Editorial

Predicting long-term prognosis in severe alcoholic hepatitis

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To the Editor,

The global burden of cirrhosis and hepatocellular carcinomas is substantial accounting for approximately 2 million deaths annually or a proportionate total of 3.5% of all deaths worldwide. Approximately 2 billion people consume alcohol worldwide and upwards of 75 million are diagnosed with alcohol-use disorders and are at risk for developing alcohol-related cirrhosis and HCC (1). Chronic alcohol misuse is associated with a spectrum of liver injury within which 10–20% of individuals develop cirrhosis. Alcoholic hepatitis of varying degrees of severity develops in a subset of alcohol misusers. *Severe* alcoholic hepatitis, defined by a Maddrey's discriminant function of $\geq$ 32 (2) or a model for end-stage disease (MELD) score >20 (3) typically presents as an acute and florid episode of acute hepatic decompensation. Although the exact incidence of alcoholic hepatitis is unknown, its prevalence in heavy drinkers has been estimated at 20% (4). Approximately 50% of patients with severe alcoholic hepatitis have cirrhosis at the time of their acute presentation, and these patients have a very poor prognosis with reported mortality rates of 50% at 90 days (5,6). Currently, corticosteroids are the only therapeutic option for patients with severe alcoholic hepatitis (5,6). Nevertheless, a significant proportion of patients do not respond, and frequently experience severe adverse effects, such as infection, even if administered for only a short period of time. (7) Very few, if any, therapeutic options are available for corticosteroids non-responders and mortality rates as high as 80% have been recorded (5,6)

Several scores can be used to determine outcome in patients with alcoholic hepatitis as well as identifying those who may benefit from treatment which is a significant management priority. 'Static' scores, which are obtained at baseline, include the Maddrey DF and the MELD score while the Lille model, which includes the change in serum bilirubin concentrations over the first week of treatment, is referred to as a dynamic score (8). More

recently a combined MELD/Lille model calculated 7 days after initiation of corticosteroids has been used to successfully to predict short term survival (9). However, the overall predictive abilities of these scores are modest and there is a need for more accurate identification of patients who will respond to corticosteroids, ideally using information available at baseline rather than at day 7 (10).

Trépo and colleagues have taken up this challenge and have recently adopted the novel approach of determining outcomes in patients with severe alcoholic hepatitis utilizing transcriptome profiling (11). They determined a 123-gene prognostic signature from formalin fixed, paraffin-embedded liver biopsy material obtained from 73 patients with severe alcoholic hepatitis, prior to treatment with corticosteroids. An integrative clinical and molecular prognostic score was then developed based on the regression coefficient of a multivariable Cox regression model including the gene signature and the MELD score. This assignment system, the gene signature MELD (gs-MELD) outperformed other clinical models at predicting survival at 90 and 180 days in a validation cohort of 48 patients with severe alcoholic hepatitis, using a predefined cut-off value of >2.66 to define poor prognosis (11). Subsequently, a prognostic gene signature, employing the top 114 genes, was implemented in a Food and Drug Administration (FDA)-approved platform (NanoString) ready for clinical deployment having been validated against the original microarray. Results can be obtained within 2 days.

In this issue of the journal the same authors (12, having shown that the gs-MELD scoring system accurately predicts 90 and 180 day survival in patents with severe alcoholic now report data on the predictive validity of the score for determining long-term survival in the same population. This post-hoc analysis was undertaken using follow-up data from the 48

patients with severe alcoholic hepatitis who comprised the validation cohort in the index publication (11). All had severe alcoholic hepatitis on liver biopsy and all received methyl prednisolone 32 mg daily for 4 weeks. As reported in the initial paper, 26 patients were classified as having a good prognosis (score < 2.66), and in this group survival was 96% at 90 days and 84% at 180 days. In contrast, 22 patients were classified as having a poor prognosis (score ≥ 2.66) and in these survival was significantly lower at 43% at 90 days and 34% at 180 days.

Patients from this cohort were then followed for 5 years from the first day of treatment. Drinking behaviour, which is know to substantially influence long–term outcome in patients with severe alcoholic hepatitis who survive the initial episode, was monitored and reported as 'return to drinking' yes or no. At the end of the follow-up period 61% (95% CI: 41-81) of the original patients with a low gs-MELD score were alive compared to 26% 95% CI: 11-55) of those with a high gs-MELD score (p = 0.001). Likewise, the survival rate in the 19 individuals who remained abstinent from alcohol was 81% (95% CI: 58-96) compared with only 22% (95% CI: 10-47) of the 29 individuals who continued to drink ($p < .001$). Both the gs–MELD score (subdistribution hazards ratio [SHR] 5.78, 95% CI: 2.17-15.38) and a return to drinking (SHR 12.18 (CI 3.16-46.95) were significantly associated with long-term mortality. The correlation between the gs-MELD score and alcohol consumption was not significant.

