

We would like to take this opportunity to express our sincere gratitude to the reviewers who identified parts of the manuscript that needed corrections or modification and for their careful review. Based on the instructions provided in the decision letter and comments provided by the reviewers, we have carefully revised the manuscript.

Manuscript NO:47204.

Our responses to the reviewers' comments are as follows:

Response to Reviewer 1 (ID: 03009708)

Thank you for reviewing our manuscript. We appreciate your acceptance of our manuscript.

Response to the Reviewer 2 (ID: 03647890)

Thank you for reviewing our manuscript. Our responses to your comments are as follows:

- 1) Authors couldn't show any histological data of liver tissues. I think authors should add pathological data and information of HCC stage to this manuscript.

Response to 1)

Thank you for your valuable comment. In our study, the patients with and without HCC did not undergo histopathologic examination. However, a recent

study reported the relationship between pathological data and HCC stage. We have indicated that the AC2 level was associated with tumor stage and AC2 expression in HCC tissue was decreased according to tumor stage in the Introduction section (page 8, lines 8 and 9). In addition, we have indicated that the patients with HCC were categorized into two groups according to the median cutoff value for total tumor volume (low, <6.3; high, ≥6.3) and the patients with HCC with total tumor volume ≥6.3 had a significantly higher VEGF/AC2 ratio versus those with total tumor volume <6.3 in the Results section (page 13, line 6-10). We believe that AC2 was associated with the HCC stage.

We hope and believe that the revised manuscript is acceptable for publication and look forward to the publication of our manuscript in *World Journal of Gastrointestinal Oncology*.

Sincerely,

Hiroaki Takaya