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ORIGINAL ARTICLE

Multicentric evaluation of model for end-stage liver disease-based allocation and survival after liver transplantation in Germany – limitations of the 'sickest first'-concept

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Summary

Since the introduction of model for end-stage liver disease (MELD) in 2006, post-orthotopic liver transplantation (OLT) survival in Germany has declined. The aim of this study was to evaluate risk factors and prognostic scores for outcome. All adult OLT recipients in seven German transplant centers after MELD implementation (December 2006–December 2007) were included. Recipient data were analyzed for their influence on 1-year outcome. A total of 462 patients (mean calculated MELD = 20.5, follow-up: 1 year) were transplanted for alcoholic cirrhosis (33.1%), hepatocellular carcinoma (26.6%), Hepatitis-C (17.1%), Hepatitis-B (9.5%), primary sclerosing cholangitis (5.6%) and late graft-failure after first OLT before December 2006 (8.7%). 1-year patient survival was 75.8% (graft survival 71.2%) correlating with MELD parameters and serum choline esterase. MELD score >30 [odds ratio (OR) = 4.17, confidence interval: 2.57–6.78, 12-month survival = 52.6%, *c*-statistic = 0.669], hyponatremia (OR = 2.07), and pre-OLT hemodialysis (OR = 2.35) were the main death risk factors. In alcoholic cirrhosis (n = 153, mean MELD = 21.1) and hepatocellular carcinoma (n = 123, mean MELD = 13.5), serum bilirubin and the survival after liver transplantation score were independent outcome parameters, respectively. MELD >30 currently represents a major risk factor for outcome. Risk factors differ in individual patient subgroups. In the current German practice of organ allocation to sicker patients, outcome prediction should be considered to prevent results below acceptable standards.

Introduction

The identification of those patients with a high priority and also suitability for orthotopic liver transplantation (OLT) is a major challenge in transplantation medicine. This challenge is aggravated by a critical shortage of liver allografts, the determination of priority based upon an assessment of mortality on the waiting list, and the

prediction of factors suggesting a favorable outcome following OLT. Since 2002 and 2006, the model for end-stage liver disease (MELD) has been implemented in the USA and the Eurotransplant network, respectively, in an attempt to replace more subjective assessment criteria for OLT candidate stratification. The suitability of the MELD score is based on a study by Wiesner *et al.* [1] that showed the prediction of 3-month mortality of waiting list candidates with a *c*-statistic of 0.83, which was recently confirmed by an analysis of a large patient cohort from the United Network for Organ Sharing (UNOS) database [2]. However, the initial development of MELD never intended its subsequent utilization as an allocation instrument for liver transplantation. The assessment of MELD as predictor of mortality following OLT has led to controversial reports [3–6], and *c*-statistics to predict 3-month mortality have been reported to reach only 0.54 [7] and 0.63 [2]. To improve the accuracy of MELD for the assessment of time to death, an incorporation of additional parameters such as sodium and age has been discussed [8].

Model for end-stage liver disease-based allocation stratifies patients with abnormal coagulation, creatinine and serum bilirubin levels for OLT, who are thus characterized by a higher degree of morbidity, complexity of disease, and longer hospital treatment time [9]. However, patients with renal failure, who would be prioritized for transplantation, have been shown to suffer from a poorer outcome [10]. In Germany, the introduction of MELD has considerably changed the clinical practice of waiting list management. Although sicker patients are more likely to be eligible for OLT, a significant reduction in outcome has been reported that was associated with longer surgery time and poorer renal function [11].

Against this background, prognostic models are being studied that can contribute to the identification of those patients characterized by both a critical need for OLT as well as the likelihood of a positive outcome. In an analysis performed before the introduction of MELD in Germany, our group developed a prognostic score for survival after liver transplantation (SALT) with a *c*-statistic of 0.785 [5]. This score does not incorporate donor parameters, in contrast to a recent score devised in the USA (survival outcomes following liver transplantation) with a *c*-statistic of 0.70 [2]. The most significant risk variables were re-transplantation and pre-OLT life support, but variables that are not available at the time of placement on the waiting list including cold ischemia time, donor age and allocation origin were also incorporated. The prediction of outcome is therefore likely not only to depend upon individual risk variables but also on the selection of patients, the overall severity of disease at OLT, and the allocation system.

It was the aim of this study to evaluate, in a multicentric approach, risk factors and prognostic scores for 1-year patient and graft survival following OLT, especially after the introduction of the MELD-based allocation system in Germany.

