

## ORIGINAL ARTICLE

# The difficulty in defining extended donor criteria for liver grafts: the Eurotransplant experience

Gerd R. Silberhumer,<sup>1</sup> Axel Rahmel,<sup>2</sup> Vincent Karam,<sup>3</sup> Mithat Gonen,<sup>4</sup> Georg Gyoeri,<sup>1</sup> Barbara Kern,<sup>1</sup> Rene Adam,<sup>3</sup> Ferdinand Muehlbacher,<sup>1</sup> Xavier Rogiers,<sup>5</sup> Andrew K. Burroughs<sup>6,7</sup> and Gabriela A. Berlakovich<sup>1,7</sup>

1 Department of Transplant Surgery, Medical University Vienna, Vienna, Austria

2 Eurotransplant, Leiden, The Netherlands

3 European Liver Transplant Registry (ELTR), Paris, France

4 Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

5 Transplantation Centre, Gent University Hospital and Medical School, Gent, Belgium

6 Liver Transplant Unit, The Royal Free Sheila Sherlock Liver Center, The Royal Free Hospital, London, UK

7 European Liver and Intestine Transplant Association (ELITA), Birmingham, UK

## Keywords

donor evaluation, extended liver donor criteria, liver transplantation, organ quality.

## Correspondence

Gerd R. Silberhumer MD, PhD, Department of Transplant Surgery, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

Tel.: +43 1 40 400 6870;

fax: +43 1 40 400 6872;

e-mail: gerd.silberhumer@meduniwien.ac.at

## Conflicts of interest

All authors have declared no conflict of interest.

Received: 22 November 2012

Revision requested: 14 December 2012

Accepted: 28 June 2013

Published online: 10 August 2013

doi:10.1111/tri.12156

## Introduction

Outcome data after orthotopic liver transplantation have continued to improve throughout the last decades. Nevertheless, transplant centers face the problem of rising numbers of patients on their waiting lists in contrast to a limited number of stable available donor grafts [1–3]. Even the use of living donors and donors after cardiac death (DCD) could not overcome this imbalance [4]. Therefore, transplant physicians and organ sharing networks try to allocate, so-called, “extended criteria organs” very aggres-

## Summary

Donor criteria for liver grafts have been expanded because of organ shortage. Currently, no exact definitions for extended donor grafts have been established. The aim of this study was to analyze the impact of donor-specific risk factors, independent of recipient characteristics. In collaboration with Eurotransplant and European Liver Transplant Register, solely donor-specific parameters were correlated with 1-year survival following liver transplantation. Analyses of 4701 donors between 2000 and 2005 resulted in the development of a nomogram to estimate graft survival for available grafts. Predictions by nomogram were compared to those by Donor Risk Index (DRI). In the multivariate analysis, cold ischemic time (CIT), highest sodium, cause of donor death,  $\gamma$ -glutamyl transferase ( $\gamma$ -GT), and donor sex (female) were statistically significant factors for 3 months; CIT,  $\gamma$ -GT, and cause of donor death for 12-month survival. The median DRI of this study population was 1.45 (Q1: 1.17; Q3: 1.67). The agreement between the nomogram and DRI was weak ( $\kappa = 0.23$ ). Several donor-specific risk factors were identified for early survival after liver transplantation. The provided nomogram will support quick organ quality assessment. Nevertheless, this study showed the difficulties of determining an exact definition of extended criteria donors.

sively to limit the number of patient deaths on the waiting list. Several studies have demonstrated the safe use of such extended criteria grafts with acceptable outcomes [5–7].

During the last decades, several studies have tried to define parameters and cut-off values for extended criteria organs, but there is still no general definition accepted within the transplant community [8–10]. Several risk factors such as older donor age, prolonged cold ischemic time (CIT) and hypotension, steatosis and high sodium values have been widely accepted, although their impact differs significantly in the reported studies [11–15].

Because of this inhomogeneity, the aim of this study was to identify solely donor-related risk factors for developing a clinical evaluation tool for risk assessment of deceased liver donors. This study reflects the current situation in Eurotransplant (ET) and is based on merged data from ET database and European Liver Transplant Registry (ELTR).

## Materials and Methods

### Data collection

Data were received for all liver transplantations performed within the ET area between 2000 and 2005 from the ET database, Leiden, Netherlands and ELTR, Paris, France [2,3]. ET and ELTR databases were merged. Both registries randomly undergo data review in a standardized manner. The ELTR registry underlies a strict data audit by independent members of participating countries. During the audits in each center, 10% of liver transplant files are analyzed and additionally evaluated by the ELTR data manager. In ET donor, data undergo a plausibility check at the time of data acquisition. In addition, the registry management randomly cross-checks the documented donor data.

Median data completeness of the merged database was 69% (Q1: 64%, Q3: 100%). Almost 70% of risk factors reached more than 80% data completeness.

