ORIGINAL PAPERS

Graft survival after liver transplantation: an approach to a new Spanish risk index

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ABSTRACT

Introduction: several indicators are available to assess liver graft survival, including the American DRI and the European ET-DRI. However, there are significant differences between transplant programs of different countries, and the previously mentioned indicators might be not valid in our setting.

Objectives: the aim of the study was to describe a new national liver graft risk indicator based on the results obtained from the Registro Español de Trasplante Hepático (RETH) and to validate the DRI and ET-DRI indicators.

Methods: the RETH includes a Cox analysis of factors associated with graft survival; the graft risk index (GRI) indicator was defined based on these results. The variables considered are dependent upon the donation conditions (*age, cause of death, blood compatibility* and *cold ischemia time*) and the transplant recipient (*age, underlying disease, hepatitis C virus, transplant number, UNOS status* and *surgical technique*). A logistic regression curve was obtained and graft survival curves were calculated by stratification. Precision was assessed using the ROC analysis.

Results: a GRI of 1 represents a probability of graft loss of 23.25%; each point increase in the GRI score multiplies this probability by 1.33. The best discrimination of GRI was obtained by stratification. The DRI ROC area was 0.54 (95% CI, 0.50-0.59) and the ET-DRI ROC area was 0.56 (95% CI, 0.51-0.61), compared to 0.70 (95% CI, 0.65-0.73) ($p < 0.0001$) for the GRI.

Conclusions: both the DRI and ET-DRI do not seem to be useful in our setting. Hence a national indicator is more desirable. The GRI requires a national study in order to further streamline and assess this indicator.

Key words: Liver transplantation. Graft survival. Prognostic score. External validation.

INTRODUCTION

Graft outcome is one of the factors that most conditions the subsequent evolution of patients undergoing a liver transplantation. This risk is carefully assessed by transplant teams and depends on donor-related variables, even more so when organ donors are managed using expanded criteria. Furthermore, variables associated with the donation-transplant process, which may differ from one program to the next, are also assessed. Finally, recipient-related variables are also studied, even more so when previously defined transplant indication limits are extended for new recipients. Therefore, indicators have been established to assess both liver graft and recipient survival post-transplantation. These include: MELD and CTP (1), NDDF (2), SOLD (3), DRI (4), SOFT (5), D-MELD (6), BAR (7), ET-DRI (8), NN-CCR and NN-MS (9), NN_{top15} (10), and DLI (11) (Supplementary Table 1). However, significant differences exist between donation-transplantation programs in different countries and organizations, both with regard to donor characteristics and transplant outcome (Supplementary Table 2). These differences are most remarkable for donor age and ethnicity, number of brain-dead donors (DBDs) *vs* cardiac-dead donors (DCDs), causes of brain death and liver bipartition, among others. All the above mean that donors and recipients are quite different between countries and/or regions. Hence a region/site specific scoring system would be more appropriate for liver graft acceptance and allocation.

The Registro Español de Trasplante Hepático (RETH) records the experience with liver transplantation in Spain, including systematic data, for all liver transplants.

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Supplementary Table 1. *Survival indicators in liver transplantation*

