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Predicting outcome after liver transplantation

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Chapter 7

Identification and validation of the predictive capacity of risk factors and models in liver transplantation over time

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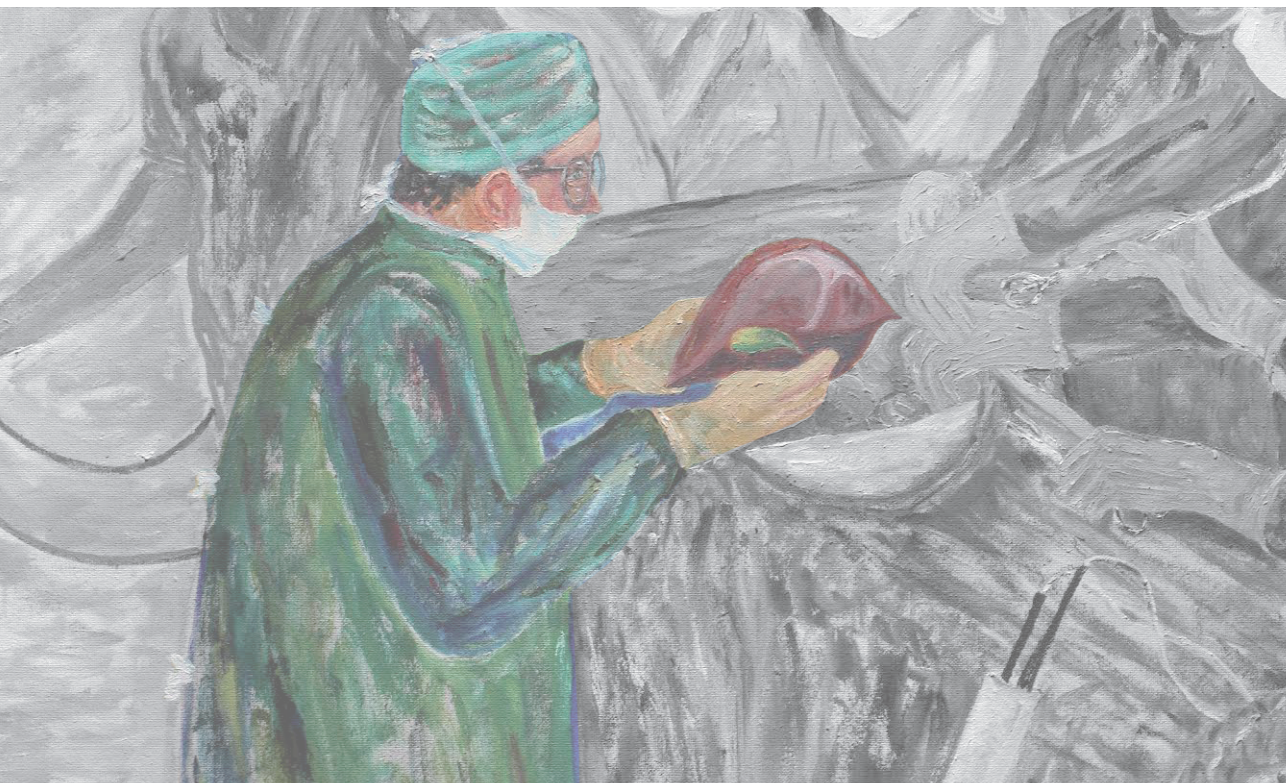

ABSTRACT

Introduction

Outcome after liver transplantation (LT) is determined by donor, transplant and recipient risk factors. Objective of this study is to analyze the predictive capacity of LT risk factors and models and how these factors vary in time and per outcome type.

Methods

All LTs performed in the Netherlands from 1.1.2002 till 31.12.2011 were analyzed with multivariate analyses at 3-month, 1-year and 5-year for patient and death-uncensored graft survival. Investigated risk models were compared with concordance indices.

Results

Recipient age, MELDNa, ventilatory support, diabetes mellitus, HCC, previous malignancy, HCVAb, HBVAb, perfusion fluid, and Eurotransplant-donor risk index (ET-DRI) had significant impact on outcome at one or multiple time points. Significant factors at 3-month patient survival (recipient age, MELDNa, ventilatory support) were used to compose a concept model, which showed a higher c-index than the balance-of-risk (BAR), donor risk index (DRI), ET-DRI, donor-recipient model (DRM) and simplified recipient risk index (sRRI) for long-term patient and death-uncensored graft survival.

Conclusion

In this study, the effects of recipient risk factors and models on different outcome types and time points were shown. Short-term patient survival mainly depends on recipient risk factors, long-term graft survival on donor risk factors and is more difficult to predict. Next to the CM, the DRM has a higher predictive capacity to other risk models for (long-term) patient and death-uncensored graft survival. The DRI and ET-DRI best predicted death-censored graft survival. Knowledge about risk factors and models is critical when using these for waitlist management and/or help in organ allocation and decision-making.

INTRODUCTION

Outcome after liver transplantation (LT) is determined by multiple factors among which donor, transplant and recipient risk factors play a crucial role. Previous studies have identified several of these risk factors and computed risk models in an attempt to predict outcome. The survival outcomes following liver transplantation (SOFT) score (1), donor model for end-stage liver disease (D-MELD) (2), the balance of risk (BAR) score (3) and risk model by Burroughs et al. (4) all use combinations of donor, transplant and recipient factors in one model, whereas the donor risk index (DRI) (5) and Eurotransplant donor risk index (ET-DRI) (6) consist of donor and transplant factors.

Donor and transplant risk is best indicated by the DRI5 for the United Network for Organ Sharing (UNOS) region and ET-DRI (6) for the Eurotransplant region. Our recent study on donor-recipient matching demonstrated that the use of a combination of a donor risk model with a recipient risk model in a donor-recipient model (DRM) had a better prediction of outcome after LT than a donor model or recipient model alone. (7) One of the drawbacks of this study was the fact that the recipient model only consisted of basic recipient related factors registered in the Eurotransplant database, used to create a "simplified" recipient risk index (sRRI). A recipient risk model that encompasses more factors might even be more useful for prediction of patient or graft survival after LT.

When evaluating donor risk models and donor-recipient risk models computed with data from large registries (Organ Procurement and Transplantation Network, European Liver Transplant Registry, Eurotransplant and the UK) in the past decade (Table 1), it is remarkable that every model is either based on patient survival or graft survival, with either short or long-term follow-up. Ideally, relevant information on pre-transplant risk factors that influence post-transplant outcome should be available at the time of an organ offer. However, when choosing one of the above described models, one should already have the desired end point in mind at that time. A sophisticated tool to assess the specific risks of the recipient at multiple time points, that looks at patient as well as graft survival, does not yet exist. Furthermore, when analyzing and reporting results and comparing them with the literature, these results should always be interpreted in the light of donor quality and recipient risks involved.

