

Point by point response

Manuscript NO.: 74199, Letter to the Editor – World Journal of Gastroenterology

Dear Editor and reviewers,

First of all, we are thankful for the positive response on our manuscript and the comments raised. We have made the requested additions to the manuscript by reviewer 2 or made comments to them. The manuscript was proofread and edited by language scientific editing company. All additions and changes in the manuscript are highlighted in red font in the redline version of the manuscript.

(1) Science editor:

The letter explored the effects of metformin in Swedish patients with colorectal cancer and type 2 diabetes on cancer-specific survival and inflammatory factors. The data from this study warrant further study. however, as the reviewers suggested, authors need to refine the necessary research procedures such as the Ethics statements.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade A (Excellent)

Answer: Thank you for this positive response. We have added the Ethics statement to the manuscript and added a copy of ethic approval. We have gone through the language and done some minor changes and added PMID to all references.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Answer: Thank you for this positive response. We have made all requested revisions.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The letter entitled “Effects of diabetes type 2 and metformin treatment in Swedish patients with colorectal cancer on cancer specific survival and inflammatory factors” provided some extra evidence for the relationship between DM and patients with CRC. It is interesting to find that controversial data for predictive factors of CRC patients. Regarding the object of study, the authors should declare the Ethics statements.

Answer: Thank you for this positive response. We have added the Ethics statement to the manuscript that “The investigation was approved by the Regional Ethical Review Board in Linköping, Sweden, and informed consent was obtained from each participant.” We have added a copy of ethic approval and example of informed consent. We have also made changes to the text according to the feedback from the proofreading company.

Reviewer #2:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade D (Rejection)

Conclusion: Rejection

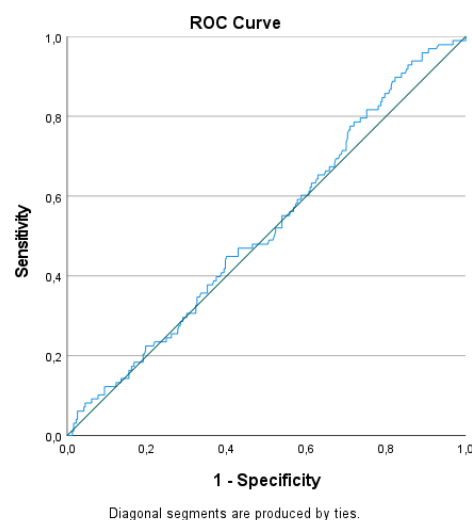
Specific Comments to Authors: Overview The letter explored the effects of metformin in Swedish patients with colorectal cancer and type 2 diabetes on cancer-specific survival and inflammatory factors. However, we do not think the article can be published because the analysis information is too simple and lack necessary information. Details 1. Clinical trials need to provide ethical approval documents or ethical approval numbers, and conduct clinical registration. In addition, as non-own data, the original data need to ask for specific authorization information. 2. The inclusion and exclusion criteria are not clear enough. The diagnostic criteria should be explicitly quoted and the exclusion criteria specified, such as recent trauma, surgery, or tumor. Criteria for inclusion and exclusion of the patient should be listed, including the diagnostic criteria cited, reasons for exclusion, etc., with a flow chart if necessary. For instance, patients staging criteria should be clearly marked. 3. The survival rate alone cannot fully reflect the experimental results, so the area under the survival march should be calculated and compared. In addition, basic patient information and relevant biochemical test data should be attached, as should other prognostic, pathological or biological

markers.

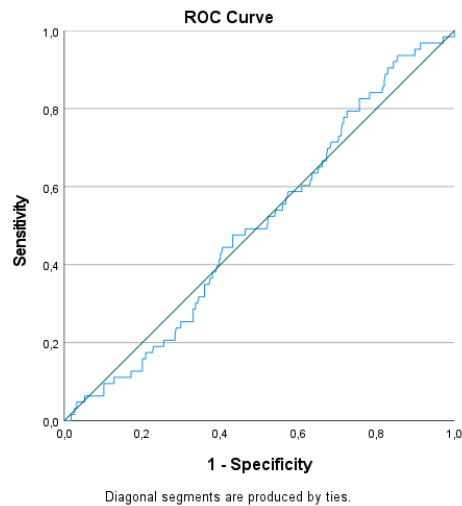
1. *Answer: We have added an ethical statement that “The investigation was approved by the Regional Ethical Review Board in Linköping, Sweden, and informed consent was obtained from each participant.” We have added a copy of ethic approval and example of informed consent.*
2. *We have specified the inclusion criteria which were all consecutive patients who underwent surgical resection for primary colorectal adenocarcinomas between 1996 and 2019 at the Department of Surgery, Ryhov County Hospital, Jönköping, Sweden.*

For sub analysis of association with DM and metformin to our previous studies against chemokines and other inflammatory factors, where these two factors were not previously included, the inclusion criteria in those published papers were based on patients and blood samples that were included in the database at that point. Since we refer to previously published papers we don't specify more about the inclusion criteria in the different sub analysis in this letter to the Editor. With respect to analysis of IGFBP7 we added those patients that have been added to the biobank since the previous study in 2009, which we believe is clear as it is written now.

3. *We appreciate the reviewer's suggestion to include ROC-analysis. For reviewer purpose we attach the results based on survival time of those with DM or not:*



As well as a ROC-curve for those with metformin treatment:



Both curves have an area under the curve of 0.52 and 0.50, which corresponds to the Kaplan-Maier results and confirms that there is no association between DM or metformin treatment and survival.

In the manuscript there are available basic patient information on other prognostic, pathological or biological markers such as stage, localization etc of the whole cohort. As a letter it is not optimal to add this information for each sub analysis, which is for most of the cases reported in the published papers we refer to. As suggested we have also included another biochemical marker such as CEA levels and found no association to either DM or metformin. We have added this to the text.

We have also made changes to the text according to the feedback from the proofreading company.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This letter can be accepted in this style

Answer: Thank you for the positive response.

Sincerely, Dick Wågsäter, professor, on behalf of the authors.