

## **Association of CK19 expression with efficacy of adjuvant TACE after hepatic resection in hepatocellular carcinoma patients at high risk of recurrence**

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Association of CK19 expression with efficacy of adjuvant TACE after hepatic resection in hepatocellular carcinoma patients at high risk of recurrence

Journal of Clinical and Translational Research

Dear Dr. Xiang,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jan 19, 2022.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author.

You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This manuscript was an original article which retrospectively investigated the association between CK19 expression and efficacy of adjuvant TACE after hepatic resection in patients with HCC at high risk of recurrence. The authors demonstrated that adjuvant TACE can significantly prolong OS and PFS of CK19-negative patients, while it may prolong only PFS of CK19-positive patients.

This study was conducted well, and the methods used are appropriate. The data are presented clearly. In general, this is a well-written paper that presents interesting data. This article will be of interest to clinicians and researchers involved in this field. The following minor issue should be addressed:

Minor

1. (Table 2, 3) I recommend that the authors provide not only positive data but also negative ones in the single factor analyses.

Reviewer #2: This is a retrospective study investigated the association of CK19 expression with efficacy of adjuvant TACE after resection in HCC patients at high risk of recurrence.

Major strength: Interesting topic. Well written manuscript with inclusion of the large sample size.

Major weakness: retrospectively design, patients from single center.

Tumor recurrence is the leading cause of death for patients with HCC after surgery, especially for those with high risk of recurrence. Several HCC official guidelines in Asian (China, Japan, Korean) recommend adjuvant TACE for such patients. However, none of them divided patients into subgroup based on CK19 expression. Not all patients will benefit from adjuvant TACE. Therefore, it is necessary to select the best benefit subsets before TACE.

Concern: The authors only cite the China HCC official guideline. I suggest they also cite HCC official guidelines from APASL, Japan, and Korea.

Reviewer #3: This is a well-written manuscript that provides relevant and timely information on the role of a biomarker in the postoperative evolution of HCC. The manuscript is well structured and easy to follow. The research is conducted properly, and all details on how the retrospective study was conducted were clear.

I have a few suggestions to improve the overall flow of information:

1- It is important to provide more information of the principles of TACE, and how this procedure acts against tumor cells and improve prognosis.

2- The role of cytokeratin-19 should be clarified. How this protein works, and how does it increase the aggressivity of the cancer. The authors described briefly the biological roles of this marker in the discussion, but I suggest a more detailed description of its roles in HCC to clarify why it's potentially deleterious.

3- In the statistical analysis section, the authors mention that continuous variables had "abnormal" distributions, and therefore 2-tailed P-values were reported. Which statistical tests were used? Parametric (T-test) or non-parametric (Mann-Whitney U)? Since the distribution is abnormal, a parametric t-test cannot be used, and this may affect the P-values tremendously.

4- The results are interesting and show the impact of CK19 positivity and TACE on survival. However, the authors may clarify more in the discussion what this study adds to the literature. Is this information already known and this study validates what is known? Or does it add new information?

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Authors' response

Dear Michal Heger,

Thank you for giving us the opportunity to revise our manuscript "Association of CK19 expression with efficacy of adjuvant TACE after hepatic resection in hepatocellular carcinoma patients at high risk of recurrence" (JCTRes-D-21-00187). Below we reply point-by-point to the editor and the reviewers' comments, and we indicate where we have made changes in the revised manuscript.

We hope the revised text can be judged suitable for publication in *Journal of Clinical and Translational Research*, and to that end, we would be happy to answer any further questions that you or the reviewers may have.

We look forward to hearing from you,

Jian-Hong Zhong

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Reviewer #1: This manuscript was an original article which retrospectively investigated the association between CK19 expression and efficacy of adjuvant TACE after hepatic resection in patients with HCC at high risk of recurrence. The authors demonstrated that adjuvant

TACE can significantly prolong OS and PFS of CK19-negative patients, while it may prolong only PFS of CK19-positive patients.

This study was conducted well, and the methods used are appropriate. The data are presented clearly. In general, this is a well-written paper that presents interesting data. This article will be of interest to clinicians and researchers involved in this field. The following minor issue should be addressed:

Minor

1. (Table 2, 3) I recommend that the authors provide not only positive data but also negative ones in the single factor analyses.

