Author's response to reviews

Title: Expressions of HIF-1alpha and VEGF in colorectal cancer: correlations with clinical outcomes and prognostic implications

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Author's response to reviews: see over
Dear editors:

Here is a manuscript by Dan Cao, Mei Hou, Jiang Ming, Yang Yu, Hongfeng Gou entitled “Expressions of HIF-1alpha and VEGF in colorectal cancer: association with clinical outcomes and prognostic implications”. It’s submitted to be considered for publication oncology as a research article. This paper is new, neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal. The manuscript was revised by a scholar of medical English for grammar.

We believe this research may be of particular interest to the readers of your journal. Although HIF-1 alpha and VEGF were reported to be expressed in many types of cancers, few number of studies investigating the prognostic role of these factors in solid tumors, in particular, in human colorectal cancer, have yet been reported. The aim of our study was to investigate the effects of HIF-1 alpha and VEGF expressions on clinical outcomes and prognosis implications in CRC. Our results suggest that HIF-1 alpha and VEGF could be biomarkers of tumor infiltration evaluation and poor prognosis in colorectal cancer. Therefore, as effectiveness of targeting VEGF have been proved, biological agents targeting HIF1- alpha might be more effective in CRC which has the potential to improve outcomes in future perspective.

All authors have given their approval for the submission of the paper.

Correspondence and phone calls about the paper should be directed to Dr. Mei Hou at the following address, phone, and e-mail address:

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Details of my revisions:
I have revised my manuscript to include the statement of ethical approval and informed consent for this study in the Methods section. The present study involving the human
tissue samples was approved by the medical ethics committee of West China Hospital of Sichuan University. Informed consents from patients were obtained for the use of resected tumor specimens.

Response to the comments of both reviewers:

Reviewer1:

1. In Abstract part: It is incorrect that multivariate analysis is used to evaluate the relation HIF-1 alpha expression to tumor stage, lymph node metastasis, and liver metastasis. In addition, it should add “prognosis” in Key Words.

   **Comments:** In Abstract part: “multivariate analysis” is revised to “univariate tests” used to evaluate the relation HIF-1 alpha expression to tumor stage, lymph node metastasis, and liver metastasis. In addition, I have added “prognosis” in Key Words.

2. In Statistical analyses part: It should add Cox Hazard Propotional Model (multivariate) to analysis the prognostic importance of HIF-1 and VEGF.

   **Comments:** In Statistical analyses part: I have already added Cox Hazard Propotional Model (multivariate) to analysis the prognostic importance of HIF-1 and VEGF.

3. In Table 1 title part: It is incorrect to use the univariate analysis.

   **Comments:** In Table 1 title part, I think it is reasonable to use the univariate analysis (chi-square test) to evaluate the relationship between HIF-1alpha (VEGF) and clinicopathologic factors in initial research. Then we use multivariate analysis (logistic regression).

Reviewer2:

Minor essential revisions:

1. There are some linguistic and grammatical errors that should be corrected.

   **Comments:** It is too difficult to ask a native English speaking colleague to help me copyedit my paper. The manuscript was revised by a scholar of medical English for grammar by word for the second time.

2. Immunohistochemical staining and scoring system is not well defined, especially for HIF-1 alpha.

   **Comments:** In Immunohistochemistry and Scoring criteria, immunohistochemical staining
and scoring system is revised to define the positive and negative expressions of HIF-1 alpha and VEGF in detail.

3. Tables should also include %-values in addition to total number of patients.

**Comments:** We have added %-values in tables

4. Figures: Immunohistochemistry pictures should also contain a positive control as reported by Zhang et al.

**Comments:** I have added pictures expressing HIF-1 alpha and VEGF intensely served as the positive controls reported by Zhong and Shibusa.

5. The discussion and conclusions are not well balanced. The discussion part is quite redundant. It's too long and only defining the results of other trials, but there is little comment about the results of this study.

**Comments:** The discussion part is reduced in explaining the results of other trials. There are more analysis and comment about the results of our study.

**Major compulsory revisions:**

Major criticism is the lack of novelty. The study does not appear novel enough for publication in its current form, requiring additional analysis and extensive revision. It is not clear to this reviewer what the conclusion of this study would be, as other reports have already been published on this topic. Authors need to emphasize the significance of their study compared to already published reports. We already have many published studies proving the effectiveness of agents targeting VEGF. Some of these targeting agents are already approved and used in standard treatment of metastatic colorectal cancer.

**Comments:** I think our study is novel in aspect of clinical implication. Although HIF-1 alpha and VEGF were reported to be expressed in many types of cancers, few number of studies investigating the prognostic role of these factors in solid tumors, in particular, HIF-1 alpha in human colorectal cancer, have yet been reported. The aim of our study was to investigate the effects of HIF-1 alpha and VEGF expressions on clinical outcomes and prognosis implications in human colorectal cancer. And our results suggest that HIF-1 alpha and VEGF could be biomarkers of tumor infiltration evaluation and poor prognosis in colorectal cancer. It is promising that as effectiveness of targeting VEGF have been proved, biological agents targeting HIF1- alpha might be more effective at CRC, which has
the potential to improve outcomes in future perspective.

Additional revision:

There are minor spelling errors in two authors' name: “Jiang Ming, Yang Yu” should be revised to “Ming Jiang, Yu Yang”