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המכון למחלות דרכי העיכול והכבד
Department of Gastroenterology and Hepatology

17.2.2018

To: Ya-Juan Ma-Science Editor,

Editorial Office-Baishideng Publishing Group

Dear Editor,

We appreciate your decision to allow the submission of a revised version of our paper entitled "Analysis of aggressiveness factors in Hepatocellular carcinoma patients undergoing transarterial chemoembolization". We carefully read the reviewers comments and thank them for their concise and thorough evaluation. The manuscript was revised in accordance with every comment.

Following is our detailed response in a point-by-point fashion.

We hope you find the manuscript suitable for publication in *World Journal of Gastroenterology*

Yours

Oren Shibolet MD

Director of the Department of Gastroenterology and Hepatology

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Point by point response:

Reviewer 1: This is very interesting paper about TAE for HCC. Author concluded that aggressiveness index (MTD, AFP, PVT and Nodules) was strongly correlated with survival in TAE for HCC. I ask some question. According to author's discussion, a study of 109 patients who underwent TACE from 2006 to 2012, did not show any single component of Child-Pugh score which includes bilirubin was a predictor of survival (28). But in Japan, Child-Pugh and K-ICG are predictive factor for TAE for HCC. Please tell me your data about Child-Pugh score, single component of Child-Pugh and the prognosis of TAE for HCC.

Comment: We thank the reviewer for his comment. A sentence explaining the results of the study by Barman et al. and the data on single CPT components was added in the discussion on page 13.

Reviewer 2: The papers regarding correlation between 'aggressiveness index of hepatocellular carcinoma'(AgI) using 4 parameters, maximum tumor diameter, AFP, presence or absence of PVT and the number of tumors were published already(Ref number 15,16 and 17) and laboratory parameters. This paper analyzed the relation between AgI and 8 laboratory parameters, albumin, ALP, GTP, AST, bilirubin, platelets, WBC and lymphocyte. It is well known that the prognosis of HCC depends on both tumor aggressiveness and liver function, so that degree of cirrhosis. The parameters composing of laboratory parameters (albumin, bilirubin and platelets) are related liver function, some like GPT, AST and ALP are not related with liver function but ongoing liver injury, WBC and lymphocyte are not relevant to liver function. Can authors explain the meaning or hypothesis why the 5 irrelevant parameters included for this analysis? Another consideration is that why authors didn't use other factors better reflecting liver function including prothrombin time, and ICG clearance test that reflects very well of degree of cirrhosis. Reviewer also have question about the authors excluded variants of HCC such as combined cholangiocarcinoma or sarcomatous variants, both are more aggressive than ordinary HCC. Another is DCP or PIVKA II as a tumor marker. This is more sensitive for early detection and better marker rather than a-FP in some reports.

Comment: We thank the reviewer for the concise and important comments. References 15-17 were corrected. We added paragraphs in the discussion page12 explaining why we chose the 8 laboratory parameters for our analysis. All were previously shown to correlate with HCC aggressiveness in other scores. We further explain why we didn't use ICG clearance and DCP in our study. We fully agree with the reviewer that these are excellent predictors of liver function (references were added to show this). However, they are not routinely used in our center and are not in wide clinical use in Europe and the USA. A sentence stating this was added.

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Mixed cholangio-HCC and sarcomatous HCC are very rare and may have a distinct aggressiveness pattern. We added a sentence in the methods section and in the discussion explaining why we did not include these variants in our analysis.

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