Only deceased liver donors procured by transplant centers within the ET area were considered for analysis. DCD, donors for split liver transplantation and recipients younger than 18 years were excluded from analysis.

This initial study revealed significantly poorer outcomes for emergency transplantation and re-transplantation compared with chronic liver failure. For the final donor risk factor analyses, it was decided to focus only on deceased donors that were reported for first transplantation in the standard allocation setting for chronic liver diseases.

Factors provided by the ET database included: cause of brain death, donor age, sex, multiorgan donor Y/N, duration of stay in the intensive care unit, cardiac arrest/hypotension Y/N, use of catecholamines Y/N, body mass index, known insulin-dependent diabetes mellitus and alcohol abuse, activated partial thromboplastin time, sodium (highest during intensive care unit stay and latest pre-transplantation), potassium, creatinine (highest and latest), erythrocytes count, leukocytes count, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, total bilirubin,  $\gamma$ -glutamyl transferase ( $\gamma$ -GT), lactate dehydrogenase, amylase, lipase, alanine phosphatase. Donor data are stored anonymously in the ET database.

Factors provided by ELTR database included: indication for transplantation [alcohol-induced, re-transplantation, hepatocellular carcinoma (HCC), biliary, hepatitis C virus, hepatitis B virus, metabolic, and others], sex mismatch, CIT, cause of graft failure, follow-up time with patient- and

graft survival. In the case of multifactorial cirrhosis, only the main underlying disease was considered for subgroup classification resulting in eight groups of indication for transplantation.

### Outcome measures/statistical methods

Graft survival was defined as the time period from transplantation to either recipient death or re-transplantation. All donor-related factors were correlated with post-transplant graft survival to define extended donor criteria. Primary endpoints were survival or death/re-transplantation at 3 and 12 months of follow-up. Age was categorized in 5-year steps (age 5), CIT in 15-min steps (CIT 15).

Statistical analyses were performed using SAS Version 9 (SAS Institute Inc., Cary, NC, USA) and R version 2.10 (<http://www.r-project.org>). Survival curves were generated using Kaplan–Meier estimates and compared by log-rank tests for univariate analysis with categorical variables. Continuous variables were compared using hazard ratio estimates and confidence intervals.

Stepwise Cox regression was used for multivariable modeling, adjusted for overfit using 10-fold cross-validation, as implemented in SAS and in R [16,17]. A predictive summary of the multivariate model was provided with a nomogram. Predictive accuracy of the nomograms was assessed using the area under the receiver operating characteristic curve (AUC). An AUC of 1.0 indicates perfect discrimination, whereas an AUC of 0.5 indicates no discrimination by the nomogram.

### Comparison Donor Risk Index versus nomogram

The Donor Risk Index (DRI) described by Feng *et al.* was calculated for each patient in our data set [12]. To facilitate the comparison of DRI and the nomogram, we categorized them into three groups based on the observed tertiles in our data DRIs.

### Ethics

The study protocol has been reviewed by the Institutional Ethics Committee and has been performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008.

### Results

A total of 6982 deceased liver donors were procured within the ET area from 2000 to 2005. The 700 (10.0%) donors used for split liver transplantation and the 149 (2.1%) organs imported into the ET area were excluded from this analysis. Therefore, the resulting initial study population consisted

of 6133 deceased liver donors. In an initial analysis, emergency transplantation ( $P = 0.01$ ) and re-transplantation ( $P < 0.01$ ) were associated with significantly poorer 3- and 12-month survival rates compared with indications for chronic liver failure. Therefore, these patients were excluded for definite donor risk factor analyses, leaving 4701 patients.

### Study population for risk factor analyses

Donor factors for the final study population are described in detail in Table 1. Mean donor age was  $42.8 \pm 17.4$  years (median 45 years), 44.1% of the donors were female. Donor death was classified as cardiovascular (61.3%), trauma (30.4%), suicide (4.0%), respiratory (3.6%), and other reasons (0.7%).

Indications for transplantation were grouped as alcohol-induced (24.3%), biliary disease (15.6%), malignancy (16.5%), hepatitis C (15.7%), metabolic (7.8%), hepatitis B (7.3%), and others (12.9%). No significant differences regarding the graft survival owing to indications for transplantation could be found.