Patients and methods

Patients

We performed a retrospective analysis of all adult (>18 years) patients from seven German transplant centers (Berlin, Essen, Hannover, Heidelberg, Mainz, Münster, Regensburg), who received an OLT during the first year after the introduction of MELD-based allocation (December 17, 2006–December 16, 2007). Living donor transplantations (including domino), multiple organ, and high urgency transplantations because of fulminant hepatic failure without chronic liver disease were excluded, as, in these situations, organs are not allocated by the MELD-System. Required minimum follow-up was 1 year.

Patient characteristics including age, gender, etiology of liver disease and history of hemodialysis before OLT, graft type (split versus full organ) and biochemical parameters were retrospectively analyzed regarding their influence on 1-year graft and recipient survival. Pretransplant biochemical parameters [international normalized ratio (INR), serum bilirubin (BILI), serum creatinine (CREA), choline esterase (CHE), serum sodium (Na)] were recorded at the last re-evaluation before OLT and on the day of OLT. The time point of last re-evaluation before OLT depends on the actuarial MELD score and the re-certification schedule required by Eurotransplant. Accordingly, it ranges between 1 week and 3 months. We chose these two time points because parameters obtained at the last re-evaluation were used for organ allocation, while values on the day of transplantation were considered to represent more adequately the recipient's overall condition immediately at the time of OLT. On the basis of original laboratory data at each time point, we calculated the laboratory MELD (lab-MELD) score as described by Wiesner *et al.* [1]. Patients who were dialyzed before OLT received a set creatinine value of 4 mg/dl. In addition, the SALT score was calculated as 'SALT = 0.04*age (years) + 0.003*CREA (μmol/l) − 0.349*CHE (kU/l)' at both time points [5]. Waiting list mortality data were not incorporated into the analysis.

Statistical analyses

Data were collected using the ACCESS Database software (MS Office 2003; Microsoft Corporation, Redmond, WA, USA) and were further analyzed using the SPSS 15.0 software package for Windows (SPSS Inc., Chicago, IL,

Table 1. Analysis of age, biochemical parameters, MELD, and SALT scores of patients who survived 1 year after OLT, or died. Patients who died within 12 months after OLT were compared with those, who survived (by Mann–Whitney *U*-test); NS, not significant. The data entry rate is indicated in column 2 for each parameter.

		Recipient outcome 1 year post-OLT		
	Data entry rate (%)	Survived (mean ± SD, median)	Died (mean ± SD, median)	*P*-value
Age at OLT (years)	100	53.6 ± 9.3, 54.1	53.6 ± 9.5, 53.1	NS
Biochemistry at last re-evaluation				
CREA (μmol/l)	97.2	125.2 ± 84.7, 91.1	171 ± 121.3, 126.6	<0.001
BILI (μmol/l)	97.8	139.2 ± 275, 49.8	296.2 ± 700.7, 107.5	<0.001
INR (ratio)	97.6	1.55 ± 0.57, 1.4	1.9 ± 1.18, 1.56	<0.001
CHE (kU/l)	68.2	3.48 ± 2.12, 2.93	2.91 ± 1.94, 2.37	0.020
Na (mmol/l)	80.1	136.2 ± 5.2, 137	135.7 ± 7.4, 136	NS
Biochemistry on day of transplantation				
CREA (μmol/l)	99.8	117.3 ± 91.2, 88.4	156.8 ± 150.9, 121.4	0.001
BILI (μmol/l)	99.6	120.6 ± 182.3, 44.5	239.6 ± 267.5, 107.7	<0.001
INR (ratio)	99.6	1.49 ± 0.52, 1.33	1.79 ± 0.91, 1.52	<0.001
CHE (kU/l)	61.0	3.64 ± 2.34, 3.2	3.1 ± 2.05, 2.4	0.054
Na (mmol/l)	96.1	136.6 ± 5.3, 138	136.9 ± 7.1, 137	NS
Pretransplant MELD				
At last re-evaluation	97.4	18.96 ± 9.59, 16.33	25.45 ± 11.21, 26.61	<0.001
On day of transplantation	98.7	17.99 ± 9.22, 15.62	24.68 ± 10.8, 24.28	<0.001
Pretransplant SALT				
At last re-evaluation	68.2	1.26 ± 0.93, 1.45	1.65 ± 0.89, 1.73	0.001
On day of transplantation	61.0	1.22 ± 1.0, 1.35	1.55 ± 0.91, 1.64	0.020

OLT, orthotopic liver transplantation; MELD, model for end stage liver disease; SALT, survival after liver transplantation; INR, international normalized ratio; BILI, serum bilirubin; CREA, serum creatinine; CHE, choline esterase; Na, serum sodium.

