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Spleen in hepatocellular carcinoma: More complexity and importance than we knew

To the Editor:

We read with interest in the article by Marasco and colleagues, which was recently published by *Journal of Hepatology*.[1] In their prospective cohort study, the authors present important data regarding the importance of spleen stiffness measurement (SSM), a non-invasive marker of portal hypertension evaluated by transient elastography (TE), for predicting the late recurrence (24 months post-surgery) of hepatocellular carcinoma (HCC) after liver resection. Their study showed that the usage of SSM at 70 kPa is an optimal cut-off value to predict the late recurrence of HCC, both the positive and negative predictive values are 75%. As the data show, none of the patients in late HCC recurrence group had an F1/F2 grade of liver fibrosis. Furthermore, compared to the no HCC recurrence and early HCC recurrence group (with a spleen stiffness of 35 kPa and 40 kPa, respectively), the late HCC recurrence group had a higher SSM value of 54.2 kPa. Those results indicate that the severity of liver fibrosis or cirrhosis and spleen stiffness are closely related to the development of *de novo* tumors after curative HCC resection without the presence of microsatellites and vascular invasion. The measurement of spleen stiffness is very important and will potentially guide clinicians to customize a tailored surveillance program after curative treatment for HCC patients with pre-surgery SSM >70 kPa; however, the risk of HCC is complex and requires additional considerations.

Firstly, the virus etiology, viral load, pre- and post-operative antiviral therapy should be fully considered. It is well acknowledged that hepatitis virus infection is associated with a remarkable increase in the risk of developing HCC compared with virus-negative patients, among which individuals with hepatitis C virus (HCV) infection have the highest risk. An earlier study showed that high viral load was associated with late recurrence in hepatitis B virus (HBV)-related HCC and pre- and post-operative antiviral therapy play crucial roles in reducing late recurrence.[2] In the study by Marasco and colleagues, the bias may partly come from virus etiology (HBV or HCV), unclarified virus load and antiviral therapy strategies (nucleotide drugs for HBV and interferon or direct-acting antivirals for HCV), as well as from races/ethnicities. For example, a computed tomography-based model had a high accuracy for prediction of hepatic venous pressure gradient in individuals with alcoholic and HCV dominant cirrhosis, but not for HBV-related cirrhosis in China.[3] Thus, we are concerned that the applicability of SSM in predicting the late recurrence of HCC should not be generalized to populations with different races/ethnicities and etiologies of HCC without further validation.

Secondly, studies showed that shear wave elastography (SWE) had a better sensitivity and specificity for the diagnosis of liver fibrosis/cirrhosis.[4] Factors such as ascites, obesity, aminotransferase abnormalities, extrahepatic cholestasis and high central venous pressure, can limit the validity of TE measurements. And the failure rate for TE was significantly higher than SWE (13% *vs.* 3–4.5%),[5] especially when spleen width was <12 cm. In addition, spleen stiffness values are usually higher than liver stiffness values, with maximum values of 75 kPa and 150 kPa for TE and SWE, respectively.[5] Considering the optimal SSM cut-off value is 70 kPa in this article, it may be preferable to choose SWE to estimate spleen stiffness values and evaluate the HCC recurrence risk after surgery in the future.

Thirdly, spleen stiffness during liver cirrhosis can be partly ascribed to immune alteration in the spleen. Since immune cells and factors are commonly involved in fibrosis and spleen fibrosis contributes to spleen stiffness,[6] it is rational to anticipate that the disordered spleen immunity in virus-related cirrhotic patients plays an essential role in spleen fibrosis and the consequent stiffness. Our previous study revealed that in cirrhotic patients with portal hypertension, macrophages within enlarged spleens were disturbed and secreted pro-inflammatory and pro-fibrogenic cytokines,[7] further supporting the immune role of the spleen in its stiffness. Likewise, spleen immunity can also be educated by cancer cells and impact on the development of HCC. The involvement of spleen immune cells in malignancies has been reported in our previous study[8] and 2 recent studies.[9,10] Spleen-resident or spleen-derived immune cells may foster a tumor-facilitative immune microenvironment in the liver by releasing cytokines, or by directly altering the hepatic leukocyte pool after being recruited. Therefore, from an immune point of view, the proposal by Marasco *et al.* that SSM may predict HCC late recurrence is reasonable. Given the central place positioned by spleen immunity, the combination of SSM and immune parameters of spleen and/or blood would have a higher value in predicting HCC late recurrence.

In summary, late recurrence could be regarded as *de novo* tumor, the study by Marasco *et al.* enables clinicians to provide a more individualized tailored surveillance program, especially for patients with high SSM before HCC resection. Validation studies from a more diverse population are warranted and

future studies need to carry out sub-analysis for virus etiology (HBV or HCV), viral load and antiviral therapy strategies with different methods of spleen stiffness measurement (SWE). Again, future studies need to clarify whether the combination of SSM and immunological parameters could be better for predicting late recurrence of HCC.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Supplementary data

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Liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection: A comment for moving forward

To the Editor:

Predicting risk factors of hepatocellular carcinoma (HCC) recurrence has become a hot topic in the last decade.[1] In a recent issue of *Journal of Hepatology*, Marasco and coworkers[2] performed a prospective study which included 175 patients with HCC who underwent hepatic resection. The post-operative and 90-day mortality rates following resection were nil. Patients were followed up for at least 24 months from inclusion or until HCC recurrence. The authors found that risk factors of early recurrence (<2 years) included viral etiology, HCC grading (3 or 4), resection margins <1 cm, and being beyond the Milan criteria, while spleen stiffness measurement (SSM) (hazard ratio 1.046, 95% CI 1.020–1.073) was the only risk factor of late tumor recurrence (≥2 years).[2] Therefore, they concluded that spleen stiffness seems to be a crucial predictor of the late recurrence of HCC, since it is directly correlated to the degree of liver dis-