

We thank the reviewers and editors for the critical assessment of our manuscript. Here are our point-to-point responses to the comments.

## A) REVIEWERS'S COMMENTS

### Reviewer #1:

**Specific Comments to Authors:** 1. *Please describe more thoroughly about your inclusion and exclusion criteria.*

**Our response:** Thank you for the comments. The study was based on the bioinformatics analysis on the TCGA PanCancer Atlas dataset, and we have added TCGA sample inclusion criteria in the revised Materials and methods section. Specifically, we stated that "There are certain sample inclusion criteria for the TCGA PanCancer Atlas on colorectal adenocarcinoma. The biospecimens were collected from newly diagnosed colorectal adenocarcinoma patients undergoing surgical resection, regardless of histologic grade or tumor stage. The patients had not received prior chemoradiation therapy. The histological sections contained an average of 60% tumor cells with less than 20% necrosis".

2. *Although there may a link between somatic mutation in FAT cadherin family members and clinicopathologic features in patients with CRC. The authors should provide data of the functional outcome such as protein expression of these somatic mutations in FAT cadherin family to support their conclusion.*

**Our response:** Thank you for the comments. The study was based on the bioinformatics analysis on the TCGA PanCancer Atlas, and we could only extract the available information provided by the TCGA dataset. There has no available information on protein expression of FAT1-4 in the dataset. Moreover, even if we do have the information on protein expression level, the protein expression level does not necessarily correlate with the protein function, given our findings, presented in Table 2, that somatic mutations were significantly enriched in the extracellular cadherin domain that is critical for its function in signaling transduction. We have discussed this limitation in the revised discussion section, and we believe that "the underlying

**molecular mechanisms related to the prognostic role of the FAT family in colorectal cancer need further experimental validation.**

3. The authors concluded that FAT cadherin family genes mutation profile defines a subtype of CRC with favorable clinicopathologic characteristics. However, many other factors such as MSI status, TP53 mutation, histopathological subtypes of CRC, may influence pathological features and prognosis. The authors should address how to avoid the effects of other potential confounders.

**Our response:** Thank you for the comments. In our revised Discussion section, we stated that *“we tried to address the impact of MSI status, a confounding factor, by analyzing the MSS samples. However, there are still additional potential confounding factors, such as histopathological subtypes, TP53 mutation status, and intratumoral spatial and temporal heterogeneity. The ability of our study to address these potential confounding factors is hampered by intrinsic limitations of the TCGA database, and the landmark cancer program heavily focused on cancer genomics datasets. A randomized, large-scale clinical cohort is necessary to validate our conclusion and to establish somatic mutations in FAT family genes as independent prognostic factors for colorectal carcinoma in future studies.”*

**Reviewer #2:**

**Specific Comments to Authors:** Dear authors, Thank you for sharing your experiences on colorectal cancer deep in the molecular science and article entitled “Somatic Mutations in FAT Cadherin Family Members Constitute an Underrecognized Subtype of Colorectal Adenocarcinoma with Unique Clinicopathologic Features”. It is written good in medical language and punctuation and grammar. The given information is important and actual. I recommend to acceptance and publishing the article. Sincerely

**Our response:** Thank you for the comments. We greatly appreciate the positive feedback from the expert reviewer like you.

**Reviewer #3:**

**Specific Comments to Authors:** *Thank you for the opportunity to review this manuscript. This is an important result for understanding the clinicopathologic features in CRC patients with somatic mutation in FAT cadherin family members. There is one comment as follows. Minor comment 1. The authors should discuss limitations of this study.*

**Our response:** **Thank you for the comments. The limitations of our study are added in the Discussion section. Please also see our responses to Item 3 raised by Reviewer #1.** *Specifically, we state: “Our study has several limitations. First, our findings were obtained from a bioinformatics study on somatic mutation profiles through the TCGA PanCancer Atlas dataset. The protein expression levels of individual FAT family members were not systemically examined in the study, and the underlying molecular mechanisms related to the prognostic role of the FAT family in colorectal cancer need further experimental validation. Second, all the patients in the study were untreated, with no therapy response data and a short follow-up. Therefore, the evaluation of advanced-stage colorectal carcinoma is relatively limited. Third, we tried to address the impact of MSI status, a confounding factor, by analyzing the MSS samples. However, there are still additional potential confounding factors, such as histopathological subtypes, TP53 mutation status, and intratumoral spatial and temporal heterogeneity. The ability of our study to address these potential confounding factors is hampered by intrinsic limitations of the TCGA database, and the landmark cancer program heavily focused on cancer genomics datasets. A randomized, large-scale clinical cohort is necessary to validate our conclusion and to establish somatic mutations in FAT family genes as independent prognostic factors for colorectal carcinoma in future studies.”*

## **B) EDITORIAL OFFICE’S COMMENTS**

**Authors must revise the manuscript according to the Editorial Office’s comments and suggestions, which are listed below:**

**(1) Science editor:**

*The manuscript has been peer-reviewed, and it's ready for the first decision.*

**Our response:** **Thank you for providing professional editorial service to our manuscript. We greatly appreciate the positive editorial decision.**

**(2) Company editor-in-chief:**

*The title was invited to submit to World Journal of Clinical Oncology, author submitted to World Journal of Gastrointestinal Oncology. This has been corrected and update in the Manuscript information section.*

**Our response: Sorry for the confusion, and thank you for the correction. To polish the language, we have also sent our revised manuscript to a professional company for English language editing.**