The objective of this study is to analyze the predictive capacity of risk factors and models in LT in the Netherlands and to determine how these factors vary in time (short versus long term) and for different outcome types (patient versus graft survival). Furthermore, we compare these various risk factors with existing risk models.

Table 1. donor and/or recipient risk models in the past decade with different end points (patient/graft survival) at different time points (short/longterm survival)

Authors	Year	Model	N	Factors	Registry	Endpoint	
						Patient survival	Graft survival
Adam et al.	2000	normalised intrinsic mortality risk	22,089	D,T,R	ELTR	1,3 and 5 year	-
Burroughs et al.	2006	3-month and 12-month mortality	34,664	D,T,R	ELTR	3-month, 12-month	-
Feng et al.	2006	DRI	20,023	D,T	OPTN	-	3 year
Rana et al.	2008	SOFT	21,673	D,T,R	OPTN	3-month	-
Halldorson et al.	2009	D-MELD	17,942	D,R	OPTN	1, 4 year	1, 4 year
Dutkowski et al.	2011	BAR	37,255	D,T,R	UNOS	3-month	-
Braat et al.	2012	ET-DRI	5,723	D,T	Eurotransplant	-	2.5 year
Blok et al.	2015	sRRI	4,466	R	Eurotransplant	-	3.3 year
Collett et al.	2016	DLI	7,929	D,T	UK	-	1, 2, 5 and 10 year

D, donor; T, transplant; R, recipient; DRI, donor risk index; SOFT, survival models following liver transplantation; D-MELD, donor model for end-stage liver disease; BAR, balance of risk; ET-DRI, Eurotransplant donor risk index; sRRI, simplified recipient risk index; DLI, donor liver index; UNOS, united network for organ sharing; ELTR, European Liver Transplant Registry

PATIENTS AND METHODS

Study design

Data from all LTs (including repeated transplants) performed in the Netherlands from January 1st, 2002 till December 31st, 2011 were included. Patients transplanted with a combined transplant were excluded, except for patients transplanted with a combined liver-kidney transplantation. All livers were recovered from deceased donors and were transplanted into adult recipients (≥18 years). Donor, transplant, basic recipient factors and follow-up data were obtained from the Netherlands Organ Transplant Registry, with consent of the scientific advisory committee and the department heads of the three Dutch liver transplant centers. Detailed information on recipient characteristics and follow-up were obtained directly from the transplant centers.

Statistical analysis

All available recipient characteristics (Table 2) were included in the statistical analysis. The ET-DRI was calculated to include donor risk in the multivariate analyses.6 In case of missing values for donor gamma-glutamyltransferase (GGT) and/or cold ischemia time median values were used (GGT 28 U/L in 1.8% missing of the total, CIT 7.67h in 0.9% missing of the total) to calculate the ET-DRI. For all recipients the most recent model for end-stage liver disease (MELD) score before transplantation was calculated using the original formula with a lower

limit of 1 for all variables and with creatinine capped at 4 mg/dl. (8) If patients received renal replacement therapy according to Eurotransplant, the creatinine value was set at 4 mg/dl (as of 16.12.2006, implementation of the MELD score for liver allocation in the Eurotransplant region). (9) The MELD score was capped at 40 and was rounded to the nearest whole value (range 6-40). For the MELD sodium (MELDNa) score the formula from the original study by Kim et al. (10) was used. The BAR score was calculated, according to the formula described by Dutkowski et al. (3). The factor major abdominal surgery was defined and analyzed as follows: all types of major abdominal surgery such as bowel surgery exploratory laparotomy, previous LT, liver surgery etc. (examples of non-major previous abdominal surgery: appendectomy, laparoscopic cholecystectomy, pylorotomy) and categorized as either no major abdominal surgery, previous LT or other major abdominal surgery. The factor perfusion fluid was categorized as UW/other/unknown versus HTK. A separate analysis of UW versus HTK, after exclusion of other and unknown, showed similar results (data not shown). To not lose too many patients for the study we included the other/unknown patients in the UW group, as they showed similar results (data not shown).

To determine a set of prognostic factors for further study, multivariate analyses were performed using Cox regression models with backward elimination and forward selection. Before multivariate analyses all recipient laboratory values with a non-normal distribution (ALT, AST, GGT, creatinine and bilirubin) and the ET-DRI were converted to a logarithmic scale. All analyses were first performed three times; with the separate MELD components (creatinine, INR and bilirubin), the calculated MELD score and the calculated MELDNa score. Both models (MELD and MELDNa) were significant, but because MELDNa was the more significant model, this was used in all analyses. Next, all multivariate Cox-regression analyses were performed separately for the endpoints patient survival and death-uncensored graft survival (defined as the period between the date of transplantation and date of retransplantation or date of recipient death [with a functioning transplanted organ], whichever occurred first, with administrative censoring applied at 3-months, 1-year and 5-years follow-up administrative censoring was calculated after 'x' months, specific emphasis for the factors that were significant at 3-months and so on.

All analyses were anonymized for transplant center. Subsequently, multivariate analyses were performed, using all prognostic factors that were selected (significant at 0.05 level) in at least one of the previous analyses.

Z-values were calculated for all significant factors from the multivariate analysis. The z-value is the quotient of the regression coefficient of a risk factor and its standard error, with a significance level at 1.96 (standard error). Negative values have a protective effect for graft failure or patient death. Harrell's concordance index (c-index) (11) was calculated to indicate

the predictive capacity of the combination of factors at that specific time point and outcome type. The maximal c-index of the combination of all factors in the multivariate analysis was also calculated in order to get an indication of the maximal value that could be reached in this database (Supplemental data). Of course, such a model would be totally overfitted and this was only done to obtain an upper bound for a c-index in a clinical prediction model, based on currently registered variables. A concept model (CM) was constructed with the significant factors at 3-months patient survival as a proof of principle and was compared with the BAR score, DRI, ET-DRI, sRRI and DRM by calculating c-indices for all models over time (from 3-months till 5-years post-transplant outcome). For all analyses, a Wald p-value of $p<0.05$ was considered significant. Analyses and the calculation of the c-index were performed with R (version 3.3.2).

A separate analysis of death-censored graft survival (defined as the period between the date of transplantation and date of retransplantation or the date of reregistration on the waiting list if followed by recipient death) was also performed and is added as supplementary material (Supp. figures 1 and 2, sup. tables 1 and 2). Note that using this definition of death-censored graft survival, patients that were reregistered on the waiting list, but were not retransplanted nor died, were not regarded as graft failure.

