ORIGINAL ARTICLE

Does the meld system provide equal access to liver transplantation for patients with different ABO blood groups?

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SUMMARY

This study investigates the relationship between blood group and waiting time until transplantation or death on the waiting list. All patients listed for liver transplantation in the Netherlands between 15 December 2006 and 31 December 2012, were included. Study variables were gender, age, year of listing, diagnosis, previous transplantations, blood group, urgency, and MELD score. Using a competing risks analysis, separate cumulative incidence curves were constructed for death on the waiting list and transplantation and used to evaluate outcomes.In 517 listings, the mean death rate per 100 patient-years was 10.4. A total of 375 (72.5% of all listings) were transplanted. Of all transplantations, 352 (93.9%) were ABO-identical and 23 (6.1%) ABO-compatible. The 5-year cumulative incidence of death was 11.2% (SE 1.4%), and of transplantation 72.5% (SE 2.0%). Patient blood group had no multivariate significant impact on the hazard of dying on the waiting list nor on transplantation. Age, MELD score, and urgency status were significantly related to the death on the waiting list and transplantation. More recent listing had higher probability of being transplanted. In the MELD era, patient blood group status does not have a significant impact on liver transplant waiting list mortality nor on waiting time for transplantation.

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Introduction

The introduction of the MELD system represented a fundamental change in the approach of patients listed for liver transplantation. No longer were patients prioritized according to waiting time, but the principle of transplanting the sickest patients first was applied. The aim of the MELD system was to reduce waiting list mortality and other inadvertent outcomes during waiting time, such as clinical deterioration, and ultimately development of contra-indications against liver transplantation [1–3]. The MELD system aims to provide equal access to transplantation, with patients prioritized according to their clinical status, without compromising post-transplantation outcome [4]. But the idea that the MELD system truly ensures equal access to liver transplantation for all patients remains open to debate [5,6]. This article focuses on the equality of access to liver transplantation between patients with different blood groups.

The initial intent in the MELD system is to encourage ABO-identical transplantations. However, in case of high urgency and in some situations of regular urgency

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with recipient MELD scores above 30, patients with blood groups A, B, and AB can be transplanted with ABO-compatible grafts from donors with a different blood group [7]. As this option does not exist for patients with blood group O, a potential inequality in access to liver transplantation exists. The fact that patients with blood group O experience longer waiting times to transplantation and that a lower fraction of these patients is transplanted has been demonstrated in the pre-MELD era [8,9]. However, in the MELD era, the effect of recipient blood group status on waiting time and waiting list mortality has not yet been assessed.

The aim of this study was to investigate whether in the MELD era, a potential disparity exists in waiting time and waiting list mortality, for liver transplant candidates from different blood groups.

Methods

All patients having spent any time on the waiting list for liver transplantation in the Netherlands between 15 December 2006 and 31 December 2012 were included in this study. The start of the study period marked the introduction of the MELD allocation system in the Eurotransplant (ET) region. Patients were followed until 31 December 2013 to ensure that all patients had at least a potential of one-year actual follow-up.

Allocation was performed by Eurotransplant, according to the Eurotransplant Liver Allocation System (ELAS) algorithms [7].

Study variables collected were patients' gender, age at listing, year of listing, diagnosis, number of previous transplantations, donor and recipient blood group status, urgency status for transplantation, and MELD score both at listing and at removal from the waiting list. MELD score was defined as lab-MELD points, including potential standard exceptions (SE) and nonstandard exceptions (NSE) points.

Waiting time for removal was defined as the time between the date of listing and the date of removal from the waiting list, either after transplantation or after another event. These other events were categorized as death on the waiting list, development of contra-indications, improvement of liver disease, or listing in a foreign center.