**Table 1.** Donor and recipient data.

Factors	Study group <i>n</i> = 4701
Gender	
Male (%)	55.9
Female (%)	44.1
Age (years)	44 (30; 55)
BMI (kg/m <sup>2</sup> )	24 (22; 26)
Cause of death	
Cardiovascular (%)	61.3
Trauma (%)	30.4
Suicide (%)	4.0
Respiratory (%)	3.6
Other (%)	0.7
CIT (h)	9.5 (7.6; 11.5)
Sodium latest (mmol/l)	146 (141; 152)
Sodium highest (mmol/l)	148 (143; 154)
Potassium (mmol/l)	4.0 (3.6; 4.4)
CRP (mg/dl)	1.7 (0.9; 2.9)
AST (U/l)	32 (19; 55)
ALT (U/l)	24 (14; 45)
γ-GT (U/l)	23 (13; 51)
Bilirubin (mg/dl)	0.6 (0.4; 0.9)
PTT (s)	36 (30; 41)
Alkaline phosphatase	73 (52; 115)
Amylase (U/dl)	94 (46; 186)
Lipase (U/l)	105 (53; 197)
LDH (U/l)	300 (208; 453)
Creatinine (mg/dl)	0.8 (0.7; 1.1)

Data are presented as median and (lower; upper quartile).

CIT, cold ischemia time; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PTT, partial thromboplastin time; LDH, lactate dehydrogenase.

Graft survival rates were 87.2% for 3 months and 81.2% for 12 months. The re-transplantation rate was 10.7%. Infection-related deaths (20.6%) were the main cause of death in our study population, followed by, liver complications (17.3%; 5.3% as a result of primary nonfunction and dysfunction), unclassified causes (13.7%), and cardiovascular-related deaths (8.4%). Multiorgan failure occurred in 5.8% of patients and 6.5% of patients died intraoperatively. HCC recurrence caused only 3.4% of deaths within the first year after transplantation.

### Univariate analysis

In the univariate analysis age, cause of donor death, creatinine, γ-GT, high sodium, and CIT were significant factors for 3- and 12-month graft survival. In addition, donor sex and the latest sodium were only significant to the 3-month survival rate. Detailed data are shown in Table 2a. All other investigated values did not show significance at any follow-up time point.

### Multivariate analysis

In the multivariate analysis CIT, high sodium, cause of donor death, γ-GT, and donor sex (female) were statistically significant for the 3-month graft survival rate. For the 12-month survival rate, only CIT, γ-GT, and cause of donor death remained statistically significant factors. Detailed data are shown in Table 2b.

### Nomogram

Based on the Cox proportional hazards regression model, nomograms for 3 months (Fig. 1a) and 12 months (Fig. 1b) were developed. All clinically relevant variables served as a basis for this nomogram. The cross-validated AUC was 0.570 (95% confidence interval: 0.543–0.596) for the 3-month nomogram and 0.559 (0.536–0.582) for the 12-month nomogram. In Table 3, the use of the nomogram is explained by an example for an optimal organ donor and an extended criteria liver donor. Estimations of 3-month survival are provided in Table 3a, 12-month survival in the Table 3b.

### Donor Risk Index

The mean DRI for this study population was 1.45 (Q1: 1.17; Q3: 1.67).

### DRI versus Nomogram

The AUC for the DRI was 0.555 at 3 months and 0.557 at 1 year, values that are both lower than the cross-validated

**Table 2.** Univariate (A) and multivariate (B) analysis of risk factors for survival at 3 months and 12 months.

Factor	3 months		12 months	
	HR (CI)	<i>P</i> -value	HR (CI)	<i>P</i> -value
<b>A</b>				
Donor death	1.038 (1.016–1.060)	0.01	1.053 (1.028–1.078)	0.01
Age 5	1.022 (1.000–1.043)	0.048	1.032 (1.014–1.051)	<0.01
Sex	1.167 (1.020–1.366)	0.02	1.021 (0.997–1.046)	0.08
BMI	1.000 (0.981–1.020)	0.97	1.004 (0.988–1.021)	0.61
CIT 15	1.010 (1.006–1.014)	<0.01	1.009 (1.006–1.013)	<0.01
Sodium	1.009 (1.001–1.017)	0.03	1.006 (0.999–1.013)	0.09
Potassium	1.019 (0.991–1.049)	0.19	1.022 (0.998–1.047)	0.07
Creatinine	1.032 (1.008–1.056)	<0.01	1.033 (1.011–1.056)	<0.01
AST/ALT	1.000 (0.999–1.001)	0.96	1.000 (0.999–1.001)	0.98
$\gamma$ -GT	1.001 (1.000–1.002)	<0.01	1.001 (1.000–1.002)	<0.01
Alkaline phosphatase	1.000 (0.999–1.001)	0.78	1.000 (0.999–1.001)	0.91
Amylase	1.000 (1.000–1.000)	0.40	1.000 (1.000–1.000)	0.29
Highest sodium	1.012 (1.004–1.019)	<0.01	1.008 (1.001–1.015)	0.02
Highest creatinine	0.964 (0.876–1.062)	0.46	0.988 (0.920–1.061)	0.74
LDH	1.000 (1.000–1.000)	0.42	1.000 (1.000–1.000)	0.25
Bilirubin	1.006 (0.956–1.058)	0.82	0.992 (0.943–1.044)	0.77
<b>B</b>				
CIT 15	1.010 (1.005–1.015)	<0.01	1.009 (1.005–1.013)	<0.01
$\gamma$ -GT	1.001 (1.000–1.002)	0.03	1.001 (1.000–1.002)	0.01
Donor death	1.242 (1.008–1.529)	0.04	1.323 (1.333–1.545)	0.02
Highest sodium	1.015 (1.002–1.028)	0.02	1.009 (0.998–1.021)	0.11
Sex	1.275 (1.023–1.589)	0.03	1.021 (0.997–1.046)	0.08
Age 5	1.016 (0.987–1.045)	0.26	1.019 (0.995–1.044)	0.12
Creatinine	0.937 (0.810–1.084)	0.38	0.998 (0.987–1.009)	0.71
Sodium	0.998 (0.986–1.010)	0.66	0.995 (0.891–1.112)	0.93

