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ORIGINAL ARTICLE

The value of MELD and sodium in assessing potential liver transplant recipients in the United Kingdom

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Summary

As the result of the widening gap between supply and demand of organs for liver transplantation, efforts to improve allocation have become an increasingly important yet controversial subject. The MELD score has been adopted in the USA but its usefulness has rarely been examined in Europe. We carried out an intention to treat analysis of 422 patients placed on our transplant waiting list over a 5-year period. We examined multiple variables to investigate the value of MELD, sodium and other factors in predicting post-transplant outcomes. MELD at transplant was the most important indicator of post-transplant outcomes. In addition, delta-MELD and hyponatreamia were significant at predicting, which patients placed on the waiting list would not proceed to transplant. While a move to allocating solely by MELD is not justified in the UK allocation system, there is value in using MELD, delta-MELD and hyponatreamia in making decisions regarding the allocation of organs. This may subsequently help to improve overall outcomes.

Introduction

The success of liver transplantation in the treatment of patients with end-stage liver disease has led to an increasing gap between the supply and demand for organs. The shortage of liver grafts first became a problem in the USA and as waiting lists lengthened and deaths on the waiting lists increased much work was performed to improve the efficiency of organ allocation.

This led to the Model for End-stage Liver Disease (MELD) score being introduced by UNOS in February 2002 as the system by which donor livers should be allocated in the USA. The MELD score was first described in 2000 and similarly to the Childs score was intended as a model to predict outcome among patients with chronic liver disease undergoing Transjugular Intrahepatic Portosystemic Shunt (TIPSS) [1]. It has since been validated as an accurate tool for predicting a 3-month mortality in different groups of patients with end-stage liver disease [2] including those on liver transplant waiting lists [3]. MELD uses three readily measurable, objective parameters of Bilirubin, Creatinine and INR in a logarithmic formula to produce a score between 6 and 40. The wider range of MELD when compared with Childs score more easily allows the sickest patients to be prioritized.

In the UK, it has been agreed that organs should be allocated to give the maximal outcome. Donor livers are offered to patients with end-stage liver disease who are perceived to have a post-transplant survival at 5 years of >50% with a quality of life acceptable to the patient [4]. Each centre is responsible for the allocation of the organs at their own centre although patients with fulminant hepatic failure are given national priority. Figures from UK Transplant show that as the shortage of organs becomes more severe, waiting times in the UK are lengthening with increasing waiting list mortality [5]. MELD has yet to be used as a tool for organ allocation in the UK.

The usefulness of MELD may further be enhanced if it can also predict post-transplant outcomes. Predicting post-transplant outcome is important, as this would enable a more rationale utilization of scarce resources to achieve their maximum benefit. Developing an accurate model to predict post-transplant outcome is likely to prove difficult because of the numerous donor, recipient and centre

variables likely to impact on this. Indeed an analysis of over 17 000 transplants concluded this and that disease specific models were likely to be needed [6]. There is no consensus on the usefulness of MELD in predicting post-transplant outcome [7–11]. Predicting post-transplant outcome does not usually take into account the mortality on the waiting list, something well predicted by MELD. We hypothesize that in an intention to treat analysis of all patients placed on the waiting list the usefulness of MELD in predicting post-transplant outcome should be clearer, a view shared in a recent article by Richard Freeman [12].

Since its introduction, it has been argued that the addition of serum sodium values may improve the accuracy of MELD in predicting pretransplant mortality risk [13–15]. The value of pretransplant sodium values in predicting post-transplant outcome has yet to be looked at. The aims of this study were to evaluate the impact of MELD, the rate of change of MELD and other factors, such as serum sodium on outcomes in a British population of potential liver transplant patients at a single centre.

Table 1. Studied variables.

Recipient variables	Donor variables
Age	Age
Primary disease	Grade of steatosis
Waiting time	Cold Ischaemic time
Blood group	
Retransplantation	
BMI	
Childs score	
Albumin	
MELD at listing	
MELD at removal	
d-MELD	
dx-MELD	
Bilirubin at listing	
Bilirubin at removal	
Creatinine at listing	
Creatinine at removal	
INR at listing	
INR at removal	
Sodium at removal	

Methods

All patients listed for liver transplant between 1 July 1998 and 30 June 2003 at St James's University Hospital, Leeds were included in this retrospective study. This data included all patients who were removed from or died on the waiting list during this period. We analysed data for those transplanted and those removed from the list first separately and then together. Patients were removed from the waiting list after discussion at multidisciplinary meetings when the clinical judgement was that the patient no longer had a 50% 5-year survival probability in line with the UK guidelines. Patients transplanted for acute liver failure, paediatric recipients and those with incomplete data were excluded.

