

June 9, 2022

Dear Editor-in-Chief,

Thank you very much for giving us the opportunity to address the reviewers' comments by submitting a revised version of our manuscript (76626) entitled “*Identification of predictive factors for post-transarterial chemoembolization (TACE) liver failure in hepatocellular carcinoma patients: A retrospective study*” for your favorable consideration for publication in **World Journal of Clinical Cases**.

Following the extensive and insightful comments and suggestions made by the reviewers and Editorial Board, now we have revised the manuscript and provided clarifications/suggestions as suggested by the reviewers. The point wise answers to comments are also provided below for your consideration. The manuscript has been revised accordingly and I hope the revised manuscript would be acceptable for publication in your esteemed journal.

All the authors approved the authorship changes. We are looking forward to hearing from you.

Yours Sincerely,



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Responses to Editors' and Reviewers' Comments

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an interesting and well-written real-life study that highlights the relevance of the technique and the importance of patient selection regarding transarterial chemoembolization (TACE) as a treatment for hepatocellular carcinoma (HCC). The message is clearly expressed; a double embolization technique to treat large size HCC tumors (> 50 mm) is prone to severe complications. Large size HCCs (> 50 mm) not suitable for surgery are difficult tumors to treat, as they are frequently associated with tumor microinvasion, which results in TACE failure. Improving the chemoembolization technique is a solution, but this study clearly shows the limits of the technique. This is the main interest of the current strategies which consist in combining treatments (Kudo et al, TACTICS trial. Gut. 2019), or proposing a systemic treatment in first intention (Reig et al, « BCLC strategy for prognosis prediction and treatment recommendation », J Hepatol 2022), with chemoembolization secondarily, to treat the residuals. We have moved from "palliative" chemoembolization aimed at slowing tumor progression to "curative" chemoembolization aimed at achieving complete tumor necrosis, with radiological response correlated to survival (Gillmore R et al, EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol. 2011). In this context, patient selection with non-surgical hepatocellular carcinoma using an up-to-seven criteria model (as highlighted by the authors through reference #3 Giannini et al AJG 2016) or a score (HAP score : Kadalayil et al, Ann Oncol 2013), are methods to avoid this post chemoembolization toxicity. As the authors remind us in the discussion, the criteria associated with overtoxicity are well identified and should be taken into account for the treatment strategy. In this study, a majority of patients had cirrhosis; non-tumor portal thrombosis was reported in nearly 20% of patients, and there were also patients with pre-treatment ascites (table 1). The abstract is pertinent, the introduction correctly states the problem. The embolization method (procedure) is well explained, the presentation of the results is clear. The descriptive study is associated with a multivariate analysis, which supports the results. Finally, the authors propose a nomogram as an aid to decision making. The discussion is well conducted; no alternative solution is envisaged to treat these large size lesions (> 50 mm), but this is not the purpose of the article. It is necessary to check whether the

presentation of the references corresponds to that requested by the journal (PMDI to be cited).

Answer: Thanks for the reviewer's favorable comments. We have considered the issues mentioned by the reviewer and revised the Discussion section. The reference style was also revised according to the author guidelines of the journal (Page 9 - 10).

Reviewer #2:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Rejection

Specific Comments to Authors: We read with interest the paper entitled “ Identification of predictive factors for post-transarterial chemoembolization (TACE) liver failure in hepatocellular carcinoma patients: a case-control study” by Min Yuan et al. it is a retrospective case-control study carried out on 199 HCC patients undergoing TACE, 70 of whom developed post-TACE liver failure. The authors retrospectively analyzed data from these patients and concluded that microsphere plus gelatin embolization and main tumor size > 5 cm were risk factors for post-TACE liver failure while previous history of HCC resection could protect from this complication. Although the authors addressed an interesting issue in the field of HCC treatment, the paper has several drawbacks that limit its scientific impact Study design is retrospective According to standard statistical definition the present study cannot be defined as a case-control study. This is a retrospective observational study carried out on an unselected cohort of patients undergoing TACE with or without post TACE liver failure. As stated in materials and methods, microspheres and gelatin sponge particles were administered only to patients with HCC > 5 cm. Thus, these two variables are redundant and should not be included together in univariate and multivariate analysis since they identify the same patient. The two groups of patients are very inhomogeneous as to the treatment received in association with TACE and this make difficult to compare them as to the end point of post-TACE liver failure According to the above-mentioned statistical drawbacks, this study is not reliable to build up a predicting risk model. Moreover, every predicting model should be internally and externally validated in ad hoc different cohorts beside the original training cohort before being proposed for clinical employment. Looking at the ROC diagrams the accuracy performance of this predicting risk model is quite low (never exceeding the value of 0.6) According to international guidelines, vascular invasion is a well-known contraindication for TACE and some patients with vascular invasion were included in the study. According to BCLC algorithm patients with extrahepatic metastases are not suitable for TACE. To better understand the results, patients should be staged in keeping with BCLC staging system. The authors should