Age 5, age categorized in 5 year steps; ALT, alanine aminotransferase; AST, aspartate aminotransferase;  $\gamma$ -GT, gamma glutamyl transferase; BMI, body mass index; CIT, cold ischemia time; CIT 15, cold ischemia time categorized in 15 min steps; CRP, C-reactive protein; LDH, lactate dehydrogenase.

AUC of the nomogram. The agreement between the two predictors was weak ( $\kappa = 0.23$ ) (Table 4a). Multiple patients showed comparable outcomes, although they were classified differentially according to DRI and the nomogram (Table 4b). For example, 81% of the patients who were low-risk DRI and intermediate by nomogram were 1-year survivors and 78% of those who were high-risk DRI and intermediate by nomogram survived the first year after transplantation.

## Discussion

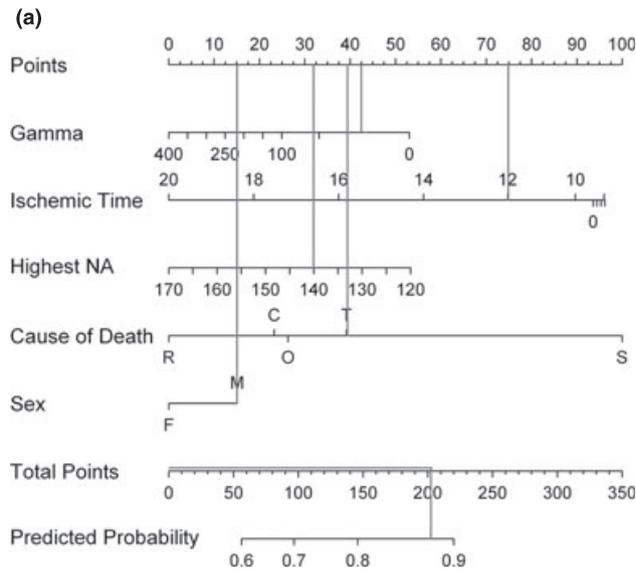
Growing liver transplant waiting lists, combined with increasing waiting list mortality rates, resulted in the adoption of several different strategies to combat the issue of organ shortage. The use of extended criteria donors (ECD) has been promoted recently, as several studies have shown acceptable long-term results with these organs [8,9,18].

This collaborative study between ET and ELTR initially aimed at creating a precise definition of extended criteria

deceased liver donors solely based on donor-related factors, independent of medical recipient conditions. In contrast to the currently established DRI by Feng *et al.*, special donor conditions such as DCD and split liver grafts with well-known significantly higher risk of organ failure were excluded from analysis [13]. In addition, recipients with acute liver failure or those that required re-transplantation were excluded from the study population (Group B) because significantly poorer graft survival was found with these indications in this and previous studies [19].

Furthermore, by limiting our analyses to 3 and 12 months after transplantation, we aimed at decreasing the impact of recipient-related risk factors. In contrast to the findings in Mells and Neuberger, our results show that causes of post-transplant death change significantly with longer follow-up time [20].

Although the focus of this study was the classical diseased heart-beating liver donor, this manuscript highlights the difficulties of defining ECD. Nevertheless, we were able to demonstrate the interdependency of previously reported



Formula:

$$\text{Prob}\{\text{cens3} = 1\} = \frac{1}{1 + \exp(-X \hat{\beta})}, \text{ where}$$

$X \hat{\beta} =$

$$\begin{aligned} & 3.633797 \\ & -0.005231303\{\gamma\text{-GT}\} + 8.578671 \times 10^{-7} (\{\gamma\text{-GT}\} - 8)^3 \\ & -9.90527 \times 10^{-7} (\{\gamma\text{-GT}\} - 23)^3 + 1.326599 \times 10^{-7} (\{\gamma\text{-GT}\} - 120)^3 \\ & +0.00473088\{\text{cit}\} - 0.001401043(\{\text{cit}\} - 5.986667)^3 \\ & +0.002762421(\{\text{cit}\} - 9.533333)^3 - 0.001361378(\{\text{cit}\} - 13.18333)^3 \\ & -0.01167339 \{\text{highest Na}^+\} \\ & +0.03336522\{O\} - 0.25467140\{R\} + 0.84004321\{S\} + 0.17447850\{T\} \\ & +0.1656467\{M\} \end{aligned}$$

and  $\{c\} = 1$  if subject is in group  $c$ , 0 otherwise;  $(x)_+ = x$  if  $x > 0$ , 0 otherwise.