USA). Patient and graft survival was determined by Kaplan–Meier survival analysis. For individual parameters, groups were compared by log-rank test. Continuous variables are presented as means ± standard deviations as well as medians, and were compared by Mann–Whitney *U*-test. Categorical variables were compared by chi-squared test. The validity of prognostic scores such as MELD and SALT was tested using the area under the receiver operator characteristic (ROC) curve. Multivariate analysis was performed by logistic regression. Data entry was complete for patient characteristics and nearly complete for the MELD parameters (INR, BILI, CREA). Serum sodium and serum choline esterase values were not available for some patients (Table 1). Therefore, not the entire cohort of patients had a complete set of parameters and consequently, these patients were not available for multivariate analyses. All tests were two-tailed and a *P*-value of 0.05 or less was considered statistically significant.

The Ethics Committee of Hannover Medical School approved the study and its execution.

Results

Demographics and outcome

A total of 468 patients met the inclusion criteria of this study. Since six patients were lost to follow-up, the final population consisted of 462 patients (68.4% men) with a mean age of 53.6 ± 9.4 years (range 18.3–73.5 years), a mean calculated MELD of 20.5 ± 10.4 at last re-evaluation, and of 19.6 ± 10 on the day of OLT. The main reasons for OLT were alcoholic liver disease (33.1%), hepatocellular carcinoma (HCC) (26.6%), Hepatitis-C (17.1%), Hepatitis-B (9.5%) and primary sclerosing cholangitis (PSC) (5.6%). In 8.7% of all patients, a re-transplantation was performed because of chronic graft dysfunction occurring after one or more previous OLTs. These previous OLTs had all been performed before December 16, 2006 (Table 2).

All patients were followed up for at least 1 year after OLT. One-year patient survival was 75.8%, and 1-year graft survival was 71.2% because 10.2% of all recipients required an urgent re-transplantation because of initial graft nonfunction. Patients who required urgent re-transplantation had a significantly reduced 1-year survival of only 53.2% ($P < 0.001$).

Outcome parameters

Biochemical parameters (CREA, BILI, INR, Na and CHE), age at OLT, and two calculated scores (MELD and SALT) were further analyzed by Mann–Whitney *U*-test for a possible association with 1-year patient survival (Table 1). The MELD parameters INR, CREA and BILI correlated significantly with 1-year survival both on the day of OLT

Table 2. Analysis of risk factors for recipient mortality and graft loss at 12 months after OLT. The absolute number and the percentage of patients with the respective risk factor are given for each parameter. Odds ratios (OR) are calculated for patients positive for each risk factor compared with those without the risk factor, and both groups were compared regarding patient- and graft 1-year survival by chi-squared test.

