May 8, 2017

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Editors-in-Chief, *World Journal of Gastroenterology*

Ya-Juan Ma, Science Editor, Editorial Office, *World Journal of Gastroenterology*

RE: Manuscript NO: 33459

Dear Editors,

My co-authors and I are pleased to submit a revised version of our original research article "Real World Treatment Patterns of Gastrointestinal Neuroendocrine Tumors: A Claims Database Analysis" for publication in *World Journal of Gastroenterology (WJG)*. 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 *WJG*.

Thank you for your consideration.

Responses to reviewers

Ya-Juan Ma: Please add postcode.

> We have added postal codes for all of the authors listed on the title page.

Windows 用户 : Please read the core tip then provide the audio core tip:

 Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, don't allow to have the noise.

> We have attached an audio core tip file to our resubmission.

asdasd: **COMMENTS**

Background

To concisely and accurately summarize the related background of the article and to enable the readers to gain some basic knowledge relevant to the article, thus helping them better understand the significance of the article.

Research frontiers

To briefly introduce the hotspots or important areas in the research field related to the article.

Innovations and breakthroughs

To summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, from the other related or similar articles so as to allow the readers to catch up the major points of the article.

Applications

To summarize the actual application values, the implications for further application and modification, or the perspectives of future application of the article.

Terminology

To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers, but are essential for the readers to understand the article.

Peer-review

To provide the comments from peer reviewers that most represent the characteristics, values and significance of the article, and allow the readers to have an objective point of view toward the article.

> We have added a COMMENTS section to the manuscript with the required text and headings on pages 13-15.

Anonymous: The article is aimed to describe real world treatment patterns of gastrointestinal neuroendocrine tumors. The title is "Real World Treatment Patterns of Gastrointestinal Neuroendocrine Tumors: A Claims Database Analysis". 1. This is a retrospective study. 2. Several factors influence the outcome of the study. Some limitations might be occurred. Please discuss these factors. 3. Please add the limitations of the study in the discussion section. 4. Please also add the conclusion part in the text. 5. What are the new knowledges from this study? 6. Please recommend the readers "How to apply this knowledge for routine clinical practice?".

> Thank you for your comments.

> In response to comment 2 and 3, we believe that we have covered the limitations throughout the Discussion section (specific sections noted below). If the reviewer has a specific concerns, we would be happy to address them.

On pages 10-11: Each of these findings must be considered in light of what is known about the disease as well as the inherent limitations of the data source. Treating NET patients is a complex process. Treatments are individualized based on tumor size, location, and pathology, as well as whether the tumor is functional, type and extent of symptoms, and speed of progression. Our data did not include this level of detail. Insurance companies aggregate information on inpatient and outpatient services (generally reported as ICD-9-CM or ICD-10), procedures (ICD-9 procedure codes and CPT codes) and pharmacy claims (NDC) as claims are submitted for payment by providers, healthcare facilities, and pharmacies. So for example, while GI NET can be identified by using a list of ICD-9-CM codes, presence of advanced disease must be inferred by observing the use of pharmacologic treatment. Another limitation of the date source is that the available length of time for analysis is relatively brief, so conclusions regarding average duration of use may not be representative of long-term treatment patterns.

On page 11: There are several possible explanations for the frequent use of CC. Patients observed to initiate cytotoxic treatment may have been treated in the past with other agents and either progressed or were intolerant to those agents. We reviewed data for 6 months before the first pharmacologic treatment, but treatments more than 6 months in the past would have been missed. It may also be that some of the patients had a pathology finding suggesting chemotherapy would be beneficial, or a different type of GI tumor that was incorrectly coded as NET. Our data were de-identified, meaning we could not confirm the diagnosis in medical records, physician or patient surveys, or by other means.

On page 12: First, although median follow-up was over 15 months, many patients were eventually lost to follow-up when they disenrolled from a plan included in our databases. One third of patients were continuing to use their index treatment when they were lost to follow-up. Whether (or when) these individuals progressed to second-line treatment cannot be determined using these databases. If these patients were systematically different from the ones who remained under observation, our results would be biased…

On pages 12-13: In cases where Medicare had primary responsibility, we would have missed claims for pharmacologic or liver-directed therapy and thus underestimated treatment. The magnitude of this problem is impossible to know using our current data source. A study using Medicare data and examining patients over 65 only might be less likely to suffer from this bias. Finally, it may indeed be the case that some patients stop therapy completely. Such patients may be terminal and choose not to

undergo further treatment, or they may be relatively asymptomatic and decline to be treated on that basis. Further research with detailed clinical data would be needed to confirm which, if any, of these explanations is the most accurate.

In response to comment 4, the study conclusion can be found on page 13, as follows:

In this large, claims-based, retrospective study of real world pharmacologic treatment patterns, we found that 60% of GI NET patients began therapy with somatostatin analogues and about one-third with cytotoxic chemotherapy. The relatively long time to discontinuation of somatostatin analogues, as well as their use in combination with other agents, suggests they may be well tolerated and potentially have sustained effectiveness. We also found that over half of the patients discontinued treatment after first line and only less than 10% of the patients received second-line treatment despite the availability of a number of different options. To address the limitations of this study and expand knowledge of real world treatment patterns, a study using more detailed clinical information such as medical charts or physician surveys is warranted. In addition, future studies should consider using databases that would allow for greater longitudinal follow-up, such as registries, to assist in the further understanding of treatment patterns and length of therapy.

In response to comments 5 and 6, in the COMMENTS section (pages 13-15), we have added descriptions of what this study adds in terms of current research and future applications.