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Change in model for end-stage liver disease score on the transplant waiting list predicts survival in patients undergoing liver transplantation

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Summary

Allocation of donor livers through the model for end-stage liver disease (MELD) score has resulted in a fall in waiting list deaths in the United States. Change in MELD score (ΔMELD) whilst awaiting transplant has been suggested as a method of refining organ allocation. Our aims were to analyse the effect of ΔMELD between listing and transplant, and examine its impact on patient survival, intensive care stay and hospital stay in 402 patients transplanted for chronic liver disease at a single centre. Patients who had a ΔMELD score of >+1 point were more likely to die in hospital following transplant ($P < 0.05$) and had a significantly worse 12- and 36-month survival post transplant ($P < 0.0001$) when compared with patients with ΔMELD ≤+1 (77.8% vs. 91.9% at 12 months; 72.1% vs. 83.6% at 36 months). This difference persisted even when in-hospital deaths were excluded ($P = 0.0148$). In a Cox-proportional hazards model, factors associated with reduced survival were ΔMELD ($P = 0.008$), and transplant from intensive care ($P < 0.001$). In conclusion, change in MELD score whilst on the transplant waiting list has a significant effect on survival post-transplant although MELD score at the time of transplant appears to have the most significant effect on resource utilization.

Introduction

The guiding principles of organ allocation are those of efficiency of organ use and urgency of need [1]. This is in addition to the ethical and legal requirements of equity, transparency and nondiscrimination. In the late 1990s, it became apparent that waiting time for a liver had become the major determinant of organ allocation in the United States of America (USA). As a result, there were a substantial number of deaths on the waiting list. Consequently, the final rule by the Department of Health and Human Services was issued, dictating that the role of waiting times should be minimized and that other factors, such as severity of disease, should receive greater priority [2]. This resulted in the introduction of the model for end-stage liver disease (MELD) as a means of organ allocation in the USA.

The MELD score is derived from a methodology to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts (TIPSS) [3]. This model identified the objective variables of creatinine, bilirubin and INR and cause of underlying liver disease as key in determining outcome [3]. Subsequently, the model was validated in other groups with liver disease and was shown to retain a high concordance with 3-month mortality [4]. In a subsequent study, removal of aetiology of the liver disease, was shown to not significantly alter the concordance for predicting mortality [5]. MELD score was subsequently validated prospectively in 3437 patients with chronic liver disease placed on the Organ Procurement and Transplant Network (OPTN) waiting list over a 25 month period and was shown to be a significantly better predictor of 3-month mortality when compared with the Child-Turcotte-Pugh (CTP) score [6]. Other

subsequent modifications of the score were to cap the serum creatinine levels at 4.0 mg/dl, to allocate extra points to patients who had undergone dialysis twice in the previous 7 days, and to cap the total MELD score at 40 thus avoiding futile transplantation. This organ allocation system was put into effect in February 2002 in the USA.

An argument against the implementation of MELD score in organ allocation is the problem of operating on sicker patients and their potential for greater resource utilization, decrease in both graft and patient survival, and by inference prolonged intensive care unit (ICU) and hospital stays. CTP score is not predictive of short-term outcome following liver transplantation (LT), but has been shown to correlate with resource utilization [7,8]. A report of 42 patients, found that MELD score was no better than CTP score in predicting post-LT resource use, or indeed, 1-year survival [9].

More recently, there has been interest in examining waiting list mortality by evaluating the change in MELD score (ΔMELD) over time. An increasing MELD score over 30 days was associated with increased mortality on the waiting list [10], although, the effect of ΔMELD in the 30 days prior to transplant was not shown to have an effect on post-transplant outcome [11]. Moreover, the effect of ΔMELD on post-transplant survival and resource utilization, from the time of listing to transplantation has not been examined. The aim of this study was to examine whether patient survival post-LT in a single UK transplant centre correlated with pretransplant CTP and MELD scores and the effect of disease aetiology on these outcomes. We also aimed to study whether MELD score and the ΔMELD whilst on the transplant waiting list affected post-transplant outcome and resource utilization.

Materials and methods

All patients registered for adult liver transplantation with UK Transplant (UKT) between January 2000 and December 2003 from King's College Hospital, London were identified. This was cross-referenced with the databases held at our transplant centre. Seven hundred and forty-two patients were listed for a total of 787 times. Patients were excluded on the basis of non-NHS entitled listings ($n = 122$), super-urgent listings for acute liver failure ($n = 138$), listings for multiple organ transplant ($n = 14$), an underlying diagnosis of amyloid ($n = 15$) and still awaiting transplantation ($n = 3$). Five patients were listed, delisted and subsequently relisted and transplanted and thus their original listings were excluded. Application of these listing criteria left a total of 490 listings in 472 patients.