Reference						Study						Results	
Quote	Author	Year	Country (ISO 3166alfa-3)	Design	Patients (years)	Methodology	Variables: Donor	Variables: Process	Variables: Recipient	Indicator (range)	Graft survival	Patient survival	Validation‖ (AUC-ROC [95% CI] or "c-statistic")
1	Brown *Liver Transpl* 8:278	2002	USA	S	42 (1998-2000)			3	3	MELD (6;40)		3 months	1.00 (0.88-1.12)¶
								5	5	CTP (5;15)			1.49 (0.65-3.41)¶
2	Desai *Transplantation* 77:99	2004	USA	MS (UNOS)	2,565 (as of 2001)	MELD Logistic regression Multivariate analysis		7	7	NDDF		3 months	0.54 (0.50-0.59) 0.65 (0.61-0.69)
3	Ioannou *Liver Transpl* 12:1594	2006	USA	MS (UNOS)	20,301* (1994-2003)	Logistic regression Multivariate analysis	3	13 1	9	SOLD	90 days 1, 2, 5 years		Plotted comparison of observed vs predicted survival
4	FENG *Am J Transplant* 6:783	2006	USA	MS (SRTR)	20,023 (1998-2002)	Logistic regression Multivariate analysis	7	8 1		DRI	3 months 1 year 3 years		0 < DRI ≤ 1 91.9 (91.0-92.7)** 87.6 (86.6-88.7)** 81.2 (79.9-82.6)**
													2 < DRI 80.3 (78.1-82.6)** 71.4 (68.8-74.1)** 60.0 (56.9-63.2)**
5	Rana *Am J Transplant* 8:2537	2008	USA	MS (UNOS)	2,.673 (2002-2006)	Logistic regression Multivariate analysis	4	18 1	13	SOFT (-5;71)		3 months	0.83 (0.82-0.83)
6	Halldorson *Am J Transplant* 9:318	2009	USA	MS (UNOS)	17,942† (2003-2006)	Donor (age) x MELD	1	4	3	D-MELD	1 year	1 year	≥ 1,600 *vs* < 1,600†† Graft 45% *vs* 77.3% Patient 66.9% *vs* 81.4%
7	Dutkowski *Ann Surg* 254:745	2011	USA & DEU	MS (UNOS & Zurich)	37,255 (2002-2010)	DRI, MELD, D-MELD, SOFT Logistic regression Multivariate analysis	1 (Edad)	6 1 (TIF)	4	BAR		7 years	0.5, 0.6, 0.6, 0.7 0.7
8	Braat *Am J Transplant* 12:2789	2012	EUR	MS (ET)	5,723 (2003-2007)	DRI + 4 Logistic regression Multivariate analysis	3	1		ET-DRI	3 months 1 year 3 years		0 < ET-DRI ≤ 1 90.3 (82.7-97.9)** 83.6 (74.0-93.2)** 81.6 (71.6-91.6)**
													2 < ET-DRI 77.7 (75.5-79.9)** 67.5 (65.1-69.9)** 58.2 (55.4-61.0)**

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Supplementary Table 1 (Cont.). *Survival indicators in liver transplantation*

Reference						Study						Results		
Quote	Author	Year	Country (ISO 316$_{6alfa-3}$)	Design	Patients (years)	Methodology	Variables: Donor	Variables: Process	Variables: Recipient	Indicator (range)	Graft survival	Patient survival	Validation[I] (AUC-ROC [95% CI] or "c-statistic")	
9	Briceño *Am J Transplant* 9:318	2014	ESP	MS(11)	1,003[‡] (2007-2008)	MELD, D-MELD, P-SOFT, SOFT, BAR, DRI					3 months		all < 0.67 *vs* NN-CCR p = 0.001	all < 0.61 *vs* NN-MS p = 0.001
						Neural networks (Positive-graft survival model)	57			NN-CCR			0.8060	
						Neural networks (Negative-graft loss model)	19	12	26	NN-MS			0.8216	
10	Lau *Transplantation* 101:e125	2017	AUS	S	180 (1988-2013)	DRI, SOFT					30 days		DRI: 0.680 (0.669-0.690) SOFT: 0.638 (0.632-0.645)	
						Neural networks (multilayer perception)	12	15	3	NN_{Top15}			0.818 (0.812-0.824)	
11	Collett *Transplantation* 101:786	2017	GBR	MS (UKTR)	7,929[§] (2000-2014)	Logistic regression Multivariate analysis	7 2	7 1	 3	DLI	1, 2, 5, 10 years		0.5500	

Reference: S: single-center study; MS: multicenter study; UNOS: United Network for Organ Sharing; SRTR: Scientific Registry of Transplants Recipients ET: Eurotransplant; UKTR: United Kingdom Transplant Registry. *Combined transplants and re-transplants excluded. [†]Re-transplants, acute liver failure, and donation after cardiac death excluded. [‡]Split, living donor, and combined transplants excluded. [§]Recipients < 16 years, heterotopic or auxiliary liver and blood incompatibility excluded.
Study: MELD: model for end-stage liver disease; CTP: Child-Turcotte-Pugh score; NNDF: newly derived discrimination function; SOLD: score of liver donor; DRI: donor risk index; SOFT: survival outcome following liver transplantation; D-MELD: donor-MELD; BAR: balance of risk score; ET-DRI: Eurotransplant donor risk index; NN-CCR: neural network-correct classification rate; NN-MS: neural network-minimum sensitivity; DLI: donor liver index.
Results: [I]Except when indicated, AUC-ROC (95% CI): area under the ROC curve (95% confidence interval); [¶]Linear regression OR (95% CI); **Adjusted survival; †[I]Kaplan-Meier.