RESULTS

Donor, transplant and recipient factors

Included were 1,012 deceased donor LTs, including 161 repeated transplants (16%), performed in the Netherlands in adult recipients, with a mean follow-up of 7.9 years. Recipient characteristics are shown in Table 2. Median recipient age was 52 years, with the majority of patients being transplanted for cholestatic disease (19%) or alcoholic cirrhosis (15%) or viral cirrhosis due to HBV or HCV (14.8%).

Donor and transplant factors are shown in Table 3. Median donor age was 49 years, the majority of donors had a cerebrovascular accident as cause of death (66%) and 18% of all allografts were obtained from donation after circulatory death donors. Overall median ET-DRI donor risk was 1.67.

Multivariate analysis of recipient risk factors

A multivariate Cox regression analysis for two types of outcome (patient survival and death-uncensored graft survival) at three time points (3-month, 1-year and 5-year survival) was performed. All the available recipient factors (Table 2), perfusion fluid (UW/other or HTK), transplant center, second warm ischemia time and the ET-DRI were included. This resulted

Table 2. recipient characteristics in the Netherlands (with univariate analysis)

Recipient factor	
Age, median (IQR), years	52 (43 – 59)
Age category, N (%)	
18-39	201 (20)
40-49	232 (23)
50-59	352 (35)
60-69	225 (22)
≥70	2 (0.2)
Sex, N (%)	
Male	629 (62)
Female	383 (38)
BMI, median (IQR)	24.8 (22.4 – 27.8)
Etiology (primary reason for LT)	
Acute liver failure, primary	92 (9.1)
Cirrhosis, alcoholic	156 (15)
Cirrhosis, hepatitis C related	115 (11)
Cirrhosis, hepatitis B related	37 (3.7)
Cirrhosis, metabolic	54 (5.3)
Cirrhosis, other	143 (14)
Cholestatic, PBC/PSC/other	196 (19)
Retransplant, acute liver failure	36 (3.6)
Retransplant, chronic liver failure	125 (12)
Other/unknown	58 (5.7)
Donor/recipient bloodgroup compatibility	
Identical	938 (93)
Compatible	74 (7.3)
Liver/kidney transplantation	31 (3.1)
High urgent status at transplantation	153 (15)
Medical history, N (%)	
Diabetes mellitus	208 (21)
Angina pectoris	27 (2.7)
Cerebrovascular disease	16 (1.6)
Hypertension	186 (18)
Cardiac intervention	27 (2.7)
Previous LT (reTX)	161 (16)
Previous major abdominal surgery (incl. reTX)	286 (28)
Hepatocellular carcinoma	179 (18)
Other malignancy	27 (2.7)
Previous encephalopathy	250 (25)
Previous ascites	448 (44)

Table 2. recipient characteristics in the Netherlands (with univariate analysis) (continued)

Recipient factor	
Serology, N (%)	
HBsAg positive	74 (7.3)
HBcAb positive	183 (18)
HCVAb positive	148 (15)
HIVAb positive	2 (0.2)
Clinical factors at transplant, N (%)	
Encephalopathy	138 (14)
Ascites	352 (35)
Admitted at ICU	132 (13)
AST	83 (51 – 167)
ALT	55 (31 – 134)
GGT	79 (43 – 172)
Bilirubin	59 (26 – 194)
INR	1.4 (1.2 – 1.8)
Creatinine	83 (64 – 117)
Sodium	138 (135 – 141)
MELD score	16.4 (11.5 – 24.2)
MELDNa score	18.3 (12.5 – 26.2)

in six separate analyses. The hazard ratios of the factors that were significant at one or more points in time are shown in Table 4. The c-index for the optimal combination of the significant factors at that specific time point, for that specific outcome type was calculated. The log-hazard ratios are shown in the supplemental data (Supplemental Figure 3).

Figure 1 shows the z-values of the significant factors over time for either patient survival (Figure 1A) and death-uncensored graft survival (Figure 1B). The z-value is the reflection of the importance of that factor at that time point. These figures demonstrate that the risk of every factor varies over time (short vs. long term) and changes when looking at either patient or graft survival. For example, in Figure 1A, the importance of the factor HCVAb for decreased patient survival is negligible until about 6 months and becomes and remains significant as of that point.

As a demonstration of this concept, the validity of the significant recipient risk factors at 3-month patient survival, recipient age ($p<0.001$), MELD-Na ($p<0.001$) and ventilatory support ($p<0.001$), were used to compose a 'concept model' (CM). This model is the most suited to predict 3-month patient survival in this database; $p<0.001$, c-index 0.69 and used in the following analyses as a surrogate recipient risk model and subsequently for the sole reason to function as a proof of principle.

Table 3. donor and transplant characteristics for deceased donor liver transplants performed in adults from 2002 -2011 in The Netherlands

Donor factor	
Age, median (IQR), years*	49 (38 – 57)
Sex, N (%)	
Male	508 (50)
Female	504 (50)
BMI, median (IQR)	24.4 (22.5 – 26.3)
Cause of death, N (%)*	
Traumatic	230 (23)
CVA	666 (66)
Anoxic	67 (6.6)
Other	49 (4.8)
GGT, median (IQR), U/L*	28 (17 – 53)
HBcAb positive	18 (1.6)
HCVAb positive	n/a
DCD*	182 (18)
Transplant factor	
Transplant center	
#1	353 (35)
#2	240 (24)
#3	419 (41)
Perfusion fluid	
UW	672 (66)
Unknown/other	73 (7.2)
HTK	267 (26)
Allocation, N (%)*	
Local	305 (30)
Regional	424 (42)
Extra-regional	283 (28)
Rescue allocation, N (%)*	60 (6)
Split liver transplantation*	23 (2.3)
2nd WIT, median (IQR), minutes	36 (28 – 44)
CIT, median (IQR), hours*	7.7 (6.4 – 9.3)
ET-DRI, median (IQR)	1.67 (1.45 – 1.93)
*Factor in ET-DRI	

CVA, cerebrovascular accident; HBcAb, hepatitis B core antibodies; HCVAb, hepatitis C antibodies; DCD, donation after circulatory determination of death; UW, University of Wisconsin perfusion fluid; HTK, histidine tryptophan ketoglutarate perfusion fluid; WIT, warm ischemia time; CIT, cold ischemia t