Risk factor	*n* (%)	12-month patient survival (%)	OR (CI) for death 12 months post-OLT	*P*-value	12-month graft survival (%)	OR (CI) for graft loss 12 months post-OLT	*P*-value
All patients	462 (100)	75.8			71.2		
Indication							
Alcoholic cirrhosis	153 (33.1)	80.4	NS	NS	75.8	NS	NS
HCC	123 (26.6)	80.5	NS	NS	73.2	NS	NS
Hepatitis-C	79 (17.1)	79.7	NS	NS	73.4	NS	NS
Hepatitis-B	44 (9.5)	81.8	NS	NS	72.7	NS	NS
PSC	26 (5.6)	92.3	0.25 (0.06–1.06)	**0.043**	88.5	0.31 (0.9–1.04)	**0.046**
PBC	18 (3.9)	61.1	NS	NS	61.1	NS	NS
AIH	20 (4.3)	65	NS	NS	65	NS	NS
Previous liver transplantation	40 (8.7)	60	**2.26 (1.16–4.43)**	**0.015**	60	NS	NS
Demographics							
Age > 65	44 (9.5)	75	NS	NS	65.9	NS	NS
Male	316 (68.4)	76.8	NS	NS	72.2	NS	NS
Dialysis pretransplant	47 (10.2)	59.6	**2.35 (1.26–4.4)**	**0.006**	55.3	**2.19 (1.18–4.04)**	**0.011**
Split graft	18 (3.9)	61.1	NS	NS	50	**2.58 (1–6.65)**	**0.043**
Biochemical parameters at re-evaluation							
BILI > 70 μmol/l	197 (43.6)	65.5	**2.83 (1.81–4.43)**	**<0.001**	59.4	**2.88 (1.89–4.38)**	**<0.001**
INR > 2	92 (20.4)	65.2	**1.99 (1.21–3.27)**	**0.006**	55.4	**2.48 (1.54–3.99)**	**<0.001**
CHE < 2.6 kU/l	142 (45.1)	69.7	**1.71 (1.02–2.87)**	**0.04**	65.5	NS	NS
Na < 130 mmol/l	44 (11.9)	61.4	**2.07 (1.07–4.0)**	**0.028**	52.3	**2.47 (1.3–4.68)**	**0.005**
CREA > 100 μmol/l	212 (45.9)	67.9	**2.21 (1.43–3.41)**	**<0.001**	64.2	**1.89 (1.26–2.84)**	**0.002**
Predictive scores at re-evaluation							
MELD > 20	198 (44)	66.2	**2.63 (1.69–4.11)**	**<0.001**	60.6	**2.56 (1.69–3.9)**	**<0.001**
MELD > 30	95 (21.1)	52.6	**4.17 (2.57–6.78)**	**<0.001**	46.3	**4.12 (2.56–6.62)**	**<0.001**
SALT > 1.7	121 (38.4)	66.9	**2.03 (1.21–3.41)**	**0.007**	62	**1.87 (1.14–3.05)**	**0.012**

OLT, orthotopic liver transplantation; MELD, model for end stage liver disease; SALT, survival after liver transplantation; OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; INR, international normalized ratio; BILI, serum bilirubin; CREA, serum creatinine; CHE, choline esterase; Na, serum sodium; AIH, autoimmune hepatitis.
Bold entries indicate statistical significance of $P < 0.05$.

and at the time of last re-evaluation. In addition, CHE and the SALT score at the time of last re-evaluation correlated significantly with 1-year patient survival.

For 1-year graft survival (data not shown) again INR, CREA and BILI as well as MELD and SALT were significantly correlated with outcome ($P < 0.02$), whereas CHE failed to reach statistical significance ($P = 0.086$) in this analysis.

However, the continuous variables, age and sodium, were not observed to show a correlation with 1-year graft or patient survival.

Risk factors

Using the ROC-analysis, cut-off values for biochemical parameters, for age, as well as the MELD and SALT scores were determined and used to define risk factors for survival. These were further analyzed by chi-squared test to determine their influence on 1-year patient and graft survival together with other categorical variables such as indication for OLT, gender, and graft type (Table 2).

Although the outcome was different for the various indications, only patients with PSC had a significantly better 1-year survival of 92.3%. Conversely, patients with a history of previous OLT before December 2006 who required re-transplantation had an expected higher risk of death 12 months after OLT [odds ratio (OR) = 2.26]. All biochemical parameters that correlated with outcome as continuous variables were found to be significant risk factors with their respective cut-off points leading to an OR between 1.7 and 2.8. With this approach, hyponatremia (Na < 130 mmol/l) at the time of re-evaluation was a significant risk factor for 1-year graft (OR = 2.47) and recipient (OR = 2.07) survival. In 10.2% of all patients, hemodialysis was initiated before OLT. These recipients had a considerably decreased 1-year survival of 59.6% with an OR of 2.35.

A MELD Score of more than 30 points at re-evaluation was the strongest risk factor for recipient death at 12 months after OLT (OR = 4.17). As shown in Fig. 1a, these recipients (21.1% of the entire study population) had an actuarial 12-month survival of only 52.6%, while the survival for all other MELD groups was significantly better ($P < 0.001$). The area under (AU) the ROC curve (*c*-statistic) of MELD was calculated as 0.697 [confidence interval (CI): 0.627–0.767] for 3-month patient survival and 0.669 (CI: 0.609–0.730) for 1-year patient survival.

By using the previously coined SALT score [5], we identified additional risk groups (Table 2, Fig. 1b) regarding 12-month patient survival. In patients with a SALT score of more than 2.5 at the time of re-evaluation, 1-year survival was reduced to 55%. The *c*-statistic for SALT was lower than that for MELD with 0.645 (CI: 0.563–0.728) for 3-month and 0.626 (CI: 0.556–0.695) for 1-year patient survival.