The death rate on the waiting list was calculated for each calendar year, in concordance with UNOS definitions, by dividing the number of patients who died in a given year by the sum of the (partial) years that all patients spent waiting during the study period in that particular calendar year [10]. The death rate on the waiting list was expressed as deaths per 100 patient-years at risk. Patients who had to be removed from the waiting list due to contra-indications were followed until death in order to assess the postdelisting survival for this patient group. To calculate the expanded death rate per 100 patient-years at risk, the same computation was performed as for the death per 100 patient-years on the waiting list, but this time, patients who had to be removed from the waiting list due to contra-indications were grouped among the patients who died on the waiting list, as the intention to transplant these patients is not achieved and their outcome is ultimately unfavorable.

Transplantations were defined as ABO-identical if the recipient and the donor had the same ABO blood group type and as ABO-compatible in the case that either a blood group O graft was transplanted in a patient with a different blood group or a group A or B graft was transplanted in a patient with blood group AB. All other transplantations were defined as ABO-incompatible. Patients were classified as high urgency listings in case they were listed as high urgency at the moment of transplantation. Pediatric patients were defined as patients listed below the age of 18 years. Indications for transplantation were classified as alcohol, viral (mainly hepatitis B or C), biliary (mainly primary biliary cirrhosis, primary sclerosing cholangitis, or biliary atresia), or other.

Study variables were compared between patients according to their blood group status, and statistical differences were assessed using Pearson's chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables.

Separate cumulative incidence curves were constructed for the outcome death on the waiting list and for the outcome transplantation. The four potential outcomes of a patient listed for transplantation (transplantation, death on the waiting list, withdrawal from the list, alive still on the waiting list) form competing risks. This makes survival analysis using Kaplan–Meier estimates unreliable [11]. For analysis of these competing risks, we used the proportional hazards model for cause-specific hazard functions. These functions describe the rate of each outcome (a "cause") given that the individual is still on waiting list. Because of the small number of patients removed from the waiting list due to improvement of disease or listing in a foreign center ($n = 7$; 1.4%), we have treated these patients as censored (i.e., still on waiting list) at the time of the withdrawal. In the multivariable analysis, the outcome of patients who were removed from the waiting list due to contra-indications was considered as death on the

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waiting list. Effects of study variables on the outcomes "death" and "transplantation" were explored by fitting proportional hazard regression models. Age and MELD score were treated as continuous variables; the entry year was dichotomized as prior to 2010 or later. Because of retransplantations, patients could enter the waiting list several times. To take these entries into account as a separate category would require a much larger study. As we are interested in waiting times, we have chosen to treat reentries as separate patients. We used likelihood ratio tests (performed at 5% significance level) to select variables for a best fitting regression model. Computations were carried out using library mstate of statistical package R [12,13]. P-values less than 0.05 were considered statistically significant.

Results

Waiting list dynamics

The study group consisted of a total of 460 patients who spent time on the waiting list for liver transplantation during the study period. These patients entered the list 517 times: 412 patients were listed once, 41 patients were listed twice, six patients were listed three times, and one patient was listed five times. Of the 517 list entries, 416 (80%) concerned the first transplantation; 82, 15, 3, and 1 concerned the second to the fifth transplantation, respectively.

Dynamics of the waiting list are shown in detail in Fig. 1.

Of the patients removed from the waiting list, 375 (72.5%) were transplanted, 46 (8.9%) died on the waiting list, 15 (2.9%) developed contra-indications for transplantation, 5 (1.0%) showed improvement of their disease, and 2 (0.4%) were listed for transplantation in a foreign center.

Demographics

Of all patients included in the study, 277 (53.6%) had blood group O, 177 (34.2%) had blood group A, 52 (10.0%) had blood group B, and 11 (2.1%) had blood group AB. Patient gender, age at listing, high urgency