Supplementary Table 2. *Activity at OPTN, ET, and ON during 2016**

	OPTN	ET	ONT
Population			
Countries (ISO 3166$_{alfa-3}$)	USA	AUS BEL HRV DEU HUN LUX NLD SVN	ESP
Inhabitants (million) (UNFPA)	**324.1**	**134.4**	**46.1**
Density (inhabitants/km^2)	**35**	**198**	**92**
Donation: global activity			
All donors	**15,949**	**3,479**	**2,390**
Donors, dead/living	**9,971** (*62.5*) / **5,978** (*37.5*)	**2,021** (*58.1*) / **1,458** (*41.9*)	**2,019** (*84.5*) / **371** (*15.5*)
Donation rate (pmp)	**30.8** / **18.6**	**14.5** / **10.7**	**43.8** / **8.1**
Dead donors: characteristics			
Type:			
Total	**9,971**	**2,021**	**2,019**
DBD	***8,287*** (*83.1*)	***1,803*** (*89.2*)	***1,524*** (*75.5*)
DCD	***1,684*** (*16.9*)	***218*** (*10.8*)	***495*** (*24.5*)
Uncontrolled	–	*5 (2.3)*	*125 (45.5)*
Controlled	–	*213 (97.7)*	*270 (54.5)*
Sex:			
Female	**4,014** (*40.3*)	**917** (*45.4*)	**836** (*41.4*)
Male	**5,957** (*59.7*)	**1,104** (*54.6*)	**1,183** (*58.6*)
Age:			
Mean	**26 (18-34)**	**55**	**60.1 ± 17.1**
Age groups			
< 65	**9,343** (*93.7*)	**1,496** (*74.1*)	**919**‡ (*44.5*)
≥ 65	**628** (*6.3*)	**525** (*25.9*)	**1,100**‡ (*54.5*)
70-79			*456 (22.6)*
≥ 80			*198 (9.8)*
Cause of death:			
Trauma	**2,783** (*27.9*)	**373** (*18.5*)	**303** (*15.0*)
Anoxia/stroke/natural	**6,856** (*68.8*)	**1,549** (*76.6*)	**1,236** (*61.2*)
Other	**362** (*3.3*)	**99** (*4.9*)	**480** (*23.8*)
Liver transplants			
Offered donors	**8,152**	**1,978**	**1,669**
Removed livers			**1,537**
Unused donors	**741**	**411**	**414**
Liver transplants:	**7,841**	**1,732**	**1,159**
Donors, dead/living	**7,496** / **345**	**1,610** / **122**	**1,131** / **28**
Rate (pmp)	**24.2**	**12.9**	**25.1**
Waiting list:			
Patient on active list	**24,604**	**4,172**	**2,115**
Died while on list	**1,883** (**7.7**)	**501** (**12.0**)	**78** (**3.7**)
Global mean $_{(days)}$			**150**
Adults / children			**153** / **91**

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Supplementary Table 2 (Cont.). *Activity at OPTN, ET, and ON during 2016**

	OPTN		ET		ONT	
	Liver transplants					
Per blood group†:						
0	**1,162**	**1,274-2,401**	.	.	**125.8**	**40-279**
A	**1,445**	**1,139-1,920**	.	.	**78**	**20-206**
B	**385**	**347-428**	.	.	**84**	**21-187**
AB	**127**	**112-148**	.	.	**67.2**	**8-145**
Transplant type:						
Pediatric < 15 years	**515**	***(6.6)***	**182**	***(10.5)***	**59**	***(5.1)***
Unorthodoxl:						
DCD	**447**	***(5.7)***	**117**	***(6.8)***	**134**	***(11.6)***
Living donor	**345**	***(4.4)***	**122**	***(7.0)***	**28**	***(2.4)***
Domino	**9**	***(0.1)***	**15**	***(0.9)***	**5**	***(0.4)***
Split	**186**	***(2.4)***	**82**	***(4.7)***	**2**	***(0.2)***

DBD: donor brain dead; DCD: donor cardiac dead. ***Data in absolute value (%).*** *Based on: OPTN, Organ Procurement and Transplantation Network. Available from: https://optn.transplant.hrsa.gov/data/; ET : Eurotransplant. Available from: http://statistics.eurotransplant.org/; ONT: Organización Nacional de Trasplantes. Available from: http://www.ont.es/infesp/Paginas/Memorias.aspx; Newsletter Transplant 2017. Available from: http://www.ont.es/publicaciones/Documents/. †$OPTN_{2011\text{-}2014}$: mean and 95% confidence interval; ONT_{2016}: median and interquartile range. ‡Data < or ≥ 60 years.

