortunately, detailed clinical information on BD severity was not uniformly available in our retrospective cohort, limiting our ability to incorporate this into the analysis. We agree that future studies should stratify patients according to disease severity and medication response to provide a more nuanced understanding of the risks.

Third, as Dr. Zhuo highlighted, unmeasured confounding factors such as diet, lifestyle, and genetic background may have affected our results. Although we adjusted for several known covariates and performed propensity score matching, residual confounding cannot be ruled out. This limitation is inherent in retrospective observational studies and underscores the need for prospective, multicenter studies to validate our findings.

Fourth, with respect to potential biases, we acknowledge the inherent limitations of retrospective data collection, including possible inaccuracies in medication records and missing information. To mitigate these issues, we relied on comprehensive medical records at a tertiary referral center and performed sensitivity analyses, but we agree that prospective data collection would provide greater accuracy.

Fifth, we recognize the challenge of distinguishing intestinal BD from other inflammatory bowel diseases, particularly Crohn disease. In our study, all diagnoses were made based on a combination of endoscopic findings and established clinical criteria, with input from experienced gastroenterologists and rheumatologists at our institution. Nonetheless, as Dr. Zhuo points out, misclassification remains a potential concern.

Finally, Dr. Zhuo commented on the classification of PPI dosage and duration. We agree that the categorization we employed was relatively simplified due to the constraints of retrospective data availability, although several previous studies have used similar classifications.[3] We attempted to capture broad patterns of exposure, but we acknowledge that more detailed analysis, including intermittent and variable dosing, would provide additional insight.

In conclusion, we appreciate Dr. Zhuo's valuable comments,[1] which underscore important limitations and future research directions. Despite these limitations, we believe our findings provide meaningful evidence of an association between PPI use and increased risk of intestinal BD. We hope that our work stimulates further prospective research to elucidate the underlying mechanisms and to guide safer clinical practice in managing patients with BD.

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