The role of the model for end-stage liver disease-sodium score and joint models for 90-day mortality prediction in patients with acute-on-chronic liver failure

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pibrentasvir for 8 or 12 weeks, the modified intent-to-treat SVR12 was smaller in the 679 patients infected with genotype 3 (95.8%) than in the 2,900 patients infected with genotypes 1, 2 and 4 (97.6% to 98.5%), but no predictive factors of virological failure have been identified. Thus, recommendations on treatment duration in patients infected with genotype 3a and compensated cirrhosis are based on moderate-quality evidence." Thus, the recommendation is: "Treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with: […] (iii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (A1). In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 weeks, but more data are needed to consolidate this recommendation (B1)."

As indicated in the EASL recommendations: "Simplified, genotyping/subtyping-free, pangenotypic anti-HCV treatment must be used to improve access to HCV treatment and increase the global infection cure rates in any setting where genotype and subtype determination is not available, not affordable and/or would limit access to therapy (A1)". In such context, the collective benefit is preferred to an individual benefit, as far as the duration of glecaprevir/pibrentasvir administration or the addition of ribavirin to sofosbuvir/velpatasvir are concerned: "Lower SVR12 rates may be achieved in patients infected with HCV genotype 3 and compensated (Child-Pugh A) cirrhosis than in other patients, but efficacious retreatment strategies exist in individuals with virological failure."

The issue of patients infected with genotype 3b, an HCV subtype inherently resistant to NS5A inhibitors relatively frequent in China and South-East Asia but rare in Europe, is discussed in another section of the EASL Recommendations: "In settings where sequence analysis of the NS5A region by means of population or deep sequencing is available and affordable, patients infected with subtypes 1l, 4r, 3b, 3g, 6u and 6v and patients infected with other infrequent subtypes harbouring ≥1 RAS(s) known to confer resistance to NS5A inhibitors should be considered for treatment with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, pending data with dual pangenotypic regimens (B2)." It is said elsewhere that: "Virological studies are required in countries in Africa, Asia and South America to determine the epidemiology, distribution and prevalence of HCV subtypes inherently resistant to NS5A inhibitors and thus to optimize treatment decisions without the need for individual HCV genotype and subtype determination." This implies that the triple combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks may be indicated as first-line treatment in regions where HCV subtypes inherently resistant to dual NS5A inhibitor-containing regimens are highly prevalent and reliable HCV genotype and subtype determination is not available or affordable.

The EASL panel confirms that "Renal function, including creatinine and eGFR, should be ascertained (A1)" whenever possible, as part of regular medical care. Finally, "Given the high SVR12 rates expected with these regimens across all groups of patients if adherent, testing for SVR can be omitted (except in patients with high-risk behaviours and risk of reinfection who require SVR testing 12 weeks after the end of treatment and yearly thereafter whenever possible) (B1)."

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Reference

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EASL Recommendations on Treatment of Hepatitis C Panel*
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The role of the model for end-stage liver disease-sodium score and joint models for 90-day mortality prediction in patients with acute-on-chronic liver failure

To the Editor:

With great interest we read the article by Hernaez *et al.*[1] The authors showed that the model for end-stage liver disease sodium (MELD-Na) score underestimated the observed mortality risk in patients with acute-on-chronic liver failure (ACLF). As a result, patients with ACLF might be underserved in the MELD-Na-based allocation of donor livers. We agree with the authors that the MELD-Na score is not optimal for patients with ACLF, but we have a few additional comments on their paper.

First, the authors state that "it is unclear whether MELD-Na captures clinical severity" in patients with ACLF. Considering the available literature, it is clear that the disease course of ACLF is not captured by MELD-Na, especially for patients with ACLF-3.[2] In their large UNOS analysis, Sundaram *et al.* already showed that ACLF death and waiting list removal rates are independent of MELD-Na score, as mortality rates were highest in MELD-Na <25 and ACLF-3 patients.

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Second, the authors question the accuracy of MELD-Na mortality prediction in patients with ACLF. The CLIF score, specifically developed for patients with ACLF, achieved a 90-day mortality concordance statistic (c-index) of 0.76, whereas the MELD-Na had a c-index of 0.67.[3] The c-index shows how accurate the model can discern between life and death, by pairwise patient comparisons in the given data. The discrimination of both scores is not optimal. Given that the MELD-Na was not developed for patients with ACLF, but for chronically ill patients at listing for liver transplantation (LT), its discrimination seems respectable. The current allocation system is based on MELD-Na because, for the majority of patients with chronic liver disease, MELD-Na offers excellent performance.[4,5] Still, the authors showed that MELD-Na and thus transplant chances increased with higher ACLF grades, with median MELD scores of 24, 27 and 32 for ACLF grade 1–3 respectively. The authors do not focus on the c-index as the main model performance indicator but assess the calibration instead. The expected and observed mortality rates in patients with ACLF were compared. One could question the assessment and main focus of calibration if the model captures few relevant factors in these patients. Even in cirrhotic patients, for whom MELD-Na was designed, the MELD-Na becomes less reliable with increasing disease severity.[4,5]

Third, the authors showed that LT was not often considered/performed in patients with ACLF. Many patient-specific and center-level factors influence the evaluation for LT. Still, ACLF showed a positive association with LT, which was higher than for non-ACLF patients. Patient exclusion from transplantation is most likely due to expected futility. The fact that the allocation system is MELD-Na based, does not change that. As Nadim *et al.* stated: "while scoring systems for ACLF may help centers decide who to transplant, the scores do not affect organ allocation; it is still the MELD score that ultimately determines organ allocation in most countries, including the US".[6] Granting exception points or status 1 may be the best option for the small number of patients with ACLF listed for LT.

Finally, Hernaez *et al.* note that "future research should also focus on developing and validating prognostic scores that incorporate dynamic changes in patients clinical course" and that they "did not capture longitudinal changes of ACLF scores over time". Traditional Cox models, like the MELD-Na, make assumptions that often do not hold in the data and use only 1 measurement in time for survival prediction. Thus, dynamic changes are not modeled and longitudinal data is ignored. For dynamic prognostic modelling of longitudinal data, the joint model (JM) is an appropriate method to capture changing disease severity.[7] The JM adequately links longitudinal measurements to survival analysis by combining mixed-effect and Cox models. It considers all past measurements, changes in values and the rate of change at every point in time and uses this for patient-specific predictions that are updated based on every new available measurement. This is valuable for ACLF patients. In simulation studies, the JM outperformed Cox models with less biased results.[8–10]

In conclusion, the MELD-Na underestimates mortality in patients with ACLF because it uses only some of the relevant prognostic factors for mortality. The JM should be considered for the dynamic prediction of patient-specific survival based on repeated measurements.

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Conflict of interest
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Author names in bold designate shared co-first authorship

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