Therefore, it is a tool that can be used to gain insight into our own experience. The goal of the study was to describe a new liver graft risk indicator based on the RETH results. The indicator combined donor, process and recipient related factors to facilitate decision making on organ acceptance and allocation to specific patients. Attempts were also made to validate and compare this indicator with the American DRI and European ET-DRI in our setting.

MATERIAL AND METHOD

Data sources

The description of the new indicator was based on data collected from the RETH annual report (12). This report includes donor characteristics and outcome for all liver transplants performed in Spain. Specifically, it contains systematic data of 22,846 liver transplants carried out at 24 transplant centers from 1984 to 2016. This is a public report that is available online. Data from 600 adult (above 15 years of age) liver transplants performed consecutively in our center were used for the validation of the aforementioned indicators. The data were collected prospectively and the characteristics are described below. The study was compliant with the Spanish Organic Law 15/1999 for the protection of personal data. It was also approved by the Aragon ethics committee, $Code_{CEICA}$ PI18/0097, on April 24th 2018.

GRI description

The study methodology for the design and validation of the GRI is summarized in table 1:

- The RETH report includes a Cox proportional hazards regression analysis of the factors associated with overall graft survival. Results are expressed as CoxPH (RR) values with their corresponding 95% confidence intervals (95% CI) (Table 1A).
- Based on the Cox regression equation [$\ln(\lambda_t) = a + b_1x_1 + b_2x_2 + \ldots + b_nx_n$], an indicator may be defined as an exponential (inverse logarithm) of a linear risk score. Three indicators were defined by grouping together variables with statistically significant differences (SSDs) according to the multivariate analysis: donor risk index (dRI), recipient risk index (rRI) and graft risk index (GRI), where GRI = dRI x rRI (Table 1B).
- The new indicator (GRI) was validated and compared to the American DRI and European ET-DRI in our series (Table 1C).

Two events were considered for indicator assessment:

- Event 1. Graft survival (GS): defined as the time elapsed from the transplant to either re-transplantation or recipient death from any cause, whichever comes first.
- Event 2. Failure-free graft survival (ffGS): defined as the time elapsed from the transplant date to the either re-transplantation or recipient death with an associated chronic graft dysfunction, whichever comes first.

GRI logistic function

The Hosmer-Lemeshow goodness of fit test ($p > 0.05$) was used to assess model fit. Values were subsequently obtained for the logistic regression curve: regression coefficients (β_0 y β_1) with their corresponding standard errors, Wald statistic and odds ratio (OR) = $e^{(\beta 1)}$, with the confidence interval.

Indicator comparisons: values, graft survival and hazard ratio by stratification

Graft survival curves were calculated via indicator-related risk groups using Kaplan-Meier estimations. The HR for

Table 1. *GRI description: variables included (1A), formula (1B) and examples in comparison with DRI and ET-DRI (1C)*

1A. Statistically significant variables for overall graft survival included in the GRI*					
Variables		**RR**	**95% CI lower**	**95% CI upper**	**p-value**
Donor age	Age < 50	1.00	.	.	
	Age 50-74	1.28	1.22	1.35	< 0.05
	Age > 75	1.69	1.54	1.84	< 0.05
Cause of brain death	TBI	1.00	.	.	
	AS	1.12	1.06	1.20	< 0.05
	Anoxia	1.13	1.01	1.25	< 0.05
	Tumor	1.44	1.14	1.82	< 0.05
	Other	1.26	1.12	1.43	< 0.05
UNOS status	Home	1.00	.	.	
	ICU	1.58	1.36	1.87	< 0.05
	Hospital	1.42	1.31	1.55	< 0.05
	Medical care	1.08	1.02	1.14	< 0.05
Recipient HCV	No	1.00	.	.	
	Yes	1.39	1.33	1.49	< 0.05
Blood compatibility	Isogroup	1.00	.	.	
	Compatible	1.19	1.08	1.34	< 0.05
	Incompatible	1.99	1.61	2.34	< 0.05
Recipient age	Recipient < 60	1.00	.	.	
	Recipient child	1.33	1.13	1.50	< 0.05
	Recipient ≥ 60	1.66	1.40	1.86	< 0.05
Cause of transplantation	Cholestasis	1.00	.	.	
	SALF	1.10	0.93	1.30	NS
	Cirrhosis	1.15	1.04	1.28	< 0.05
	Cancer	1.33	1.19	1.48	< 0.05
	Metabolic	1.05	0.90	1.25	NS
	Other	1.58	1.36	1.83	< 0.05
Transplant number	1st	1.00	.	.	
	2nd	1.38	1.26	1.51	< 0.05
	> 3	1.68	1.33	2.12	< 0.05
Cold ischemia time	< 6	1.00	.	.	
	6-12	1.16	1.11	1.22	< 0.05
	> 12	1.31	1.16	1.48	< 0.05
Technique	Classic	1.00	.	.	
	Extracorporeal	1.14	1.09	1.20	< 0.05
	Piggy-back	1.32	1.18	1.48	< 0.05
Date (year)	≥ 2011	1.00	.	.	
	2002-10	1.85	1.71	2.00	< 0.05
	≤ 2001	1.33	1.24	1.44	< 0.05