The MELD score was calculated, using biochemical data at both time of listing and at time of transplantation: $\text{MELD} = [0.957 \times \ln(\text{creatinine mg/dl}) + 0.378 \times \ln(\text{bilirubin mg/dl}) + 1.12 \times \ln(\text{INR}) + 0.643] \times 10$ [6]. Patients were stratified according to MELD score at assessment and at transplantation into four categories: MELD ≤10, MELD 11–18, MELD 19–24 and MELD >24. For patients who were transplanted, the MELD score at listing was subtracted from MELD score immediately before transplantation to give ΔMELD.

Patients were then stratified into two groups by virtue of their ΔMELD score: ≤ +1 and >+1. The mean ΔMELD was 0.6 and thus the cut-off value was obtained by rounding this to the nearest integer. The listing and transplant MELD scores, ICU and hospital stays, hospital survival, and 90-day, 6, 12, 24, 36 and 48 month survival was calculated. Patients who were alive at the end of 48 months were censored.

In accordance with current United Network for Organ Sharing (UNOS) policy MELD scores were limited between 6 and 40. Patients with hepatocellular carcinoma were not awarded additional points in this study. The length of ICU and hospital stay post-transplant and number of ICU admissions in the post transplant hospital stay were collected from hospital records and the Riyadh Intensive Care programme® (Medical Associated Software House, London, UK).

Statistical methods

Categorical variables are expressed as percentages and analysed using the chi-squared test. Continuous variables are reported as medians and inter-quartile ranges (IQR) and analysed using nonparametric tests. Survival curves were computed using Kaplan–Meier methods and compared using log-rank tests. Receiver-operator-characteristic (ROC) curves were generated based on 90-day survival or transplantation as an end-point. The area under the curve was used for the c-statistic. Univariate and multivariate analysis was performed using a Cox regression model. Statistical analyses were performed with SPSS software (SPSS® 11.0 for Windows, ©SPSS Inc., Chicago, IL, USA).

Results

Outcome of listing

The demographics of patients at the time of listing and their outcomes on the transplant waiting list are shown in Table 1. Thirty-six patients were removed from the transplant list. The reasons for removal from the transplant list were; improvement in hepatic function ($n = 11$), progression of hepatocellular carcinoma beyond transplant criteria ($n = 5$), development of contraindications to transplantation/multiple organ failure (MOF)

Table 1. Baseline characteristics of all patients listed and in relation to their outcome on the transplant waiting list. *P*-values relate to comparisons the outcome groups. The diagnosis of HCC relates to the 71 patients known to have an HCC at the time of listing in all diagnostic groups.

Median (IQR)	All listings ($n = 490$)	Transplanted ($n = 402$)	Died ($n = 52$)	Delisted ($n = 36$)	*P*-value
Age (years)	54 (44–61)	54 (45–61)	58 (48–63)	50 (43–61)	=0.118
Gender (M:F)	305:185	247:155	35:17	23:13	=0.698
Time on list (days)	68 (26–129)	67 (26–130)	62 (13–114)	82 (23–120)	=0.046
Child-Pugh score	9 (8–11)	9 (7–10)	11 (10–12)	9 (8–11)	<0.001
CP grade (A:B:C)	49:211:201	42:190:148	0:7:42	7:14:11	<0.001
MELD score	15 (11–18)	14 (11–18)	18 (16–24)	18 (10–22)	<0.001
Diagnosis					
Alcohol-related	117 (23.9%)	90 (22.4%)	14 (26.9%)	13 (36.1%)	=0.465
Hepatitis C virus	104 (21.2%)	85 (21.1%)	12 (23.1%)	7 (19.4%)	
Redo LT	54 (11%)	40 (10%)	6 (11.5%)	8 (22.2%)	
Autoimmune hepatitis	30 (6.1%)	25 (6.2%)	2 (3.8%)	3 (8.3%)	
Budd–Chiari syndrome	4 (0.8%)	4 (1%)	0	0	
Cryptogenic	40 (8.2%)	36 (9%)	5 (9.6%)	2 (5.6%)	
Hepatitis B virus	21 (4.3%)	20 (5%)	1 (1.9%)	0	
Primary biliary cirrhosis	40 (8.2%)	36 (9%)	4 (7.7%)	0	
Primary sclerosing cholangitis	40 (8.2%)	33 (8.2%)	5 (9.6%)	2	
Other	40 (8.2%)	33 (9%)	3 (5.8%)	1 (2.8%)	
Hepatocellular carcinoma	71 (14.5%)	64 (15.9%)	0	7 (29.4%)	=0.006