specify how many patients belonged to intermediate and how many belonged to advanced stage. In table 1 Child-Pugh score should be reported (as % of patients belonging to A,B,C class, and mean value) Language and style deserve a mother-tongue deep revision

Answer: We appreciate the constructive comments of the reviewer.

(1) We have revised the study type as retrospective study and deleted the phrase of “case-control” in the revised version.

(2) Microspheres plus gelatin sponge particles were administrated only to patients with HCC > 5 cm, while not all the subjects with tumor size > 5 cm received combination embolization of microspheres and gelatin. Hence, we adjusted these two variables in the univariate and multivariate regression models.

(3) In this retrospective study, we have adjusted the inhomogeneous baseline characteristics in the regression models, and declared the potential biases in the limitation of the Discussion section (Page 10). We hope this could be acceptable for the reviewer and the journal.

(4) The predictive performance of the model was not promising in this retrospective study, we also presented this limitation. Even though, the factors mentioned in our preliminary analysis should be considered for the TACE decision-making in the clinical practice (Page 10).

(5) In our study, the China Liver Cancer Staging (CNLC) from “Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China (2019 edition)” (PMID: 32164061) were used for decision-making of TACE procedure. According to this guideline, HCC patients with CNLC stage Ib – IIIb should be considered for the TACE therapy. Even extrahepatic metastases (IIIb) are suitable for TACE. We have added this information in the “Treatment procedure of TACE” part of the Materials and Method section. The CNLC staging were also provided in Table 1. The univariate logistic regression model indicated that the CNLC staging did not affect the occurrence of post-TACE liver failure significantly (OR = 1.1, 95% CI = 0.75 – 1.61, p = 0.639). Thus, the CNLC staging was not entered into the multivariate model.

(6) The Child-Pugh and MELD scores have been presented in Table 1 in the revision. The univariate logistic regression model did not find the significances of the Child-Pugh and MELD scores for the occurrence of post-TACE liver failure (OR = 1.05, 95% CI = 0.81 – 1.36, p = 0.706 and OR = 0.95, 95% CI = 0.88 – 1.02, p = 0.143, respectively). Thus, the Child-Pugh and MELD scores were not entered into the multivariate model.

(7) We have reedited the English language under the help of AJE (<https://www.aje.cn/>, verification code FF11-5276-98A8-AF4F-E32C).

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: In the treatment of HCC patients, post-TACE liver failure is a major concern. The authors' conclusion in a retrospective analysis that microsphere plus gelatin embolization is a risk factor for the development of post-TACE liver failure in HCC patients is a relevant finding. I have only few comments about this paper. As already highlighted by the authors, there is no uniform/standard definition of post-TACE liver failure, making it difficult to interpret the results compare them with other studies. The inclusion of “increase in ascites” in the definition brings subjectivity, which needs to be addressed in the discussion. Over 90% of HCC patients in both groups were cirrhotic. Were there any differences in the severity of cirrhosis (e.g., CTP/MELD scores) between the two groups?

Answer: Thanks for the reviewer's positive comments. We have discussed the definition subjectivity of “increase in ascites” as a limitation in the Discussion section in the revised version (Page 11). Besides, the CTP and MELD scores have been provided to assess the severity of cirrhosis in Table 1 of the revision.