*RETH Results Report (Memoria de Resultados del RETH), available from: http://www.sethepatico.org. RR: risk ratio; CI: confidence interval; NS: not significant; AS: acute stroke; SALF: severe acute liver failure; TBI: traumatic brain injury; ICU: intensive care unit; UNOS: United Network for Organ Sharing; HCV: hepatitis C virus.

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Table 1 (Cont.). *GRI description: variables included (1A), formula (1B) and examples in comparison with DRI and ET-DRI (1C)*

1B. Prospective GRI formula

Prospective GRI calculation = dRI x rRI = $\exp^{\text{donor factors}}$ x $\exp^{\text{recipient factors}}$

GRI = $\exp^{[(0.247 \text{ if donor age} \geq 50 - \leq 74) + (0.525 \text{ if donor age} \geq 75) + (0.113 \text{ if DBD} = \text{AS}) + (0.122 \text{ if DBD} = \text{anoxia}) + (0.365 \text{ if DBD} = \text{tumor}) + (0.231 \text{ if DBD} = \text{other}) + (0.174 \text{ if ABO} = \text{compatible}) + (0.688 \text{ if ABO} = \text{incompatible}) + (0.148 \text{ if ischemia time 6-12 h}) + (0.270 \text{ if ischemia time} > 12 \text{ h})]}$ x $\exp^{[(0.285 \text{ if child recipient}) + (0.507 \text{ is recipient age} \geq 60) + (0.329 \text{ if recipient HCV-positive}) + (0.322 \text{ if OLT number} = 2) + (0.519 \text{ if OLT number} \geq 3) + (0.140 \text{ if cirrhosis}) + (0.285 \text{ if cancer}) + (0.457 \text{ if other than cholestasis, fulminant, or metabolic}) + (0.457 \text{ if UNOS} = 1) + (0.351 \text{ if UNOS} = 2) + (0.077 \text{ if UNOS} = 3) + (0.131 \text{ if extracorporeal bypass}) + (0.278 \text{ if piggy-back})]}$

1C. Examples comparing GRI, DRI and ET-DRI

		Factor	Reference example	Example 1	Example 2	Example 3	Example 4 (max GRI)
Donor	1	Age	**35**	64	*78*	*80*	*82*
	2	Cause of DBD	**Trauma**	*Acute stroke*	*Acute stroke*	*Anoxia*	*Tumor*
	3	ABO	**Isogroup**	Isogroup	Isogroup	*Compatible*	*Incompatible*
	4	Ischemia T	**< 6**	< 6	*6 - 12*	*> 12*	*> 12*
dRI			**1**	**1.433**	**2.195**	**2.977**	**6.347**
Recipient	5	Age	**45**	55	*62*	*64*	*64*
	6	HCV	**No**	*Yes*	*Yes*	*Yes*	*Yes*
	7	OLT #	**First**	First	First	*Third*	*Third*
	8	Disease	**Cholestasis**	*Cirrhosis*	*Cirrhosis*	*Cirrhosis*	*Other*
	9	UNOS	**4**	4	4	*2*	*1*
	10	Bypass	**Classic**	*Piggy-back*	*Piggy-back*	*Piggy-back*	*Piggy-back*
rRI			**1**	**2.111**	**3.504**	**8.365**	**12.769**
Overall GRI			**1**	**3.025**	**7.691**	**24.903**	**81.045**
$DRI_{(Feng)}$			0.954	1.686	1.914	1.916	1.770
$ET\text{-}DRI_{(Braat)}$			0.956	1.651	1.865	1.866	1.730

Example of reference in boldface (Risk 1); variables modified from reference in italics. In DRI and ET-DRI calculations variables not included in the GRI were considered to have a value of 0 (risk 1).

each risk group was estimated *versus* a standard group using a Cox regression model.