($n = 13$) and miscellaneous causes ($n = 7$). Twelve patients who were delisted were still alive at the end of the study period whereas the remainder had died. Fifty-two patients died whilst they were on the waiting list. The causes of death in these patients were sepsis ($n = 19$), variceal bleed ($n = 11$), MOF as a result of end-stage liver disease ($n = 9$), intracranial haemorrhage ($n = 1$) and unknown ($n = 12$).

Of the 65 patients who died on the waiting list or were delisted due to development of MOF, the median listing MELD score was 18 (IQR 16-24) and Child-Pugh score (CPS) was 11 (IQR 10–12), whereas the MELD score of those who were transplanted was 14 (IQR 11–18) and CPS was 9 (IQR 7–10) (both $P < 0.001$).

The ability of the MELD score at listing to predict 90-day survival on the waiting list and overall survival on the waiting list gave c-statistics of 0.788 (95% CI: 0.719–0.857) and 0.713 (95% CI: 0.647–0.779), respectively. The CPS was not significantly different from this with c-statistics of 0.787 (95% CI: 0.720–0.854) and 0.711 (95% CI: 0.645–0.777).

Outcome of transplantation

A total of 402 transplants were performed on patients listed during the study period with 11 patients having two transplants performed electively during that time. The demographics of the cohort are shown in Table 1. The commonest indications for liver transplantation were alcohol-related cirrhosis (22.4%) and hepatitis C virus-related cirrhosis (21.1%). Mean MELD score immediately prior to transplantation was 15.4 (median 14, IQR 11–19). ΔMELD ranged from −15 to +16 with a median of 0 and there were no differences in ΔMELD according to aetiologies.

Three hundred and twenty-nine patients (81.8%) patients were transplanted from home after a median 72 days (IQR 35–140) days on the transplant waiting list. Their median MELD score at listing and at transplant was 14 (IQR 11–17) and median ΔMELD was 0 (IQR −2 to +2). Fifty-three patients (13.2%) were hospitalized (non-ICU) at the time of transplantation and their median MELD score was 16.5 (IQR 13–20) at the time of listing. This had increased to a median MELD score of 19 (IQR 13–25) at the time of transplantation and their median ΔMELD was +1 (IQR 0 to +4). The 20 patients (5%) who were transplanted from the intensive care unit had a median MELD score of 19 (IQR 12–30) at listing and this had increased to 20 (IQR 14–27) at the time of transplant. Patients were admitted to intensive care for management of variceal bleeding, sepsis or deterioration in their end-stage liver disease. There was no significant difference in location at the time of transplant and their ΔMELD grouping ($P = 0.07$). ICU stay post LT ranged from 0 to 120 days with a median stay of 2 days. The median number of ICU stays was 1 with a range of 1–4 stays. The median hospital stay was 20 days with a range of 1–248 days (in those who left hospital, hospital stay ranged from 7 to 248 days). The 1- and 3-year survival of all patients was 86.8% and 80.3%, respectively.

The survival data and resource utilization for the ΔMELD groups are shown in Table 2. Patients whose

Table 2. The ICU, hospital stays and outcome post-transplant, dependent on ΔMELD score > or ≤ +1.

Median (IQR)	ΔMELD ≤ +1	ΔMELD > +1	*P*-value
ICU stay post LT (days)	2 (1–5)	2.5 (1–8)	0.235
Hospital stay (days)	20 (14–34)	22 (15–39)	0.089
Left ICU (%)	96	92	0.05
Left hospital (%)	95	89	0.025
Child-Pugh score at listing	9 (7–10)	9 (8–11)	0.230
MELD at listing	14 (11–18)	14 (10–17)	0.152
MELD at transplant	13 (10–16)	18 (13–23)	<0.001
Time on waiting list (days)	64 (26–123)	71 (28–143)	0.224
90 day survival (%)	95.3	90.4	0.0001
180 day survival (%)	94.9	84.7	0.0001
1 year survival (%)	91.9	77.8	0.0001
2 year survival (%)	88.1	72.1	0.0001
3 year survival (%)	83.6	72.1	0.0001