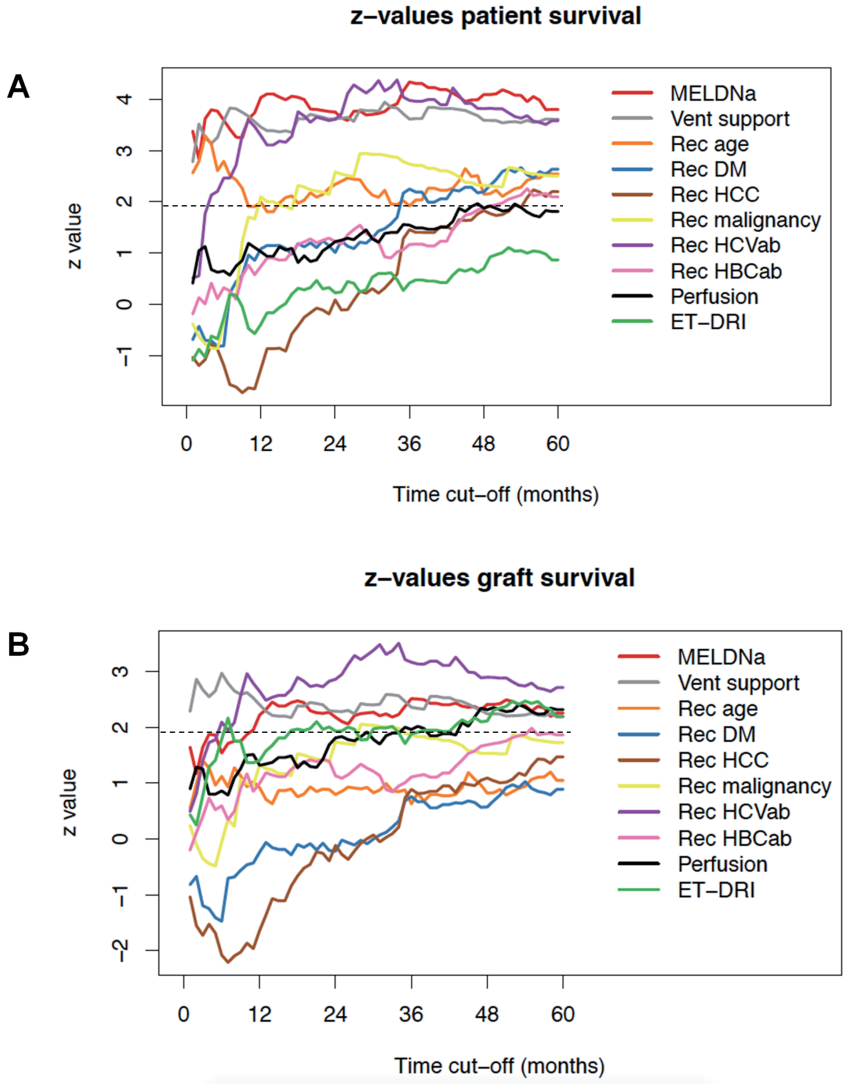

Figure 1. Z-values for recipient risk factors, perfusion fluid and (log-)ET-DRI over 5-years follow up for patient survival (1A) and death-uncensored graft survival (1B)

Comparison of risk models

As a first step the BAR score and ET-DRI were validated in our dataset for the type of outcome and time point they were originally constructed for. The BAR score was validated for 3-month patient survival; p<0.001, c-index 0.69. The ET-DRI was validated for 5-year graft survival; p=0.002, c-index 0.55.

Table 4. results of the multivariate analysis of recipient risk factors according to 3-months, 1-year and 5-years patient- and death-uncensored graft survival

	Patient survival Exp. coefficient (95% confidence interval)			**Death-uncensored graft survival** Exp. coefficient (95% confidence interval		
Recipient factor	3-months	1-year	5-years	3-months	1-year	5-years
Recipient age	1.03 (1.01-1.05)	1.02 (1.001-1.03)	1.02 (1.004-1.03)			
Ventilatory support	3.00 (1.63-5.54)	2.33 (1.38-3.94)	2.26 (1.37-3.73)	2.01 (1.16-3.47)	1.65 (1.01-2.70)	
MELDNa	1.05 (1.02-1.08)	1.05 (1.03-1.07)	1.03 (1.01-1.05)		1.02 (1.01-1.04)	1.01 (1.00-1.03)
HCVAb positive		1.94 (1.28-2.94)	1.99 (1.41-2.84)		1.44 (1.01-2.05)	1.49 (1.11-1.99)
HCC			1.49 (1.05-2.10)			
Malignancy			1.87 (1.02-3.44)			
Diabetes mellitus			1.50 (1.12-2.02)			
HBcAb positive			0.64 (0.44-0.93)			
Donor/transplant factor						
Perfusion fluid (HTK vs. UW/other)			1.37 (1.04-1.81)			1.30 (1.02-1.67)
Combined liver-kidney transplant					0.14 (0.02-0.99)	0.30 (0.10-0.93)
logET-DRI						1.84 (1.08-3.13)
C-index	0.69 (± 0.031)	0.68 (± 0.03)	0.68 (± 0.02)	0.59 (± 0.02)	0.59 (± 0.02)	0.59 (± 0.02)

Next, the c-indices of the DRI, ET-DRI, BAR-score, sRRI, DRM, CM and combination of CM with ET-DRI were calculated (all as continuous models) for the two outcome measures and three time points, in order to compare their predictive capacity. The c-indices of these models are depicted in Figure 2; for patient survival (Figure 2A) and death-uncensored graft survival (Figure 2B), the values are described in Table 5.

The change in the predictive capacity of the models is demonstrated over time with the difference in c-indices per outcome type (patient vs. graft survival). The BAR score and CM seem to have the highest c-index for short-term patient survival (Figure 2A), but this decreases over time. As of circa 14 months' follow-up the CM has the highest predictive capacity for patient survival. For death-uncensored graft survival (Figure 2B) the BAR and CM have comparable predictive capacity at short-term survival, but the CM, CM/ET-DRI and DRM have the highest predictive capacity at the long-term follow-up.

To show the absolute maximum of what may be possible to achieve, the maximal c-indices of the combination of all significant factors (Supplemental Figure 4) and the combination of all available factors (Supplemental Figure 5) were calculated for all three outcome measurements. Of course, such models are totally overfitted and therefore not usable in (clinical) practice.

