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Meeting the Eastern perspective in hepatitis B related ACLF

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Chronic hepatitis B (CHB) related liver disease affects millions of patients worldwide,[1] and acute decompensation superimposed on cirrhosis, now termed acute-on-chronic liver failure (ACLF) has a high short-term mortality, and acute reactivation of CHB frequently sets off ACLF. Effective viral suppression and liver transplantation are the mainstays of management. From both a clinical and public health perspective, accurate prediction of patients at highest risk of decompensation and thus most likely to benefit from expensive and scarce resources is highly valuable. Use of the Model for End-stage Liver Disease (MELD) score to determine liver transplantation need has become ingrained as the *de facto* method for establishing short-term mortality in patients with chronic liver disease since its institution in the US transplant system in 2002; however, many refinements have been suggested to address the imperfections of MELD, which is appropriate given that the face of cirrhosis and chronic liver disease will continue to change as clinical advances arise in the care of these patients.

The authors of this article evaluate several outcome/mortality prediction models in CHB-related ACLF by comparing iterations of MELD in a cohort of 232 Chinese patients with CHB who participated in a previous study of an acute liver decompensation assist device system.[2] These alternate versions of MELD include additional parameters of clinical care as well as previously validated prediction methods, including Child-Turcotte-Pugh (CTP) score. Using sophisticated statistical methodology, the authors conclude that integrated MELD, or iMELD, which incorporates age and sodium along with the traditional MELD score, is the most robust model to predict short- and long-term mortality. The authors also speculate that refinement of the CTP score with additional parameters may improve its applicability (CTP-based model was modified by extending scoring to 18 points via an additional stratification for more elevated laboratory values). Most significantly, the authors suggest that predictive models like MELD, iMELD, MELD-Na, and others may need to be re-examined in selected populations given that origination, specification, and validation of the models were done using predominantly Caucasian populations from the US and Europe, which may introduce ethnic/genetic-based biases, biases related to differences in the prevalence of various etiologies of liver disease (i.e. CHB prevalence is higher in Asia but less in Europe and North America), as well as differences due to treatment effects across geographic regions.

Many of the authors' results and conclusions point to an "East-West divide" in liver disease demographics, etiologies, and treatments when considering past studies that originated and validated several of the most commonly used models. This is a reasonable concern given that the results of clinical studies are only as generalizable as the population studied. In this article, the foundational definitions and analyses used present a few problems related to generalizability to chronic liver disease patients both outside and inside China. The study group's use of the Chinese Society of Hepatology definition of ACLF is unique and likely constrained by inclusion criteria inherent to the original study of the acute liver assist device, but that would be an issue with any paper as the definition is not uniform across regions. This represents an East-West discrepancy and perhaps deserves a collaborative approach among the major hepatology societies

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worldwide to provide a focused definition so that clinical research would be more readily generalizable. The inclusion of patients who received treatment via an acute liver assist device (nearly half of the cohort) also hampers the applicability of their conclusions to all similar patient populations, including Chinese patients and thus the results should be interpreted with caution. It is also unclear why so few patients were prescribed antiviral therapy, as this has been shown to modify liver disease related outcomes in CHB patients.[3] A sensitivity analysis with stratification by treatment with an acute liver assist device or antiviral therapy would be interesting and would lend support to the notion that future research directions should concentrate on isolating the effects of antivirals in outcomes related to HBV cirrhosis, ACLF in HBV, and HBV flares, particularly in studies with Asian patients where CHB is far more prevalent.

Nonetheless, this comparison of different mortality prediction models raises several interesting more general questions in addressing suitability of current methods to assess patient appropriateness for liver transplantation in the setting of ACLF. First, use of survival-based versus utility-based models is one area of controversy in determining the best way to predict need for transplantation. While utility of transplantation and transplant-free survival outcomes are closely related, they are not the same as utility takes into account potential recipients' ages and thus estimates expected life-years saved *vs.* predicting a raw survival time expectation. Second, the evaluated time horizon in studies of either survival- or utility-based measures is not standard, and this has been interpreted and applied in many ways with vastly different recommendations regarding MELD and transplant hazard and benefit.[4-6] One standard conclusion is that the longer the time horizon studied, the lower the recipient's MELD score needs to be at the time of transplantation to receive benefit. This is not surprising given that cirrhosis is a progressive disease for most patients. Third, it is unclear whether the etiology of cirrhosis affects the incidence of ACLF, impacts outcomes of acute decompensation episodes, or influences expected utility from liver transplantation. This is especially pertinent in the case of HBV and HCV cirrhosis given these conditions have successful suppressive and curative treatments respectively. Obviously in the setting of ACLF, this makes a big difference because HBV therapies are likely to be easier to implement quickly with higher short-term impact on outcome than in the setting of HCV or other etiologies of underlying chronic liver disease. Once again, these questions point to major differences across Eastern and Western regions related to chronic liver disease and ACLF expectations and management strategies.

In conclusion, Shen, *et al.*'s analysis of several prognostic models of ACLF in CHB is provocative by highlighting substantial differences in characterization and evaluation of chronic liver disease based on the geographic region of the cohort. Through their robust analysis, the authors have demonstrated that prognostic models are not equally effective and that the differences in model performance may be inherent to the model but also possibly to characteristics of the study cohort. They also revisit the concept of modifying a prognostic tool to attempt to tailor it to a more relevant therapeutic climate and demographic. Perhaps most illustratively, the authors' work reinforces a basic tenet of clinical research interpretation: readers must perform their own generalizability tests for each peer-reviewed study to ensure the results and conclusions will apply to their patients. This paper also emphasizes that our methods of prioritization of patients for liver transplantation is not "one size fits all," particularly in the cases of patients where portal hypertension severity and MELD (or other scoring system) score do not move in parallel fashion. These results suggest that further refinement of our methods of patient assessment for liver transplantation through periodic reevaluation are key to make certain that, as a hepatology and transplant community, we are providing faithful service to our patients. Lastly, this study underscores the cooperative work hepatology societies can do to better define disease processes to aid in standardizing clinical study focus while simultaneously recognizing the inherent limitations of standardizations when treating unique patients.

CONFLICT OF INTEREST STATEMENT

The authors do not have any commercial associations that might pose a conflict of interest in connection with the submitted manuscript.

SUPPORT

None.

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