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Forum Feedback

MELD is not enough—enough of MELD?

To the Editor:

The recent review [1] on MELD confirms that interest in assessing prognosis in cirrhotic patients has been revived. However, several drawbacks of MELD, which deserve some comment, have not been considered.

Firstly, use of MELD for allocation is a 'justice' and not a 'utility' score, as it does not consider outcome after liver transplantation (LT). One reason is that donor factors are not considered [2]. As a result, both pre-LT MELD and change

in MELD [3] do not correlate with post-LT survival, with only a *c*-statistic of 0.58 in the UK [4]. In the USA, survival after transplantation was unchanged [1]. Secondly, the *c*-statistic for 3-month survival on the waiting list is as low as 0.75 [5]. Use of MELD outside the USA, has also given poor predictive accuracy in individual patients and poor generalisability [6].

Thirdly, the component variables of MELD may be difficult to assess, which may be one reason for poor

concordance values. Lean body mass influences creatinine concentration, with underestimation in malnourished cirrhotics [7]. Most importantly in terms of 'equity' the normal range for women is lower than for men [7]. This has not been accounted for, and systematically discriminates against women. Significant variations of INR [8] and serum creatinine measurement are found, particularly with high bilirubin levels and persistent ascites due to different laboratory methodologies [7].

Fourthly, as acknowledged [1], severe symptoms, metabolic disease and quality of life cannot be encompassed in the current MELD allocation system. Although variceal bleeding, ascites, hepatorenal syndrome and spontaneous bacterial peritonitis did not add to the predictive power of the original MELD [1], this is unlikely to be true. Recently, encephalopathy [9], and hyponatraemia and ascites [10] were again recognized to correlate significantly with mortality in cirrhotics, particularly in patients with low MELD scores. Thus, these clinical events need to be considered.

In terms of allocation systems, the ideal approach should evaluate both pre-operative recipient and donor characteristics [2] and validate these. It may be possible to provide matching criteria for donor and recipient. This occurs by clinical experience in centre based prioritization systems, which has been shown to correlate with MELD scores [4]. It may reflect 'justice' to be top of an allocation list, but this sickest patient will be hoping that the best donor is found to achieve the best chance of survival.

Finally, the reality is that MELD is also being used in several different clinical scenarios [1]. This highlights other problems, especially when comparing MELD to other prognostic models. The original MELD was developed for predicting survival after TIPS: when compared to Child-Pugh (CP) score [11,12], there was no significant difference and the *c*-statistic for 12-month survival was less than 0.80. Given this, it is not clear whether the perceived superiority of MELD in non-transplant settings is related to using serum creatinine as a variable. Indeed, predictive accuracy of modified CP score incorporating creatinine was found to be similar (*c* statistic=0.72) [13] or only marginally worse compared to MELD (*c* statistic=0.83 vs 0.95, *p*=0.047) [14].

All comparisons of CP scoring to MELD demonstrate little difference. This is surprising as CP has never been evaluated nor validated statistically. Currently, there is interest in redefining MELD point thresholds for allocation for hepatocellular carcinoma or metabolic disease [1]. However, more fruitful evaluations could arise from re-visiting CP scoring. The potential value of CP is not only its simplicity, but that it is intrinsically a staged prognostic score from well compensated to decompensated liver disease, although missing the terminal phase with renal dysfunction. The original points allocation and division between A, B and C grades was arbitrary, and CP scores have 'ceiling and floor effects' with respect to the cut offs

for the laboratory variables. The original Child's classification and CP should be re-assessed statistically and validated. More work needs to be done on the addition of markers of renal function [7], to construct a Child-Pugh D grade. Once new modified CP models are validated, as has been done with MELD, then these can be formally compared. This should involve new statistical techniques, which are likely to be better than the *c*-statistic [15]. It is important that comparisons are made in each clinical scenario in which the models are applied.

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MELD in liver transplantation: the da Vinci code for the Holy Grail?

To the Editor:

We read with interest the paper published in a recent issue of *Journal of Hepatology* under the heading of Forum on Liver Transplantation [1]. The model for end-stage liver disease (MELD) has become the prevailing criteria for organ allocation in liver transplantation. Abundant studies have shown that the MELD system is superior or at least equal to the traditional Child-Turcotte-Pugh (CTP) system in terms of outcome prediction for patients with end-stage liver disease [2–6]. It possesses the advantage of minimal variability and wide-range continuous scale to assess underlying disease severity compared to the traditional CTP scoring system. However, the MELD system may not serve all patients well and could have certain limitations. We have investigated the impact of the occurrence of cirrhosis-related complications (esophageal varices bleeding, spontaneous bacterial peritonitis or hepatic encephalopathy) on patient survival in comparison with the MELD score. Patients with these complications had a similar baseline MELD score compared to those without complications, yet they had a much poorer prognosis. Among 290 patients with CTP score of 7 or more, the mean MELD score was 11.6 ± 2.9 for patients with complications ($n=67$), compared to a mean MELD score of 12.2 ± 3.2 ($P=0.184$) for those without complications ($n=223$) at disease presentation (unpublished data). Interestingly, the presence of complications had a very similar profile of predictive accuracy for short and intermediate term mortality compared to the MELD system by using the c-statistic method for the area under receiver operating characteristics curve. These findings suggest that while these patients have a poor prognosis and early transplantation referral is recommended, they do not necessarily have a higher MELD score and the priority for transplantation could be down-staged in the MELD era.

As indicated by the author, patients with hepatocellular carcinoma (HCC) awaiting liver transplantation are a particular group in organ allocation. The UNOS has arbitrarily set up a MELD score of 24 for stage 2 (T2) HCC patients based on an anticipated 15% risk of drop out from the waiting list. However, this score could be overestimated according to our recent survey [7], because patients with small HCC can often be effectively treated with various loco-regional tumor ablation therapies that slow down the rate of tumor progression. The tumor progression (or de-listing) rate for T2 stage HCC at 1-year

was 13.8%, approximately equal to the 1-year mortality rate of 13.9% for patients with MELD score range of 10–14 in the cirrhosis group without HCC [7].

According to the current UNOS policy, the priority of liver transplantation is determined based on a single-point estimation of MELD score. The change of MELD score over time (Δ MELD), which measures the dynamic change of liver reserve, may provide updated information of disease severity and could alter the ranking status. However, the prognostic value of serial determinations of MELD score has not been fully elucidated in a recent study [8]. By contrast, our recent study showed that increasing MELD score is associated with the onset of ascites and hepatic encephalopathy, and Δ MELD is superior to initial MELD and CTP score to predict the outcome in patients with advanced cirrhosis [9].

We are convinced that the MELD system is particularly useful as a tool to fairly allocate donor organs in a large patient population as a whole. Nevertheless, patients awaiting transplantation could have different clinical scenarios and may not be equally weighted even they have the same MELD score. Analogous to the situation of pursuing the Holy Grail from *the Da Vinci Code* according to a recent famous novel, the MELD ‘code’, which leads to a presumably right way of defining the priority of organ allocation, does not necessarily reveal the fundamental myth or adequately solve the controversies in the current practice of organ transplantation. Since the patient population awaiting transplantation is intrinsically heterogeneous, other more potent biological markers with a better predictive ability should be continuously explored for further refinement.

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