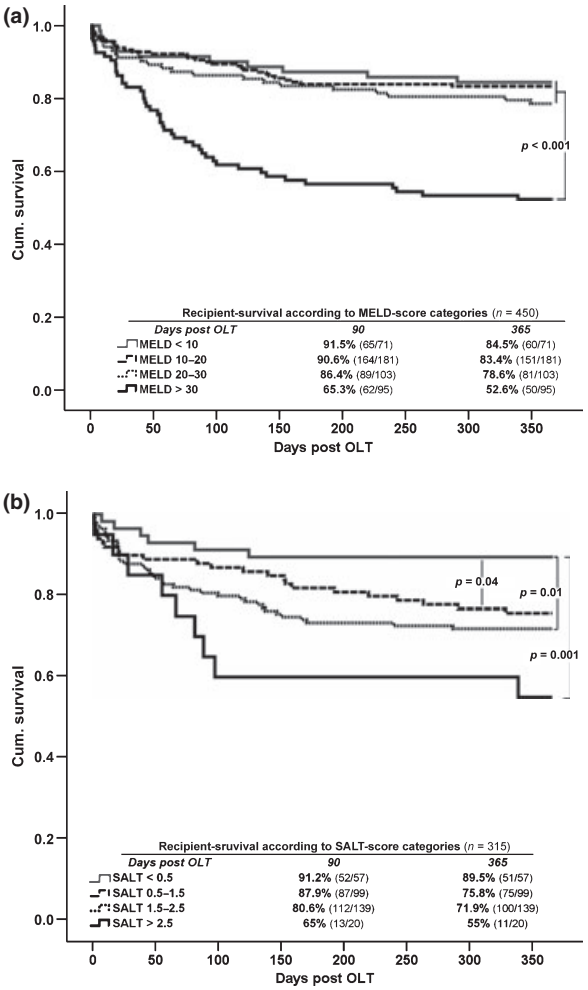

Figure 1 (a) Kaplan–Meier graph of recipient survival by MELD score. Different categories of MELD were compared by log-rank test. (b) Kaplan–Meier graph of recipient survival by SALT score. Different categories of SALT were compared by log-rank test.

Multivariate analysis

Risk factors and continuous variables at the time of re-evaluation that were significant in univariate analyses were subjected to multivariate analyses ($n = 314$). Logistic regression (Method: Enter) identified MELD at re-evaluation as the only parameter that significantly correlated with 1-year survival ($P < 0.001$). When only the individual laboratory data (BILI, INR, CREA, CHE) were entered instead of the calculated MELD or SALT scores, the biochemical parameters CREA ($P = 0.023$) and BILI ($P = 0.049$) at re-evaluation were found to correlate independently with 1-year recipient survival.

Subgroup analyses

The two major OLT indications, alcoholic cirrhosis and HCC were separately evaluated for parameters that correlate with 1-year patient survival (Table 3). Parameters that reached a *P*-value of <0.1 in a univariate test were then subjected to multivariate analysis.

In the alcoholic cirrhosis group ($n = 153$, 77.8% men, mean age 55.5 years, mean calculated MELD = 21.1), higher BILI and higher MELD score at re-evaluation as well as a hyponatremia (Na < 127 mmol/l) were significantly correlated with 1-year recipient mortality. The age at OLT reached near significance. Following logistic regression, BILI at re-evaluation remained as the only predictive parameter.

Table 3. Subgroup analysis for predictive parameters with impact on 1-year recipient survival. Univariate analysis was performed with Mann–Whitney *U*-test for continuous or chi-squared test for categorical variables. Logistic regression identified significant risk factors. In this multivariate analysis, only cases with a complete data entry set could be included (respective number of cases is given).

Indication	Univariate analysis		Multivariate analysis
Alcoholic cirrhosis		*P*-value	
	BILI	0.013	BILI;
	MELD	0.034	Number of cases = 109
	Age	0.071	($P = 0.002$,
	Na < 127	0.042	*c*-Statistic = 0.649)
HCC		*P*-value	
	CHE	0.021	SALT;
	Age	0.033	Number of cases = 96
	SALT	0.007	($P = 0.006$,
	Na < 127	0.025	*c*-Statistic = 0.695)

MELD, model for end stage liver disease; SALT, survival after liver transplantation; BILI, serum bilirubin; HCC, hepatocellular carcinoma; CHE, choline esterase; Na, serum sodium.

