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**Manuscript NO:** 53252

**Title:** Validation of the Six-and-Twelve Criteria among patients with hepatocellular carcinoma and performance score 1 receiving transarterial chemoembolization

Jan. 8 2020

Dear editors:

The authors thank the reviewers for their valuable comments and suggestions, which have improved our manuscript furtherly. Please find our point-by-point responses to their comments in the following document.

**Reviewer 1 (02353723) report:**

The study of Wang et al. represents a valid attempt to scientifically support the use of TACE for patients with HCC and performance score 1. In general, the manuscript is well written, but the abstract needs some changes and the discussion should be extended at least mentioning some other possible therapeutical approaches.



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**Comment 1:** ABSTRACT: Change “trans-arterial” with transarterial, as reported in the remaining part of the manuscript.

**Response:** Thank you very much for the suggestion. We have changed “trans-arterial” to “transarterial” in all four places throughout the whole manuscript (Highlighted in Page 1, 5, 6).

**Comment 2:** ABSTRACT: Change “while numbers of patients...” with while a large number of patients.

**Response:** Thank you for this suggestion. We have revised it in the manuscript accordingly (Highlighted in Page 5).

**Comment 3:** ABSTRACT: In a retrospective study you do not “screen for eligibility” but “select” patients.

**Response:** Thank you for this suggestion. We have used word of “selected” in the revised version (Highlighted in Page 5).

**Comment 4:** ABSTRACT: In the materials and methods you mention for the first time the “6&12 Criteria” without any explanation. Move here the definition that you report in the results.



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**Response:** Thank you for this suggestion. We have moved the definition to the right place and revised the abbreviation in METHODS part (Page 5, 6).

**Comment 5:** ABSTRACT: The C index also defined as “concordance statistic” (measure of goodness of fit for binary outcomes in a logistic regression model) is too specific to be mentioned in the abstract. Try to express the concept differently or omit it.

**Response:** Thank you for the suggestion, with which we totally agree. We have replaced it with “predictive ability” to represent this information (Highlight in Page 6).

**Comment 6:** ABSTRACT: CONCLUSION should be CONCLUSIONS

**Response:** Thank you for this suggestion. We have revised it accordingly (Highlighted in Page 6).

**Comment 7:** THE CORE TIP: “Current study retrospectively included...” should be “The current study retrospectively included...”

**Response:** Thank you for this suggestion, according to which we have revised this mistake in the manuscript (Highlighted in Page 7).

**Comment 8:** STUDY POPULATION: Also, in this case “... retrospectively screened for



eligibility.” Should become “retrospectively selected”

**Response:** Thank you for this suggestion. Accordingly, we have revised it to “retrospectively selected” (Highlighted in Page 9).

**Comment 9:** STUDY POPULATION: How you obtained a written informed consent from all patients before treatment initiation if your study was retrospective? Retrospective studies that guarantee anonymity do not need informed consent.

**Response:** Thank you for this comment. Patients receiving TACE treatment in the participating centers of our study must have signed an informed consent form before surgery. All the informed files covered a specific notice, main idea of it was that “I have known that the relevant materials of the treatment process such as my anonymized medical history may be used for scientific research in the future and I agree with it”.

**Comment 10:** STUDY POPULATION: Since a mixture of doxorubicin, cisplatin, epirubicin or oxaliplatin was selected according to the practice of each center, you should evaluate or at least make a comment in the discussion about the effect of the different cocktails on OS.

**Response:** Thanks for the comment and suggestion. As a highly complex technical procedure, TACE is operator-dependent and heterogeneity exists in the techniques and



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agents used, which might explain variations in outcomes in patients with HCC. However, there is no consensus on the optimal chemotherapeutic agent to use in TACE. Worldwide, the most popular anticancer drug injected is doxorubicin. In addition, A recent RCT comparing TACE with transarterial embolization (TAE) found no differences in terms of tumor response and overall survival, which questioned the effects of chemotherapy agents. Considering these points, using the mixture of doxorubicin, cisplatin, epirubicin or oxaliplatin might have little effect on our current analysis (Highlighted in Page 17).

**Comment 11:** RESULTS: (1) Table 1 is a little bit confusing. Associate the legends “Number (%) / mean  $\pm$  S.D. / median [IQR]”, to each parameter/line instead of placing them on the top of the column.

**Response:** Thanks for the suggestion. We have revised it in the manuscript accordingly (Table 1 in Page 40).

**Comment 12:** DISCUSSION: A wider review of the literature and a comment on the possible alternative techniques such as TARE, would make the discussion more complete (see Facciorusso et al. doi: 10.4254/wjh.v7.i16.2009)

**Response:** Thank you very much for the comment and suggestion. Although TACE was



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the most commonly used treatment for patients with unresectable HCC, sorafenib was the firstly recommended systemic therapy to advanced disease, and was approved to be effective worldwide. Furthermore, combining TACE and sorafenib might be a “good marriage” for unresectable HCC. In addition, systemic chemotherapy with doxorubicin or FOLFOX did not demonstrate survival benefits. Major emphasis has been focused on the efficacy of transarterial radioembolisation (TARE). In cohort studies, TARE showed tumor response rates between 40% and 90%, and survival was comparable to that obtained with TACE and sorafenib. However, RCTs failed to demonstrate a survival benefit from TARE compared with sorafenib. Recently, lenvatinib was found to be non-inferior to sorafenib, offering another treatment option for patients with advanced HCC; however, large multicenter real-world studies are highly needed. We have added these points in the revised manuscript (Highlighted in Page 17, 18).

**Reviewer 2 (02936084) report:**

Manuscript titled “Validation of the Six-and-Twelve Criteria among patients with hepatocellular carcinoma and performance score 1 receiving trans-arterial chemoembolization” by Wang Z. The authors have investigated treatment outcomes of TACE in HCC with ECOG score of 1 alone and propose a specific prognostic model. The idea is very good. The study is well-designed. The manuscript was well, concisely and coherently organized. I recommend to accept this article after reviewing the statistical methods.



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**Response:** Thank you very much for the consideration and suggestion. We have invited the biostatistician (Prof. Jielai Xia) of the Department of Health Statistics in our university to review the statistical methods used in this article. He has signed a Biostatistics Statement that already upload to the editorial office. Any comments in detail will be appreciated.