ROC curves

DR, ET-DRI and GRI accuracy to predict graft survival was assessed using the area under the curve in a ROC curve analysis, where 1 represents a perfect discrimination and 0.5 represents a discrimination that is not above the level of chance.

A Wald p-value < 0.05 was considered as significant. All analyses were carried out using the IBM® SPSS® Statistics, version 22.0 software (©Copyright IBM Corporation 1989 to 2013, Chicago, IL, USA).

RESULTS

DRI, RRI and GRI description and calculation

The indicators DRI, RRI, and GRI were obtained based on the data collected from the Cox logistic regression analysis of overall graft survival in the RETH (Table 1). Table 1 includes an example of GRI with a score of 1 and an example of maximum risk (GRI: 81.045) with their corresponding DRI and ET-DRI scores.

Validation series

Data from 600 liver transplants performed in our center were used for the validation of the new indicators, DRI and ET-DRI. The data with regard to the validation series are listed in table 2.

GRI logistic function

A Hosmer-Lemeshow analysis showed that the observed probabilities were similar to those expected for the three indicators: DRI (p = 0.883), ET-DRI (p = 0.317) and GRI (p = 0.210). Figure 1 shows the logistic equation curve and the values observed by GRI interval. A GRI of 1 represents a graft loss likelihood of 23.25%; each point increase in the GRI multiplies this graft loss probability by 1.33 (95% CI: 1.24-1.44).

Indicator comparisons: values, graft survival and hazard ratios by stratification

No statistically significant differences in the mean DRI were seen between groups with and without graft survival: 1.54 (95% CI: 1.50-1.58) *vs* 1.60 (95% CI: 1.55-1.65), respectively. Moderate statistically significant differences were obtained for ET-DRI: 1.51 (95% CI: 1.47-1.55) *vs* 1.60 (95% CI: 1.56-1.63), p < 0.05, respectively.

Table 2. *Principal cohort characteristics*

Variables*	Transplants n = 600	
Age (years)	**54.2 ± 9.7** ***55 (48-61)*** *15-69*	
Sex: male (*vs* female)	447	(74.6)
Blood group:		
0	252	(41.9)
A	283	(47.2)
B	49	(8.2)
AB	16	(2.7)
MELD	**16.2 ± 5.9**	
Child-Pugh (n = 464)		
A	78	(16.8)
B	165	(35.6)
C	221	(47.6)
UNOS:		
ICU	50	(8.3)
Hospital	102	(17.0)
Continuous care	277	(46.2)
Home	17	(28.5)
Causes:		
Cholestasis	**6**	**(1.0)**
Metabolic	**10**	**(1.7)**
Cancer	**16**	**(2.7)**
Fulminant	**20**	**(3.4)**
Other	**84**	**(14.0)**
Retrasplants	*78*	
Cirrhosis	**464**	**(77.3)**
Enolic	234	(39.0)
Viral	181	(30.2)
HBV	27	(4.5)
HCV	154	(25.7)
Coinfection with HCV + HBV	*3*	
Coinfection with HCV + HIV	*10*	
Cryptogenic	22	(3.7)
Autoimmune	15	(2.5)
Biliary	12	(2.0)
Total cirrhosis with HCC	*120*	
Waiting list:		
Mean	**80.4 ± 103**	
Time according to blood group		
0	***47***	***(13-122)***
A	***49***	***(11-112)***
B	***36***	***(9-109)***
AB	***26***	***(6-73)***

HCV: hepatitis C virus; HIV: human immunodeficiency virus; MELD: model for end-stage liver disease; UNOS: United Network for Organ Sharing; HCC: hepatocellular carcinoma; HBV: hepatitis B virus. *Quantitative variables are expressed as: **mean ± standard deviation, median (interquartile range),** and *range*. ***Qualitative variables*** are expressed as n (%).

