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Reply to correspondence concerning: "Role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection"

To the Editor:

We read with great interest the letters by Wei *et al.*, Xiang *et al.* and Huo *et al.* commenting on our recently published manuscript[1] regarding the role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma (HCC) after resection.

According to Wei *et al.*, the risk of HCC recurrence should be stratified, taking into account the etiology of the underlying liver disease, the viral load and the ethnicity of the patients enrolled. We agree with the suggestion that all these co-factors could affect individual susceptibility to HCC recurrence; however, in our enrolled population which only included Caucasian patients, the prevalent etiology (93 patients, 59.2%) at enrollment was hepatitis C virus (HCV)-related liver disease. As already outlined, all our patients with HCV were enrolled prior to the direct-acting antiviral (DAA) era and had active infections. Thirty-nine (38) out of 93 (41.9%) patients with HCV reached the DAA era without experiencing HCC recurrence; 38 out of the 39 patients (97.4%) achieved a sustained virologic response, and 5 of them developed late HCC recurrence. Thus, it was not possible to assess a potential effect of HCV eradication with DAAs on HCC recurrence. However, all patients with hepatitis B virus infection (36 patients out of 157 [23%]) were on nucleoside/nucleotide analogues with a virologic response at enrollment.

Moreover, as far as the better accuracy of shear wave elastography (SWE) for the diagnosis of liver cirrhosis is concerned, the literature available and the studies cited support only some possible technical advantages;[2] however, the European Federation of Ultrasound in Medicine and Biology (EFSUMB) guidelines and the European Association for Study of Liver (EASL) still recommend transient elastography for hepatic cirrhosis and severe fibrosis assessment.[2,3] Furthermore, spleen stiffness measurement (SSM) using transient elastography is considered to be a validated tool for the assessment of portal pressure[4] and the prediction of clinical complications.[5,6] Regarding the ceiling effect, in our population, only 13 patients out of the 157 enrolled (8.3%) had an SSM = 75 kPa, and thus it was possible to assert that a ceiling effect of 75 kPa does not seem to impair its reliability and accuracy.[7]

Finally, considering the possible role that spleen immune alterations play in fostering a tumor-facilitative immune microenvironment in the liver, we suggest that combining "new parameters" with a simple SSM could improve the prediction of late HCC recurrence. As with any predictive model, any external validation is welcome and necessary.

We agree with Xiang *et al.* that liver stiffness measurement (LSM) is a good predictor of late HCC recurrence. In fact, we found a significant association at univariate analysis, confirming the results of other authors who evaluated the role of LSM exclusively.[8,9] However, at multivariate analysis the SSM was still the only predictor of late HCC recurrence after liver resection. This result is not completely unexpected since SSM has been demonstrated to be more accurate than LSM in the assessment of portal hypertension[10] and its complications;[5] thus, in a competing variable model, SSM was a stronger predictor of late HCC recurrence than LSM. Unlike previous reports[8,9] in which only LSM was evaluated, we would point out that this is the first time that the prediction of HCC recurrence was also evaluated using the SSM. In fact, the correlation between the LSM and portal hypertension is lost for values of hepatic venous pressure gradient ≥10 mmHg, when extrahepatic factors of portal hypertension are involved (*i.e.* hyperdynamic circulation, *etc.*); thus, the degree of portal hypertension is better mirrored by the SSM.[11] According to the suggestion, we used SSM (52.8 kPa[10]) as a surrogate marker of clinically significant portal hypertension (CSPH) to assess the predictive role of CSPH for late HCC recurrence, finding that SSM ≥52.8 kPa was a predictor of late HCC recurrence (hazard ratio 2.531; 95% CI 1.198–5.349; $p = 0.015$).

Moreover, according to the evidence available in the literature[12] which points out that the majority of late HCC recurrences occur in cirrhotic patients, we expected to be unable to stratify patients at risk of recurrence according to their METAVIR grade. Thus, we did not plan on including METAVIR grade in the predictive model. In fact, as far as the fibrosis histologic grade is concerned, in our population, the late recurrences were found more frequently in patients with METAVIR F4 than in those with F3, and no recurrences were observed in the few patients with F1-F2. However, a *post hoc* analysis with METAVIR grade documented its predictive role only at univariate analysis; this may have been due to a suboptimal sample size. In addition, many other variables considered more accurate in stratifying the disease progression in F4 patients, such as LSM and SSM, platelet count, spleen length and platelet count to spleen length ratio, were included.

Finally, we agree with Xiang *et al.* that in the American Association for the Study of Liver Diseases (AASLD) guidelines,[13] HCC patients with macrovascular invasion or multiple nodules are not recommended for curative hepatic resection. In our study, we refer to post-surgical pathological staging. The patients with macrovascular invasion and multiple nodules found at surgical and pathological evaluation had previously been judged suitable for surgery by imaging; thus, they were clearly under-staged before surgery. However, this finding was not new because previous studies[14–16] on explanted livers have already highlighted the critical problem of imaging staging before surgery, finding an underestimation or overestimation of the tumor burden in approximately 25% of cases.

Huo *et al.* suggest including the albumin-bilirubin (ALBI) score in our predictive model. The ALBI score, which was introduced in 2015,[17] is a validated tool for assessing underlying liver function for the prognosis of HCC. Since the study was designed in 2008 and patients were enrolled up to January 2014, we did not plan to include the ALBI score in our predictive model. However, according to this suggestion, a *post hoc* analy-

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sis to assess the role of ALBI in predicting HCC early and late recurrences was carried out. It was found that, in our cohort, it was not a predictor of these events (early HCC recurrence: HR 1.521; 95% CI 0.978–2.366; $p = 0.063$; late HCC recurrence: HR 1.448; 95% CI 0.769–2.726; $p = 0.251$).

In conclusion, even if other variables, such as those suggested by Wei *et al.*, Xiang *et al.* and Huo *et al.*, could be investigated in additional studies regarding their predictive role in HCC recurrences, we believe that the SSM represents a clinically useful predictive tool for this purpose, being directly correlated with the degree of liver disease and portal hypertension which are both involved in carcinogenesis.

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Conflict of interest
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Authors' contributions
All the authors contributed equally to the response.

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Author names in bold designate shared co-first authorship

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