In the HCC group (n = 123, 84.6% men, mean age 58.1 years, mean calculated MELD = 13.5), a lower CHE, a higher SALT score, hyponatremia (Na <127 mmol/l) at re-evaluation and higher age at OLT were significant predictive parameters for the recipient's death at 1 year after OLT. The SALT Score was the only significant parameter that was confirmed in a multivariate analysis (logistic regression, method: backward-stepwise). As shown in Fig. 2b, recipients with a SALT score >2 at re-evaluation had a highly significant reduction of 3- and 12-month survival. The area under the ROC curve for the SALT score in patients transplanted for HCC was calculated as 0.726 (CI: 0.544–0.907) for 3-month and 0.695 (CI 0.560–0.829) for 1-year patient survival. In contrast (Fig. 2a), MELD was not a good predictor of post-OLT survival in patients transplanted for HCC and was significant only for 3-month survival.

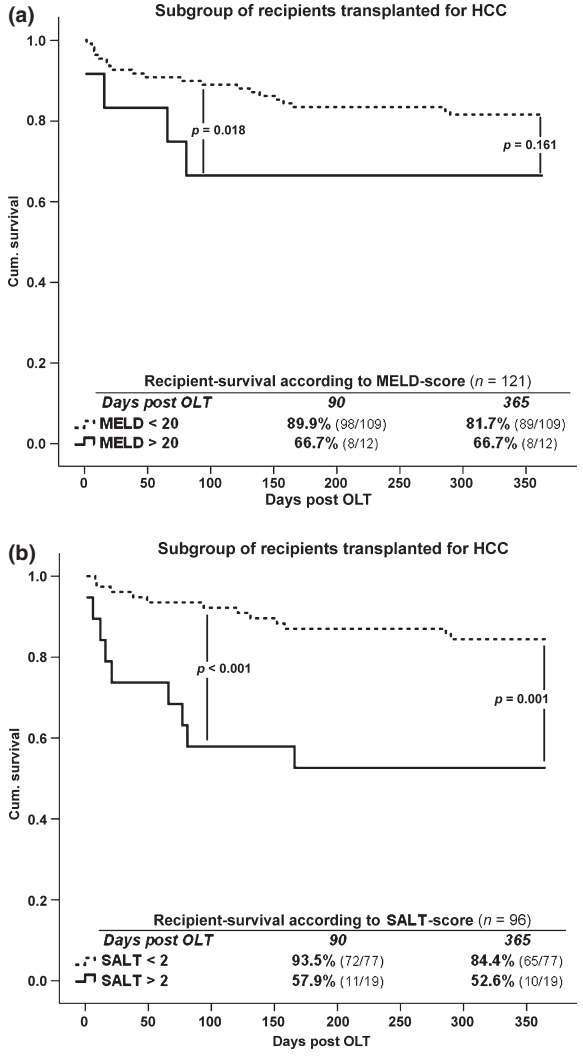

Figure 2 (a) Kaplan–Meier survival analysis of patients transplanted for HCC. Recipients with a MELD score of more or less than 20 at the time of re-evaluation were compared by log-rank test. (b) Kaplan–Meier survival analysis of patients transplanted for HCC. Recipients with a SALT score at re-evaluation of more or less than 2 were compared by log-rank test.

Analysis of primary transplants only

A separate analysis of primary transplants that excludes re-OLT and split liver OLT resulted in similar findings as the above data. In this analysis, 407 patients remained (71% male, mean age 54.2 years, mean calculated MELD at re-evaluation: 19.9). OLT indications were: alcoholic liver disease (36.9%), HCC (29%), Hepatitis-C (17.7%), Hepatitis-B (10.3%), and PSC (3.9%). One-year patient survival was 77.9%, and 1-year graft survival was 73.2% because 8.4% of all recipients required an urgent re-transplantation. Patients who required urgent re-transplantation had a significantly reduced 1-year survival of only 58.8% (P = 0.005). Significant risk factors in this group were: hemodialysis before OLT (OR = 2.26, P = 0.025), BILI > 70 (OR = 3.59, P < 0.001), INR > 2 (OR = 1.88, P = 0.023), Na < 130 (OR = 2.48, P = 0.007), CREA > 100 (OR = 2.24, P = 0.001), MELD > 20 (OR = 2.8, P < 0.001), SALT > 1.7 (OR = 2.1, P = 0.01), MELD > 30 (OR = 4.9, P < 0.001). AU-ROC (c-statistic) of MELD was calculated as 0.711 for 3-month patient survival and 0.679 for 1-year patient survival. AU-ROC (c-statistic) of SALT was calculated as 0.647 for 3-month patient survival and 0.629 for 1-year patient survival. In primary transplants, logistic regression (Method: Enter) identified MELD at re-evaluation as the only parameter significantly correlating with 1-year survival (P < 0.001). Eighteen patients had received a split liver OLT. Of these, four had a MELD >30 at re-evaluation. Two of these four patients did not survive 1 year demonstrating that split liver OLT was avoided in patients with MELD >30.

