August 15, 2017

Dr. Ya-Juan Ma, MSc
Science Editor, *World Journal of Gastroenterology*

RE: Manuscript NO: 35217 - Manuscript revision

Dear Dr. Ma,

My co-authors and I are pleased to submit a revised version of our original research article "Factors associated with carcinoid syndrome in patients with gastrointestinal neuroendocrine tumors" for publication in *World Journal of Gastroenterology*. We appreciate the consideration of our manuscript and the opportunity to revise and resubmit in response to the feedback. We have incorporated these valuable suggestions into the manuscript to the best of our ability.

Specific responses to each suggestion are noted below, including page references to where corresponding changes can be found in the revised manuscript. Changes have also been highlighted within the manuscript.

We look forward to working with you to move this manuscript towards publication in *World Journal of Gastroenterology*.

Sincerely,

Michael S. Broder, MD, MSHS

Reviewer comments:

1. The nature of retrospective study; case-control study using US administrative claims may cause several confounders and details e.g. the database is not designed for research, and may had misclassification. Additionally, the CS cases with minor symptoms such as cutaneous flushing, diarrhea with few bowel movements/day may underdiagnosed[1].

   We agree that there are important limitations to the method and the database. We have revised the discussion to include the following statements (pg. 12):
   "GI NET and CS diagnoses were identified from healthcare claims coded for reimbursement, not research, and misclassification was possible. Errors in coding could bias our analysis. Specifically, patients with CS who have less severe symptoms may never be coded as having the syndrome."

2. The authors have to discuss why the number of 25% of both population of GI-NETS cases in development dataset and validation dataset had carcinoid syndrome (CS) which was higher than those previous reports of 3-21% of NET patients[1, 2]

   We appreciate the reviewer's point—our estimate is on the higher side of prior estimates. Halperin 2017 reported 19% of NET patients had CS but also reported that 32% of GI- NET patients had the syndrome. Given that many prior estimates of CS frequency were based on clinical data and ours on insurance claims, we feel the discrepancy between our study and others is not unexpected. See response to number 6 below.

3. The number of new cases of NETs in 2012 is reported from 6.98 cases per 100,000 individuals thus this study included 2162 cases which should be derived from 30,974,212 population by calculation. Therefore, this number is not equivalent to the information in methods which mentioned that the newly diagnosed cases with GI NETs is included during the 1/1/2010 - 12/31/2014 and the PharMetrics Plus database is comprised of 150 million patients enrolled in US health insurance plans, with an annual capture of 40 million. Is it correct?

   The reviewer appears to be concerned about the discrepancy between the incidence of NET as reported in SEER and the relative size of our cohort of GI-NET patients in relationship to the overall database we used. The most important reasons for the lack of comparability of these numbers are, first, that the cited publication reports the incidence of NET overall, and our study only included GI-NET. Second, SEER, the source of data for cited number, is a coordinated system of population-based cancer registries located across the US, whereas the insurance claims used in the present study are a convenience sample. Third, the current study was not designed to estimate incidence and captured cases over a 5-year period. For a more complete discussion, we direct the reviewer to a recent publication attached, accepted since the current manuscript was submitted, that uses claims data to estimate GI-NET incidence (Epidemiology of gastrointestinal

neuroendocrine tumors in a US commercially insured population DOI:10.4158/EP171879.OR).


Epidemiology of GI NET

4. In addition, the key diagnosis of CS is still doubtful, for example the standard guideline recommends a 24-h urinary 5-HIAA analysis should be performed for all patients with a small intestinal primary NET, as well as those with symptoms suggestive of the carcinoid syndrome[3] but it's not well noted in this study.

   We appreciate the reviewer's comment and agree with the cited standard. We have clarified the recommended diagnostic methods in the Discussion (pg. 12): "The current study included more GI-NET subjects than prior studies. The rate of CS among GI-NET patients in our study was higher than in some prior studies[20], and it was lower than at least one other.[17] The criteria we used to identify CS were more restrictive than the study by Halperin et al. Current recommendations for diagnosing CS include measuring 5-HIAA.[1,21] We incorporated that recommendation into our identification algorithm, requiring two claims with an ICD-9-CM code for CS and a claim for either a urine 24-hour 5-HIAA or a serum serotonin in the period surrounding that diagnosis, whereas the prior study required two claims for CS, diarrhea, or flushing."

5. The predictive factor for CS were liver disorder [OR 3.38 (2.07 - 5.51)], enlargement of lymph nodes [OR 2.13 (1.10 - 4.11)], and abdominal mass [OR 3.79 (1.87 - 7.69)] were interesting and give some new information. However, the tumor burden and the behavior of aggressive tumor progression may be key important factors instead of the reported predictors[3].

   We agree with the reviewer that many factors other than those we identified may be important predictors. Indeed, as we note in the Discussion (pg. 12, para. 2), the factors we identified are likely to be related to other, more proximate factors such as tumor burden or aggressiveness. These theories are not mutually exclusive. We were not able to examine burden or aggressiveness directly, as these concepts are not coded in claims.

6. Finally, the strength of this study is the high number of sample size in both dataset compared to previous report[4]. In addition, the clinical presentation of this study is different from the large study from Japan[5]. The authors should add discussion in this aspect.

   We appreciate the reviewer's suggestion and while we do not have the information to discuss differences in clinical presentation, we have added the following text to the discussion (pg. 12):

"A strength of this study was that it was drawn from two very large underlying databases covering nearly 200 million patients enrolled in US health insurance plans. The rate of CS among GI-NET patients in our study was higher than in some prior studies[20], and it was lower than at least one other[17]."

References (from the reviewer's comments):

1. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol 2017;18:525-534.

2. Ducreux M. Carcinoid syndrome in neuroendocrine tumors: a prognostic effect? Lancet Oncol 2017;18:426-428.

3. Singh S, Asa SL, Dey C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. Cancer Treat Rev 2016;47:32-45.

4. Salyers WJ, Vega KJ, Munoz JC, et al. Neuroendocrine tumors of the gastrointestinal tract: Case reports and literature review. World J Gastrointest Oncol 2014;6:301-10.

5. Ito T, Igarashi H, Nakamura K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. J Gastroenterol 2015;50:58-64.

References (from the manuscript):

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Neuroendocrine Tumors Version 2. 2016.

17. Halperin DM, Shen C, Dasari A, Xu Y, Chu Y, Zhou S, Shih Y-CT, Yao JC. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol* 2017;18:525–34 [PMID: 28238592 DOI: 10.1016/S1470-2045(17)30110-9].

20. Ito T, Igarashi H, Nakamura K, Sasano H, Okusaka T, Takano K, Komoto I, Tanaka M, Imamura M, Jensen RT, Takayanagi R, Shimatsu A. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. J Gastroenterol 2015;50:58-64. [PMID: 24499825 DOI: 10.1007/s00535-014-0934-2].

21. Singh S, Asa SL, Dey C, Kennecke H, Laidley D, Law C, Asmis T, Chan D, Ezzat S, Goodwin R, Mete O, Pasieka J, Rivera J, Wong R, Segelov E, Rayson D. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. Cancer Treat Rev 2016;47:32-45. [PMID: 27236421 DOI: 10.1016/j.ctrv.2016.05.003].