**Figure 1** (a) Nomogram for 3-month survival estimation. Blue bars illustrate the use of the nomogram. The “optimal donor” of Table 3 serves as example for 3-month survival estimation. (b) Nomogram for 12-month survival estimation. Each axis represents one of the significant variables of the multivariate analysis. Variable-specific values have to be correlated (straight upward) with the top point axis. Finally, all points of each variable have to be added and the total sum can be linked with the survival axis in the lowest row. Gamma,  $\gamma$ -glutamyl transferase (U/l); ischemic time (h); highest NA, highest documented sodium during ICU stay (mmol/l). Cause of death: R, respiratory; C, cardiovascular; T, trauma; S, suicide; O, other. Sex: F, female; M, male.

donor risk factors in accordance with currently established literature [18,21,22].

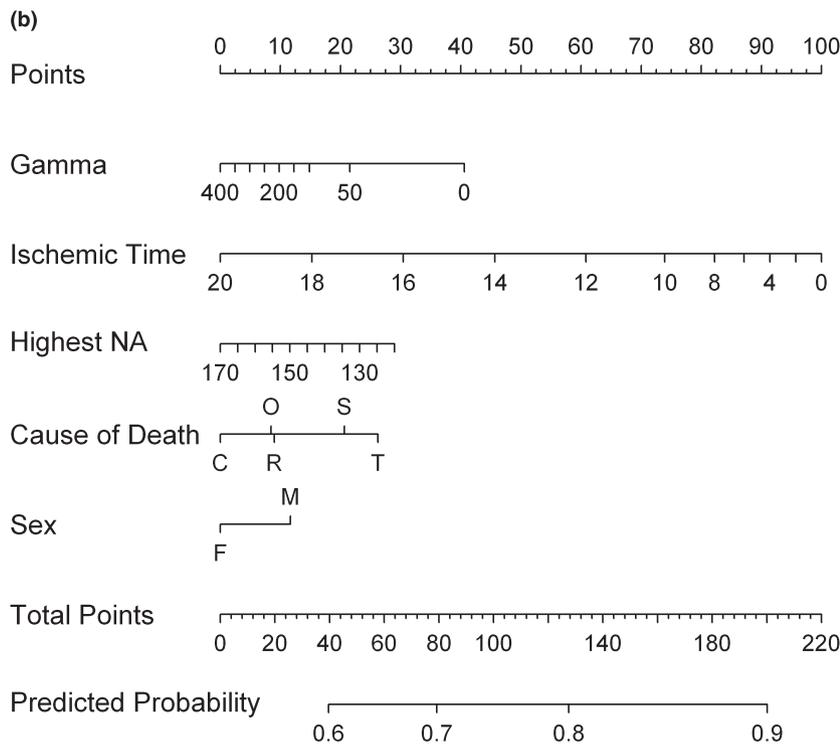
### Donor age and cause of donor death

In this study population, donor age was only a predictor of post-transplant survival in the univariate analysis without revealing any cut-off value. The general increase in mean donor age might be reflected in an alteration of the causes of donor death, as well [1]. Currently, more than 60% of organs are procured from donors who have died from cardiovascular disease [23]. Our data reveal a statistically

significant negative effect of cardiovascular donor death for 3- and 12-month survival following transplantation. Nevertheless, the question has to be raised, if cardiovascular cause of death should be considered as standard as it represents more than 60% cases and trauma-related death a protective factor?

### Sex mismatch and donor sex

Female donors showed a negative impact on 3-month post-transplantation survival, a phenomenon that can be attributed to Alloimmunity mechanisms and hormonal



Formula:

$$\text{Prob} \{ \text{cens12} = 1 \} = \frac{1}{1 + \exp(-X \hat{\beta})}, \text{ where}$$

$X \hat{\beta} =$

$$\begin{aligned} & 2.633942 \\ & -0.005201531 \{ \gamma\text{-GT} \} + 9.233355 \cdot 10^{-7} (\{ \gamma\text{-GT} \} - 8)^3 \\ & -1.066119 \times 10^{-7} (\{ \gamma\text{-GT} \} - 23)^3 + 1.427838 \times 10^{-7} (\{ \gamma\text{-GT} \} - 120)^3 \\ & -0.02401290 \{ \text{cit} \} - 0.0007968789 (\{ \text{cit} \} - 5.986667)^3 \\ & + 0.001571198 (\{ \text{cit} \} - 9.533333)^3 - 0.0007743188 (\{ \text{cit} \} - 13.18333)^3 \\ & -0.006476537 \{ \text{highest Na}^+ \} \\ & + 0.09455751 \{ O \} + 0.10042977 \{ R \} + 0.23034898 \{ S \} + 0.29289681 \{ T \} \\ & + 0.1303845 \{ M \} \end{aligned}$$

and  $\{c\} = 1$  if subject is in group  $c$ , 0 otherwise;  $(x) = x$  if  $x > 0$ , 0 otherwise.

