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Reply to: “It takes two “eyes” to see in depth”

To the Editor:

We appreciate Ripoll and colleagues’ comments regarding our study demonstrating that cardiac index (CI) is an independent predictor of disease outcomes in cirrhosis.[1] As stated by Dr. Ripoll and colleagues, our study is the first attempt to give a precise definition of hyperdynamic circulation by using the upper limit of normal CI (>4.2 L/min/m^2) as a cut-off. We also described a hypodynamic circulatory state (CI <3.2 L/min/m^2). Interestingly, these two states had a worse prognosis compared to patients with a normodynamic circulation (CI ≥3.2 L/min/m^2 and ≤4.2 L/min/m^2). We would like to remark that using CI (as opposed to cardiac output) or systemic vascular resistance index (SVRI, as opposed to SVR) corrects for body surface and decreases the risk of error when comparing different patients.

Ripoll *et al.* appropriately question whether adding SVRI to these cardiodynamic states could provide further granularity. We should note that, in each multivariable model assessing decompensation or survival as outcomes,[1] we introduced mean arterial pressure and this parameter was not found to be independently predictive of outcome.

Furthermore, we performed a new analysis to confirm the lack of an added predictive value of SVRI to sub-staging based on CI. To categorize patients into a “vasodilated” or “non-vasodilated” stage, we used two SVRI cut-offs: 1,700 dynes-sec/cm^{-5}/m^2 (a discriminating level often used in intensive care units) or 1,970 dynes-sec/cm^{-5}/m^2 (the lowest level of normal in adults).

Fig. 1 shows the proportion of patients in vasodilated *vs.* non-vasodilated states in the context of each of the clinical stages of cirrhosis and their circulatory subcategories. At each stage of cirrhosis, the hyperdynamic circulatory state was closely associated with a very high proportion of patients in the vasodilated state (independently of SVRI cut-off used), ranging from 90% (in compensated patients) to 100% (in decompensated patients), indicating that CI alone is sufficient to identify truly hyperdynamic patients.

Regarding the hypodynamic circulatory state, when vasodilation is determined by a SVRI cut-off of 1,700, each of the clinical stages of cirrhosis was associated with a high proportion of patients in a non-vasodilated state, ranging from 88% to 100%, indicating that in this setting CI alone is sufficient to identify a hypodynamic circulatory state. Similar results are observed when using the SVRI cut-off of 1,970, except in patients with refractory ascites, where 37% of hypodynamic patients were also vasodilated (at rest and in the supine position). This may indicate that this subgroup of patients is enriched with patients transitioning from a normo-hyperdynamic state to the hypodynamic one due to a primary deterioration of cardiac inotropic activity.[1,2]

Regarding the normodynamic circulatory state, around 25% and 60% of compensated patients with clinically significant portal hypertension (CSPH) are vasodilated, defined by SVRI <1,700 or <1,970, respectively (Fig. 1). The corresponding figures for decompensated patients were about 50% and 80%, respectively. This identifies the normodynamic group as the group where “two eyes” may provide further depth of perception.

We agree with Ripoll *et al.* that post-capillary pulmonary hypertension (pcPH) may not necessary reflect the presence of left ventricular dysfunction. Nevertheless, pcPH is a well-established definition of severe diastolic dysfunction and heart failure with preserved ejection fraction.[3–5] Although, pcPH was present in compensated patients with CSPH and in any cardiodynamic group of both the compensated and decompensated stages (see Fig. 2 in[1]), we cannot rule out that administration of an average of 46 g of albumin (after a large volume paracentesis) to patients with refractory ascites the day before the hemodynamic assessment may have increased intravascular volume above the level of maximum load tolerance of the left ventricle (and pericardium) (see Table 1 in[1]). However, data supporting this view are derived from studies where hemodynamic evaluation was performed soon after a rapid infusion of high dose of either albumin in cirrhotic patients[6] or saline in