Discussion

Against the background of a continued organ shortage, the assessment of a survival benefit for an OLT candidate is a major challenge. In particular, in Germany, MELD-based allocation has led to an increase in mean MELD score values at the time of OLT [2,11]. Although waiting list mortality has been shown to decrease [6,12–14], decreased survival rates have also been observed [11], which contrasts analyses from the UNOS database in the USA [2,6,12] and indicates that in different transplantation settings, factors predicting outcome may vary. We therefore report a multicenter study aimed at analyzing risk factors for mortality or graft loss following OLT with the participation of seven major German transplantation

centers to analyze this development. All OLTs performed between December 2006 and December 2007 immediately after the implementation of MELD-based allocation were studied representing half of all OLTs in Germany.

The results of this study illustrate the dilemma of an association of 1-year post-OLT mortality with BILI, CREA and INR, the parameters employed to calculate the MELD score. Age as a risk factor for mortality after OLT has been described in a number of studies [2,11], but could not be confirmed in this study population. This might be due to the special subset of multimorbid patients, in whom age no longer plays such a prominent role. When individual risk factors were determined, the strongest mortality risk factor for 1-year survival was a MELD score >30. Expectedly, also hyponatremia, re-transplantation, and pre-OLT dialysis were associated with increased mortality [2,10,15]. Presently, the timely allocation of an organ to a patient without an accepted exceptional MELD (match-MELD) condition in German transplant centers is only likely with a MELD score exceeding 30 with an increasing trend. According to the original data of Wiesner *et al.* [1] patients with a MELD between 30 and 39 have an expected 3-month survival of 47.4%. In our analysis (Fig. 1a), the group of patients with a MELD >30 is characterized by a 3-month survival following OLT of 65.3% and a 1-year survival of 52.6%. This indicates that current practice selects those patients with the poorest prognosis following OLT. This finding remains even when re-OLT and split liver OLT are excluded from the analysis. The *c*-statistic for this prediction was 0.697 (CI: 0.627–0.767) and 0.669 (CI: 0.609–0.730) for 3- and 12-month survival, respectively, which is higher than the *c*-statistic for 3-month survival recently reported by Rana *et al.* [2] who analyzed a UNOS cohort. These data indicate that analyses from the UNOS database in the USA (with a significant lower MELD-level at OLT) may not be fully applicable to the situation and current allocation practice of OLT in Germany and that separate analyses such as the one presented here are useful.

The stratification of patients by MELD has significantly altered the variables that define mortality. This is illustrated by an analysis of the SALT score that was developed in a cohort of patients with a mean MELD of 14.5 prior to the initiation of MELD-based allocation [5]. In this cohort, the SALT score predicted outcome with a *c*-statistic of 0.785 (CI: 0.644 to 0.926), which, in the present overall cohort (mean MELD = 20.5), was reduced to only 0.626 (CI: 0.556–0.695), although higher SALT scores >2 still indicated a significantly reduced survival of 55% after 12 months (Fig. 1b). In the present study cohort with considerably higher MELD – and thus morbidity – age was no longer discriminatory for outcome (Table 1) and therefore represents the likely explanation for a reduced predictive value of SALT, which includes age for its calculation. Therefore, the changed criteria for organ allocation appear to impact the risk factors for outcome.

However, individual groups of OLT candidates require additional attention. When our analysis was expanded to subgroups, MELD was not a superior post-OLT-mortality predictor for all patient groups. Two of the major indications for OLT are alcoholic cirrhosis and HCC. In alcoholic cirrhosis hyponatremia of <127 mmol/l, elevated BILI and MELD were significantly associated with 1-year mortality with BILI (and not MELD) as the only predictive risk parameter in the multivariate analysis. This group is characterized by a mean MELD score of 21.1, which is very similar to that of the overall group (20.5), yet the risk factors for outcome were observed to be different. The second large indication group is HCC characterized by an expected lower mean lab-MELD of 13.5, due to the fact that these patients are all prioritized through an exceptional match-MELD. In this subgroup age, CHE, hyponatremia <127 mmol/l and the SALT score, but not MELD, were significantly associated with 1-year mortality. Multivariate analyses identified SALT as the only predictive risk factor (*c*-statistic of 0.726). Also in this subgroup, MELD was not identified as major outcome predictor (Fig. 2a and b). These two sub-analyses indicate that outcome prediction requires individual approaches for different indications and selection criteria.