We collected key demographic, clinical, survival and donor data that had been prospectively recorded in the UK transplant database, our internal transplant records and from the hospitals computer records. A number of recipient and donor variables were analysed (Table 1). Outcome endpoints were post-transplant graft failure, 90-day mortality post-transplant and overall mortality. Graft failure was censored in that several patients were successfully retransplanted and some others died with a functioning graft.

The MELD score was calculated using the UNOS formula:

$$\mathrm{MELD} = \{0.957 \times \mathrm{In(Creatinine)} + 0.378 \times \mathrm{In(Bilirubin)} + 1.12 \times \mathrm{In(INR)} + 0.643\} \times 10$$

where INR is the international normalized ratio of prothrombin time. Bilirubin and creatinine were measured in mg/dl with minimum values being 1.0 for all variables. Where patients were on renal support, a value of 4.0 mg/dl was used with this also being the upper limit of creatinine values. Finally, the calculated MELD score was rounded to the nearest integer.

MELD scores were calculated at the time of listing and at the time of removal from the waiting list, be it because of transplantation or because the patient died or became too ill for transplantation. A pretransplant delta-MELD (d-MELD) was calculated by subtracting listing MELD from removal MELD with a figure for rate of change, dx-MELD calculated by dividing d-MELD by the time spent on the waiting list. The MELD variables of bilirubin, INR and creatinine were similarly analysed at the time of listing, at removal from the list and a delta figure calculated as the difference between these figures. Sodium was analysed at the time of removal from the list.

Most factors were analysed as continuous variables but for body mass index (BMI), which is the weight in kilograms divided by the height in metres squared, a cut-off value of 30 was chosen. Similarly cut-off values were chosen for serum sodium at 130 mmol/l and for cold ischaemic time at 12 h. These cut-offs reflect work published previously and allow conclusions to be more directly clinically applicable.

The grade of steatosis was classified as none, mild, moderate or severe as assessed subjectively by the senior surgeon carrying out the organ retrieval in line with guidelines from The Royal College of Surgeons of England Transplant Audit. Statistical analysis was carried out using the SPSS Package (SPSS Inc., IL, USA) Chi-square test was performed for categorical variables and '*t*' test for

continuous ones. Significant variables on univariante analysis were further analysed in a logistic regression model.

Results

Between 1 July 1998 and 30 June 2003 481 patients were transplanted in our unit using nationally allocated organs. We excluded 45 paediatric patients and 52 acute liver failure patients leaving 384 adult transplants. In addition, 38 nonsuperurgent patients were removed from the waiting list during this period because they died or became too sick to transplant before subsequently dying and so these were also included in our analysis. Two patients were removed from the waiting list because their clinical condition improved and so no longer needed transplant and so these were excluded.

Our study population of 422 patients had a median age of 45 years with 56% being male and 83% of white origin (Table 2). They spent a median of 41 days waiting for a transplant and at a median follow-up of 35 months 74% of those transplanted were alive with a functioning graft. The median MELD at listing was 17 [IQR 12–21 (Interquartile ranges between 25th and 75th quartile)] and at removal from the list was 18 (IQR 13–25) with the value for d-MELD 1 (IQR −1–5) for the time waiting.

Table 2. The characteristics of the studied population.

Median age	45 years (IQR 30–54)
Male (%)	55.6
White (%)	83.2
Median waiting time	41 days (IQR 13–87 days)
No. transplants	
None	38
One	361
Two	16
Three	7
Median follow-up	35.1 months (IQR 19–53)
(of transplanted 384)	
Alive with functioning graft (%)	283 (73.7)
Graft failure (%)	55 (14.3)
Death (%)	46 (12.0)
MELD scores for entire group of 422	
Median MELD at listing	17 (IQR 11.9–20.8)
Median MELD at removal	18 (IQR 13.1–24.8)
Median D-MELD	1.1 (IQR −0.8–4.9)
Median Dx-MELD	0.01 (IQR −0.02–1.1)
Diagnosis (%)	
Primary biliary cirrhosis	76 (20)
Alcoholic liver disease	69 (18)
Hepatitis C	41 (11)
Sclerosing cholangitis	35 (9)
Autoimmune cirrhosis	25 (6)
Cryptogenic cirrhosis	22 (6)
Hepatitis B	16 (4)
Others	100 (26)

