Published in final edited form as:

Gastroenterology. 2015 August ; 149(2): 281–283. doi:10.1053/j.gastro.2015.06.020.

MELDing the Lille Score to More Accurately Predict Mortality in Alcoholic Hepatitis

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Persons who consume >25 g of alcohol a day are at risk of developing hepatic steatosis, alcoholic hepatitis, and cirrhosis. Alcoholic cirrhosis is the eighth most common cause of mortality in the United States and the second highest cause of mortality among all gastrointestinal diseases.¹ Although women are at greater risk for alcohol-related liver disease for any given level of alcohol consumption, overall morbidity and mortality is greater in men, likely owing to their higher levels of total alcohol consumption.² The cost associated with hospitalization of patients with cirrhosis in the United States is approximately \$10 billion a year, and approximately 40% of these patients have alcoholic cirrhosis. Alcoholic cirrhosis may lead to portal hypertension and complications like variceal bleeding, ascites, hepatorenal syndrome, hepatic encephalopathy, and hepatocellular carcinoma. Of all the forms of alcoholic liver disease, acute alcoholic hepatitis is associated with the greatest risk of short-term mortality, between 30% and 50% at 3 months. Alcoholic hepatitis has been associated with multiorgan failure when superimposed on chronic liver disease, a condition more recently termed, “acute-on-chronic liver failure.”³ Management of the patient with alcoholic hepatitis requires intensive care in those with multiple organ failure, specific treatments aimed at reversing the hepatic injury, and interventions toward alcohol rehabilitation. Corticosteroids improve survival at 28 days, although the magnitude of benefit may not be as great as previously believed.⁴ Among those patients who respond to steroids, complete abstinence from alcohol is associated with improved survival at 1 year.⁵ No medical therapy alone is associated with improved survival beyond 6 months, and liver transplantation remains the best option for patients with liver failure who are rehabilitated from alcohol abuse. There is a subset of patients in whom all interventions, either medical or psychosocial, are futile. Given the bleak outcome in patients with alcoholic hepatitis, the National Institute in Alcohol Abuse and Alcoholism has funded several consortia with the specific goal of studying the mechanisms of alcohol-induced liver injury, and translating these mechanisms into novel therapeutic interventions.

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Conflicts of interest

The authors disclose no conflicts.

In patients with alcoholic hepatitis, the risk for mortality is related to severity of liver disease, the attending complications of infection and multiple organ failure, inflammatory response,⁶ histology,⁷ risk for continued alcohol abuse, and perhaps genetic polymorphisms.⁸ Identifying whether the course of implemented therapy is having the intended effect is also critical, so that the therapy and its inherent toxicities can be obviated if a benefit is unlikely to be conferred. Such is the example with corticosteroid therapy, whereby initial studies showed that a lack of improvement in bilirubin after 1 week of therapy indicated futility.⁹ There is, therefore, the need for accurate risk scores to stratify patients for mortality at both baseline state and at interval times after initiation of therapy.

Risk scores may be stratified as “static,” which predict prognosis at specific time points, and “dynamic,” which scrutinize mortality risk over varied time intervals to ascertain response to implemented therapy. At baseline, in patients with alcoholic hepatitis, the Maddrey Modified Discriminant Function (MDF) has been the most widely used risk score.¹⁰ More recently, the Model for End-stage Liver Disease (MELD) score has been validated in several different groups of varying severity of liver disease and geographical location.¹¹ The Glasgow Alcoholic Hepatitis Score,¹² and the age, bilirubin, International Normalized Ratio (INR), creatinine (ABIC) score¹³ have not received the same degree of scrutiny in US patient cohorts. In international clinical practice, an MDF of ≥ 32 or more recently a MELD score of ≥ 20 have been used to initiate treatment, usually with steroids. Since the initial description of the bilirubin-based early biological response, the model has been further refined with additional laboratory and demographic features and termed the Lille Score.¹⁴ A Lille score of >0.45 after 1 week of steroid therapy is used to trigger discontinuation of steroids because these patients have high mortality despite continuing steroids. The MELD score and the MDF are static scores, whereas the Lille score, which looks at the change over 1 week, is a dynamic score. The utility of risk scores is gauged by their discrimination and calibration. Discrimination is defined by the c statistic, which is the receiver operating area under the curve. For example, using the MELD score, a c statistic of 0.8 indicates that 8 out of 10 times a patient with a higher score will die before the patient with a lower score. A highly discriminant score such as the MELD is best used in patient populations, for example, in prioritizing organ allocation for liver transplantation. In clinical practice, calibration relates to how closely the predicted and observed mortality are at specific time points. A horse race may be used to provide examples of discrimination and calibration. Discrimination is determining which horse is most likely to win; calibration is accurately predicting the timing of each horse in the race, clearly a much more difficult proposition. Calibration is even more difficult when patients receive differing standards and durations of treatment, including intensive care. Calibration is important for the individual patient in determining need for change in therapy and counseling. Thus far, static and dynamic scoring systems have not been combined in patients with alcoholic hepatitis to determine whether they can better discriminate or calibrate mortality risk.

