Reply to: "Outcome of critically ill cirrhotic patients admitted to the ICU: The role of ACLF"

To the Editor:

We sincerely thank Professor Senzolo and colleagues for their interest in our article and for sharing their experience in Padua. Senzolo and colleagues compared the data obtained in 28 patients with ACLF from Padua to the ICU outcome of our cohort of 71 patients admitted to the intensive care unit in Leuven. They questioned the fact that patients in Leuven had a better survival than previously reported in the literature. They specifically raised the possibility that differences in the patient population and liver disease severity may explain the differences in survival in their ACLF cohort compared to those in Leuven. Recently, the prospective multicenter CANONIC study defined ACLF as a severe disease entity with high associated mortality and showed that survival correlated with the number of failing organs.[1] However, until now it has remained unclear if ACLF is associated with a worse prognosis than other ICU indications, as no studies have specifically addressed this question in carefully matched patient cohorts.

The purpose of our study was to assess whether patients with ACLF and comparable disease severity had similar outcomes when admitted to the ICU. For this reason, the APACHE II score was used to compare liver disease to non-liver disease populations upon admission to the intensive care. Our study utilized the unique opportunity of interrogating the large prospective EPaNIC database.[2] This prospective study performed at our institution included 4,640 ICU patients allowing us to carefully match 71 patients with ACLF, defined by the Chronic Liver Failure (CLIF) criteria, to 71 patients with sepsis and 71 medical ICU patients using propensity score matching. Propensity score matching allowed us to reduce bias due to confounding variables, a statistical tool often utilized in large ICU studies including heterogeneous populations. When these comparisons were performed using rigorous statistical analysis, we could clearly demonstrate comparable outcomes for ACLF patients when matched to other ICU cohorts.

The difference in outcome in ACLF between the Padua and Leuven cohorts may indeed be explained by important differences between the groups including higher CLIF-sequential organ failure assessment (CLIF-SOFA) scores, and the type of organ failure as mentioned by Senzolo and colleagues. It may however also be explained by a delay in ICU support. As mentioned by the authors, 85.7% of their population already fulfilled ACLF criteria while still admitted to the liver ward and were then subsequently admitted to the ICU due to further worsening of organ failure, reflected by an increase in ACLF grade, as well as a high number of these patients requiring organ support following ICU admission. In contrast our patients were admitted much earlier to the ICU because of ACLF development. In this way the Padua cohort probably better mimics the population studied in the CANONIC trial. Another consequence of the fact that patients remained in the liver ward longer, is the fact that the calculated CLIF-SOFA scores upon ICU admission in the Padua, better correlated with the ICU outcomes published in the literature. Indeed, Gustot and coworkers showed that the final ACLF grade and prognosis are better predicted by the CLIF-SOFA score on day 3 to 7 after disease onset.[3] The CLIF-SOFA score in our study was calculated at the time of ICU admission and not on day 3–7, as the intent of the study was to evaluate the outcome of patients with ACLF compared to ICU patients without ACLF and therefore to establish whether ICU care is justified in this population. Overall, the findings generated from the studies from Padua and Leuven may therefore justify earlier referral of patients with ACLF to the ICU as worsening of organ failure may further negatively impact on survival in this disease.

Senzolo and colleagues do raise a very important point that warrants pertinent discussion. The CLIF criteria defines ACLF based on the unweighted sum associated with organ failure in patients with cirrhosis. A patient with cirrhosis may therefore fulfill the CLIF criteria for ACLF despite having relatively preserved liver function but associated extrahepatic organ failure. As suggested by Senzolo and colleagues, it is currently unclear if patients with more severe liver failure, as part of their ACLF syndrome, have worse outcomes compared to patients where liver dysfunction is less pronounced. Although ACLF as a syndrome is accepted by all major liver disease societies including EASL, AASLD and APASL controversy exists regarding the sequence of events leading to ACLF. According to the CLIF consortium and EASL, extrahepatic organ failure may precede or be disproportional in severity to liver dysfunction in ACLF. APASL places the emphasis on jaundice and encephalopathy occurring before other signs of decompensation and does not require underlying cirrhosis to be present. It is clear that studies are required to define the importance of the sequence of organ failure and the degree of liver dysfunction needed to be present, to separate "organ failure occurring in cirrhosis" from "liver centered" ACLF, as the prognosis of these entities may differ. It is also conceivable that cirrhotics with predominant non-hepatic multi-organ failure may benefit much less from liver transplantation than "liver failure centered ACLF".

Conflict of interest

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

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.01.001.

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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