In predicting 90 day mortality (Table 3), the significant factors on univariante analysis were MELD at listing ($P = 0.02$), MELD at removal ($P = 0.006$), d-MELD ($P = 0.05$), retransplantation ($P = 0.03$), listing bilirubin (0.03), removal creatinine ($P = 0.006$), d-creatinine ($P = 0.01$) and d-bilirubin values (0.04). However, on logistic regression only MELD at removal, retransplantation, listing bilirubin and d-bilirubin values remain significant.

The factors which predict overall mortality post-transplant (Table 3) on univariante analysis were MELD at listing ($P = 0.03$), MELD at removal ($P = 0.003$)), d-MELD ($P = 0.05$), retransplantation ($P = 0.04$), albumin ($P = 0.04$), Childs score ($P = 0.036$), listing creatinine ($P = 0.01$), listing bilirubin ($P = 0.03$) and removal creatinine ($P = 0.006$). On logistic regression only MELD at removal remains significant.

The factors significant at predicting overall graft failure (Table 3) on univariante analysis were MELD score at removal ($P = 0.04$), retransplantation ($P = 0.009$), hyponatreamia ($P = 0.02$) and Childs score (0.008). However, when analysed using logistic regression, only MELD score at removal and Childs score remained significant. MELD at removal is the only common factor significant on logistic regression for each post-transplant outcome we looked at. Further, we looked at the 1- and

Table 3. How variables affected outcomes in the transplanted group with *P*-values on univariante analysis.

Variable	90-day mortality	Overall mortality	Graft failure
Donor Age	0.37	0.73	0.84
Steatosis	1.0	0.7	0.16
Cold isch. time	0.82	0.60	0.59
Recipient age	0.34	0.54	0.56
MELD at list	0.02	0.03	0.16
MELD at Removal	0.006*	0.003*	0.04*
d-MELD	0.05	0.05	0.06
dx-MELD	0.086	0.057	0.78
BMI >30	0.82	1	0.55
Re-transplant	0.03*	0.04	0.009
Albumin	0.16	0.04	0.497
Sodium rem. <130	0.53	0.07	0.02
Waiting time	0.22	0.07	0.14
Childs score	0.324	0.036	0.008*
Listing bilirubin	0.03*	0.03	0.16
Listing INR	0.21	0.39	0.60
Listing creatinine	0.09	0.01	0.25
Removal bilirubin	0.08	0.06	0.07
Removal INR	0.33	0.16	0.17
Removal creatinine	0.006	0.006	0.17
Primary disease	0.18	0.08	0.22
d-creatinine	0.01	0.05	0.37
d-bilirubin	0.04*	0.54	0.69
d-INR	0.58	0.18	0.19

*Significant on logistic regression.

3-year survival rates depending on MELD at the time of transplant (Table 4). This shows patients with higher MELD scores have a significantly poorer post-transplant outcome even beyond 1 year.

When we added the group who were removed from the waiting list for our intention to treat analysis (Table 5), the only comparable outcome was overall mortality and we excluded the donor factors, which were now irrelevant to this analysis. The factors significant on univariante analysis were MELD at removal ($P < 0.001$), rate of change of MELD ($P = 0.05$), hyponatreamia ($P = 0.001$), albumin ($P = 0.04$), Childs score ($P = 0.036$), listing creatinine ($P = 0.03$), removal bilirubin ($P = 0.03$) and removal creatinine ($P = 0.02$). On logistic regression, we again found that MELD at removal remained significant and also that removal creatinine was significant.

We then drew receiver operator characteristic (ROC) curves for MELD at removal against our primary outcomes for the transplanted group producing *c*-statistics: MELD at removal versus graft survival: $c = 0.60$ MELD at removal versus overall mortality: $c = 0.58$. The mortality at 90 days was not sufficient to make an ROC curve valid.

We then drew an ROC curve for the intention to treat group first with MELD at removal against overall mortality and then to see what benefit adding sodium to the predictive power: MELD at removal versus overall mortality $c = 0.61$ MELD and sodium at removal versus overall mortality $c = 0.67$.