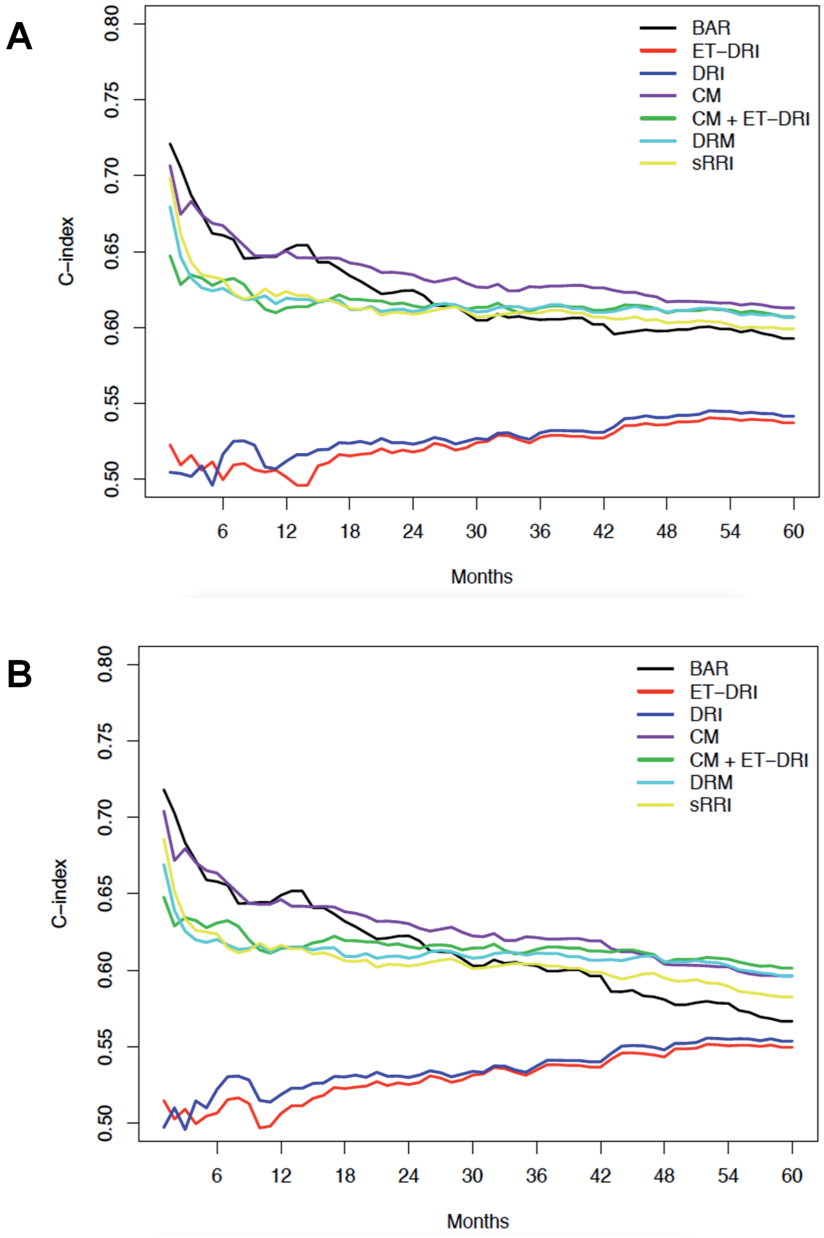

Figure 2. Concordance indices of risk models over 5-years' time for patient survival (2A) and death-uncensored graft survival (2B)

Table 5. c-indices of the investigated risk model for patient survival (PS), death-uncensored graft survival (DUGS) and death-censored graft survival (DCGS) at 3-months, 1-year and 5-years

Risk model	Time point					
	3-months		1-year		5-years	
	PS	*DUGS*	*PS*	*DUGS*	*PS*	*DUGS*
BAR	0.70	0.70	0.65	0.64	0.59	0.56
ET-DRI	0.51	0.51	0.50	0.51	0.54	0.55
DRI	0.50	0.51	0.51	0.52	0.54	0.55
CM	0.68	0.67	0.65	0.64	0.62	0.60
CM + ET-DRI	0.63	0.64	0.61	0.61	0.61	0.60
DRM	0.64	0.64	0.62	0.61	0.61	0.60
sRRI	0.66	0.65	0.63	0.61	0.60	0.58

DISCUSSION

This study provides insight into the changing importance of recipient risk factors over time (short vs. long term) and per outcome type (patient vs. death-uncensored graft survival vs. death censored graft survival). This was demonstrated by analyzing a decade of LT in the Netherlands, with a long-term follow-up (mean 7.9 years). This knowledge can be used to assess risks involved in clinical decision making.

Besides a great variety in the factors that are used in studied risk models (either donor, transplant and/or recipient risk factors), these models are incomparable when looking at the predicted outcome type (patient vs. graft survival) and follow-up (short vs. long-term outcome). This makes it even more difficult to perform a valid comparison with regard to their capability of predicting outcome after LT, reflected by the c-index. The BAR score and ET-DRI were validated in the dataset for their original endpoint and outcome type. Additionally, a multivariate analysis was performed including all (available) recipient risk factors and significant donor and transplant factors (ET-DRI and perfusion fluid) in order to determine which factors influence outcome after LT. As shown in Figures 1A and B, the importance of the significant factors varies over time and across outcomes. Factors with an absolute z-value>1.96 are significantly associated with outcome (Tables 4 and 5). The significant factors at 3-month patient survival (recipient age, ventilatory support and MELDNa) were used to construct a concept model to demonstrate a proof of principle. This shows that the combination of factors significant at short-term (3-month) patient survival are important to indicate short-term patient risk and are also important at long-term patient and graft survival (purple line in Figures 2A and B).

With regard to patient survival, in our database, the CM was comparable to the BAR-score for short-term outcome and seemed superior to all other models for long-term outcome. When looking at death-uncensored graft survival, the CM and BAR had comparable c-indices short-term, but the CM was comparable to the combination of ET-DRI with the CM and the DRM (long-term). When looking at death-censored graft survival (supplementary data), the ET-DRI has our preference to the other models. Our results clearly show that patient survival mainly depends on the condition of the recipient, whereas death-censored graft survival predominantly depends on the quality of the liver graft. Death-uncensored graft survival reflects both, which is a consequence of its definition, i.e.; the period between the date of transplantation and date of retransplantation or date of recipient death, whichever occurred first. The complex procedure of LT is very difficult to predict. In this study, we have shown the, in our opinion, best predictive models with their limitations. Although limited, these models are still much better than not-validated, sometimes only theoretical parameters or even expert opinion. Furthermore, predictive models are essential in case-mix correction and/or outcome analysis. The results of our analyses actually show that the risk factors that were significantly associated with outcome, are also relevant after a longer period of time. These factors are most relevant at the time of transplantation, when selecting a suitable recipient.

For evaluation of outcome or for deciding whether to accept an organ offer or not, it is essential to understand the differences of predictive tools with regard to time and outcome. When comparing outcome data between various centers, regions or countries, the data suggest that the DRM (combination of ET-DRI and sRRI) has the highest potential. Of all previously described models, the DRM gives a valid prediction of long-term patient and death-uncensored graft survival (c-index of 0.60). Furthermore, the DRM consist of a combination of donor, transplant and recipient factors, that are all available in most databases (UNOS and Eurotransplant). Donor quality is probably best reflected in death-censored graft survival analyses. The DRI and ET-DRI models best predict this outcome type, which is why we therefore prefer these models to describe donor quality. For short-term patient survival, one could either use the BAR score or CM. We prefer the latter because this model only include recipient factors. In fact, the CM has the same parameters as the BAR, except for donor age, MELDNa and retransplantation. Interestingly, retransplantation was not identified as a risk factor in this database.

