Response to: "Towards optimally replacing the current version of MELD"

On building a better mousetrap

To the Editor:

We thank Dr. Kartoun for his interest in our manuscript with regard to leading liver transplant allocation models that have demonstrated enhancements beyond the existing model for end-stage liver disease (MELD)-Na score.[1,2] In agreement with the general sentiment of Dr. Kartoun's letter, we believe that there is room for improvement of MELD and other prognostic models.

If we may reiterate the main points made in our manuscript, there are at least three applications for prognostic models in chronic liver disease – (1) for liver transplant allocation, (2) prognostication for patient management and (3) for continuous monitoring of patient status for care optimization.[2] Clearly, MELD was developed for the first purpose, but has been used frequently for other purposes as well, because of familiarity, convenience, and direct applicability in potential transplant candidates, as well as wide acceptance of its predictive accuracy. We also outline ways in which models may be improved for patient management purposes, using large amounts of data in electronic records and modern modeling techniques.

With regards to the specific question about MELD 3.0, a wide array of variables was extracted as potential predictors of waitlist survival, including demographics, clinical status, and laboratory values (including components of the MELD and Child-Pugh scores and additional variables). Consistent with principles outlined in the development of the original MELD score, variable selection for MELD 3.0 was conducted so that the included variables were: (1) measurable in an objective fashion, (2) broadly generalizable, (3) devoid of unnecessary volatility without biological significance, and (4) reportable to the Organ Procurement and Transplant Network (OPTN) without causing an undue burden. For instance, potentially subjective variables, such ascites and encephalopathy, and those with ambiguous policy implications, such as age, were excluded *a priori* from the development of MELD 3.0.[3] While additional variables such as lactate, blood urea nitrogen, white blood cells, and total cholesterol may provide additional prognostic insight to MELD-based models,[4–6] they do not fulfill all of the principles outlined above.

We thank Dr. Kartoun for highlighting the strengths of the MELD-Plus model. It has been shown to be more discriminating compared to the MELD-Na in the Mass General Brigham and IBM Explorys database,[4] which suggest that it may have a role in patient management scenarios. On the other hand, for the reasons highlighted above it is not quite suitable for allocation of organs for transplant. This discussion, however, remains helpful in highlighting the various purposes of prognostic models and just because one model is optimal for one purpose, it may not necessarily be the best for other purposes.

We would like to take this opportunity to update the reader that MELD 3.0, developed based on the OPTN data and tested on the liver simulated allocation model,[7] has been adopted by the OPTN Board to replace the current MELD-Na to determine the organ allocation priorities in the US. Congruent with the direction of this dialogue, we continue to look for opportunities to improve policy and clinical tools to optimize patient outcomes.

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Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose as described by the Journal of Hepatology.

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Supplementary data

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Non-invasive tests for evaluating treatment response in NAFLD

To the Editor:

We read with great interest the intriguing and clinically very relevant study by Rinella *et al.,* wherein they used non-invasive tests (NITs) to evaluate the therapeutic response to obeticholic acid (OCA).[1] The study is based on the 18-month interim results from the phase III REGENERATE trial, in which 931 patients with non-alcoholic steatohepatitis (NASH) and fibrosis stage F2 or F3 were randomized to receive placebo or two different OCA doses. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase as well as fibrosis scores, including FIB-4, enhanced liver fibrosis (ELF), FibroMeter, FibroTest and FibroScan-AST score, were determined and vibration-controlled transient elastography (VCTE) was assessed during the study period of 18 months. A reduction of aminotransferases, the different fibrosis scores and VCTE was observed in OCA- compared to placebo-treated patients. AST and ALT reduction was most evident in patients with improvement of fibrosis ≥1 stage. Aminotransferase levels, however, also improved in OCA-treated patients with no change or even with worsening in fibrosis stage, suggesting that these changes are unrelated to fibrosis. This is in line with a previous study showing that aminotransferases decrease with improvement of histological disease activity in non-alcoholic fatty liver disease (NAFLD), but do not significantly correlate with worsening of NAFLD.[2]

In Rinella *et al.*'s study, ELF score changes were more pronounced in patients with fibrosis worsening than with improvement, whereas FIB-4 changes equally reflected fibrosis worsening and improvement.[1] The FIB-4 score was developed to rule-in or -out advanced fibrosis by using two cut-off values.[3] However, a long-term follow-up study of NAFLD patients revealed that changes of FIB-4 are only weakly associated with fibrosis progression in NAFLD.[4] The ELF score considers markers of extracellular matrix remodeling and revealed a high diagnostic performance for the detection of advanced fibrosis in NAFLD.[3]

An early NIT, which detects early signs of fibrogenesis, remains to be established. We suggest that the M30 cell death biomarker, which measures caspase-cleaved cytokeratin-18 (CK-18) fragments after their release from apoptotic hepatocytes, might be very useful to detect fibrosis changes in response to treatment. Studies in HCV-mediated liver damage revealed that M30 is a sensitive NIT that can already be elevated in patients with normal aminotransferase levels but fibrotic liver injury.[5,6] Moreover, patients with NAFLD and low FIB-4, who would not be considered for further risk stratification according to current guidelines, might benefit from serological M30 detection. We have very recently observed in a NAFLD cohort (n = 103) that patients with low FIB-4 but elevated M30 levels had NASH in the majority of cases, from which more than half showed histological signs of fibrosis (43% with F2/F3 fibrosis). Since inflammation and apoptotic liver injury triggers fibrogenesis, M30 levels significantly correlate with liver fibrosis.[7–10] Indeed, CK-18 cleavage is an early event in hepatocyte apoptosis that is causally linked to stellate cell activation and fibrogenesis. Although M30 is not primarily a fibrosis marker, its level encompasses a biological plausibility that should be useful for monitoring therapeutic effects on fibrosis. Rinella *et al.* found a robust dose-dependent reduction of M30 levels in OCA-compared to placebo-treated patients with NASH at month 18. Despite the important findings, however, no information was provided on M30 levels at different time points in the course of treatment with respect to changes in the fibrosis stage. With regard to the close correlation of M30 with liver injury and fibrogenesis, it would be interesting to know how this biomarker reflects fibrosis progression or regression, as shown for other NITs.

Since apoptosis is an early event in the pathogenesis of NAFLD and fibrosis development,[7] the M30 marker might detect a broader range of disease severity and therefore might represent a suitable NIT for monitoring the NAFLD course. M30 is currently used in various clinical studies evaluating novel drugs in NAFLD. Further data from these trials are required to evaluate the suitability of M30, as a single marker or in combination with other parameters, for monitoring disease progression and treatment response in NAFLD.

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