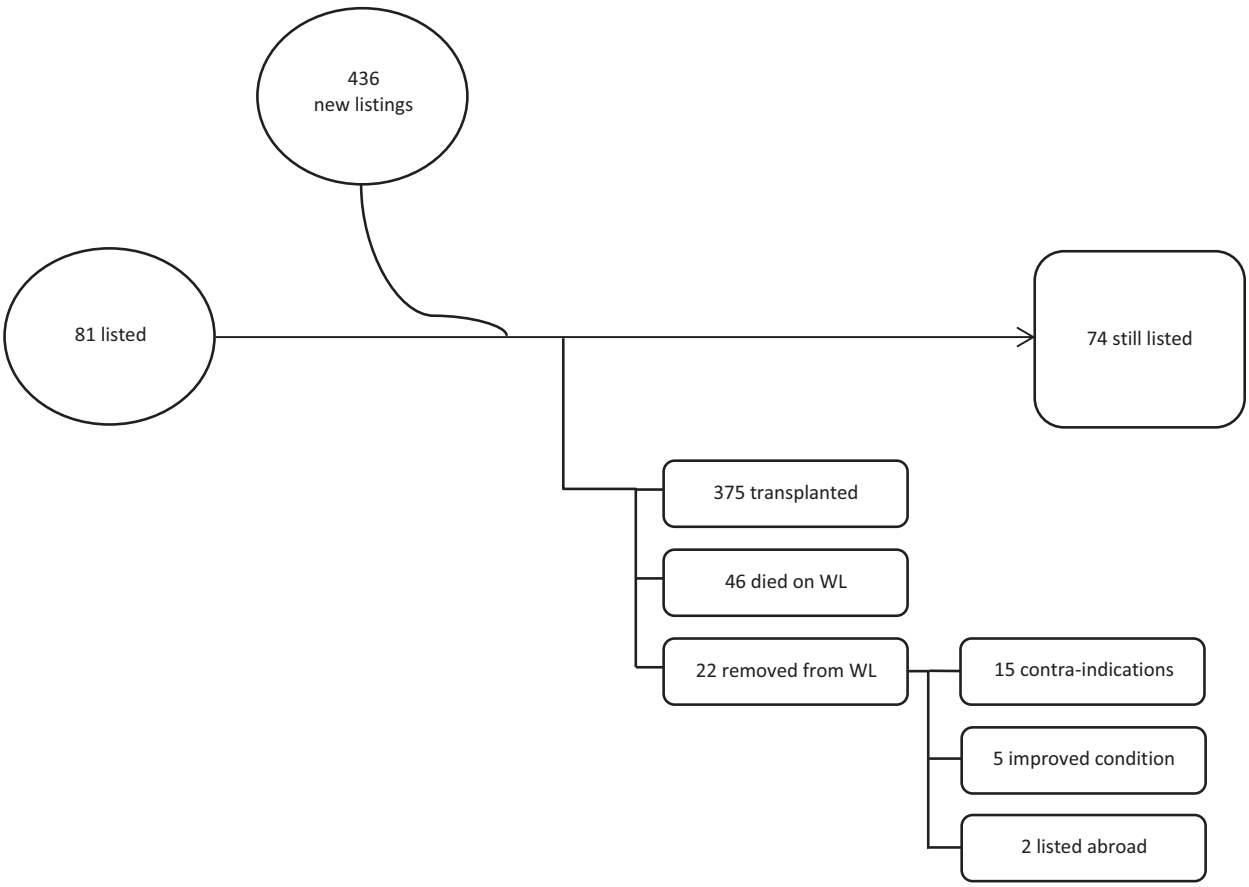

Figure 1 Waiting list dynamics.

Table 1. Demography.

	ABO blood group				
	O *n = 277*	A *n = 177*	B *n = 52*	AB *n = 11*	*P*-value
Male gender	162 (58.7%)	108 (61.0%)	32 (61.5%)	6 (54.5%)	0.921
High urgency status	48 (17.3%)	25 (14.1%)	11 (21.2%)	2 (18.1%)	0.621
Pediatric patients	80 (28.9%)	44 (24.9%)	19 (36.5%)	2 (18.2%)	0.337
Age of adult patients (yrs, mean ± SD)	48.1 ± 13.8	50.2 ± 13.2	47.0 ± 14.7	52.8 ± 11.2	0.361
Etiology					
Alcohol	25 (9.0%)	17 (9.6%)	5 (10%)	2 (18%)	0.621
Cholestatic	103 (37.2%)	48 (27.1%)	17 (33%)	3 (27%)	
Viral	23 (8.3%)	17 (9.6%)	5 (10%)	0 (0%)	
Other	126 (45.5%)	95 (53.4%)	25 (48%)	6 (55%)	
Median MELD listing	16	17	20.5	20	0.130

status at transplantation, disease etiology, and MELD score at listing showed no significant differences between patients with different blood groups (Table 1).