ΔMELD was >+1 were significantly less likely to survive ICU and hospital. However, there was no difference in ICU or hospital stays between the two groups, even when in-hospital deaths were excluded. Patients whose MELD score increased by greater than 1 point whilst on the waiting list had a significantly decreased post-LT survival up to 36 months (see Fig. 1) and this survival disadvantage persisted even when in-hospital mortality was excluded from analysis ($P = 0.0148$). The rate at which the MELD score changed, or the time on the waiting list was not a factor in the difference in survival post-LT between the two groups.

The changes in the different components of the MELD score between the ΔMELD groups were examined and the results are presented in Table 3. There was a significant difference in creatinine levels between the groups at listing and both groups demonstrated significant changes in INR, bilirubin, creatinine and MELD score between listing and transplantation.

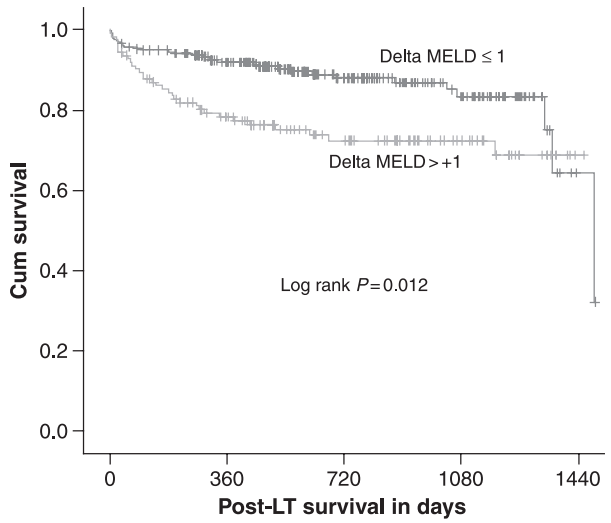

Figure 1 Kaplan–Meier curve demonstrating significant differences in survival in patients classified according to ΔMELD ≤+1 or ΔMELD >+1 ($P = 0.012$, log-rank test).

Table 3. This demonstrates how the differing components in the MELD equation, changed between listing and transplant between the ΔMELD groups.

Median (IQR)	ΔMELD ≤+1	ΔMELD >+1	*P*-value
Listing creatinine (μmol/l)	95 (79–118)	89 (76–104)	0.004
Transplant creatinine (μmol/l)	94 (80–112)	100 (84–138)	0.003
P-value	0.031	<0.001	
Listing INR	1.19 (1.06–1.37)	1.21 (1.06–1.37)	0.870
Transplant INR	1.17 (1.06–1.3)	1.37 (1.16–1.68)	<0.001
P-value	0.01	<0.001	
Listing bilirubin (μmol/l)	53 (29–85)	46 (26–112)	0.828
Transplant bilirubin (μmol/l)	38 (23–67)	76 (41–193)	<0.001
P-value	<0.001	<0.001	
Listing MELD	14 (11–18)	14 (10–17)	0.136
Transplant MELD	13 (10–16)	18 (14–23)	<0.001
P-value	<0.001	<0.001	

The outcome and resource utilization dependent upon the MELD score at transplant and at listing were also examined and is shown in Table 4. The survival curve dependent upon the MELD score at transplant is shown in Fig. 2. The ICU stay and hospital stay increased significantly as MELD scores increased (be it at time of listing or at transplant). However, there was only a significant worsening in survival in patients with higher MELD scores at the time of transplant and post-LT survival was not related to the MELD score at the time of listing.

The risk factors associated with death in a univariate analysis in a Cox regression model are shown in Table 5. In multivariate analysis, factors that were significant were transplantation from intensive care ($P = 0.002$) and ΔMELD >+1 ($P = 0.008$).

Discussion

This study shows that ΔMELD, whilst on the waiting list for LT, can significantly impact on the survival of the recipient. This study also demonstrates a significant increase in resource utilization as MELD score increases. Our results also show that in a UK transplant population, with shorter waiting times than in the US, use of MELD as an isolated variable is equivalent, but not superior, to CPS as a means of minimizing waiting list deaths. In the UK, allocation of donor livers is based primarily upon waiting time, although individuals may be prioritized within a centre, based on clinical need. This system is adequate as long as waiting lists remain short. However,

Table 4. This shows resource utilization, in-hospital mortality and survival dependent on MELD score at transplant and at time of listing.