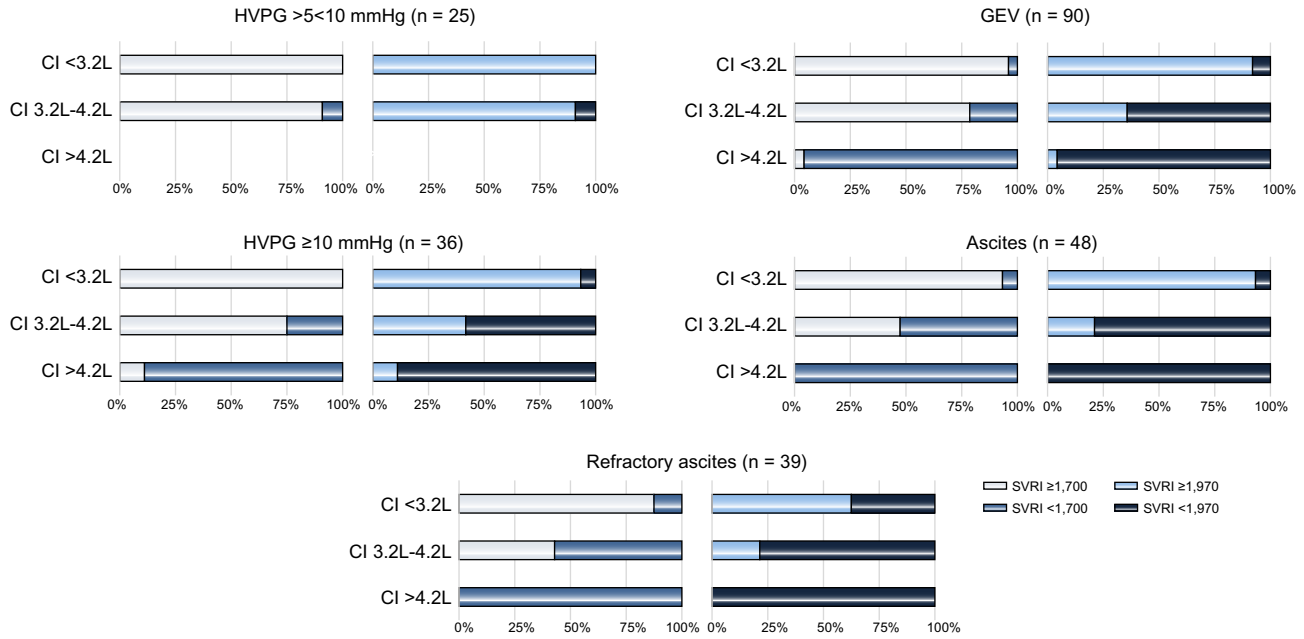

Fig. 1. Systemic vascular resistance index in patients stratified according to the five prognostic stages and the three cardiodynamic circulatory states described in.[1] CI, cardiac index; GEV, gastroesophageal varices; HVPG, hepatic venous pressure gradient; SVRI, systemic vascular resistance index.

healthy individuals[7]. On the other hand, in patients with ascites controlled by diuretics we may have underestimated the proportion of patients with pcPH due to a drug induced decrease of central volemia. Our survival data show that presence of pcPH in patients with ascites (refractory or controlled by diuretics, all with a normal ejection fraction at echocardiography as reported in the Methods session of[1]) is a predictor of death independent of cardiodynamic state, model for end-stage liver disease, and C-reactive protein (CRP).

Ripoll *et al.* also suggest that adding left ventricle stroke work index (LVSWI) to pcPH would provide a holistic view of patients' hemodynamics.[8] This indirect parameter relates ventricle performance to the pressure of work and its formula includes CI. We found that average baseline LVSWI values were different among cardiodynamic states and it progressively decreased throughout the prognostic stages in both hypodynamic and hyperdynamic patients (see Fig. S2 in[1]). These factors multiply the possible sources of error in the individual patient in comparison to CI. So, since our cardiodynamic states have been created based on CI and given that CI and pcPH are independent predictors of death, we think that, at least in decompensated patients, we already have a holistic evaluation of heart function at rest and in the supine position.

A final comment is warranted regarding the interrelationship between inflammation and heart dysfunction. Our study shows increasing CRP levels with each clinical stage, constituting an independent predictor of decompensation/death. Increased CRP levels occur as early as CSPH develops, suggesting that bacteria (or bacterial product) translocation may occur even before decompensation. The fact that CRP levels were not different among cardiodynamic states and that CRP levels and CI were independently predictive of outcomes, raises the possibility that cardiac response to inflammation may differ among patients with cirrhosis, requiring further investigation.

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Conflict of interest

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

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Authors' contributions

FS wrote the letter. GGC, LT, RR, and EV provided valuable intellectual input.