Figure 1 Continued.

differences [24–28]. In liver transplantation, only few elderly data are published about gender mismatch, comparable with our data [29–31].

**Cold ischemic time**

Usually, more than 12 h of CIT correlated with poor initial graft function or organ failure [13,32]. We could not identify a cut-off value as described in previous studies, but confirm a negative correlation for graft survival with prolonged CIT [8,12,13,33]. Each hour

extension of CIT roughly corresponded to a 4% (absolute) decrease in the probability of 1-year graft survival. In cases involving long distance organ shipment owing to Model for End-Stage Liver Disease (MELD) score allocation, CIT may become increasingly more important to the decision of donor acceptance, especially in case of ECD. We are aware that the exact CIT is not always predictable before organ allocation and organ harvesting. Nevertheless, delays in transportation or prolonged duration of hepatectomy might be very rare events or initially predictable.

**Table 3.** Manual for the use of the nomogram with an example of an “optimal” liver organ donor and an “extended criteria” liver donor.

Variable	Optimal			Extended		
	Example value	3 months axis points	12 months axis points	Example value	3 months axis points	12 months axis points
Sex	Male	15	12	Female	0	0
Cause of death	Trauma	40	27	CVA	25	0
Highest sodium	140 mmol/l	32	16	160 mmol/l	10	6
CIT	12 h	75	61	15 h	37	37
$\gamma$ -GT	25 U/l	41	30	100 U/l	25	15
Sum axis points		203	146		97	58
Estimated survival (%)		84	84		70	64

CVA, cerebrovascular accident; highest sodium, highest documented value during ICU stay; CIT, cold ischemia time.

**Table 4.** (A) Number of patients cross classified by DRI and Nomogram and (B) percent of patients alive at 1 year.

	Nomogram low risk	Nomogram intermediate	Nomogram high risk
<b>A</b>			
DRI low risk (%)	16	12	5
DRI intermediate (%)	13	13	8
DRI high risk (%)	4	8	21
<b>B</b>			
DRI low risk (%)	86	81	79
DRI intermediate (%)	82	81	77
DRI high risk (%)	82	78	73

DRI, Donor Risk Index.

### $\gamma$ -glutamyl transferase

Evaluation of donor organs solely based on liver-specific laboratory values is a controversial topic in medical literature [11,34–37]. In our study population, only  $\gamma$ -GT was associated with increased graft failure in the multivariate analysis for 3- and 12-month survival.  $\gamma$ -GT might reflect chronic organ damage more precisely than transaminases. Donor-related comorbidities such as cardiovascular disease, diabetes type II, chronic kidney disease, or alcohol abuse can also cause increased  $\gamma$ -GT values [38,39]. Nevertheless, one limitation of our data was the missing correlation of laboratory values with initial protocol biopsies of grafts. These are not standard, and therefore, not routinely reported to the registries in the ET area. Likewise, available ultrasound exams are generally of limited quality and therefore not considered for analyses.

### Sodium levels

Direct osmolar damage is responsible for hepatocellular swelling and dysfunction [15]. In our study, cohort high sodium value during the donor’s stay in the intensive care unit was a significant factor for post-transplant outcome,

in contrast to the last available sodium value before procurement. This supports our theory that short-term changes in sodium values result in long lasting damage within hepatocytes because of intracellular osmolarity changes, even after aggressive correction of the donor serum sodium level [40].

A further aspect of the determined risk factors is their relevance at different points in time. In our study, female donor sex and high values of sodium prior to transplantation were only significant factors for 3-month survival rates and lost significance when determining 12-month survival. Regarding long-term survival, recipient and disease-related risk factors overpower the impact of donor-related risk factor.

### Nomogram

Comparable to the correlation of the probability of death on the waiting list by MELD score, the provided nomogram might offer a tool to calculate the risk of graft failure based solely on donor-related risk factors [41]. As described in Methods section, each of the significant factors of the multivariate analysis is represented within the calculations. Evaluation of a liver donor by the nomogram will reveal interesting interactions between different donor variables, highlighting the complexity of defining an extended criteria liver donors. Examples for an optimal donor and an extended criteria liver donor are provided in Table 3.

The bias that might result from this model selection is offset using 10-folding cross-validation for model evaluation. The resulting AUCs are comparable to those nomograms that are used in predicting postresection survival in common cancers and suggest a modest ability to determine early deaths.