Table 2 (Cont.). *Principal cohort characteristics*

Variables*	Transplants n = 600	
Donor variables		
Age (years)	**52.9 ± 17.8** ***56 (40-68)*** *11-87*	
Male sex (*vs* female)	364	(60.7)
ICU days	**2.9 ± 2.1**	
Cause of death:		
AS	401	(66.8)
Trauma	144	(24.0)
Anoxia	41	(6.8)
Tumor	3	(0.5)
Other	11	(1.8)
Location:		
Local	415	(69.2)
Regional	22	(3.7)
National	163	(27.1)
Hemodynamics:		
Noradrenaline	402	(67.0)
Cardiac arrest	82	(13.7)
Diabetes insipidus	189	(31.7)
Labs:		
Sodium (mmol/l)	**147 ± 11**	*138-194*
AST (IU/l)	**51 ± 73**	*5-920*
ALT (IU/l)	**40 ± 52**	*4-497*
GGT	**65.8 ± 78.1** ***34 (17-85)*** *3-612*	
HBcAb positive	49	(8.2)
CMV positive	497	(82.8)
Steatosis:		
Mild	61	(10.2)
Moderate	3	(0.5)
Peri-transplantation variables		
Elective (*vs* emergency)	544	(90.7)
Correlation (donor vs *recipient):*		
Blood		
Isogroup	576	(96.0)
Compatible	19	(3.2)
Incompatible	5	(0.8)
Isosex	343	(57.2)
Technique:		
Preservation solution (UW)	362	(60.3)

(Continue in the next page)

Table 2 (Cont.). *Principal cohort characteristics*

Variables*	Transplants n = 600	
Technique		
Cold ischemia time (min)	**353 ± 114** ***330 (276-410)*** *125-792*	
Surgery time (min)	**325 ± 64**	
Intraoperative events:		
Post-reperfusion synd.	88	(14.7)
Mortality	0	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; HBcAb: hepatitis B virus core antibody; CMV: cytomegalovirus; UW: University of Wisconsin. Location: local, in the city; regional, < 200 km; national, > 200 km. ***Quantitative variables*** are expressed as: **mean ± standard deviation, *median (interquartile range),*** and *range.* ***Qualitative variables*** are expressed as n (%).

Table 2 (Cont.). *Principal cohort characteristics*

Variables*	Transplants n = 600	
Hospitalization course		
Primary dysfunction	7	(1.2)
Complications:		
Acute rejection	46	(7.7)
Vascular	21	(3.5)
Biliary	36	(6.0)
ICU days	**7.9 ± 8.2**	
Ward days	**15.2 ± 11.9**	
Hospitalization days	**23.0 ± 15.2**	
Re-transplantations:	**74**	**(12.3)**
Causes[3]		
Primary dysfunction	*5*	*(6.8)*
Recurrence	*14*	*(18.9)*
Chronic rejection	*18*	*(24.3)*
Vascular complication	*18*	*(24.3)*
Biliary complication	*13*	*(17.6)*
Other	*6*	*(8.1)*
Graft survival: Kaplan-Meier		
1 year	75.3 (71.6-78.6)	
3 years	66.3 (62.2-70.1)	
5 years	61.4 (57.1-65.4)	
Patient survival:		
Follow-up time (days)	**2,280.4 ± 1,978.9** ***1,880.5 (452-3,715)*** *1-6,956*	
Overall mortality	224[†]	(37.3)
Graft function		
DDG	*104*	*(46.4)*
DFG	*120*	*(53.6)*

(Continue in the next column)

Table 2 (Cont.). *Principal cohort characteristics*

Variables*	Transplants n = 600
Patient survival: Kaplan-Meier	
1 year	80.7 (77.3-83.6)
3 years	72.9 (69.0-76.4)
5 years	68.3 (64.2-72.0)

Clinical outcome variables categorized as in the RETH. DDG: died with dysfunctioning graft; DFG: died with a functioning graft. ***Quantitative variables*** are expressed as: **mean ± standard deviation, *median (interquartile range),*** and *range.* ***Qualitative variables*** are expressed as n (%). Kaplan-Meier: mean (95% confidence interval). [†]Tweny-one patients died while on the re-transplantation waiting list.

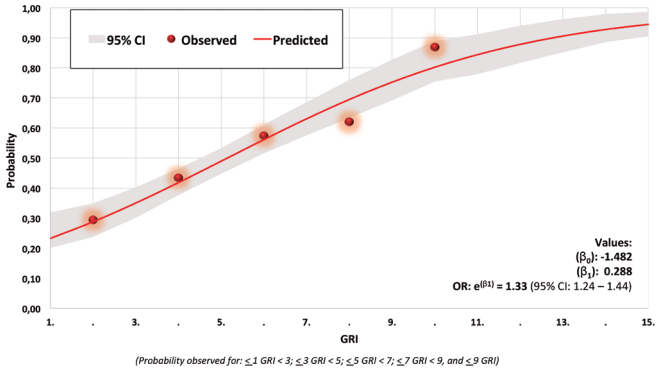

Fig. 1. *GRI logistic function: predicted event probability and 95% CI.*

Finally, GRI showed highly statistically significant differences between the groups: 4.27 (95% CI: 4.06-4.49) *vs* 6.46 (95% CI: 5.98-6.93), p < 0.0001.