Of the 517 patients listed for transplantation, 86 were removed while under HU listing. For this subgroup, SE.NSE criteria obviously did not increase their urgency. Of the remaining 431 patients not listed under HU priority, 349 patients (81.0%) were listed purely on lab-MELD and 82 patients (19.0%) were listed with SE/NSE points.

Of the 375 transplantations, 352 (93.9%) were ABO-identical, 23 (6.1%) were ABO-compatible, and none were ABO-incompatible. ABO-compatible transplantations were performed in 9 of 75 high urgency transplantations (12.0%) versus in 14 of 300 (4.7%) regular urgency transplantations ($P = 0.036$). ABO-compatible transplantations were not performed in blood group O patients, versus in 7 of 132 (5.3%) blood group A patients, in 13 of 35 (37.1%) blood group B patients, and in 3 of 7 (42.9%) blood group AB patients ($P < 0.001$).

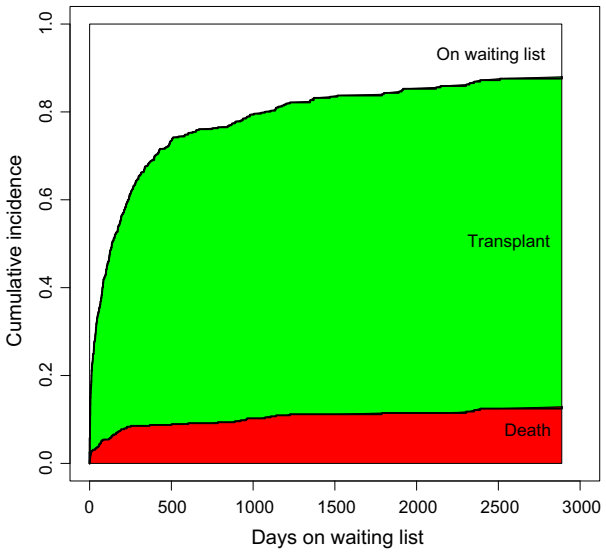

Figure 2 Cumulative incidence curves of death and transplantation from the moment of listing.

Univariate analysis

Figure 2 shows cumulative incidence curves of death and transplantation (Tx). The distance between two curves represents the probability of transplantation. After 5 years, the cumulative incidence of death was 11.2% (SE 1.4%), the cumulative incidence of transplantation was 72.5% (SE 2.0%), and 16.3% (SE 1.7%) was still on the waiting list.

A total of 46 patients died on the waiting list. The mean death rate per 100 patient-years was 10.4, with a large yearly variation, from as low as 5.0 in 2008 to as high as 14.0 in 2010. The mean expanded death rate per 100 patient-years at risk, including patients who had to be removed from the waiting list because of contra-indications, was 14.2. Table 2 shows these data according to patient blood group status. Because of the competing risks, significance testing of death rate on the waiting list and of being transplanted was only carried out in the multivariable analysis.

Median time to removal from the waiting list was 136 days. Half of the ultimate cumulative transplantation incidence (75.1%) was reached after 97 days; half of the end point cumulative death incidence (12.9%) was reached after 100 days. Median MELD scores at listing and delisting differed between the three outcome

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Table 2. Outcome parameters.

	ABO blood group					
	O *n = 277*	A *n = 177*	B *n = 52*	AB *n = 11*	All	*P*-value
Death rate per 1000 patient-years	7.2	11.8	24.6	21.8	10.4	
Expanded death rate per 1000 patient-years	10.2	17.9	28.2	21.8	14.2	
Median waiting time to transplantation (days)	106	58	117	73	85	0.331
Median waiting time to removal (days)	179	91	187	73	136	0.122
Median lab-MELD delisting	20	20	20	20	20	0.635
Median MELD delisting	25	22	25	20	24	0.260
Median change in MELD during listing	+3	0	+2	0	+2	0.004

groups ($P < 0.001$). They were lowest in the "on list" group. Overall and within the three outcome groups, MELD scores at listing did not significantly differ between the four blood groups. MELD scores at delisting did not significantly differ in the on list and in the death groups. In the transplantation group, the differences were significant ($P = 0.032$), the medians being 26, 23, 30, and 16 in groups O, A, B, and AB, respectively. The change in MELD between listing and delisting was also significantly different in the transplantation group only ($P = 0.01$). Within this group, the blood group O patients experienced most clinical deterioration during waiting time, as expressed by a median rise in MELD points of 5, compared to a rise of 2 points for blood group A, 2 points for blood group B, and 0 for blood group AB.

Of the 15 patients removed due to contra-indications, 4 patients were lost to follow-up, 1 patient was alive with a poor prognosis at the end of the study, and the remaining 10 patients died within a median of 82 days after removal from the waiting list.

Multivariable analysis

The results of the multivariable analysis are shown in Tables 3 4. Table 3 presents the results of the best fitting model which includes only significant variables. This model does not include patient blood group. Expanding the model of Table 3 by including patient blood group did not significantly improve the model fit ($P = 0.33$, likelihood ratio test). Table 4 shows the results of the expanded model. While the death risk of patient blood groups A, B, and AB was higher than that of group O, the differences are not significant, note the wide confidence intervals.

Of all study variables, only age, MELD score, and urgency status were significantly related to death on

Table 3. Results of regression analysis—best fitting model.

	HR	95%-CI	*P*-value
Outcome: death			
Age (years)			
<18	0.88	0.83–0.94	<0.001
>=18	1.07	1.04–1.10	<0.001
MELD	1.14	1.09–1.18	<0.001
HU	3.62	1.49–8.77	0.004
Outcome: transplantation			
Age (years)	1016	1.01–1.02	<0.001
MELD	1.10	1.08–1.12	<0.001
HU	6.46	4.69–8.90	<0.001
Entry after 2009	1.36	1.10–1.69	0.005

Table 4. Results of regression analysis—expanded model.

	HR	95%-CI	*P*-value
Outcome: death			
Age (years)			
<18	0.89	0.83–0.95	<0.001
>=18	1.07	1.04–1.10	<0.001
MELD	1.13	1.09–1.18	<0.001
HU	3.54	1.47–8.57	0.005
Blood group			
A:O	1.38	0.77–2.47	0.272
B:O	1.48	0.68–3.24	0.322
AB:O	1.68	0.49–5.76	0.412
Outcome: transplantation			
Age (years)	1.07	1.04–1.09	<0.001
MELD	1.10	1.08–1.12	<0.001
HU	6.78	4.90–9.37	<0.001
Entry after 2009	1.36	1.10–1.69	0.005
Blood group			
A:O	1.13	0.90–1.41	0.282
B:O	0.75	0.52–1.08	0.116
AB:O	0.95	0.45–2.04	0.900

the waiting list. For patients aged below 18 years, the risk of death on the waiting list decreased with age. For patients aged 18 years or more, the risk of death on the waiting list increased with age. The hazard ratio for 1-year increase in age for patients aged 18 years or older is 1.07, which corresponded to 1.95 for an age increase of 10 years. High urgency status and higher MELD score increased the risk of death on the waiting list.

Table 3 shows the results of the multivariable analysis for the outcome transplantation. Higher age, higher MELD score, higher urgency status, and a more recent listing all significantly impacted the "hazard" of being transplanted. The hazard ratio (HR) of age increase of 1 year was 1.016, which corresponded to 1.17 for an age increase of 10 years.

Discussion

Analyzing the outcome of patients listed for liver transplantation poses many of challenges. The variety of potential outcomes for these patients renders the usual methods for survival analysis severely biased. The simplest analysis of dividing the number of surviving patients by the total number of patients studied is obviously not relevant as it omits the time patients are exposed to the risk of being listed for liver transplantation. Particularly in survival analysis, patients are by definition exposed for various periods of time, either because patients die or because they are censored because of different lengths of follow-up within the cohort.

Usually, to account for this problem in survival analysis, the Kaplan–Meier method is used. This method accounts for the problems induced by censored patients, by creating an estimated survival figure.

However, Kaplan–Meier survival analysis in medical research should only be used in the case of no more than two potential outcomes, usually survival or death. In the case of patients listed for transplantation, patients face four potential outcomes: transplantation, death on the waiting list, withdrawal while alive, or survival while still on the waiting list. A competing risks analysis appropriately addresses the involved methodological challenges [14,15].

In our competing risks analysis, we decided to treat a removal from the waiting list due to contra-indications as death on the waiting list. The numbers were too small to include removal due to contra-indications in the multivariable analysis as a separate outcome. As prospects of this group of patients appeared to be negative—the median survival after removal due to contra-indications was only 82 days—we considered this a reasonable choice.

This study shows that patients with blood group O show significantly more clinical deterioration during waiting time for transplantation. However, this deterioration did not translate into a significant impact on risk of dying on the waiting list nor on the risk of being transplanted. Significant risk factors for waiting list mortality were age, MELD score, and urgency status. The relation between age and death on the waiting list showed an interesting direction, as for pediatric patients age was inversely related to death on the waiting list, while for adult patients, age was directly related to death on the waiting list.

As death on the waiting list and transplantation forms the two largest outcome groups for patients listed for liver transplantation, it is unsurprising that the same variables that show up in the multivariable analysis for waiting list mortality also showed up in the multivariable analysis for transplantation. Interestingly, the multivariable analysis shown in Table 3 also showed that patients listed for liver transplantation in recent years had a bigger chance of being transplanted compared to patients listed earlier in the study period. This may be explained by the donor liver grafts added to the donor pool with the introduction of living donor liver transplantation during the study period. The study group contained 3 patients transplanted with living donor liver grafts before 2010 compared to 15 patients transplanted with living donor liver grafts in 2010 or later.

Regarding blood group status, this study did not demonstrate a difference in outcome for patients listed for liver transplantation. This finding is in contrast to studies that were carried out prior to the introduction of the MELD allocation system [8,9]. Blood group O patients still suffer the disadvantage that they in case of emergency need for transplantation cannot be transplanted with ABO-compatible grafts from donors with other blood groups. The MELD allocation system offers the advantage that in case of clinical deterioration, patients with blood group O that suffer from progressive liver failure get priority over patients with the same blood group that have more stable disease. While results of this study provide some support for this theoretical benefit in clinical practice, one should keep in mind that the absence of statistical significance does not prove the absence of differences and that estimates of the relation between blood group status and outcome of patients listed for liver transplantation depend on donor availability.

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In conclusion, this study suggests that in the MELD era, ABO blood group status is no longer independently related to the outcome of patients listed for liver transplantation. Factors associated with death on the waiting list within the framework of this study were urgency status, MELD score, and age.

Author contributions

Alexander J.C. IJtsma: Participated in research design, writing of the paper, the performance of the research, data analysis. Christian S. Van der Hilst: Participated in research design, the performance of the research. Danielle M. Nijkamp: Participated in data analysis. Jan T. Bottema: Participated in data analysis. Vaclav Fidler: Participated in research design, writing of the paper, the performance of the research, data analysis. Robert J. Porte: Participated in research design. Maarten J.H. Slooff: Participated in research design, Participated in writing of the paper, Participated in the performance of the research.

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Conflicts of interest

The authors declare no conflict of interest.

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