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Correspondence

"Are the Expanded Baveno VI Criteria really safe to screen compensated cirrhotic patients for high-risk varices?"

To the Editor,

The Expanded Baveno VI criteria [1] have been recently proposed as a new screening strategy for high-risk varices (HRV), able to increase the rate of spared upper endoscopies (EGDs) and improve upon the original Baveno VI Criteria [2]. To date, few studies have investigated the performance and safety of these criteria [3,4]. The recent work by Bae et al. [4] is the first one to report a high rate (>5%) of missed HRV by the expanded criteria, questioning their efficiency in safely ruling out HRV (sensitivity 81%, NPV 93%, LR- 0.30).

We would like to present our results in a prospective multicenter cohort of patients with compensated advanced chronic liver disease (cACLD) of mixed etiology (n = 115), enrolled for the external validation of our new model for ruling out HRV [5]. Upper endoscopy (EGD) could have been spared in 19 (16.5%) patients by applying the original Baveno VI Criteria (liver stiffness (LSM) <20 kPa and platelet count (PLT) > 150×10^9/L) and in 34 (29.6%) patients by Expanded Baveno VI Criteria (LSM < 25 kPa and PLT > 110×10^9/L). However, 2 out of the 15 HRV would have been misclassified only when applying the expanded criteria, with an above-the-accepted-threshold [2] rate of missed HRV of 6% (95% Interval of confidence [IC], 1.6–19%). The etiology of the liver disease in these misclassified patients was active HCV infection and alcohol-related. Ruling-out-HRV descriptors were suboptimal (sensitivity 87% [95% IC, 60–98%], NPV 94% [95% IC, 81–98%], LR- 0.42 [95% IC, 0.11–1.58]) and in line with the results of Bae et al.

In addition, we built a nomogram (Fig. 1) as a simple visual presentation of a risk prediction model [6], based on LSM and PLT, in the entire population [5]. Indeed, according to the Baveno VI proceedings [2], a non-invasive HRV screening method is considered safe, if it is able to discriminate patients with a risk of