Median (IQR)	≤10	11–18	19–24	>24	*P*-value
MELD score at transplant					
ΔMELD>+1 [no. (%)]	7 (8.3)	63 (29.4)	36 (52.2)	24 (72.7)	<0.001
ICU stay	2 (1–4)	2 (1–5)	3 (1–7.5)	8 (2–17.5)	0.002
Hosp stay	18 (13–29.5)	20 (14–36)	23 (17–40)	24 (20–40)	0.006
Left ICU	96.5%	95.3%	92.8%	90.9%	0.535
Left hospital	95.3%	93%	89.9%	90.9%	0.6
1 year survival	88.4%	90.5%	77.9%	82.0%	0.05
3 year survival	81.0%	83.5%	71.2%	77.0%	0.05
MELD score at time of listing					
ΔMELD>+1 [no. (%)]	35 (39.8)	71 (31)	16 (27.6)	9 (32.9)	0.334
ICU stay	2 (1–3.5)	2 (1–5)	3 (1–6)	8 (3–31.5)	<0.001
Hosp stay	18 (14–36.5)	20 (14–31)	28 (17–46)	32 (20–62)	<0.001
Left ICU	97.8%	95.2%	91.5%	88%	0.154
Left hospital	95.5%	93%	91.5%	84%	0.259
1 year survival	87.7%	88.7%	83.2%	80.7%	0.73
3 year survival	80.0%	81.5%	79.7%	74.7%	0.73

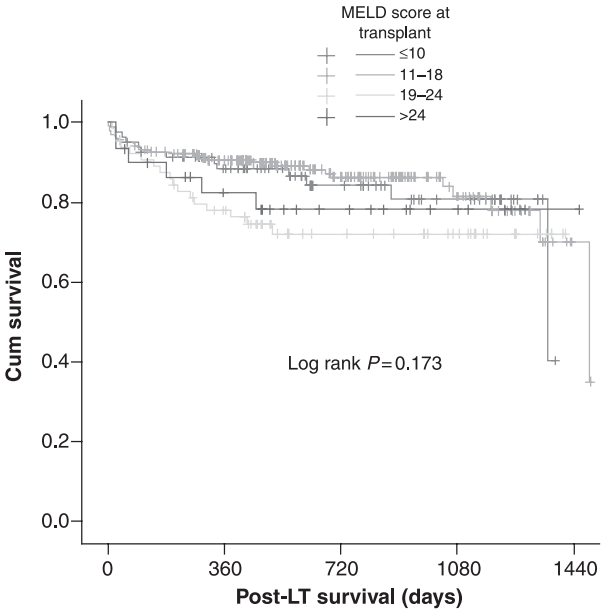

Figure 2 Kaplan–Meier curve demonstrating post transplant survival dependent upon MELD score at transplant (log-rank = 0.173).

Table 5. Risk factors on univariate analysis for patient mortality post liver transplantation in a Cox regression model.

Factor	Relative risk	95% CI	*P*-value
Male (versus female)	0.637	0.392–1.037	0.07
MELD score at LT	1.082	0.988–1.067	0.182
Transplanted from ICU (versus home)	4.175	2.035–8.565	<0.001
Transplanted from hospital (versus home)	1.437	0.723–2.855	0.3
ΔMELD	1.082	1.021–1.147	0.008
ΔMELD >+1 (vs. ≤+1)	2.217	1.351–3.637	0.002
ΔCreatinine	1.014	0.506–2.033	0.968
ΔBilirubin	1.016	0.964–1.072	0.546
ΔINR	1.454	0.999–2.117	0.051

in the scenario of lengthening lists and increasing demand for transplantation, a reappraisal of organ allocation maybe necessary. In the USA, the introduction of MELD scoring and its application to organ allocation has resulted in a decrease in waiting list deaths [11].

A study from the UK and Ireland transplant database showed that there was only a survival disadvantage, at 90 days, once the MELD score was >36 at the time of transplantation [12]. However, this cohort of patients with a MELD score >36 only accounted for 3.1% of cases transplanted [12]. The same study did not evaluate the effect of ΔMELD on patient outcome. Other studies from the USA have reported similar findings including two single centre studies of 404 and 669 patients who found that there was an increased mortality following LT only when MELD score at the time of LT was >36 (representing 11.9% of patients) or a MELD score of 25 or more (representing 27% of all patients) [13,14]. Results from our study concur with the aforementioned studies in that patients with higher MELD scores have a worse outcome following liver transplantation. Despite this there remains an acceptable 3 year survival (77%) even among the sicker patients (MELD score >24).

