Combining Data From Liver Disease Scoring Systems Better Predicts Outcomes of Patients With Alcoholic Hepatitis

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BACKGROUND & AIMS: Several models have been used to determine prognoses of patients with alcoholic hepatitis. These include static systems (the Maddrey discriminant function; age, bilirubin, international normalized ratio, creatinine [ABIC] score; and model for end-stage liver disease [MELD] score) and dynamic models (the Lille model). We aimed to combine features of all of these models to develop a better method to predict outcomes of patients with alcoholic hepatitis. **METHODS:** We collected data from several databases of patients with severe alcoholic hepatitis treated with corticosteroids in France and the United Kingdom to create a model to predict patient survival (derivation cohort, n = 538 patients). We compared the performances of 3 joint-effect models (Maddrey+Lille, MELD+Lille, and ABIC+Lille) to determine which combination had the best prognostic value, based on known patient outcomes. The model was validated using data from trials of the effects of corticosteroids in patients in the United States, France, Korea, and Belgium (n = 604 patients). **RESULTS:** We created a joint-effect model to predict patient survival after 2 and 6 months; in the derivation and validation cohorts it predicted outcome significantly better than either static or dynamic models alone ($P < .01$ for all comparisons). The joint model accurately predicted patient survival regardless of patient risk level. The MELD+Lille combination was better than the Maddrey+Lille or ABIC+Lille combination in predicting patient survival, with Akaike information criterion values of 1305, 1313, and 1312, respectively. For example, based on the MELD+Lille combination model, the predicted 6-month mortality of complete responders with MELD scores of 15–45 (Lille score, 0.16) was 8.5% to 49.7%, compared with 16.4%–75.2% for nonresponders (Lille score, 0.45). According to the joint-effect model, for 2 patients with the same baseline MELD score of 21, the patient with a Lille score of 0.45 had a 1.9-fold higher risk of death than the patient with a Lille score of 0.16 (23.7% vs 12.5%). **CONCLUSIONS:** By combining results from static and dynamic scoring systems for liver disease, we can better predict outcomes of patients with alcoholic hepatitis, compared with either model alone. This may help patient management and design of clinical trials.

Keywords: AH; Prognostic Factor; Cirrhosis; Classification.

The development of prognostic models to classify patients according to their risk of death has provided major progress in the care of patients with liver disease. The time necessary to determine a therapeutic strategy in patients with severe alcoholic hepatitis (AH) is crucial to avoid damage by intervening too early or to propose new therapies early on to patients with a high risk of short-term mortality.[1] For this reason, prognostic models at baseline (static models) and models after treatment (dynamic models) now are considered mandatory tools to determine patient outcome. Nevertheless, progress in the understanding of early prediction of mortality is still an important issue.

Pretreatment scores to measure the severity of alcoholic hepatitis such as the Maddrey discriminant function (DF); the Model for End-stage Liver Disease (MELD); age, bilirubin, international normalized ratio (INR), creatinine (ABIC); and Glasgow alcoholic hepatitis scores accurately predict short-term mortality.[2–6] Although the decision to treat usually is based on a Maddrey DF greater than 32, the

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Abbreviations used in this paper: **ABIC, age, bilirubin, international normalized ratio, creatinine; AH, alcoholic hepatitis; AIC, Akaike Information Criterion; CI, confidence interval; DF, discriminant function; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.**

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MELD score also is accurate and also could be used for this purpose[3,6] even though the optimal cut-off value for the decision to treat must be proposed by experts. With prednisolone therapy, early improvement in liver function is associated strongly with a decrease in short-term mortality. This early improvement can be assessed by recalculating static prognostic models after a short evaluation period, or by using the Lille model, which includes a measurement of response to treatment.[7] For example, a 2 or more point change in the MELD score, as well as the Glasgow AH score, or the difference in bilirubin after 7 days of treatment, are predictive of in-hospital mortality.[4,6,8] The Lille model is more accurate in this setting than repeated calculation of prognostic scores[7] and permits identification of patterns of complete, partial, and null response, each associated with a risk of early death.[9]

At present, to adapt the treatment strategy in patients with severe AH, prognosis is determined by the use of either static or dynamic models. A new notion is to combine the information from static and dynamic models to predict the risk of death on a continuum. This approach might make it possible to stratify the risk of death and provide a more precise estimation of outcome based on severity when management begins and after a short period of treatment. This approach would provide a more balanced evaluation rather than a yes/no prediction of death.