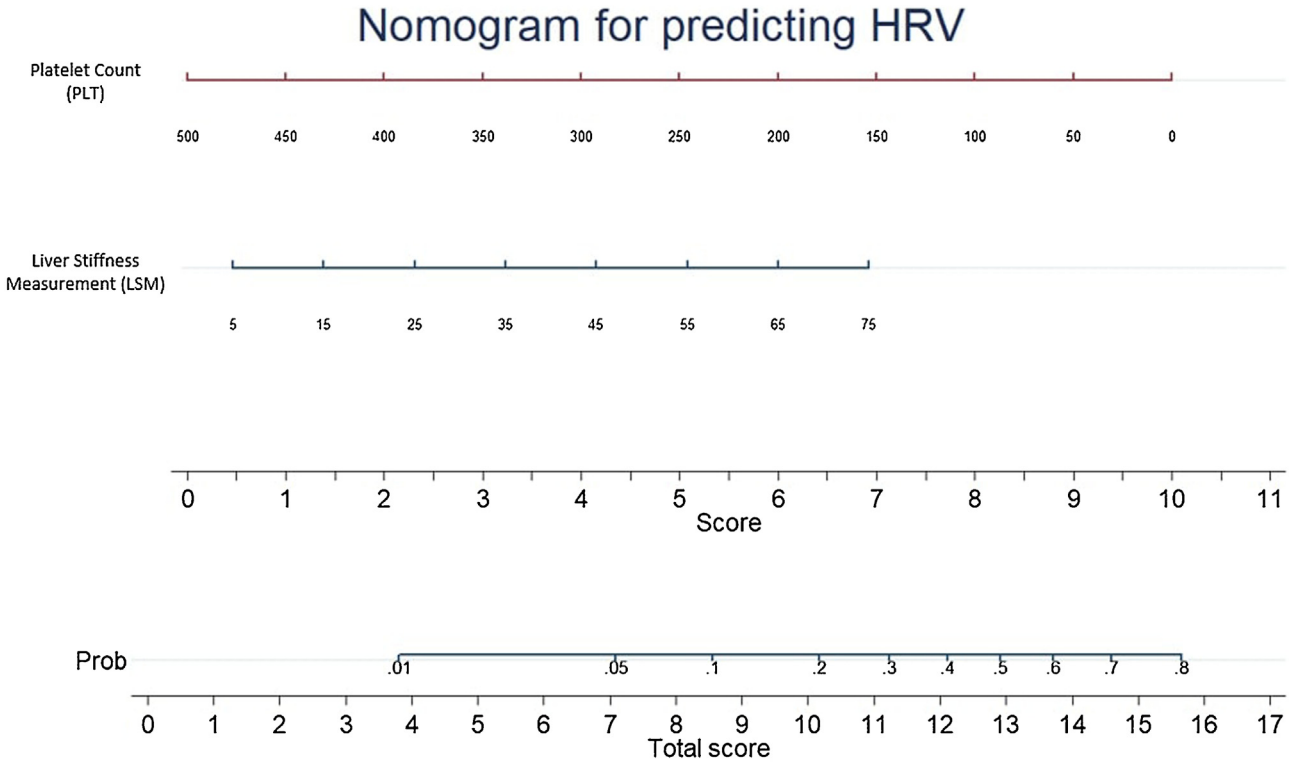

Fig. 1. Nomogram to predict the presence of high risk varices (HRV) by platelet count and liver stiffness measurements.
In nomograms with two variables, to calculate the probability of HRV, trace a vertical line from each of the predictors' axis to the first line ("Score"). Add the total points, and trace a vertical line from the "total score" axis to the risk axis (Prob) to calculate the risk of HRV.

presenting HRV <5%. This is not the case of the Expanded VI Criteria: when we apply the cut-offs to the nomogram, the model indicates an HRV risk superior to 10% and therefore is not able to identify a subset of patients with risk <5%. Interestingly, the same result can be obtained when we apply these cut-offs to the original nomogram drawn by Abraldes et al. [6] for the Anticipate Study.

In conclusion, the Expanded Baveno VI criteria represent a seemingly attractive strategy to rule out HRV, as they allow to vastly increase the rate of spared EGDs. However, this happens at the expense of the missed HRV rate, which is above the accepted threshold of 5%. Therefore, we believe that some concerns should be raised about their safety and ability to identify compensated cirrhotic patients that can avoid screening EGD. This issue should be carefully addressed by further large prospective studies evaluating screening strategies for HRV.

Conflict of interest

None declared.

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Time to revise the definition of NAFLD: A purist vision

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Dear Editor,

In 2018, Wood et al. published in *The Lancet* an analysis of individual-participant data from 600,000 current drinkers of 83 prospective studies, reporting that the threshold of alcohol consumption for lowest risk of all-cause mortality was ~100 g/week (i.e., ~14 g/day) and that a lower alcohol consumption was associated with a lower risk of cardiovascular complications [1].

In the same years, Åberg et al. published a study of nearly 6750 individuals followed for 11 years, showing that metabolic syndrome and alcohol consumption (even within the limits defining non-alcoholic fatty liver disease [NAFLD]) were associated with an increased risk of severe liver disease [2].

In another study, involving 8162 participants (56% with NAFLD) from NHANES followed for 12 years, Hajifathalian et al. documented that, among NAFLD patients, modest alcohol consumption (i.e., 0.5–1.5 drinks/day) was associated with a decrease in all-cause mortality, whereas high alcohol consumption (i.e., ≥1.5 drinks/day) was associated with an increased mortality [3].

In a recent cohort study of 4264 individuals with hepatic steatosis followed for 20 years, Younossi et al. observed that the presence of metabolic syndrome and excessive alcohol consumption were independently associated with an increased risk of death in individuals with hepatic steatosis and that the association of excessive alcohol use with mortality was significant in individuals with metabolic syndrome, but not in those without [4].

Again in 2018, using approximately 700 data sources of individual and population-level alcohol consumption, along with nearly 600 prospective and retrospective studies on the risk of alcohol use, the GBD (Global Burden of Disease) 2016 Alcohol Collaborators found that alcohol use was a leading risk factor for global disease burden, causing substantial health loss [5]. In particular, they reported that the risk of all-cause mortality, and of cancers specifically, increased with increasing levels of alcohol consumption and that the level of alcohol consumption able to minimize health loss was zero [5].

To date, the diagnosis of NAFLD is based on the following criteria: (a) hepatic steatosis on imaging or histology, (b) no excessive alcohol consumption (a threshold of 20 g/day [~140 g/week] for women and 30 g/day [~210 g/week] for men is conventionally adopted), and (c) no competing causes for hepatic steatosis [6].

Over the last decade, it has become clear that, compared to those without, patients with NAFLD have an increased risk of all-cause mortality and that NAFLD is not only associated with hepatic complications, but also with an increased risk of serious extra-hepatic complications, including cardiovascular diseases and cancers [7,8].