### DRI versus Nomogram

In addition, the DRI was calculated for all donors and correlated with outcome prediction based on the derived

nomogram. Contrasting our nomogram predictions with DRI revealed that these tools are quite different and agreement between the two is very poor. Although it is possible that they contain complementary information, we believe the differences in the underlying patient populations on which they are based are more likely to be responsible. It is of note that the nomogram had slightly better AUC than the DRI, although both leave substantial room for improvement, underscoring the difficulty of predicting outcomes following transplantation or classifying donor quality. We did not perform a statistical comparison of the two as the nomogram was developed based on a different data set, and therefore such a comparison would be inherently in favor of the nomogram. Significant differences in graft quality between United Network of Organ sharing and ET were recently discussed by Braat and Blok when presenting their Eurotransplant Donor Risk Index (ET-DRI) [42,43].

Nevertheless, the comparison of predicting tools like ET-DRI, DRI and the nomogram supports our initial statement on how difficult it is to define an extended criteria liver donor.

Readers might raise the argument that this study has some limitations as we have excluded established high-risk settings like split liver grafts and DCD, acute liver failure, and re-transplantation [13]. Rather, we are of the opinion to define donor-related risk factors even more precisely as we do not weaken the statistic power of our data because of excluding these well-established high-risk settings [13,19].

In addition, this study may be criticized for not taking into account recipient-related disease severity represented by MELD score. As a rebuttal to this argument, we want to point out once again that the focus of this study was set on the definition of solely donor-related risk factors for early graft failure in deceased heart-beating donors for first time recipients with end-stage liver disease independent of their disease severity. We are also of the opinion that including recipient conditions would weaken the statistical power of donor-related risk factors. Furthermore, the study population was defined in the pre-MELD era.

Finally, all analyzed donor factors were generated from finally procured and transplanted grafts. These grafts represent a preselected group of donors with at least a minimum level of organ quality. Organs of obviously poor quality were eliminated from use during the pretransplantation evaluation process before organ procurement. This is also reflected in a relatively low rate of primary nonfunction/primary dysfunction rate of 5%.

In conclusion, several donor-related risk factors were defined for early outcome following liver transplantation (CIT, high sodium, cause of donor death,  $\gamma$ -GT, and female donor sex for the 3-month graft survival; CIT,  $\gamma$ -GT, and cause of donor death for the 12-month follow-up). In times of organ shortage and for optimizing organ utilization, our

nomogram might provide a simple tool for organ quality assessment based on survival estimation, consequently supporting a more individualized organ allocation in the future. Nevertheless, this study shows the difficulties of developing a precise prediction tool for outcome after liver transplantation based on organ quality.

## Authorship

GRS and GAB: main investigators and designed the study. VK and RA: contributed with their knowledge of the ELTR database. AR and XR: contributed with their knowledge of the ET database. MG: statistical analyses. GG and BK: participated in the performance of the research. FM and AKB: commented on and approved the final version.

## Funding

The study was performed without any financial support. The ELTR is supported by grants from Novartis and Astellas, and receives logistical support from Hôpital Paul Brousse (Assistance Publique, Hôpitaux de Paris, Paris, France).

## Acknowledgements

The authors owe their thanks to E. de Vries, data manager of Eurotransplant for his outstanding work on supporting us with the preparation of data for statistical analysis.

## References

1. Punch JD, Hayes DH, LaPorte FB, McBride V, Seely MS. Organ donation and utilization in the United States, 1996-2005. *Am J Transplant* 2007; 7: 1327.
2. Available at: [http://www.eurotransplant.org/?id=annual\\_report](http://www.eurotransplant.org/?id=annual_report) (accessed 25 January 2013).
3. Available at: <http://www.eltr.org/> (accessed 25 January 2013).
4. Brown RS Jr. Live donors in liver transplantation. *Gastroenterology* 2008; 134: 1802.
5. Anderson CD, Vachharajani N, Doyle M, *et al.* Advanced donor age alone does not affect patient or graft survival after liver transplantation. *J Am Coll Surg* 2008; 207: 847.
6. Mullhaupt B, Dimitroulis D, Gerlach JT, Clavien PA. Hot topics in liver transplantation: organ allocation—extended criteria donor—living donor liver transplantation. *J Hepatol* 2008; 48(Suppl. 1): S58.
7. Schemmer P, Nickkholgh A, Hinz U, *et al.* Extended donor criteria have no negative impact on early outcome after liver transplantation: a single-center multivariate analysis. *Transplant Proc* 2007; 39: 529.
8. Cameron AM, Ghobrial RM, Yersiz H, *et al.* Optimal utilization of donor grafts with extended criteria: a single-center experience in over 1000 liver transplants. *Ann Surg* 2006; 243: 748; discussion 53.