To develop a predictive model of mortality that integrates both static and dynamic models, a large sample of well-characterized patients is needed as well as laboratory and clinical data at baseline, response to treatment, and appropriate statistical analysis. The relationship between each model and mortality as well as the added value provided by their combinations must be tested. If this added value is confirmed, the combined approach can be considered better.

The aim of the present study was to improve the prediction of mortality using data from well-characterized cohorts in a large database by providing a risk prediction chart for mortality based on the combination of static and dynamic models.

Patients and Methods

Study Population and Assessment of Diagnosis

The patients included in this study were found in several prospective international databases grouped into derivation and validation cohorts. The derivation cohort included the following: (1) the local Lille database of patients who were followed up prospectively after the publication of the Lille model formula; (2) patients in a randomized controlled British trial testing antioxidants vs corticosteroids[10]; (3) the local prospective database of the Medical Center of Angers, France; and (4) patients in the last randomized controlled French trial Corpentox.[11] Duplicates were discarded from this latter cohort (Corpentox) because some patients also were included in the local Lille and Angers databases. The validation cohort included the following: (1) patients in an American trial testing oxandrolone and prednisolone[12]; (2) the Lille model prospective cohort (patients included in the development and validation of the Lille model[7] from Paris, Béthune, and Lille, France); (3) patients in a Korean trial testing pentoxifylline vs prednisolone[13]; (4) a local database from Bondy, France; and (5) a local database from Brussels, Belgium. Data from another trial were available[14] but we decided to exclude them because 6-month survival date were not available for this cohort (the primary end point was 28-day survival). Study flow charts are presented in Supplementary Figures 1 and 2.

The diagnosis of AH was based on the following criteria in all cohorts: (1) recent onset of jaundice (<3 mo); (2) a history of long-standing alcoholism; (3) biological profile of alcoholic hepatitis with moderately increased transaminase and increased bilirubin levels[15]; (4) absence of recent severe gastrointestinal hemorrhage (ie, <15 days); and (5) absence of active peptic ulcers, neoplasms, and nonalcoholic liver disease (in particular, negative serologic markers for hepatitis B and C virus and for human immunodeficiency virus infection). It should be noted that information on the recent onset of jaundice and the exclusion of patients with gastrointestinal bleeding was not available in 2 trials[10,12] and 1 trial,[12] respectively. All French and Belgian subjects underwent a transjugular liver biopsy in accordance with standard clinical practice in France and Belgium.[1,16] A liver biopsy was performed in 68% of the cases in the Phillips et al[10] study. No histologic confirmation was required in the randomized controlled trial published by Mendenhall et al[12] and by Park et al.[13]

Only patients with severe AH at admission were included in the combined database, as defined by a Maddrey DF of 32 or higher. The Maddrey DF was calculated with the following formula: 4.6*(patient prothrombin time - control prothrombin time) + total bilirubin in mg/dL.[5] A few patients (3%) admitted with a Maddrey DF of 32 or higher improved before corticosteroids were begun and had a Maddrey DF of less than 32 when treatment was begun. We decided to keep these patients in the analysis because they had severe AH at inclusion. The ABIC and MELD scores were calculated with the formulas provided in the descriptions of their utility in severe AH[2,3,6] (Supplementary Table 1).

Treatment

All patients included in the present study were treated with corticosteroids. Patients in the different studies who did not receive corticosteroids were excluded (eg, if they were randomized to a placebo arm). All patients in the Corpentox study were included in the current analysis because no difference in survival was observed in the group treated with prednisolone and pentoxifylline compared with prednisolone alone. The treatment protocol with corticosteroids was slightly different depending on the study (40 mg/day in the French, Belgian, and Korean studies; 30 mg/day in the Phillips et al[10] study; 60 mg/day for 4 days then tapered down to 5 mg/day for a total of 30 days in the Mendenhall et al[12] study).

The response to treatment was assessed by the Lille model, which was calculated after 7 days of corticosteroid treatment using the following formula: exp (-R)/(1 + exp[-R]) in which R = 3.19 - 0.101 * age (years) + 0.147 * albumin (g/L) + 0.0165 * change in bilirubin (μmol/L) - 0.206 * (renal insufficiency) - 0.0065 * bilirubin day 0 (μmol/l) - 0.0096 * prothrombin time (seconds).[7] The Lille score ranged from 0 to 1, with higher scores associated with higher mortality. Change in bilirubin level was defined as the difference between total