Supplementary data

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Quantitation of anti-HBe antibodies in anti-HBc-positive liver donors

To the Editor:

There is increasing interest in quantitatively determining the presence of antibodies to hepatitis B virus (HBV) antigens both in patients with overt HBV infection and in those with occult HBV infection.[1,2] Recently, we studied a cohort of 100 hepatitis B surface antigen (HBsAg)-negative/anti-HBc-positive liver donors and found that levels of anti-HBc of IgG class above a 4.4 cut-off index (COI) correlated with the finding of intrahepatic HBV covalently closed circular (ccc) DNA, providing a novel potential tool to identify individuals with occult HBV infection (OBI) at increased risk of HBV reactivation following pharmacological immunosuppression.[3] Consistent with our results, Bae *et al.*[4] showed that among patients with resolved HBV infection undergoing allogenic hematopoietic stem cell transplantation, the finding of total anti-HBc with a titer ≥ 8 signal-to-cut-off (S/CO) ratio was independently predictive of HBV reactivation (hazard ratio [HR] 7.429, $p = 0.002$). Similarly, Yang *et al.*[5] observed that a high titer of total anti-HBc (≥6.41 IU/ml) and low anti-HBs (<56.48 mIU/ml) were significantly associated with HBV reactivation (HR 8.48 and 4.52, respectively, $p < 0.010$) in lymphoma patients with resolved HBV infection undergoing chemotherapy. However, while in the previous study, no difference was observed in anti-HBe positivity between patients with HBV reactivation and those without (39.3% *vs.* 41.7%, respectively, $p = 0.827$),[5] in our series the rate of anti-HBe positivity was significantly different between HBV cccDNA-positive and -negative individuals (55.6% *vs.* 23.3%, respectively, $p = 0.003$). On this premise, we further investigated the possible role of anti-HBe quantitation as a surrogate marker of intrahepatic HBV cccDNA in the same cohort of 100 anti-HBc-positive liver donors.[3]

The measurement of anti-HBe was performed by chemiluminescent enzyme immunoassay (CLEIA) on the fully automated system Lumipulse® G600 II (Fujirebio, Tokyo, Japan). The antibody quantitation was performed using an anti-HBe assay (Lumipulse® G HBeAb-N) calibrated against the WHO 1st International Standard for anti-HBe (Paul-Ehrlich-Institut, Langen, Germany) (Fig. 1A). Lower limit of detection (LLoD) and lower limit of quantitation (LLoQ) were estimated at 0.31 IU/ml and 0.35 IU/ml, respectively (Fig. 1B). The accuracy of recovery was 98.8% (95% CI 94.4%–103.3%) (Table S1). The coefficient of variation for repeatability of the assay (intra-run variation) was 3.1%, whereas for reproducibility (inter-run variation) it was 4.0%. Dilution parallelism of standard curve and anti-HBe-positive serum sample is reported in Fig. S1. Statistical analyses were performed using MedCalc® software, version 16.8. (MedCalc, Ostend, Belgium).

Among the 32 anti-HBe-positive donors, antibody values ranged from < 0.35 IU/ml to 14.8 IU/ml, with a median of 0.60 IU/ml. In the whole cohort of 100 liver donors, anti-HBe quantitation showed an area under the curve (AUC) of 0.713 (95% CI 0.614–0.799, $p < 0.001$) for the discrimination between HBV cccDNA-positive and -negative liver specimens; an anti-HBe titer > 0.68 IU/ml (sensitivity = 44.4% and specificity = 95.9%) allowed us to predict the presence of HBV cccDNA in the liver with a positive predictive value of 80.0%. For anti-HBc IgG, 4.4 COI was the optimal cut-off that maximized sensitivity (92.6%) and specificity (48.0%) (AUC = 0.680, 95% CI 0.577–0.771, $p = 0.002$), with a negative predictive value of 94.6%.[4] In a multivariate logistic regression model including age, gender, anti-HBe > 0.68 IU/ml and anti-HBc IgG > 4.4 COI, both antibodies were significantly and independently associated with measurable intrahepatic HBV cccDNA (odds ratio = 11.641, $p = 0.001$ and odds ratio = 7.239, $p = 0.016$, respectively) (Table 1).

We previously observed that the quantitation of anti-HBc IgG allowed the presence of intrahepatic HBV cccDNA to be ruled out in 37 out of 100 anti-HBc-positive liver donors (negative predictive value = 94.6%)[4] yet the serological prediction of

Keywords: Hepatitis B virus; HBV cccDNA; Occult HBV infection.