This study has some limitations. Since it is based on a retrospective database (from a single country), all donor-recipient combinations were already chosen by the transplant center and liver allografts were allocated centrally (by Eurotransplant). The consequence is that certain (extreme) risk factors could have been missed due to not accepting such an organ for a LT. Theoretically, in a larger study cohort there could be a chance of finding more significant risk factors; nevertheless, we proved that the above-mentioned factors are of significant impact

on outcome after LT in the Netherlands. In the end, the doctor in charge should overview all clinical data of the donor and the recipient before accepting the offer. It is difficult to weigh all factors, which is why risk models can be helpful in assessing the specific risks of the donor organ or recipient at the time of transplantation. In the analyzed models, every relevant risk factor seems to be included. A better prediction model or model with a higher c-index would therefore only be possible if other factors were added to one of these models. However, the question rises if it would even be possible to achieve such a higher c-index, because this would only be possible at the risk of overfitting the model to a specific database and thus losing the generalizability for a broader transplant population. Even though our recipient population differs from that in (for example) the United States, looking at the distribution of etiology of disease. In our database the majority of patients is suffering from biliary tract related / cholestatic disease or alcoholic disease, whereas the majority of patients transplanted in the United States has HCV-related cirrhosis or a malignancy. (12) Nevertheless, we corrected for the disease etiology in the multivariate analyses and we think our findings can also be applied in other regions such as the United States. The main point is the varying risk of etiology, such as for example HCC or HCV (see above). Another issue was the missing values of CIT and GGT. In order to calculate the risk models for every transplantation, the median values of these factors were used as imputation. Due to the limited missing number of values this will not have influenced or led to any bias in the analyses. With regard to the analyses, it would have been possible to use competing risk analyses for this study. However, competing risks only play a role in death-censored graft survival, where death of the recipient precludes graft failure. The models that we present in this manuscript for death-censored graft survival are based on so-called cause-specific hazards models. These models are valid also in the presence of competing risks and are actually recommended when interest lies in the etiology of the prognostic factors / indices involved. (13,14) The Fine-Gray model is an alternative, but we felt that the cause-specific hazards models that we present are more appropriate and closer to the proportional hazards models that were used for the other outcomes.

The three factors of the CM (recipient age, ventilatory support and MELDNa) were significantly associated with short-term patient survival. Out of those three factors, MELDNa was also significantly associated with outcome at all time points and for both patient and death-uncensored graft survival (Table 4). The impact of pre-transplant sodium in the transplant candidate on outcome has been described previously (10,15) and is a known risk factor. We choose here to use MELDNa instead of MELD because it had a higher predictive capacity in our dataset (data not shown). The MELDNa model is not (yet) being used for liver allocation in the Netherlands (nor the rest of ET). In UNOS however, the MELDNa has been incorporated for liver allocation in patients with a MELD score above 11 since January 2016. (16) Based on these data we would advocate that Eurotransplant also incorporates sodium into the MELD score. In the previously constructed sRRI the MELD score was used, because MELDNa was

not available in the Eurotransplant database, but when looking at the current data, it would be interesting to alter this to MELDNa. Even in a population where the median MELDNa at transplant is substantially higher than in our database, our findings are still useful. When a prognostic model is applied in a context where the median MELDNa is substantially higher, the resulting probabilistic predictions from that model will be different, but it doesn't mean that the contributions of the factors in that model change. That will be the case when the *effect* of the covariates is different when Na-MELD is higher or lower. In statistical terms that is the case when there is an interaction between Na-MELD and other factors. We have checked for this and we did not find any significant interactions between Na-MELD and other factors, for none of the three outcomes considered here.

A recent publication on donor-recipient matching by Briceño et al. (17) addressed the difficulties with these types of (predictive) models and gave a complete overview of the current situation with regard to existing risk models. The same authors studied the use of artificial intelligence (artificial neural networks) in D-R matching and prediction of 3-months graft survival as alternative to the current existing predictive models. (18) They also addressed the limitations of available predictive models such as the DRI, MELD (when used as predictor of post-transplant survival (19)) SOFT, D-MELD or BAR score, that all had lower areas under the curve as compared to their artificial neural networks. Interestingly they describe the high risk of overfitting, because of the high number (>55) of variables was solved by the self-learning process of the artificial neural networks, but the question remains if this system would be useable in the daily practice because of its complexity. Also, such a model would almost certainly be severely overfitted, meaning that it would fit very well on this data, but not so well on other, comparable data. Furthermore, because it is suited for one center or region specifically, it cannot be used to compare outcome data between different centers, regions or countries.

It seems that, when looking at the predictive capacity of the investigated risk models, graft survival is more difficult to predict than patient survival; the c-indices are generally lower in the graft survival figures (see supplemental material). The fact that the various models function differently with different outcome types and times is a logical consequence of their design to predict this specific outcome type or time. For example, donor risk has less impact on the prediction of patient survival (lower c-indices for DRI/ET-DRI), but this increases when looking at graft survival and when follow-up time increases. This suggests that one model would be preferable over another model for short-term survival, but another model would be more suitable when one is looking for prediction of long-term survival. Ideally one would be able to create a LT 'risk equalizer' that adjusts the risk of a certain factor according to the moment in time and the chosen outcome type. The findings presented in this study would make it possible to create such a tool and follow-up studies to verify these findings would be

interesting to undertake. In the meantime, our suggestion would be to look at patient survival for short-term prediction purposes and death-uncensored graft survival for long-term prediction purposes. Even though our results showed that long-term outcome is more difficult to predict, a reasonable risk indication can be achieved with the currently available risk models (e.g. ET-DRI and sRRI). This pre-transplantation risk indication can be used to improve donor-to-recipient matching (or selection) and optimize utilization in an era of organ scarcity.

CONCLUSIONS

In our opinion, this study contributes to the concept of risk factors and models. Although these models have their limitations, they are currently the best predictors of outcome. However, it is important to define which type of outcome and point in time one aims to predict (dynamic endpoints). A decade of LT in the Netherlands was analyzed and used to demonstrate the effects of recipient risk factors and risk models on different outcome types and post-transplantation time points. Short-term patient survival mainly depends on recipient risk factors, whereas long-term graft survival mostly depends on donor risk factors. For these purposes, respectively the BAR-model and ET-DRI showed a satisfactory discriminative capacity. Long-term outcome is more difficult to predict, but next to the CM, the DRM has a higher predictive capacity to other risk models for (long-term) patient and death-uncensored graft survival. The DRI and ET-DRI best describe donor quality and therefore best predict death-censored graft survival. Knowledge about risk factors and models is critical when using these for waiting list management and/or help in organ allocation. Moreover, correcting for quality / case-mix is essential when looking at outcome and/or comparing results.