9. Busuttill RW, Tanaka K. The utility of marginal donors in liver transplantation. *Liver Transpl* 2003; **9**: 651.
10. Merion RM, Goodrich NP, Feng S. How can we define expanded criteria for liver donors? *J Hepatol* 2006; **45**: 484.
11. Mirza DF, Gunson BK, Da Silva RF, Mayer AD, Buckels JA, McMaster P. Policies in Europe on "marginal quality" donor livers. *Lancet* 1994; **344**: 1480.
12. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783.
13. Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet* 2006; **367**: 225.
14. Angele MK, Rentsch M, Hartl WH, et al. Effect of graft steatosis on liver function and organ survival after liver transplantation. *Am J Surg* 2008; **195**: 214.
15. Cywinski JB, Mascha E, Miller C, et al. Association between donor-recipient serum sodium differences and orthotopic liver transplant graft function. *Liver Transpl* 2008; **14**: 59.
16. Harrell F. *Regression Modeling Strategies*. New York: Springer, 2001; 215.
17. Gonen M. *Analyzing Receiver Operating Characteristic Curves with SAS*. SAS Press, 2007: ISBN 978-1-59994-298-8.
18. Briceno J, Ciria R, de la Mata M, Rufian S, Lopez-Cillero P. Prediction of graft dysfunction based on extended criteria donors in the model for end-stage liver disease score era. *Transplantation* 2010; **90**: 530.
19. Sass DA, Shakil AO. Fulminant hepatic failure. *Liver Transpl* 2005; **11**: 594.
20. Mells G, Neuberger J. Long-term care of the liver allograft recipient. *Semin Liver Dis* 2009; **29**: 102.
21. Silberhumer GR, Pokorny H, Hetz H, et al. Combination of extended donor criteria and changes in the Model for End-Stage Liver Disease score predict patient survival and primary dysfunction in liver transplantation: a retrospective analysis. *Transplantation* 2007; **83**: 588.
22. Northup PG, Pruett TL, Kashmer DM, Argo CK, Berg CL, Schmitt TM. Donor factors predicting recipient survival after liver retransplantation: the retransplant donor risk index. *Am J Transplant* 2007; **7**: 1984.
23. Adam R, Hoti E. Liver transplantation: the current situation. *Semin Liver Dis* 2009; **29**: 3.
24. Briscoe DM, Sayegh MH. A rendezvous before rejection: where do T cells meet transplant antigens? *Nat Med* 2002; **8**: 220.
25. Csete M. Gender issues in transplantation. *Anesth Analg* 2008; **107**: 232.
26. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation* 1999; **99**: 2317.
27. Neugarten J, Silbiger SR. The impact of gender on renal transplantation. *Transplantation* 1994; **58**: 1145.
28. Zeier M, Dohler B, Opelz G, Ritz E. The effect of donor gender on graft survival. *J Am Soc Nephrol* 2002; **13**: 2570.
29. Brooks BK, Levy MF, Jennings LW, et al. Influence of donor and recipient gender on the outcome of liver transplantation. *Transplantation* 1996; **62**: 1784.
30. Kahn D, Gavaler JS, Makowka L, van Thiel DH. Gender of donor influences outcome after orthotopic liver transplantation in adults. *Dig Dis Sci* 1993; **38**: 1485.
31. Marino IR, Doyle HR, Aldrighetti L, et al. Effect of donor age and sex on the outcome of liver transplantation. *Hepatology* 1995; **22**: 1754.
32. Adam R, Cailliez V, Majno P, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. *Lancet* 2000; **356**: 621.
33. Busuttill RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. *Ann Surg* 2005; **241**: 905; discussion 16.
34. D'Alessandro AM, Kalayoglu M, Sollinger HW, et al. The predictive value of donor liver biopsies on the development of primary nonfunction after orthotopic liver transplantation. *Transplant Proc* 1991; **23**: 1536.
35. Durand F, Renz JF, Alkofer B, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. *Liver Transpl* 2008; **14**: 1694.
36. Verran D, Kusyk T, Painter D, et al. Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. *Liver Transpl* 2003; **9**: 500.
37. Cuende N, Miranda B, Canon JF, Garrido G, Matesanz R. Donor characteristics associated with liver graft survival. *Transplantation* 2005; **79**: 1445.
38. Meisinger C, Lowel H, Heier M, Schneider A, Thorand B. Serum gamma-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population. *J Intern Med* 2005; **258**: 527.
39. Ruttman E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H. Gamma-glutamyl transferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. *Circulation* 2005; **112**: 2130.
40. Pownner DJ. Factors during donor care that may affect liver transplantation outcome. *Prog Transplant* 2004; **14**: 241; quiz 8-9.
41. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91.
42. Blok JJ, Braat AE, Adam R, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transpl* 2012; **18**: 112.
43. Braat AE, Blok JJ, Putter H, et al. The Eurotransplant Donor Risk Index in liver transplantation: ET-DRI. *Am J Transplant* 2012; **12**: 2789.