In this issue of *Gastroenterology*, Louvet et al¹⁵ combined static scores (MDF, MELD and ABIC) with a dynamic score (Lille) to determine which combination had the best prognostic value. They concluded that the MELD + Lille combination was significantly better than the MDF + Lille, or ABIC + Lille score in predicting patient survival. They validated the data

internally using a standard tool of bootstrapped resampling. They also validated their data in an independent dataset. The derivation cohort for the model included patients from the Lille database, a British trial testing antioxidants versus corticosteroids, prospective databases in France at Angers and Lille, and patients in the recent French study comparing prednisolone treatment with or without pentoxifylline in survival of patients with severe alcoholic hepatitis.¹⁶ The validation cohort included patients from the United States, the prospective cohort used to derive the Lille model, patients from Korea and Belgium, and patients in a database from Bondy, France. Of note, dynamic data on MELD or ABIC or MDF scores after 1 week of treatment were either not available or were not analyzed. Both the MELD score and the Lille score were independent predictors of mortality, with a linear relationship between the baseline MELD score and increased risk of mortality. The combined MELD and Lille score model had better discrimination and calibration than either model alone. Thus, in patients with identical MELD scores at baseline, mortality depended on Lille scores at 1 week. Similarly, in patients with identical Lille score at 1 week, mortality was dependent on baseline MELD scores.

Although the combination of MELD score and Lille score has statistical value, how can these scores can be used in clinical practice? The MELD, ABIC, Glasgow, and MDF scores are available at initial evaluation of the patient, with the MELD score and the MDF being most widely used. These baseline scores should continue to be used to stratify mortality risk and determine type of treatment. The MDF score characterizes only severe alcoholic hepatitis (MDF > 32). Because patients with a lower MDF score still have a risk of mortality, they are not captured within this scoring system. Moreover, the MDF score was developed when the pro-thrombin time was expressed in seconds. With the pro-thrombin time now being expressed universally as the INR, the MDF becomes more difficult to calculate. Additionally, the MDF score does not include renal function, which is associated significantly with mortality. The advantage of the MELD score is that the range is wide enough that finer stratification of risk is possible. Based on the current study demonstrating the superiority of MELD score at baseline, and previous studies,^{16,17} we suggest that for future studies patients with alcoholic hepatitis be stratified at baseline into low mortality risk (MELD <11), intermediate risk (MELD 11–20), and high-risk patients (MELD >20). Furthermore, the combined MELD and Lille score at the end of a week's treatment may be used to further stratify mortality risk: low risk for mortality (<20% at 6 months), moderately high risk (20%–40%), high risk (40%–60%), very high risk (60%–80%), and pre-terminal (>80% mortality). The specific mortality risk may be determined from the nomograms in Figure 2A, B from Louvet et al.¹⁶ These risks may be used for stratification of patients as well as for power calculations in studies where mortality is an endpoint. Patients in the low risk group may be excluded in studies where mortality is an endpoint. In clinical practice, in the pre-terminal group (>80% mortality), discussions regarding withdrawal of intensive care should be initiated if patients do not qualify for urgent liver transplantation based on well-accepted criteria.¹⁸ The moderately high-risk groups may be considered for investigational medical therapies, and patients in the high, very high, and even pre-terminal risk groups may, in addition, be candidates for studies using bioartificial liver support devices. The costs associated with care of patients in specific risk groups can also be studied and results may be used in making treatment decisions. Future studies should incorporate biomarkers, as well as

genetic markers to improve the accuracy of the current combined MELD and Lille score model.

Acknowledgments

Funding

National Institutes of Health (NIH) U01 AA 21788.

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