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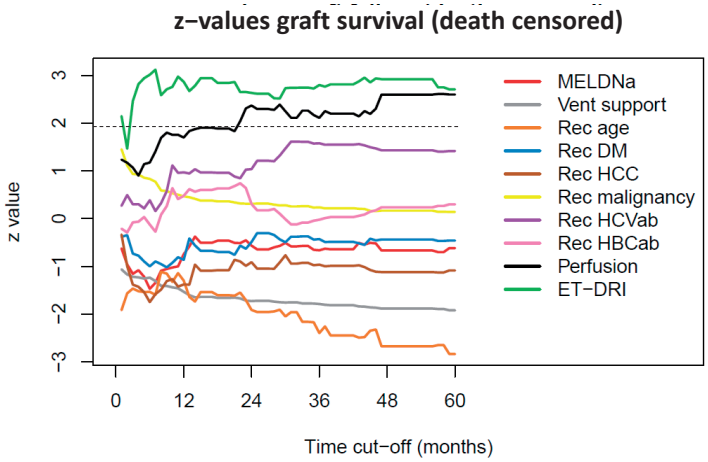
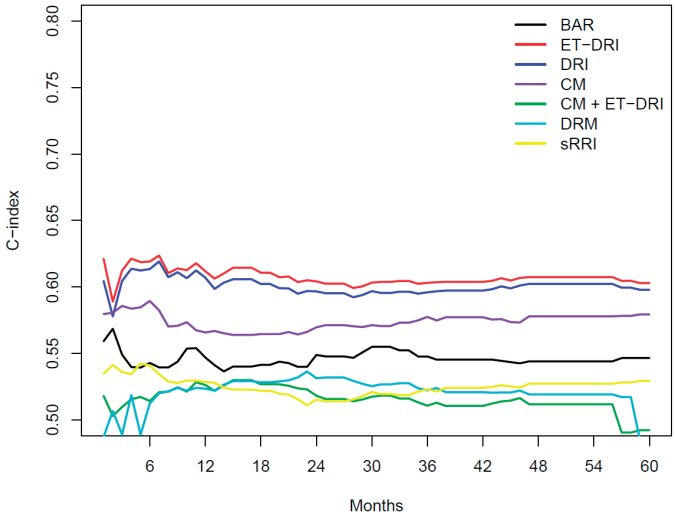
SUPPORTING INFORMATION



Supplemental Figure 1. Z-values for recipient risk factors, perfusion fluid and (log-)ET-DRI with death-censored graft survival as outcome over 5-years' time

Supplemental Table 1. results of the multivariate analysis of recipient risk factors according to 3-months, 1-year and 5-years death-censored graft survival

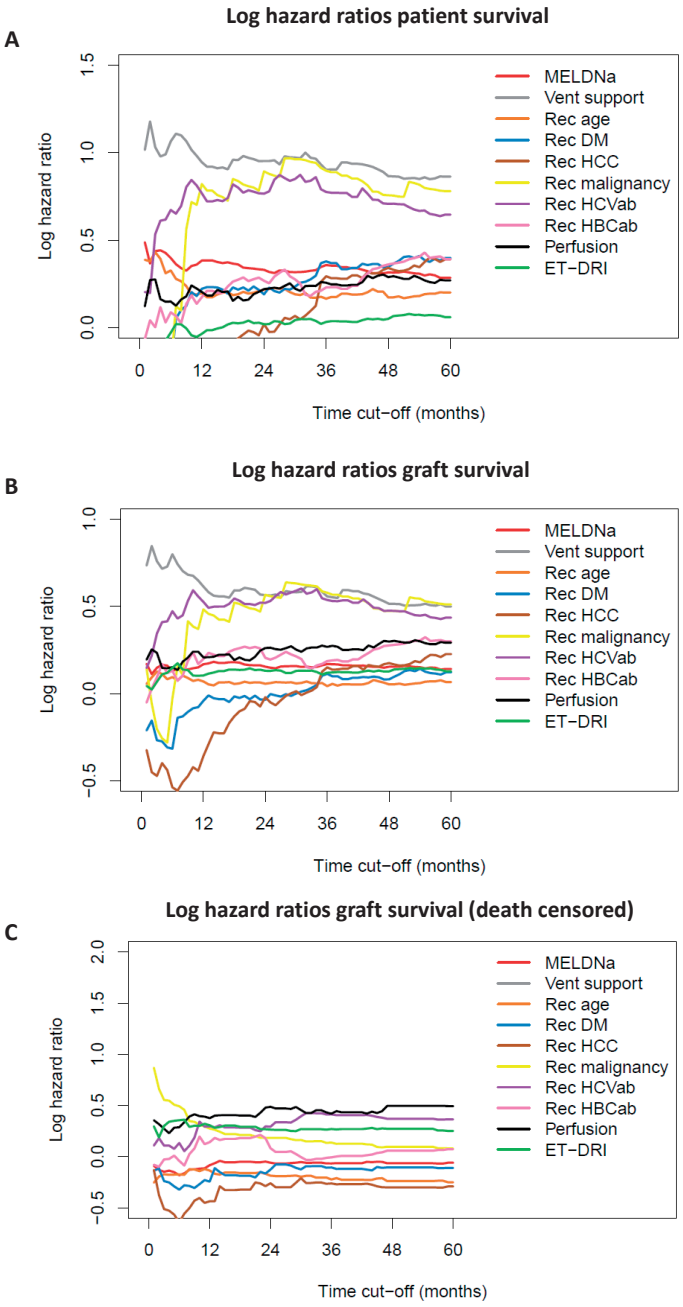
	Death-censored graft survival Exp. coefficient (95% confidence interval)		
Recipient factor	3-months	1-year	5-years
Recipient age	0.98 (0.96-0.99)		0.98 (0.97-0.998)
Ventilatory support			
MELDNa			
HCVAb positive			
BMI			0.95 (0.90-0.99)
Donor/transplant factor			
Perfusion fluid (HTK vs. UW/other)			1.57 (1.06-2.32)
Combined liver-kidney transplant			
logET-DRI	4.66 (1.60-13.6)	5.13 (2.03-13.0)	3.26 (1.36-7.81)
C-index	0.62 (± 0.04)	0.62 (± 0.03)	0.65 (± 0.03)



