

[July 27th, 2021]

Subrata Ghosh & Andrzej S Tarnawski
Editors-in-Chief
World Journal of Gastroenterology

Dear Editors:

I wish to resubmit an observational study for publication in the *World Journal of Gastroenterology*, titled “**Clinical characteristics of gastrointestinal immune-related adverse events of immune checkpoint inhibitors and their association with survival.**” (Manuscript NO.: 69501, Retrospective Study).

This study investigated the differences in the clinical features of gastrointestinal (GI) immune-related adverse events (irAE) developed in patients receiving anti-PD-1/anti-PD-L1, anti-CTLA-4 antibodies, and combination therapy with anti-PD-1 and anti-CTLA-4 antibodies. Further, we examined the correlation between the development of GI-irAE and the prognosis of patients with non-small cell lung cancer (NSCLC) and malignant melanoma (MM). We found that GI-irAEs occurred more frequently and with higher severity in patients using anti-CTLA-4 antibodies than in those using anti-PD-1/PD-L1 antibodies. In MM, but not in NSCLC patients, those who developed GI-irAEs and continued treatment with immune checkpoint inhibitors (ICIs), the overall survival was significantly prolonged. We believe that our study makes a significant contribution to the literature because there are only a few coherent reports on the clinical features of GI-irAEs for each ICI. Our study addresses this knowledge gap and reports the clinical characteristics of patients who developed GI-irAEs after receiving different ICI treatments.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *World Journal of Gastroenterology*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers' suggestions. The responses to all comments have been prepared and given below.

Responses to the Comments by the reviewer 1:

First, the general impression is that the title of the manuscript does not reflect correctly the main result of the study and the introduction section is unnecessarily lengthy. The introduction section needs to be much more concise and focused on the main questions you propose to answer, and why these questions are important. Besides, your discussion should focus on how the questions have been answered and what they mean. please also review the quality of all figures. Second, English grammar and syntax must be improved. The level of English used in this manuscript is not rigorous enough for publication, so the paper needs carefully address all language editing. Finally, please check all the cited literature for both proper formatting for this journal and any special characters that may not have translated properly as well as for their appropriate usage.

Besides, you should also include more recent references because this is an area with extensive bibliography.

Reply:

Thank you very much for your important comments. We have revised the title of the manuscript and changed it to reflect our research outcomes and the introduction to be more concise and to make the purpose of this study clearer. We also modified it to state the questions and their implications for the research results in the discussion. English grammar and syntax have been reviewed and corrected with the support of Editage (www.editage.com). We have revised all references to a format suitable for this journal and added more recent references.

Responses to the Comments by the reviewer 2:

This is a very interesting study on long-term survival of patients treated with immune checkpoint inhibitors who developed gastrointestinal immune-related adverse events. It is very well written, statistical analysis is well done, and the manuscript is very well written. Nevertheless, I believe the authors should explore more the definitions of these events. Reading the manuscript, I could not pin out exactly which adverse events were studied - was just ischemic colitis? how many of each adverse event happened? I believe this data needs to be further explored and described.

Reply:

Thank you very much for this insightful comment. We agree with this comment that we should explore more the definitions of GI-irAEs. We have added the following text to the Methods section of the manuscript: '(GI-irAEs were defined as diarrhea or bloody stools after ICI administration in patients in whom infectious enteritis could be excluded. Infectious enteritis (Clostridium difficile, other bacterial infections, or viral pathogens, such as cytomegalovirus) was ruled out using blood tests and stool samples.)' (Page 9, Lines55-58). We also have added the following text to the Results section of the manuscript: '(Among 47 patients who developed GI-irAEs after ICI administration, 39 had diarrhea, one had bloody stools, and seven had diarrhea and bloody stools. Forty-three patients (excluding four patients diagnosed with infectious enteritis) were included in the analysis.)' (Page 11, Lines111-114)

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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