Improving survival prediction models for liver transplantation candidates

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10.2 Supplement Chapter: 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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Letter

With great interest we read the article by Hernaez et al.[1] The authors showed that predicted survival by the Model for End-stage Liver Disease sodium (MELD-Na) score underestimated the observed survival in acute-on-chronic liver failure (ACLF) patients. As a result, ACLF patients 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 ACLF patients. However, we suggest several considerations for this paper.

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

Second, the MELD-Na accuracy of mortality prediction in ACLF patients is questioned. The CLIF score, specifically developed for ACLF patients, 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 ACLF patients, 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 perfor-

mance indicator but assess the calibration instead. The expected and observed mortality rates in ACLF patients 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 ACLF patients. 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 futile efforts. 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 ACLF patients 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 one measurement in time for survival prediction. Thus, dynamic changes are not modeled and longitudinal data is ignored. For dynamic prognostic modeling of longitudinal data, joint models (JM) present an appropriate method of capturing 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 survival in ACLF patients because it uses only some of the relevant prognostic factors for ACLF patient survival. Joint models should be considered to dynamically predict patient-specific survival based on repeated measurements.

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