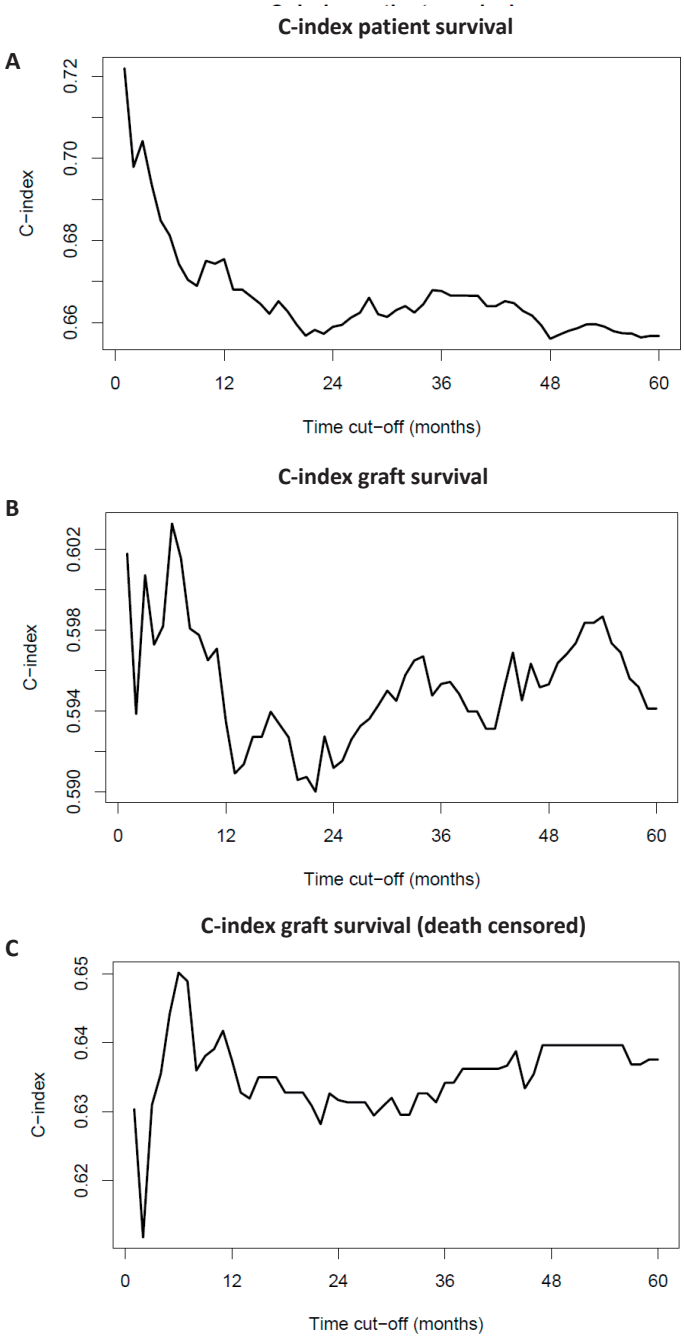
Supplemental Figure 2. Concordance indices of risk models for death-censored graft survival over 5-years' time

Supplemental Table 2. c-indices for the investigated models with death-censored graft survival as outcome:

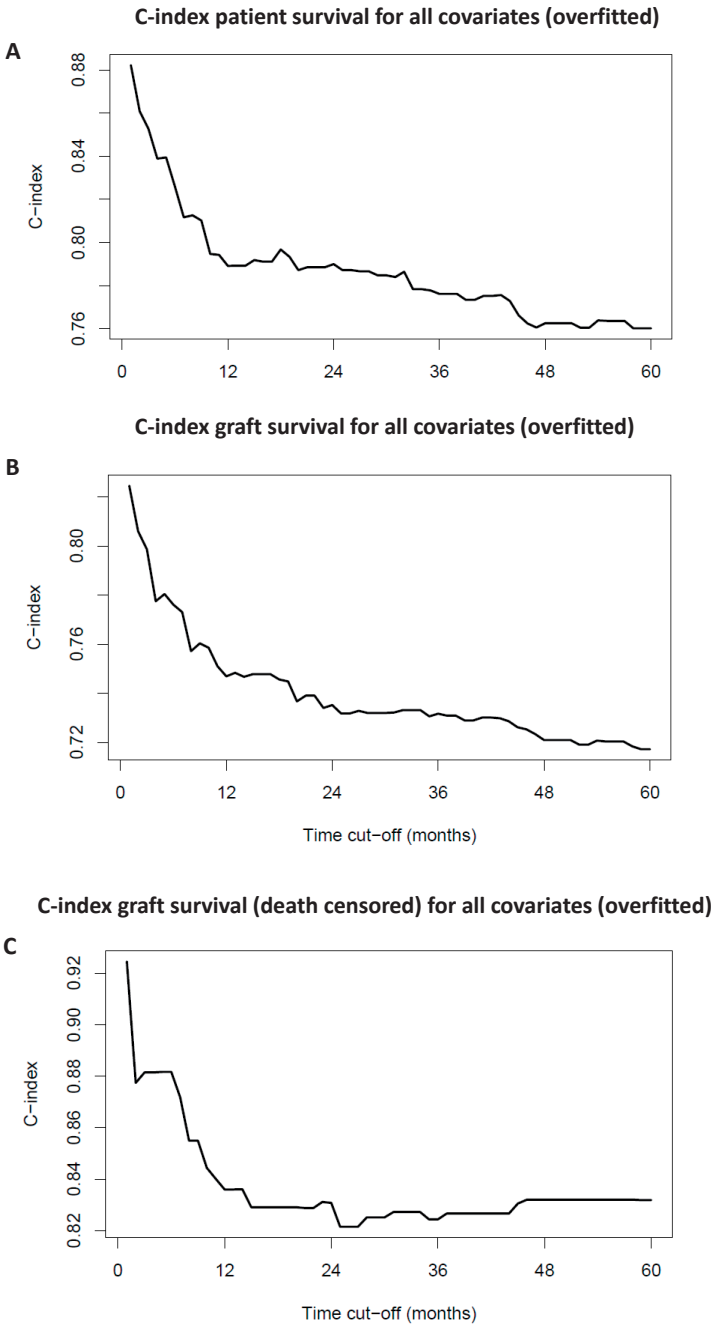
	3-months	1-year	5-years
BAR	0.55	0.57	0.55
ET-DRI	0.60	0.62	0.60
DRI	0.60	0.61	0.60
CM	0.58	0.57	0.58
CM + ET-DRI	0.51	0.53	0.49
DRM	0.50	0.53	0.
sRRI	0.54	0.53	0.53



Supplemental Figure 3. log-hazard ratios for recipient risk factors, perfusion fluid and (log-)ET-DRI over 5-years' time for patient survival (3A), death-uncensored graft survival (3B) and death-censored graft survival (3C)



Supplemental Figure 4. c-indices for the optimal combination of significant risk factors over 5-years' time for patient survival (4A), death-uncensored graft survival (4B) and death-censored graft survival (4C)



Supplemental Figure 5. highest reachable c-indices for the combination of all available factors over 5-years' time for patient survival (5A), death-uncensored graft survival (5B) and death-censored graft survival (5C)