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Column: Review

Title: New prognostic biomarkers of mortality in patients undergoing liver transplantation for hepatocellular carcinoma

Authors: Leonardo Lorente

Reviewer code: 00006459, 00052899, and 02441161

First decision: 2018-07-04

Science editor: Xue-Jiao Wang

Response to Editor comments:

Thank you very much for reconsider a revised version of the manuscript. Thank you for your comments and those from reviewers which have helped to improve the manuscript. The modifications in the manuscript according to comments of Reviewer 00006459 are written in red, and of Reviewer 00052899 are written in blue. In addition, the information about Total antioxidant capacity, other biomarker that we have recently published, are written in green. The answers to editor and reviewer, and the new version of the manuscript are enclosed.

Response to comments of Reviewer code 00006459:

This is a useful topic to review, and the topic of broad interest in hepatology. It primarily discusses markers examined by the authors. In order to create a balanced and more useful review, more information on markers that are mentioned briefly, other markers that are not mentioned, and new approaches, is needed. Specifically, markers such as C-reactive protein (CRP), PIVKA-II, need more information. What is the % of patients in which such markers and GPC-3 can be readily detected? Please add discussion of portal blood pressure, gene expression profiles of HCC, which are in the TCGA, liver Angiopoietin, liver pyroptosis, and whether receipt of DAA therapy might be of value included for predicting HCC outcome. Apoptosis is discussed, but pyroptosis is probably of value too. Recent papers that should be discussed are: 1. Faillaci, F, et al. (2018) Liver Angiopoietin-2 is a key predictor of de novo or recurrent hepatocellular cancer after HCV direct-acting antivirals. *Hepatology* epub 2018/04/01. doi 10.1002/hep.29911. PMID 29604220 2. Chu, Q, Jiang, Y, Zhang, W, Xu, C, Du, W, Tuguzbaeva, G, Qin, Y, Li, A, Zhang, L, Sun, G, Cai, Y, Feng, Q, Li, G, Li, Y, Du, Z, Bai, Y, Yang, B (2016) Pyroptosis is involved in the pathogenesis of human hepatocellular carcinoma. *Oncotarget* 7(51): 84658-65. PMC5356689. 3. Chiang, DY,

Villanueva, A (2017) Progress towards molecular patient stratification of hepatocellular carcinoma: Lost in translation? Journal of Hepatology 67(5): 893-5.

The modifications in the manuscript according to comments of Reviewer 00006459 are written in red colour.

As was suggested by the reviewer, the new version of manuscript include more information on markers that were mentioned briefly in the previous version of the manuscript (such as CRP, PIVKA-II, and GPC-3), and other markers that were not mentioned (portal blood pressure, gene expression profiles of HCC in TCGA, angiopoietin, pyroptosis, and DAA therapy).

In addition, the new version of manuscript include some references in respect to markers that were not mentioned in the previous version of the manuscript and of course including those suggested by the reviewer:

162. Faillaci F, et al. Hepatology 2018 [Epub ahead of print]

157. Chu Q, et al. Oncotarget 2016; 7: 84658-84665

168. Chiang DY, et al.? J Hepatol 2017; 67: 893-895

Response to comments of Reviewer code 02441161:

A very good review about new prognostic biomarkers of mortality in patients undergoing liver transplantation for hepatocellular carcinoma.

Thanks for the positive comments of Reviewer 02441161 about the manuscript.

Response to comments of Reviewer code 00052899:

In this review, the authors summarized the prognostic biomarkers of malondialdehyde, CCK-18, sCD40L, substance P and NLR, PLR, CRP, GPC-3, h-TERT mRNA, MMP-9, E-cadherin and beta-catenin in patients undergoing liver transplantation for hepatocellular carcinoma. Previous studies revealed that over-expression of DKK1 was implicated in invasion/metastasis of HCC after OLT. Moreover, pre-LT plasma VEGF may be a predictor of recurrence-free post-LT survival. Both them should be added in the review to broaden the scale of prognostic biomarkers.

The modifications in the manuscript according to comments of Reviewer 00052899 are written in blue colour.

As was suggested by the reviewer, the new version of manuscript include information about two prognostic biomarkers that were not mentioned in the previous version of the manuscript (DKK1 and VEGF).