Response to Reviewers :

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 33249

Title: Usefulness of the MESH score in a European hepatocellular carcinoma cohort

***Reviewer's code: 00068723**: The authors compared performance of scoring systems of hepatocellular carcinoma, focusing on MESH and BCLC. They found that MESH was more useful for selection of treatment, or management. Table 1 and table 2 were interesting. It would be more appropriate to emphasize the limitation of BCLC citing references. With the information, performance of MESH would be more convincing*

We thank the reviewer for his comments. Several references have been added to the main text concerning the limitation of the BCLC system[1, 2], and the following sentence has been added to the manuscript (page 6): « Some stage B HCC patients could be good candidates for surgery [3, 4], unlike other BCLC B HCC patients who do not benefit from the recommended treatment namely the chemoembolization [5] ».

1. Adhoute X, Penaranda G, Raoul JL, Blanc JF, Edeline J, Conroy G, et al. Prognosis of advanced hepatocellular carcinoma: a new stratification of Barcelona Clinic Liver Cancer stage C: results from a French multicenter study. Eur J Gastroenterol Hepatol. 2016;28(4):433-40. doi: 10.1097/MEG.0000000000000558. PubMed PMID: 26695429.
2. Liu PH, Su CW, Hsu CY, Hsia CY, Lee YH, Huang YH, et al. Solitary Large Hepatocellular Carcinoma: Staging and Treatment Strategy. PLoS One. 2016;11(5):e0155588. doi: 10.1371/journal.pone.0155588. PubMed PMID: 27176037; PubMed Central PMCID: PMCPMC4866714.
3. Ciria R, Lopez-Cillero P, Gallardo AB, Cabrera J, Pleguezuelo M, Ayllon MD, et al. Optimizing the management of patients with BCLC stage-B hepatocellular carcinoma: Modern surgical resection as a feasible alternative to transarterial chemoemolization. Eur J Surg Oncol. 2015;41(9):1153-61. doi: 10.1016/j.ejso.2015.05.023. PubMed PMID: 26118317.
4. Hsu CY, Hsia CY, Huang YH, Su CW, Lin HC, Pai JT, et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma

beyond the Milan criteria: a propensity score analysis. Ann Surg Oncol. 2012;19(3):842-9. doi: 10.1245/s10434-011-2060-1. PubMed PMID: 21913008.
5. Hucke F, Pinter M, Graziadei I, Bota S, Vogel W, Muller C, et al. How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. J Hepatol. 2014;61(6):1287-96. doi: 10.1016/j.jhep.2014.07.002. PubMed PMID: 25016222.

***Reviewer's code: 03646554**: The authors illustrated the value of the new scoring systems of hepatocellular carcinoma, through the comparison with other scoring systems. They found that MESH was more effective for the HCC management especially they can provide us with good prognostic information. Tables are great. It would be more clear if making the table of information of the European HCC cohort.*

We thank the reviewer for his comments. The following table (1) with the characteristics of the entire cohort has been added to the main manuscript:

Patients characteristics	**Cohort (n=581)**
Age years – Mean ±Sd	67.4 ±11.7
Male – N (%)	475 (82%)
Etiology – HCV/HBV/Alcohol/MS/others - N (%)	209 (36)/41 (7)/215 (37)/87 (15)/29 (5)
Cirrhosis – N (%)	505 (87%)
Child – Pugh stage* A / B – N (%)	323 (64) / 182 (36)
Maximal tumor diameter – Mean ±Sd	60.9 ±39.1
Tumor nodularities (1/2/≥3) – N(%)	227 (39%)/76 (13%)/278 (48%)
Infiltrative tumor- N(%)	235 (40%)
Extrahepatic metastasis – N(%)	59 (10%)
Vascular invasion – N(%)	213 (37%)
Performance status 0/1/2-4 – N(%)	276 (48%)/136 (23%)/169 (29%)
Laboratory values (Mean ±SD)	
Alkaline phosphatase (IU/L) > 200 – N(%)	112 (19%)
PT (%) – Mean ±Sd	78.0 ±15.8
Albumin (g/l) – Mean ±Sd	34.7 ±6.1
Aspartate transaminase (IU/L) – Mean ±Sd	68.7 ±60.7
Alpha-fetoprotein (ng/ml) – Mean ±Sd	5680 ±31332
Tumor stages	
BCLC (A/B/C/D) – N(%)	181 (31%)/92 (16%)/241 (41%)/67 (12%)
Treatment allocation	
Resection or RFA - N(%)	131 (23)
TACE - N(%)	175 (30)
Sorafenib - N(%)	152 (26)
Supportive care - N(%)	123 (21)

Follow-up Time –Months - Mean ±Sd	18.3 ±20.3
Deaths – N(%)	413 (71%)
Overall Survival – Months - Mean ±Sd	26.0 ±1.3

Table 1: Baseline characteristics in European hepatocellular carcinoma cohort (n=581)

HCV, hepatitis C virus; HBV, hepatitis B virus; MS, metabolic syndrom; PT, prothrombin time; BCLC, Barcelona Clınic Liver Cancer; RFA, Radiofrequency ablation; TACE, trans arterial chemoembolization.

* cirrhotic patients

Reviewer's code: 03538749: Hepatocellular carcinoma (HCC) staging system is still a controversial issue. So this letter gave me interesting news for future prediction. However, I can not know what is MESH and How the authors have used it in this letter. In addition, how to compare these staging systems? Finally, I can not get the following paper so as to know its detail. Hsu CY, Liu PH, Hsia CY, Lee YH, Al Juboori A, Lee RC, et al. Nomogram of the Barcelona Clinic Liver Cancer system for individual prognostic prediction in hepatocellular carcinoma. Liver Int. 2016;36(10):1498-506. doi: 10.1111/liv.13114. PubMed PMID: 26972815.

Liu PH et al proposed a new HCC scoring system named MESH (Model to Estimate Survival for Hepatocellular carcinoma patients) (European Journal of Cancer 63 (2016) 25-33). The MESH score has been determined from a multivariate analysis of a large HCC cohort including 1591 patients with viral underlying liver disease (HBV 54%, HCV 32%). "*The MESH score allocated 1 point for each of the following parameters: large tumor (beyond Milan criteria), presence of vascular invasion or metastasis, Child-Turcotte-Pugh score≥6, performance status≥2, serum alpha-fetoprotein level≥20 ng/ml, and serum alkaline phosphatase ≥200 IU/L, with a maximal of 6 points*". MESH score was validated in a large validation cohort (n=1591) and its prognostic value compared to others scoring systems (BCLC, HKLC, CLIP, TIS and MESIAH).

In this letter, we validate the MESH score in a European HCC cohort and we assess its usefulness for HCC management.