These figures show that while MELD at removal is important in terms of predicting outcome it is not highly specific with relatively low *c*-stats. Table 6 shows the differences between the two groups, those transplanted and those who did not proceed to transplant, for comparable variables. This shows that MELD at removal from the list ($P = 0.025$), d-MELD ($P = 0.001$), the presence of hyponatreamia ($P = 0.0008$) and waiting time ($P = 0.0002$) were all significant at identifying which patients were more likely to be removed from the list prior to transplant. On logistic regression only d-MELD and hyponatreamia remain significant.

Table 4. Differences in 1- and 3-year survival rates depending on MELD score.

MELD score	1-year survival (%)	3-year survival (%)
<15	84.5	78.4
16–17	81.8	81.8
18–23	83	79.2
>24	66.7	62.6

The difference in survival is statistically significant $P = 0.006$ (log rank).

Table 5. The intention to treat analysis of the entire population placed on the transplant waiting list.

Variable	Overall mortality
Recipient age	0.56
Blood group (non-0,A)	0.47
Weight	0.49
MELD at list	0.11
MELD at removal	<0.001*
d-MELD	0.07
dx-MELD	0.05
BMI >30	1.00
Albumin	0.04
Sodium <130 mmol/l	0.001
Waiting time	0.49
Childs score	0.036
Listing bilirubin	0.06
Listing INR	0.50
Listing creatinine	0.03
Removal bilirubin	0.03
Removal INR	0.39
Removal creatinine	0.02*
d-creatinine	0.5
d-bilirubin	0.54
d-INR	0.18

*Significant on logistic regression.

Discussion

The increasing discrepancy between the supply and demand for donor livers combined with improvements in the efficacy of liver transplantation as the treatment of choice for end-stage liver disease has resulted in the allocation policy becoming an increasingly important yet controversial topic. Allocation in the USA is carried out on the basis of disease severity scores. Initially, it was based on the Childs-Pugh (C-P) score with a limited stratification of patients, which meant waiting time became a significant factor in allocation as a way to discriminate between patients with the same C-P score. As the shortage of available livers became more severe, patients who were likely to be in need of a liver transplant would be listed earlier to increase their chance of receiving a transplant before they died on the waiting list or became too sick to transplant. In 2002, the USA allocation policy changed to the MELD system. With its wider stratification of disease severity, patients with the most severe liver disease get allocated the next available liver regardless of length of waiting time. As a result of this there are now less patients on the waiting lists and also a reduced waiting list death rate [16]. The introduction of MELD has been felt to improve the allocation system in the USA; they are able to transplant a sicker population of patients with no deterioration in results [17]. As a result of this, there is debate in Europe as to whether MELD should form part of the allocation policy and what

Table 6. A comparison between the group of patients transplanted and those who had to be removed from the waiting list during the study period with respect to the variables studied.

	Transplanted	Not transplanted	*P*-value
List MELD (mean)	17 (12–22)	17 (12–21)	0.55
Removal MELD (mean)	18 (13–24)	20 (14–34)	0.025
d-MELD (mean)	0.6 (−1.4–3.3)	4.5 (0–13)	0.001*
dx-MELD (mean)	0.74 (±2.4)	0.18 (±0.36)	0.1
Na <130 mmol/l	7% (31/446)	30% (12/40)	0.0008*
BMI >30 (%)	74 (16.6)	6 (15)	0.778
Waiting time	30 (6–78)	97 (57–165)	0.0002
Blood group (non O /A, %)	63 (16.4)	7 (17.9)	0.82
Weight	71 (61–81)	66.5 (58.5–74.7)	0.84

*Significant on logistic regression.

the role should be. In the UK, each transplant centre controls it's own allocation policy and so here patients are not put on the waiting list until they are deemed to be ready for a transplant. Once on the list numerous factors are then taken into consideration to prioritize those most in need of transplant and also to ensure donor livers are matched to the most suitable recipients to achieve the best outcome.

There has been one previous study looking at MELD in a UK population [18]. They concluded that MELD was poor at predicting 90-day post-transplant mortality throughout the UK. However, given that allocation policy varies between each of the eight centres, it may be argued that conclusions drawn from this study should be questioned. More recently transplant centres in the north of the UK have initiated a trial using MELD to allow shared allocation for the groups of patients with the highest MELD scores. This implies that there is a feeling that MELD may have a role in improving allocation in the UK.