The identification of hyponatremia as a risk factor for 1-year recipient and graft survival (Table 2) is an interesting observation regarding the ongoing discussion of an incorporation of low sodium into the MELD score for a more accurate reflection of mortality on the waiting list [8,16–18]. While low serum sodium is a risk factor for mortality associated with chronic liver disease and hepatic decompensation, little and contradictory data are available regarding its predictive impact on outcome following OLT [19–21]. In our analysis, hyponatremia is identified as a risk factor for reduced 1-year survival following OLT, which should be considered and further studied to prevent the incorporation of an additional outcome risk factor for patient stratification before OLT.

In this study, we focused on recipient parameters known at time of re-evaluation before OLT and did not analyze donor data. This way, our analysis cannot rule out the effects of increased use of extended criteria donor organs on the reduced survival rate. However, in a previous single-center study [11] we reported that donor age and cold ischemia time actually improved in the MELD era. In the United States, organ quality [22] decreased in the MELD era, but since these high-risk organs were preferentially allocated to less urgent patients, this

interestingly led to a reduced survival in patients with a lower MELD (<20). In view of this, Bonney *et al.* [23] reported that organ quality is a prognostic factor for graft survival only in patients with a low and intermediate MELD (<30), while in the high-MELD group (>30), organ quality did not affect graft survival. We report MELD >30 to represent the major risk factor for reduced 1-year survival rate, and it appears not very likely that donor organ quality represented the major factor for this.

In the existing triage-situation of organ shortage, outcome is an important limiting factor for overall benefit when grafts are allocated to recipients with a likely fatal outcome and are thus lost for patients who would do better. The lack of data on waiting list mortality may represent a limitation of this study. To optimize transplantation benefit, waiting list mortality should be balanced against post-OLT mortality. In a recent study [24], a model to calculate an individual survival benefit score for every patient on the waiting list was reported that may save more than 2000 life-years per year. The results of our study would strongly support this approach and may be helpful to initiate further efforts, to develop such a survival benefit orientated allocation system.

The retrospective character of the study is a minor limitation because all patients that were transplanted in the participating centers during the respective era were included in the analysis.

In summary, we demonstrate a change of factors associated with outcome following the implementation of MELD-based allocation in Germany. In contrast to UNOS data, MELD is identified – in the current situation in Germany – as the strongest predictor of overall 1-year post-OLT mortality. However, even in view of the presented data, we would not generally recommend to restrict OLT to patients with MELD <30. MELD was not designed for the prediction of post-OLT survival and it is a suboptimal tool in this regard. It is obvious that individual patients sharing a MELD >30 are not necessarily clinically comparable, which results from the individual parameter (BILI, CREA or INR) that primarily contributes to the overall MELD in an individual situation. Instead, it will be necessary to consider incentives for OLT, entry criteria for waiting list patients, possibly the re-evaluation of standard exception practices, and, importantly, the development and use of specific parameters for the prediction of outcome. These parameters differ in different transplant settings and are dependent on the management of allocation, in this case, the prioritization of sicker candidates on the waiting list in Germany. However, prediction of post-OLT mortality also requires individual analyses of different indication and patient groups as demonstrated for a predictive role of different parameters in HCC and in alcoholic cirrhosis. Therefore, the differentiated establishment of predictive outcome parameters appears to be necessary to prevent wasteful transplantations in cases, in which survival is predicted to be below acceptable treatment standards, and in view of more aggressive transplantation practices fuelled by the critical liver allograft shortage.

Authorship

TJW and CPS: data analysis, performed study, wrote paper. PF: collected data. JS and AP: collected and provided data. APB: provided data, edited manuscript. GO, SB and MPM: data analysis, editing of manuscript. MNS: discussions, conduct of study, data collection. HHS: editing of manuscript, data collection. HJS: writing of manuscript, analyses, data collection. PN: data collection, revisions. JK: provided data, analyses. JP: provided patient data.

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Disclosures

The authors have nothing to disclose.

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