Resource utilization following liver transplantation in the MELD era has not been fully assessed. A number of studies have summarized these factors [15–18]. Our study demonstrates an increase in ICU and hospital stay as MELD score increases. This finding was noted regardless of whether the MELD at listing, or at transplantation, was used. This may be important for counselling patients, at the time of listing, regarding of their risks of ICU and hospital stays. MELD score however, does not predict

in-hospital mortality although there may be a nonsignificant trend with increase in MELD score.

The concept of ΔMELD was suggested to be of use as a refinement to the MELD score for patients whilst on the waiting list [10]. This study found that ΔMELD over a period of 30 days was predictive of waiting list mortality and was significantly better than MELD score at the time of listing. In contrast a further study described no effect of ΔMELD on waiting list survival in 861 patients and suggested that there was a detection bias in sicker patients [19]. They also suggested that a high ΔMELD corresponds with a higher current MELD score and that it is this factor alone that affects mortality [19].

The effect of ΔMELD on post-transplant survival has also been examined [20]. In this study, using ΔMELD as the MELD at transplant minus the MELD 30 days before transplant with a cut-off of +5, the investigators found higher 1-year mortality in the high ΔMELD group. However, in multivariate analyses, MELD score at transplant, rather than ΔMELD, was found to be the significant determinant of survival [20]. In contrast, our data differs significantly in the outcome, both at the point at which ΔMELD appears to have an effect and the timescale over which it impacts upon patient survival (i.e. up to 3 years). These changes in survival also remain significant if in-patient deaths (the highest risk of death) following transplantation, or, if mortality within 90 days, are excluded (data not shown).

The reasons for the variance between our study and that of Northup *et al.* [20] may be explained by the differences in populations, and the way in which ΔMELD is calculated. Our study looked at fixed time points in the natural history of the patients on the waiting list (ΔMELD = transplant MELD − listing MELD), whereas Northup *et al.* defined ΔMELD as transplant MELD minus 30-day pretransplant MELD [20]. Thus, change in MELD score may have influenced the timing of transplantation as the selection process for being allocated an organ is dependent upon the MELD score. Of note, patients in that study, with high ΔMELD had a significantly longer time on the waiting list than those with low ΔMELD [20]. Moreover, both groups were on the waiting list for a considerably longer time than our population (mean 284 days vs. 90 days).

A further striking feature of the use of ΔMELD as a predictor of post-LT survival is that it appears to manifest its effect over the first 3 years, even if in-hospital deaths or deaths within 90 days of transplant are excluded from analysis. The reasons for this are not easy to delineate. There was an excess of patients with higher MELD scores in the high ΔMELD group, although in our total population, the majority of patients had a MELD score of <19, a level at which survival is not affected. Moreover, there was no significant difference in aetiology between the two ΔMELD groups. In addition, patients with a worsening MELD score had significant deterioration in all three biochemical parameters of the MELD score, whereas those with improving scores had stable INR and improving bilirubin and creatinine (Table 3). Previous studies have supported the hypothesis that pretransplant renal function predicts post-LT survival, particularly when the calculated creatinine clearance is <40 ml/min [21,22]. Interestingly, a modified MELD model utilizing only INR and serum creatinine was predictive of waiting list mortality in a recent publication, however, post-transplant survival was not addressed in that study [23]. However, our results suggest that it is the change in INR that may have the greatest impact upon post-LT survival. It may be that changes in INR represent a genuine, and potentially inexorable, deterioration in hepatic function over a relatively short time period, whereas changes in bilirubin and creatinine may fluctuate for reasons such as the presence of sepsis and be amenable to therapeutic measures to correct their decline.

Some limitations exist regarding the use of either MELD or ΔMELD in organ allocation. First, there is no absolute level of ΔMELD that is highly predictive of death, and this likely represents the multitude of recipient, donor, surgical and post-transplant factors that affect recipient outcome. Another limitation is that, even those patients in the worst outcome group have a 3-year survival of 72%. Despite this, the key finding from this study is that preservation or improvement of MELD parameters, whilst on the transplant waiting list, may result in a significantly improved medium-term outcome following liver transplantation.

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