**Response: We thank the reviewer. Relevant data was added in Table 2 and 3.**

Reviewer #2: This is a retrospective study investigated the association of CK19 expression with efficacy of adjuvant TACE after resection in HCC patients at high risk of recurrence.

Major strength: Interesting topic. Well written manuscript with inclusion of the large sample size.

Major weakness: retrospectively design, patients from single center.

Tumor recurrence is the leading cause of death for patients with HCC after surgery, especially for those with high risk of recurrence. Several HCC official guidelines in Asian (China, Japan, Korean) recommend adjuvant TACE for such patients. However, none of them divided patients into subgroup based on CK19 expression. Not all patients will benefit from adjuvant TACE. Therefore, it is necessary to select the best benefit subsets before TACE.

Concern: The authors only cite the China HCC official guideline. I suggest they also cite HCC official guidelines from APASL, Japan, and Korea.

**Response: We thank the reviewer. Due to HCC official guidelines from APASL, Japan, and Korea do not recommend adjuvant TACE for postoperative HCC, we did not cite these guidelines.**

Reviewer #3: This is a well-written manuscript that provides relevant and timely information on the role of a biomarker in the postoperative evolution of HCC. The manuscript is well structured and easy to follow. The research is conducted properly, and all details on how the retrospective study was conducted were clear.

I have a few suggestions to improve the overall flow of information:

1- It is important to provide more information of the principles of TACE, and how this procedure acts against tumor cells and improve prognosis.

**Response: In the second paragraph of Introduction, we add the following content.**

**‘TACE is one of the standard therapy for patients with intermediate or advanced stage HCC.’<sup>7,8</sup> The principle of TACE is to promote tumor necrosis while preserving enough**

**liver function to improve the patient's survival time. Local drug concentrations in TACE therapy were more than 10 times higher than in systemic therapy.<sup>9</sup>**

2- The role of cytokeratin-19 should be clarified. How this protein works, and how does it increase the aggressivity of the cancer. The authors described briefly the biological roles of this marker in the discussion, but I suggest a more detailed description of its roles in HCC to clarify why it's potentially deleterious.

**Response: We agree with the reviewer. We add the following content in Discussion.**

**“How CK19 might influence postoperative survival and prognosis after TACE is unclear. Based on the expression of CK19, HCC are grouped into non-proliferative and proliferative subtypes. CK19-positive HCC is an aggressive subtype characterized by invasion and angiogenesis, which lead to early tumor recurrence, chemotherapy tolerance, and worse overall survival.<sup>32,33</sup>” (p10)**

3- In the statistical analysis section, the authors mention that continuous variables had "abnormal" distributions, and therefore 2-tailed P-values were reported. Which statistical tests were used? Parametric (T-test) or non-parametric (Mann-Whitney U)? Since the distribution is abnormal, a parametric t-test cannot be used, and this may affect the P-values tremendously.

**Response: We agree with the reviewer. Mann-Whitney U test was used in the comparison of continuous variables and we add the following content in the section of Statistical analysis.**

**“Categorical variables were compared with the  $\chi^2$  or Fisher’s exact test, and continuous variables with the Mann-Whitney U test.” (p6)**

4- The results are interesting and show the impact of CK19 positivity and TACE on survival. However, the authors may clarify more in the discussion what this study adds to the literature. Is this information already known and this study validates what is known? Or does it add new information?

**Response: In the third paragraph of Discussion, we emphasized the word of “for the first time” (p10). In the sixth paragraph of Discussion, we wrote the following content.**

**“The results may help guide decision-making about adjuvant TACE in HCC patients at high risk of recurrence. The technique appears to be beneficial for most CK19-negative patients, but it may be less effective for CK19-positive patients, for whom comprehensive adjuvant therapies such as targeted therapy and immunotherapy may be better for improving OS.<sup>32,33</sup> These findings should be verified and extended in large, prospective studies.” (p11)**

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2<sup>nd</sup> Editorial decision  
08-Jan-2022

Ref.: Ms. No. JCTRes-D-21-00187R1  
Association of CK19 expression with efficacy of adjuvant TACE after hepatic resection in  
hepatocellular carcinoma patients at high risk of recurrence  
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the  
Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly  
review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Comments from the editors and reviewers: