Predicting outcome after liver transplantation

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PART I

Waitlist mortality and outcome after liver transplantation

Chapter 2

A decade of MELD-based liver allocation in Eurotransplant and its effect on liver transplant waitlist outcomes

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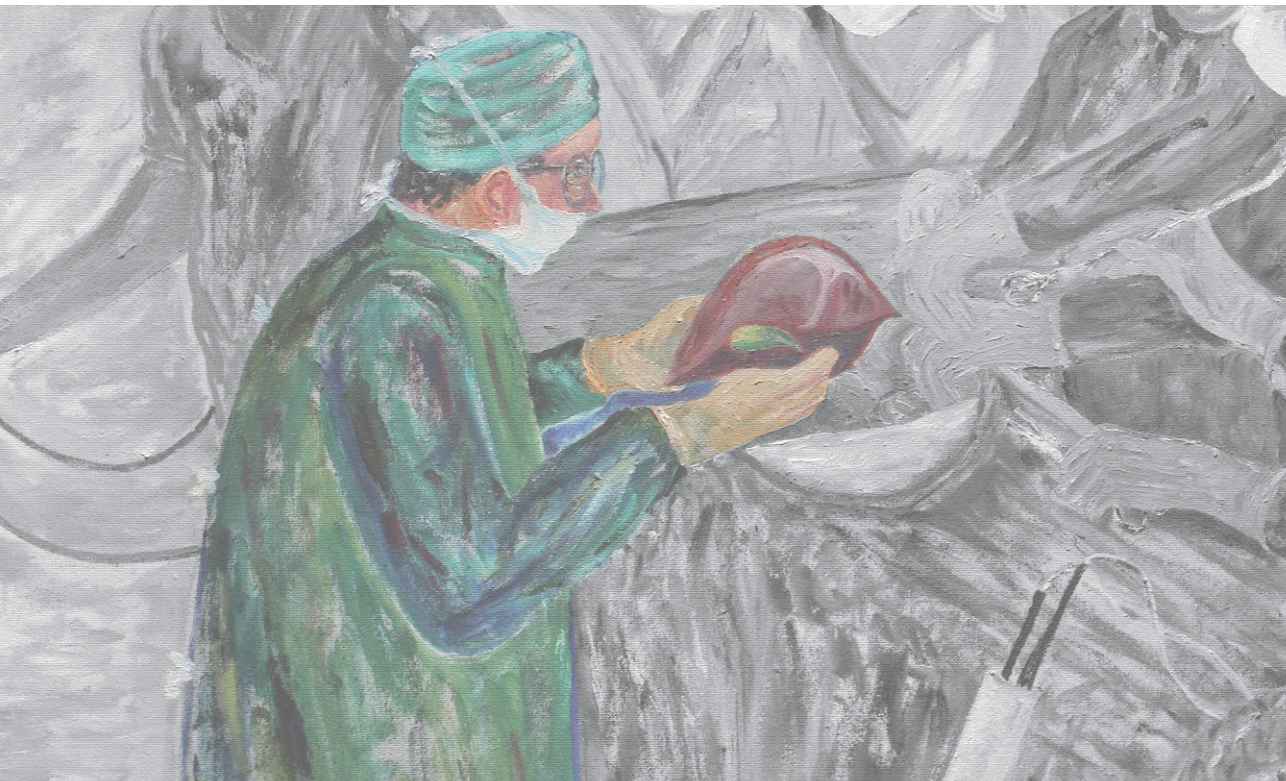


ABSTRACT

Introduction

In 2006 the model for end-stage liver disease (MELD) was implemented for liver allocation in three Eurotransplant member-states (Belgium, Germany and the Netherlands). In the past decade, no study has investigated the effect of this major allocation change on waitlist outcome in Eurotransplant.

Methods

For this purpose, a retrospective database analysis was performed, including every adult (≥18 years) patient registration on the liver waitlist from 1.1.2005 until 31.12.2015. Waitlist-outcome (death on the waitlist, transplantation, removal or staying on the waitlist within one year post-registration) was analyzed for the pre-MELD era and MELD-era with the use of competing risk analyses. Post-transplantation outcome was death-uncensored graft survival, analyzed with Kaplan-Meier survival curves.

Results

In total 26,234 patients were registered in the study period. The cumulative incidences (CI) of death (waitlist mortality) for the pre-MELD vs. MELD-era was 17% vs. 18% (p=0.29) in the whole of Eurotransplant, 17% vs. 18% (p=0.23) in the MELD countries and 15% vs. 16% (p=0.70) in non-MELD countries. The transplantation CIs were 43% vs. 50% (p<0.001), 42% vs. 49% (p<0.001) and 61% vs. 58% (p=0.93), respectively. There was a decrease in waitlist mortality in the first MELD-year from 17% to 15% (p<0.012), but this effect leveled out afterwards. Long-term graft survival was slightly decreased for patients transplanted in the MELD-era (p=0.035).

Conclusion

The implementation of MELD initially led to a (small) decrease in waitlist mortality in the MELD-countries, but this effect disappeared after a few years. The transplantation CI increased in the MELD-era, accompanied by a small decrease in long-term graft survival. This slightly poorer outcome may be explained by higher transplantation numbers due to a more liberal donor and recipient acceptance policy.

INTRODUCTION

The model for end-stage liver disease (MELD) was originally developed to predict survival in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) (1). In February 2002 it was introduced in the USA for ranking patients on the liver transplant waitlist after Kamath demonstrated a significant relation with the 3-months waitlist mortality in patients with end-stage liver disease. (2) A prospective study by Wiesner et al. showed the superiority of the MELD score over the Child-Turcotte-Pugh (CTP) score with regard to the ability of ranking patients with chronic liver disease on the Organ Procurement and Transplantation Network (OPTN) waitlist over a 3-month waiting period. (3) In 2006, on December 16th, a MELD-based liver allocation was also introduced in three Eurotransplant countries: Belgium, Germany and the Netherlands. The other Eurotransplant countries, Austria, Croatia, Hungary (which joined Eurotransplant in 2013) and Slovenia, continued to use a center-based allocation system. (4)

Several studies investigating the effect of MELD have been published, looking at its prediction of survival of patients on the liver transplant waitlist. (5) Some studies suggested a modification of the current model, either by altering the weight of existing factors (6,7) or by adding other pre-transplant values like serum sodium (8,9), serum cholinesterase (10) or serum ferritin (11). Although the MELD score was evaluated for the German situation (12,13), this was never done for the whole Eurotransplant region with regard to waitlist mortality.

Objective of this study is to evaluate the effect of the implementation of the model for end-stage liver disease as a way to prioritize patients on the liver transplant waitlist and its effect on waitlist mortality and liver transplantation in the Eurotransplant region over the past decade.

PATIENTS AND METHODS

Data selection

All adult patients (≥18 years) registered on the Eurotransplant liver transplant waitlist from January 1, 2005 until December 31, 2015 were included with exception of patients registered or transplanted in one particular German transplant center, due to validity of the data (14,15). Patients transplanted with a living or domino allograft (n = 494) were excluded. Recipient, donor, transplant factors and follow-up data were obtained from the Eurotransplant Network Information System and the Eurotransplant Liver Follow-Up Registry. The study was approved by the Eurotransplant Liver Intestine Advisory Committee with representatives from all liver transplanting Eurotransplant member states. All data were anonymized, for transplant center as well as for the single patient.

Statistical analysis

Patients were followed one year from date of listing on the liver transplant waitlist until occurrence of death, transplantation or removal from the waitlist (days from registration till previously named event). If none of the previous named events occurred within 365 days, the patient was regarded still being on the waitlist. The analyses were censored for patients registered in the pre-MELD era with an event in the MELD era (n=442). These patients did not have an event before December 16th, 2006 and were therefore still on the waitlist and subsequently censored at that date. Post-transplantation outcome was defined as time from date of transplantation till date of recipient death or retransplantation, whichever occurred first (death-uncensored graft survival). All recipients removed due to clinical deterioration ('too ill for transplantation') were regarded as 'death on the waitlist' and only patients that were removed because of clinical improvement, were regarded as 'removal from the waitlist'. Data were received in January 2017, when all included patients had at least one year follow-up.

To analyze the effect of implementation of the MELD-based liver allocation, the registrations in the pre-MELD era (from January 1st, 2005 till December 16th, 2006) were compared with the MELD era (December 16th, 2006 till December 31st, 2015), separately for countries that implemented the MELD score for liver allocation (Belgium, Germany and the Netherlands) and countries that did not (Austria, Croatia, Hungary and Slovenia). In order to calculate the Eurotransplant donor risk index (ET-DRI) (16) for all donors, the mean cold ischemia time (CIT) and gamma glutamyltransferase (GGT) were imputed in case of missing data (CIT 4,650 missing values, 36%, mean 8.73 hours and GGT 244 missing values, 1.9%, mean 79.2 U/L).

Clinical characteristics were summarized by mean and standard deviation (SD) for continuous variables or number and percentage for categorical factors. Comparison between groups was done by using Chi-square (categorical factors) or the students T- (continuous factors) tests. Cumulative incidences (CI) of death on the waitlist (waitlist mortality from here on), removal from waitlist and transplantation were calculating using competing risks methods (17), and Gray's test was used to test for differences in cumulative incidences between the different periods. Multivariate analysis was done with Cox-regression analysis. A p-value <0.05 was considered significant. Analyses were performed with SPSS version 23.0 and R version 3.2.2, with R package mstate version 0.2.8. (18)

Definitions

'MELD countries': Eurotransplant member states that incorporated on December 16th, 2006 the model for end-stage liver disease score for liver allocation purposes and for whom Eurotransplant performs patient specific liver allocation (Belgium, Germany, the Netherlands).
'non-MELD countries': Eurotransplant member states that use a center-oriented allocation.
'pre-MELD era': January 1st 2006 – December 16th 2006.

'MELD era': December 17th 2006 – December 31st 2015.
'Exceptional MELD' (excMELD): standard exception (SE) or non-standard exception (NSE).
'Laboratory MELD' (labMELD): calculated laboratory MELD score (3), minimum of 6 and capped at 40 points, with a lower limit of 1 for all variables and with creatinine capped at 4 mg/dl. If patients received renal replacement therapy, the creatinine value was set at 4 mg/dl.
'Match-MELD': highest MELD value at time of allocation, this can either be the labMELD (international allocation) or an excMELD score (standard exception or non-standard exception in national allocation).

Specific explanations on the current liver allocation rules and definitions in the Eurotransplant region are described in the recent publication by Jochmans et al. (19)

RESULTS

The total number of included patients, registered on the Eurotransplant liver transplant waitlist in the study period, was 26,234 of which 4,132 (16%) were registered in the pre-MELD era and 22,102 (84%) in the MELD era (Figure 1). The percentage of patients registered in the MELD countries vs. non-MELD countries was 91% vs. 9% (pre-MELD era) and 84% vs. 16% (MELD era), respectively (Figure 1). Overall, there was a slight increase in age at listing and age at delisting. LabMELD and match-MELD at listing and delisting tended to increase in the MELD era, but slowly decreased again as of 2013 (Table 1). Donor quality decreased over that same period, as reflected in an increase in mean ET-DRI.

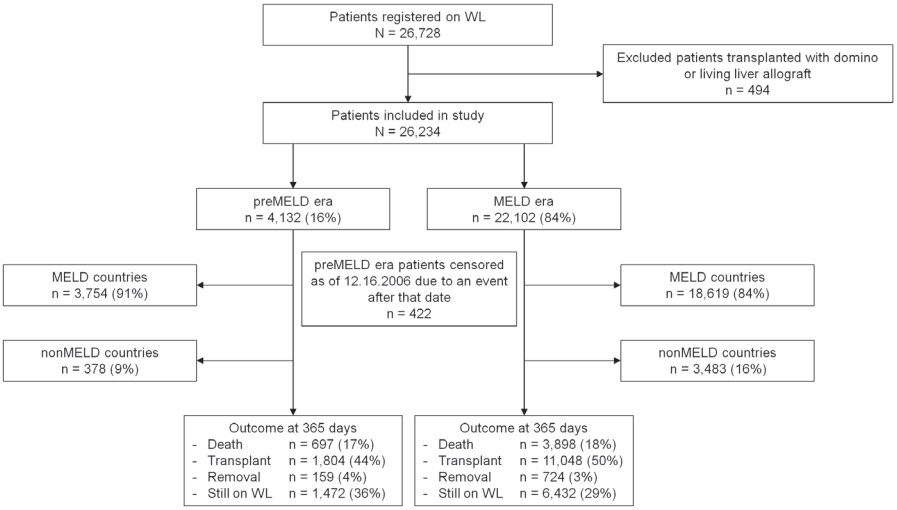


Figure 1. flowchart of all patients registered on the Eurotransplant liver transplant waitlist from 1.1.2005 – 31.12.2015

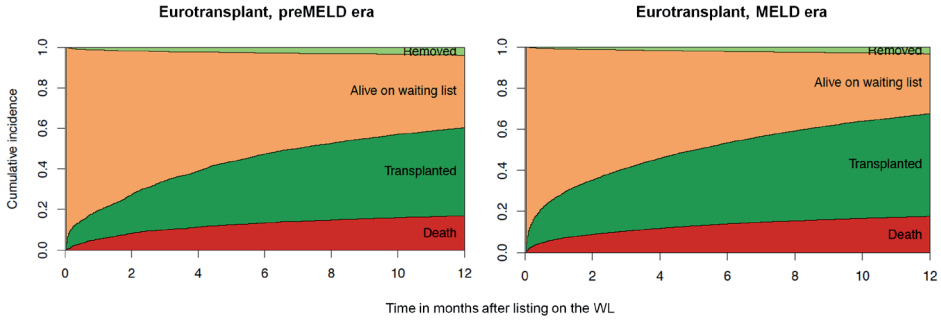
Table 1. Development of recipient age, MELD score and ET-DRI over the years for patients listed on the Eurotransplant waiting list from 1.1.2005 – 31.12-2015 (N = 26,234)

Patient factor, mean (SD)	**pre-MELD era**		**MELD era**								
Year	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Number of registrations	1,994	2,227	2,339	2,417	2,584	2,633	2,579	2,574	2,286	2,283	2,318
Age at listing (years)	50.9 (11)	51.2 (11)	51.6 (11)	52.3 (11)	52.9 (11)	52.7 (11)	53.1 (11)	53.3 (11)	53.0 (11)	53.1 (11)	53.4 (11)
Age at delisting (years)	52.4 (11)	52.7 (11)	53.0 (11)	54 (11)	54.1 (11)	53.9 (11)	54.2 (11)	54.3 (11)	53.8 (11)	54.2 (11)	54.4 (11)
LabMELD at listing	17.1 (7.7)	17.4 (8.8)	17.5 (8.9)	17.9 (8.9)	17.9 (9.4)	17.8 (9.3)	17.7 (9.5)	17.5 (9.3)	15.2 (7.0)	14.2 (6.2)	14.4 (6.4)
LabMELD at delisting	19.5 (8.9)	20.5 (9.4)	22.4 (11)	22.5 (11)	23.4 (11)	23.3 (11)	22.9 (11)	22.8 (11)	22.3 (11)	21.9 (11)	22.6 (11)
*MatchMELD at delisting	18.9 (8.8)	21.0 (9.1)	24.3 (9.3)	24.5 (9.2)	25.3 (9.9)	24.6 (10)	25.0 (9.8)	24.1 (9.6)	23.4 (9.5)	23.8 (9.4)	23.8 (9.4)
*ET-DRI	1.81 (0.4)	1.86 (0.4)	1.83 (0.5)	1.86 (0.5)	1.92 (0.5)	1.89 (0.5)	1.91 (0.5)	1.88 (0.4)	1.85 (0.4)	1.89 (0.5)	1.90 (0.4)

*Only applies to transplanted patients. Total missing values for labMELD at listing 28%, labMELD at delisting 5% and matchMELD at delisting 5%.

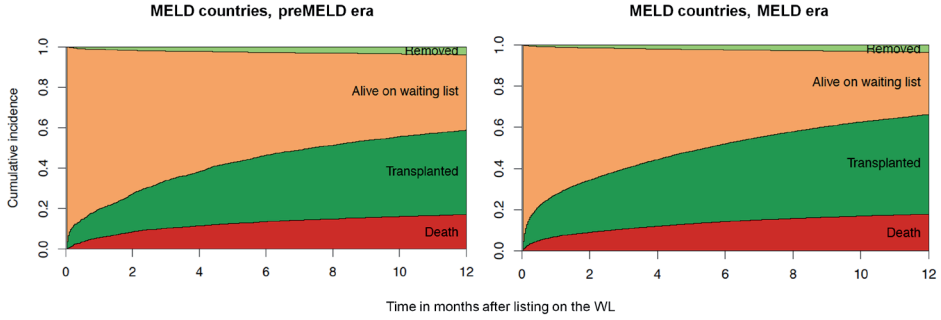
Waitlist outcome: overall

Waitlist outcome was analyzed by competing risk analyses, shown in Figures 2a (patients registered in the whole of Eurotransplant), 2b (patients registered in the MELD countries) and 2c (patients registered in the non-MELD countries), comparing the pre-MELD era with the MELD era. The figures show stacked CI-plots, where the differences between two adjacent curves (the filled areas) represent the probabilities of (from bottom to top) death on the waitlist, transplantation, still being on the waitlist within the first year and patients removed from the waitlist. The overall waitlist mortality at one year after registration was not significantly different between the pre-MELD era and the overall MELD era, respectively 17% vs. 18% (p=0.29); in the MELD countries 17% vs. 18% (p=0.23) and in the non-MELD countries 15% vs. 16% (p=0.70). The overall transplantation CI at one year significantly increased from 43% to 50% (p<0.001). This was accompanied by a significant increase in the MELD countries from 42% to 49% (p<0.001), while in the non-MELD countries the transplantation CI remained comparable (from 61% to 58%; p=0.93).



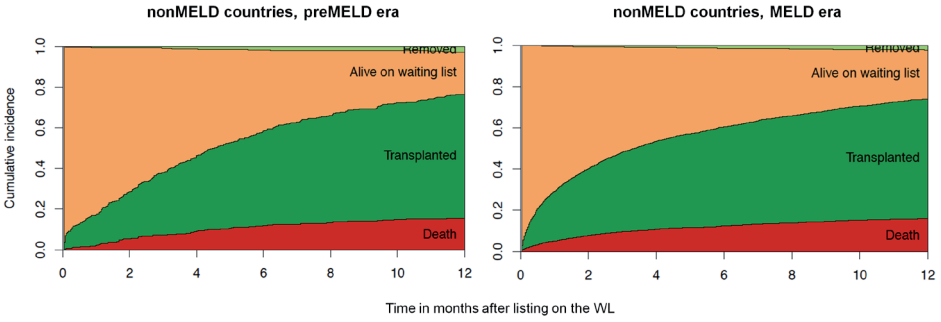
Event at 1-year	CI preMELD era	CI MELD era	p
Death	17%	18%	0.29
Transplanted	43%	50%	<0.001
Removed	3.9%	3.3%	0.051
Alive on waiting list	36%	29%	

Figure 2a. overall cumulative incidence of death, transplantation, removal or alive on waitlist for the whole Eurotransplant region, pre-MELD era (n = 4,132) vs. MELD era (n = 22,102)



Event at 1-year	CI preMELD era	CI MELD era	p
Death	17%	18%	0.23
Transplanted	42%	49%	<0.001
Removed	4.0%	3.5%	0.13
Alive on waiting list	37%	30%	

Figure 2b. overall cumulative incidence of death, transplantation, removal or alive on waitlist for the MELD countries, pre-MELD era (n = 3,754) vs. MELD era (n = 18,619)

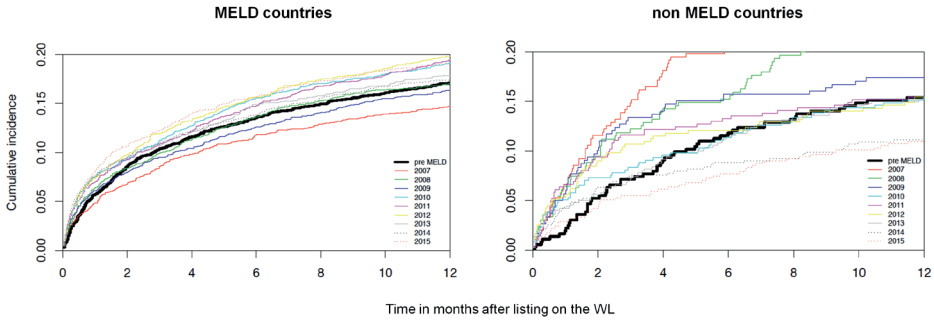


Event at 1-year	CI preMELD era	CI MELD era	p
Death	15%	16%	0.70
Transplanted	61%	58%	0.93
Removed	2.8%	2.2%	0.48
Alive on waiting list	21%	24%	

Figure 2c. overall cumulative incidence of death, transplantation, removal or alive on waitlist for the non-MELD countries, pre-MELD era (n = 378) vs. MELD era (n = 3,483)

Waitlist outcome: death

Analysis of death on the waitlist in the MELD countries per separate year shows a slight decrease in the first year after implementation of MELD, from 17% to 15% (p=0.012), but the years thereafter the effect disappeared again (Figure 3a). In the non-MELD countries there is a steep increase in the waitlist mortality in the first year of the MELD era, from 15% to 26% (p<0.001), which decreased in the following years and reached the same level in 2010 (Figure 3a). The characteristics of patients that died on the waitlist (n = 4,595) in the pre-MELD (n=697) and MELD era (n=3,898) are shown and compared in Table 2. Compared to the pre-MELD era, there is a significantly higher mean age at listing (55 vs. 53 years, p<0.001) and delisting (55 vs. 53 years, p<0.001), a higher labMELD at delisting (26 vs. 22, p<0.001) and a significant difference in etiology of liver disease (p<0.001).



Death at 1-year	pre-MELD	2007	2008	2009	2010	2011	2012	2013	2014	2015
MELD countries	17%	15%	17%	16%	19%	20%	20%	18%	17%	19%
Non MELD countries	15%	26%	22%	17%	15%	15%	15%	15%	11%	11%

Figure 3a. cumulative incidence of death on the waitlist for the MELD countries vs. non-MELD countries, per year (pre-MELD vs. 2007 - 2015)

Table 2. baseline demographics for patients that died within 1 year after listing on the transplant WL, in all Eurotransplant countries from 1.1.2005 – 31.12.2015 (n = 4,595)

	Period		p*
	pre-MELD n = 697	MELD n = 3,898	
Recipient factor, mean (SD) or n (%)			
Age (years) at listing	53.1 (9.5)	54.6 (10)	<0.001
Age category			<0.001
<40	58 (8.3)	316 (8.1)	
40-49	164 (24)	646 (17)	
50-59	288 (41)	1,582 (41)	
60-69	175 (25)	1,260 (32)	
≥70	12 (1.7)	94 (2.4)	
Sex			0.051
Male	480 (69)	2,536 (65)	
Female	217 (31)	1,362 (35)	
Blood group			0.22
ABO-O	300 (43)	1,611 (41)	
ABO-A	293 (42)	1,659 (43)	
ABO-B	87 (13)	471 (12)	
ABO-AB	17 (2.5)	157 (4.0)	
LabMELD at listing	21.0 (8.8)	20.6 (9.3)	0.64
LabMELD category at listing			<0.001
6-14	30 (4.3)	885 (23)	
15-24	64 (9.2)	1,369 (35)	

Table 2. baseline demographics for patients that died within 1 year after listing on the transplant WL, in all Eurotransplant countries from 1.1.2005 – 31.12.2015 (n = 4,595) (continued)

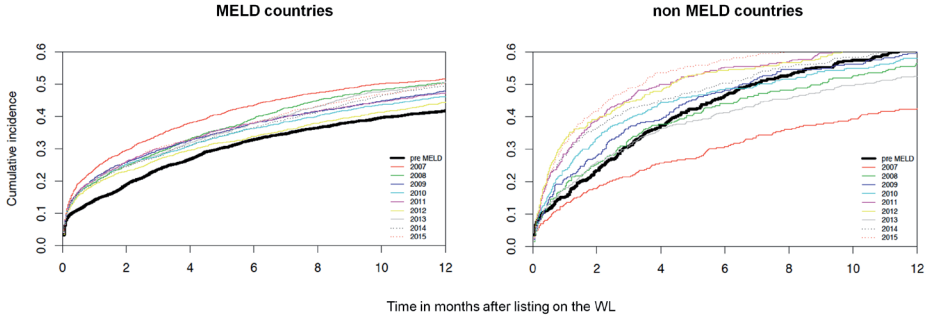
	Period		
	pre-MELD n = 697	MELD n = 3,898	p*
25-34	25 (3.6)	434 (11)	
≥35	13 (1.9)	372 (9.5)	
missing values	565 (81)	838 (22)	
Etiology			<0.001
Metabolic	27 (3.9)	162 (4.2)	
Acute	45 (6.5)	360 (9.2)	
Cholestatic	49 (7.0)	370 (9.5)	
Alcoholic	161 (23)	1,128 (29)	
Malignant	71 (10)	626 (16)	
Hepatitis B	31 (4.4)	132 (3.4)	
Hepatitis C	64 (9.2)	500 (13)	
Other cirrhosis	210 (30)	506 (13)	
Other/unknown	39 (5.6)	114 (2.9)	
Repeated transplant	98 (14)	598 (15)	0.39
Age (years) at delisting	53.3 (9.5)	54.9 (10)	<0.001
LabMELD at delist	22.4 (9.4)	26.1 (11)	<0.001
LabMELD category at delist			<0.001
6-14	107 (15)	638 (16)	
15-24	199 (29)	1,304 (34)	
25-34	94 (14)	748 (19)	
≥35	70 (10)	1,203 (31)	
missing values	227 (33)	5 (0.1)	

*T-test or chi-square test for differences between pre-MELD and MELD. **

Waitlist outcome: transplantation

Results of the competing risk analysis for transplantation per year, for MELD and non-MELD countries, are shown in Figure 3b. In the MELD countries, the transplantation CI increased after the implementation of MELD-based liver allocation, from 42% to 52% (p<0.001). In the non-MELD countries, there was a decrease in the first year of the MELD era, from 61% to 43%, (p<0.001), that increased again in the following years. Analysis of recipient, donor and transplant factors, comparing the pre-MELD with the MELD period (Table 3), demonstrated a significantly higher recipient age at listing (51 vs. 53 years, p<0.001) and delisting (51 vs. 54 years, p<0.001), significant difference in etiology of liver disease (p<0.001), a lower percentage of patients transplanted with the HU status (22% vs. 15%, p<0.001), repeated transplant (18% vs. 14%, p<0.001) and higher labMELD and match-MELD scores (19 vs. 22 and 20 vs.

25, p<0.001). Significant differences in donor risk factors led to a significantly higher mean ET-DRI in the MELD era (1.82 vs. 1.89, p<0.001).



TX at 1-year	pre-MELD	2007	2008	2009	2010	2011	2012	2013	2014	2015
MELD countries	42%	52%	50%	48%	46%	47%	44%	51%	49%	50%
Non MELD countries	61%	43%	56%	60%	58%	61%	64%	53%	61%	66%

Figure 3b. cumulative incidence of transplantation for the MELD countries vs. non-MELD countries, per year (pre-MELD vs. 2007 - 2015)

Table 3. baseline demographics for all transplanted patients in Eurotransplant from 1.1.2005 – 31.12.2015 (**n** = 12,852) per period (pre-MELD vs. MELD)

	Period		p*
	pre-MELD n = 1,804	MELD n = 11,048	
Recipient factor, mean (SD) or n (%)			
Age at listing (years)	50.9 (11)	53.3 (11)	<0.001
Age category			<0.001
<40	262 (15)	1,240 (11)	
40-49	451 (25)	2,073 (19)	
50-59	671 (37)	4,216 (38)	
60-69	407(23)	3,291 (30)	
≥70	13 (0.7)	228 (2.1)	
Sex			0.24
Male	599 (33)	3,514 (32)	
Female	1,205 (67)	7,534 (68)	
Blood group			0.022
ABO-O	573 (32)	3,858 (35)	
ABO-A	813 (45)	4,806 (44)	
ABO-B	252 (14)	1,530 (14)	
ABO-AB	166 (9.2)	854 (7.7)	

Table 3. baseline demographics for all transplanted patients in Eurotransplant from 1.1.2005 – 31.12.2015 (**n** = 12,852) per period (pre-MELD vs. MELD) (continued)

	Period		p*
	pre-MELD n = 1,804	MELD n = 11,048	
LabMELD at listing	18.9 (9.3)	18.2 (9.3)	0.13
LabMELD category at listing			<0.001
6-14	136 (7.5)	3,758 (34)	
15-24	125 (6.9)	3,365 (31)	
25-34	48 (2.7)	1,010 (9.1)	
≥35	32 (1.8)	796 (7.2)	
missing values	1,463 (81)	2,119 (19)	
Etiology			<0.001
Metabolic	65 (3.6)	518 (4.7)	
Acute	157 (8.7)	1,044 (9.4)	
Cholestatic	196 (11)	1,134 (10)	
Alcoholic	380 (21)	2,726 (25)	
Malignant	266 (15)	2,506 (23)	
Hepatitis B	53 (2.9)	356 (3.2)	
Hepatitis C	150 (8.3)	1,065 (9.6)	
Other cirrhosis	399 (22)	1,161 (11)	
Other/unknown	138 (7.6)	538 (4.9)	
HU status at transplant	387 (22)	1,656 (15)	<0.001
Repeated transplant	320 (18)	1,552 (14)	<0.001
Age (years) at delisting	51.2 (11)	53.6 (11)	<0.001
LabMELD at delist	19.3 (9.1)	21.5 (11)	<0.001
LabMELD category at delist			<0.001
6-14	415 (23)	3,709 (34)	
15-24	473 (26)	3,381 (31)	
25-34	169 (9.4)	1,945 (18)	
≥35	108 (6.0)	1,944 (18)	
missing values	639 (35)	69 (0.6)	
MatchMELD at delist	20.1 (8.9)	24.5 (9.5)	<0.001
MatchMELD category at delist			<0.001
6-14	357 (20)	1,919 (17)	
15-24	513 (28)	3,623 (33)	
25-34	178 (10)	2,965 (27)	
≥35	110 (6.1)	1,982 (18)	
missing values	639 (35)	69 (0.6)	
Donor / transplant factor			
Age (years)			
GGT (U/L)	66 (101)	82 (249) (	0.011

Table 3. baseline demographics for all transplanted patients in Eurotransplant from 1.1.2005 – 31.12.2015 (**n** = 12,852) per period (pre-MELD vs. MELD) (continued)

	Period		p*
	pre-MELD n = 1,804	MELD n = 11,048	
CIT (hours)	9.2 (2.8)	8.7 (2.8)	<0.001
ET-DRI	1.82 (0.5)	1.89 (0.5)	<0.001
Donor/transplant category			
Cause of death			<0.001
Trauma	453 (25)	2,248 (20)	
CVA	1,122 (62)	6,839 (62)	
Anoxia	173 (10)	1,403 (13)	
Other	56 (3.1)	553 (5.0)	
DCD	38 (2.1)	601 (5.4)	<0.001
Split liver	63 (3.5)	267 (2.4)	0.015
Allocation			<0.001
Local	358 (20)	2,742 (25)	
Regional	414 (23)	2,792 (25)	
Extra-regional	1,032 (57)	5,514 (50	
Rescue allocation	469 (26)	2,279 (21)	<0.001

*Differences between pre-MELD and MELD I

The outcome (death-uncensored graft survival) of transplanted patients is shown in a Kaplan-Meier survival curve in Figure 4. In the MELD countries, there is a small, but significant decrease in long-term death-uncensored graft survival in the MELD era as compared to the pre-MELD era: 70% vs. 68% at 1-year follow-up and 55% vs. 58% at 5-years follow-up (p=0.035), while donor organ quality and recipient condition decreased (over time the match-MELD increased and donor quality decreased). In the non-MELD countries, the post-transplant outcome is not significantly different between both eras: 80% vs. 78% at 1-year follow-up and 68% vs. 67% at 5-years follow-up (p=0.13).

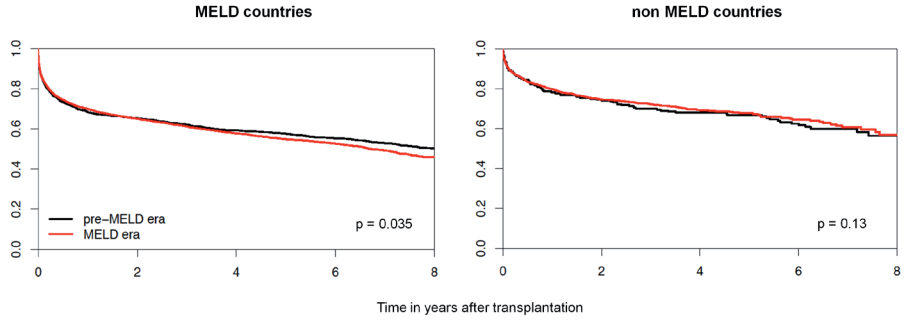


Figure 4. death-uncensored graft survival for the MELD countries and non-MELD countries, pre-MELD era vs. MELD era

DISCUSSION

In this study, the results of MELD allocation in the Eurotransplant region in the past decade are evaluated with the use of competing risk analyses. Outcome was the cumulative incidence of death (waitlist mortality), transplantation, removal or remaining on the waitlist one year after registration.

As a first step, the situation before MELD allocation (the 'pre-MELD era') was compared with the situation after the implementation of MELD (the 'MELD era'). Overall, the situation with regard to waitlist mortality was comparable for both eras. As well as for the whole Eurotransplant region as for the MELD and non-MELD countries, there was no significant difference between the pre-MELD and MELD era. When looking at the effect of MELD allocation per year (Figures 3a and 3b) a decrease in waitlist mortality is visible in the first years after implementation. This decrease seems to level out and already reaches the level of the pre-MELD era in 2008. As of 2010 the waitlist mortality is even higher as compared to the pre-MELD. Remarkably, the patients that died on the waitlist in the MELD era, were older and had a higher labMELD score at delisting. The decrease in waitlist mortality in the first MELD years is most likely related to patients with higher MELD scores being transplanted instead of dying on the waitlist (which was one of the aims of this allocation system). Since there was a switch from patients with long waiting time being on top of the waitlist to patients with the highest MELD being on top of the list (the sickest patient) in the first years of the MELD era, these 'sicker', higher listed patients could potentially have a worse outcome after LT. Another explanation for the decrease in waitlist mortality in the first MELD years could be the preselection made by the transplant centers in the pre-MELD era by not registering patients that are too sick for transplantation on the waitlist at all. Consequently, these sicker patients are not monitored on the Eurotransplant waitlist and information on their outcome is not available.

When looking at the CI of transplantation, in the non-MELD countries there was a decrease in transplantation, that reached the pre-MELD level again after 2010. In the MELD countries, there was a significant increase in the MELD era (and consequently the whole of Eurotransplant). This increase in the first years of MELD allocation in the MELD countries could partially be explained by the 4.5% increase in new (liver only) waitlist registrations together with a 12.5% increase in liver donors from 2006 to 2007 (20). Another factor is the increase in the use of higher risk donors, reflected by the higher mean ET-DRI in the MELD era, mainly caused by the higher donor age and higher percentage of donation after circulatory death (DCD) donors (in Belgium and the Netherlands). Both of these effects (decreased mortality and increased transplantation numbers) were also seen in the United Network for Organ Sharing (UNOS) in the first year of MELD allocation (reduction in waitlist mortality of 3.5% and transplantation increase of 10.2%) (21). However, long-term effects on waitlist mortality

have not been reported (yet). When looking at the outcomes after LT, there is a significant (but slight) decrease in graft survival in the MELD countries for the MELD era recipients, visible in the long-term outcomes around four years graft survival (Figure 4). This slightly decreased outcome may very well be explained by a more liberal donor and recipient acceptance policy (reflected in the significantly higher ET-DRI, recipient age, labMELD and match-MELD). According to the intention-to-treat principle this slightly higher post-transplant mortality might very well be acceptable if there is an even bigger reduction in waitlist mortality.

The advantages and disadvantages of the MELD score have already been described extensively in the current literature. (22,23) Although the MELD score seems objective, reproducible and a fair way to rank patients according to their severity of disease, it is unfortunately not without deficiencies (14,15) and its limitations are well known. (23-26). It may disadvantage patients with a high risk of waitlist mortality that is not adequately reflected by the labMELD score. The concerns with the (original) MELD score led to several new models that either reweighed the original factors (6,7) or adapted the model by adding serum sodium (9,27), sodium and albumin (28) or C-reactive protein (CRP) (29). Another study recently showed that patients with a sudden increase in MELD score had a higher risk of short-term waitlist mortality (30). However none of these newer models have been used for liver allocation purposes, except for MELDNa, which is used in UNOS as of January 2016 for patients with a MELD>11. (31) An alternative could be the use of a combination of MELDNa with a frailty index, as developed by Lai et al., that gives a more complete evaluation of the clinical status for patients with liver cirrhosis. (32)

One issue with regard to the current MELD system is the inability to give a correct reflection of the disease urgency for every liver disease, for example in HCC, leading to the (widely used) concept of the so-called "exceptions", either standard exception (SE) or non-standard exception (NSE). These (N)SE's have a great influence on the MELD score at the time of allocation (match-MELD) and consequently lead to inequity on the waitlist (33,34). This effect is also visible when looking at the labMELD and the match-MELD categories in more detail (match-MELD could either be labMELD or excMELD). There is a discrepancy in distribution between these two types of MELD categories; the frequency of patients in the higher (>25) match-MELD categories is remarkably higher as compared to the frequency of patients in the same labMELD categories (respectively 45% vs. 36%). This implies that the majority of patients in these higher categories were allocated a liver allograft based on their excMELD score, instead of their labMELD score. This transition of patients from the lower to the higher MELD ranks is therefore not based on the 'severity' of their liver function (labMELD), but on the excMELD score that is based on (N)SE points. A consequence (and intention) of this situation is that patients with an excMELD score will receive a liver allograft sooner than patients without an excMELD score. The unintended consequence is the that patients without a (N)

SE are only able to receive a liver allograft when they deteriorate and have a higher labMELD score that outranks the patients with (N)SE points. These patients with a high labMELD score are exactly the ones that have a higher risk of dying after transplantation. (35) This was also confirmed by a recent study by Umgelter et al. who demonstrated that patients with a (N)SE have an advantage with regard to waitlist outcome (transplantation or recovery) as opposed to cirrhotic patients without a (N)SE in the Eurotransplant region. They advocate an initiative to modify the SE and a reduction of NSE in order to achieve a more equitable allocation system (in the MELD countries). (36) Another solution for this situation could be to lower the (N) SE-points for patients that are eligible for such a (N)SE or prolong the period in which extra (N)SE points are awarded to a longer time span than the three months currently used. In this way, they will not compete as much with patients that have an actual high labMELD score and are in a worse clinical condition, and subsequently in higher need for a LT.

This study has some limitations, starting with its retrospective nature. Nevertheless, all (basic) patient data were actually gathered prospectively and entered in the Eurotransplant database. In this study, the MELD score at time of registration was used to follow the registered patients for one year and to analyze the effect of MELD, before and after implementation. Obviously, the MELD score could have varied throughout this year and the value at time of registration would therefore not give a perfect reflection of the actual situation, which is why the MELD score at time of death or transplantation (delisting) is given. Unfortunately, there is a large proportion of MELD scores missing from the patients listed in the pre-MELD era. In the years before MELD allocation started, there was a transition period during which transplant centers were able to register the MELD score, but were not obliged to do so. This makes it difficult to make a proper comparison of the MELD scores between the MELD era and the pre-MELD era. Another potential limitation is the fact that the MELD countries and non-MELD countries all have different allocation rules (patient vs. center oriented). The current system is very complex and consists of the allocation rules according to the law of the country involved. Liver allocation in the MELD countries (Belgium, Germany and the Netherlands) is performed on a national level by Eurotransplant. The other (non-MELD) countries use a center-based allocation. Two of these countries, Croatia and Hungary, joined Eurotransplant after the implementation of the MELD allocation system. The joining of Croatia in 2007 (37) might have influenced the CI of transplantation in the non-MELD countries in 2007, as well as the joining of Hungary could have in 2013 (suddenly lower CI of transplantation in 2007 and 2013). At the same time, besides the differences in allocation systems, there is a big difference in donation rates, that also contribute to these effects and the waitlist outcome in the different Eurotransplant countries. In two of the MELD countries (Germany and the Netherlands) the donation rates were in the lowest in ranks in 2014, whereas in Belgium and all of the non-MELD countries the donation ratios were much higher. (38) Due to differences between the Eurotransplant countries (allocation systems and donation rates), an effect of the introduction

of MELD allocation might vary quite distinctly. As described, it is extremely difficult to exactly measure the effect of the MELD allocation as it depends on such a high number of factors, that cannot all be included in a retrospective study. The biggest advantage of the MELD allocation is that it is a fair allocation system, driven by objective parameters.

In conclusion, this study evaluated the implementation of the MELD score for liver allocation in the Eurotransplant region in the past decade. Initially, the implementation of MELD led to a (small) decrease in waitlist mortality (in the MELD countries), but this effect disappeared after a few years. The CI of transplantation increased in the MELD era, but this was accompanied by a small, but significant decrease in long-term graft survival (5-years). This poorer outcome may be explained by an increased number of transplantations due to a more liberal donor and recipient acceptance policy (higher ET-DRI, higher recipient age and MELD score). Altogether, the introduction of MELD allocation in three Eurotransplant countries did not seem to deliver the intended goal of a reduction in waitlist mortality in the long run and adaptations or other allocation systems might be worth investigating.

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