Analysis of our data has shown that in those patients who were transplanted, removal MELD, the score at time of transplant, was the only common factor significant on multivariate analysis for our three primary outcomes. However, on analysis of the ROC curves, MELD at removal had a relatively low *c*-statistic (0.58–0.60) indicating it was not a highly accurate determinant of outcome. Therefore, we can conclude that MELD is important in determining outcome but a high MELD score does not guarantee a poor outcome, which would otherwise be certain without transplant. Table 4 shows how an increasing MELD leads to a significantly poorer outcome but that even among the higher MELD scores transplanted, judging from the 3-year survival rates, it is likely we are reaching the target of 50% survival at 5 years post-transplant.

There is strong evidence that the addition of serum sodium would improve the accuracy of MELD at predicting pretransplant mortality [12–14]. This is because hyponatreamia is known to be a poor prognostic sign in patients with end-stage liver disease as it develops as a result of solute free water retention. This correlates with the severity of the portal hypertension and is seen early in the cascade of events that lead to hepatorenal failure with its associated high mortality [19–21]. However, our data did not show hyponatreamia to be of any additional value in predicting outcome in the transplanted group. This could be due to patients being a self-selected group. In many centres, including ours, a sodium value of <125 mmol/l is seen as a relative contraindication to transplantation. This is because hyponatreamia can lead to problems with muscle relaxants used during anaesthesia but more significantly can result in central pontine myelinosis in the early postoperative period because of rapid correction of the hyponatreamia [22].

To study the true impact of hyponatreamia on outcome we felt that patients who were removed from the list for being too sick or for dying should also be looked at. Therefore, we analysed all the patients put on the transplant waiting list during our study period making it an intention to treat analysis of patients deemed to be in need of and be suitable for liver transplantation. However, in this analysis while hyponatreamia was significant on univariante analysis, only MELD at removal and creatinine at removal independently predicted mortality on logistic regression. The results were similar to that in the transplanted group. This is not surprising given that only an additional 10% of patients had been added to the analysis.

The impact of hyponatreamia was more apparent on subgroup analysis comparing the transplanted group with the group who did not proceed to transplant. Hyponatreamia is highly significant in predicting, which patients were not likely to proceed to transplant. In addition, on subgroup analysis we also found that d-MELD became highly significant in predicting, which patients would not proceed to transplant. d-MELD has been studied previously [23,24] but until now has not been shown to be of significant value in determining allocation or predicting outcomes. One of the problems in the calculation of

d-MELD in previous studies has been bias due to variable collection of MELD data. We sought to minimize this bias by using only the MELD scores at entry and exit from the waiting list. This assumes a linear progression of MELD while on the waiting list which is unlikely. Indeed Bambha's paper suggested that d-MELD may be of limited value due to having too short a lead time to play a role in decision-making. However, our data has shown that despite relatively short waiting times, MELD can increase considerably prior to transplant. A large prospective study designed to minimize collection bias is needed to fully clarify the role of d-MELD in allocation.

However, using our results, one can postulate that by identifying those patients who are hyponatreamic and had large d-MELD scores it may be possible to prioritize them earlier and so transplant them before they become too sick to transplant. In addition, as hyponatreamia and d-MELD were not shown to be significant predictors of post-transplant outcome then by transplanting this group of patients post-transplant outcomes should not worsen and so overall outcomes may improve.

One of the consequences of the shortage of donor livers available has been the increased use of marginal or expanded criteria donor livers for transplant [25]. It has been argued that patients with higher MELD scores have the most to gain and so the greatest survival benefit from transplant using these organs [26]. Maximizing survival benefits is a reasonable basis on which to allocate scarce organs [27]. However, unpublished data from our unit, which has been confirmed by work elsewhere [28], has shown that combining a poor quality organ with a sicker recipient will lead to much worse outcomes. Therefore, to allocate solely on disease severity may discourage the use of marginal organs due to bad outcomes. In this era of such an organ shortage a more utilitarian approach to allocation is needed that allows some flexibility rather than allocating solely on disease severity, which may encourage an increased donor pool and so improved outcomes for the population of patients in need of a transplant. MELD has been shown to correlate poorly with assessments of quality of life [29] but perhaps the gain in quality adjusted life years may be the fairest system by which to allocate available livers although a way to calculate this is someway off.

In conclusion, we feel our data support MELD as a valuable tool in assessing potential liver transplant recipients in the UK. By using MELD, d-MELD combined with a measure of hyponatreamia, it may be possible to improve overall outcomes by allocating organs more efficiently optimizing the timing of transplant and reducing waiting list deaths.

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