These data need to be scrutinized further. First, the primary endpoint was the 5-year mortality rate yet the median follow-up, as reported, was only 29 (95% CI: 4-43) months. Data for patients who were still alive, including those lost to follow-up, were censored at the date of the last follow-up visit but rather than censoring it looks as thought their data were carried forward. Further explanation is needed to clarify this. Second, the mortality data

reported at 180 days were, according to the information provided in Figure 1, unchanged at one–year meaning that no further deaths occurred in this six-month period. Likewise the numbers of deaths over the ensuing period were not substantially different between the two groups based on the numbers at risk. Thus, are the death rates at 5 –year reflecting continued attrition based on the gs–MELD scores or are they simple a reflection of the deaths occurring at 180 days? Standardizing the deaths at 180 days would answer this question. Third, the alcohol consumption data lack granularity. No information is provided on how alcohol consumption was monitored, in particular no information is provided on whether the assessments were based on self–reports or more objectively based. As there was no reported correlation between the gs-MELD and alcohol consumption a combined analysis looking at patients classified in relation to their gs-MELD score and their alcohol consumption would have been more informative. The patient numbers are small but the authors report that the gs-MELD score and recurrent alcohol consumption were independently associated with 5-year mortality in the derivation population so these two cohorts could have been combined for this exercise. Four, sex is known to significantly affect outcome in patients with severe alcoholic hepatitis (13) so sex-specific analyses are needed and would be possible with larger numbers. Finally, a number of other variables which are known to modify outcome in this patient population, for example, nutritional status where not considered and would need to be in future studies (14).

Certain practical issues also arise in relation to the application of the results of assigning the gs–MELD score. How would the score be used in the clinical situation? Although it has been shown that the score accurately predicts 90 and 180 mortality irrespective of corticosteroid treatment how would it be used guide management? Would the current static and dynamic scores still be needed as adjuncts? The authors have stated that results would be available

within two days but no information is provided on the cost-effectiveness of this approach or the cost-benefits. All of this information is necessary.

Another approach to predict mortality which should be given consideration is the use of genotyping for known genetic risk factors. Atkinson et al. (14) have convincingly shown that homozygous carriage of rs738409G in *patatin-like phospholipase domain-containing 3* (*PNPLA3*) confers a significant additional risk of mortality in the 90 to 450-day period in patients with severe alcoholic hepatitis. The number of confirmed genetic loci that modulate the risk for alcohol-related liver disease (16) is increasing and genetic risk scores will undoubtedly significantly aid management planning in both short, medium and longer terms – and this approach is easier (no biopsy) and quicker (simple genotyping of blood-derived genomic DNA) to undertake. However, combining the genotyping with transcriptome profiling would be attractive and should be seriously considered

One of the main issues, acknowledged by the authors, is that calculation of the gs-MELD score requires a liver biopsy and this is likely to limit its clinical utility (11). Both the European Association for the Study of the Liver (6) and the American College of Gastroenterology (5) guidelines recommend liver biopsy in patients with suspected alcoholic hepatitis, as in 10 to 20% this clinical suspicion is not confirmed histologically. In addition, the histological findings themselves, particularly the presence of severe fibrosis, megamitochondria, the degree of neutrophil infiltration, and cholestasis, have predictive validity (17). In patients with severe alcoholic hepatitis liver biopsy has to be performed via the transjugular route. Thus the decision to perform a biopsy has to take into account the availability of the procedure and experience of the clinical team.   Thus, it is likely that use of the gs-MELD may be confined to

research studies particularly those pharmacotherapy where indeed its use should be encouraged if not mandated.

The work undertaken by this group (11.12) is an excellent example of how combining individual genetic expression data and clinically available routine variables can be used to build a prognostic score. A particular strength of the gs-MELD scoring system is that the prognostic information is available sufficiently early to be used to guide management and avoid use of medication which, while effective is associated with a high risk of adverse effects, particularly infection . It will allow competing risk and benefit to be more objectively based.

The group (11,12) have contributed significantly and with remarkable innovation to improving the stratification of patients with severe alcoholic hepatits and to afford focused care for those at highest risk from this life-threatening condition. Further independent validation is now warranted; the question of whether or not the gs-MELD predicts longer term outcomes is moot and will need more careful study

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