Differences in graft survival between higher and lower indices are clearly seen for all three indicators. However, GRI had the best discriminating power for survival among intermediate groups of the three indicators. Furthermore, survival diminished progressively down to a GRI ≥ 9, which represents a 1-year graft survival rate of 47.5% (95% CI: 34.6-59.3) and there were highly significant differences *versus* the standard group (HR: 4.03; 95% CI: 2.63-6.19; p < 0.0001) (Table 3).

ROC curves

The area under the curve (AUC) according to the ROC analysis was 0.54 (95% CI: 0.50-0.59) for DRI and 0.56 (95% CI: 0.51-0.61) for ET-DRI. Thus, their ability to predict graft survival was not above the level of chance. The AUC for GRI was 0.70 *(*95% CI: 0.65-0.73*)* with highly significant differences when compared to the other two indices (DeLong test, p < 0.0001) (Fig. 2). With regard to the power of GRI to predict transplant futility, the fact that a GRI score ≥ 10 always forecasted graft loss should be highlighted. The specificity was 100%, the sensitivity was 14.4%, the positive predictive value was 100% and the negative predictive value was 54.2%.

Table 3. *Adjusted 1-, 3-, and 5-year graft survival and hazard ratio (HR) according to index stratification*

Indices	Cases (n = 600)		Events (n = 298)		Graft survival								
					Kaplan-Meier and 95% CI						Cox regression		
	n	%	n	%	1 year		3 years		5 years		HR	95% CI	p
DRI_{Feng} stratification													
DRI < 1.2	110	18.3	52	47.3	77.3	68.3 - 84.1	70.6	61.0-78.3	64.2	54.2-72.6			
1.2 ≤ DRI < 1.6	210	35.0	100	47.6	79.8	73.6 - 84.7	70.1	63.3-75.6	65.7	58.6-71.9	1.07	0.76-1.49	NS
1.6 ≤ DRI < 2	213	35.5	103	48.4	75.4	68.9 - 80.7	66.5	59.6-72.5	61.7	54.2-68.3	1.29	0.92-1.80	NS
2 ≤ DRI	67	11.2	43	64.2	58.0	45.1 - 68.9	46.0	33.4-57.7	42.4	30.0-54.3	2.09	1.39-3.14	< 0.001
					Log-rank p-value < 0.001								
$ET\text{-}DRI_{Braat}$ stratification													
ET-DRI < 1.2	103	17.2	47	45.6	77.7	68.4-84.6	70.5	60.7-78.3	63.7	53.3-72.4			
1.2 ≤ ET-DRI < 1.6	209	34.8	96	45.9	80.2	74.0-85.1	71.9	65.1-77.6	67.5	60.6-73.5	1.06	0.75-1.51	NS
1.6 ≤ ET-DRI < 2	227	37.8	116	51.1	75.1	68.9-80.3	64.8	57.9-70.8	59.0	51.8-65.5	1.46	1.03-2.06	< 0.05
2 ≤ ET-DRI	61	10.2	39	63.9	55.7	42.3-67.1	44.9	31.9-57.0	42.9	31.0-56.1	2.10	1.37-3.23	< 0.001
					Log-rank p-value < 0.001								
GRI stratification													
1 ≤ GRI < 3	119	19.8	35	29.4	83.8	75.8-89.3	77.1	67.8-84.0	73.2	63.2-80.9			
3 ≤ GRI < 5	240	40.0	104	43.3	81.0	75.5-85.4	70.0	63.7-75.4	67.9	61.4-73.5	1.35	0.92-1.98	NS
5 ≤ GRI < 7	122	20.3	70	57.4	72.1	63.1-79.2	63.8	54.5-71.7	55.9	46.6-64.2	1.77	1.18-2.65	< 0.01
7 ≤ GRI < 9	58	9.7	36	62.1	70.5	56.9-80.5	62.5	48.4-73.7	54.4	40.2-66.6	2.06	1.29-3.29	< 0.01
9 ≤ GRI	61	10.2	53	86.9	47.5	34.6-59.3	39.3	27.1-51.3	32.8	21.5-44.6	4.03	2.63-6.19	< 0.0001
					Log-rank p-value < 0.0001								

*% events over "n of subgroup". NS: not significant.

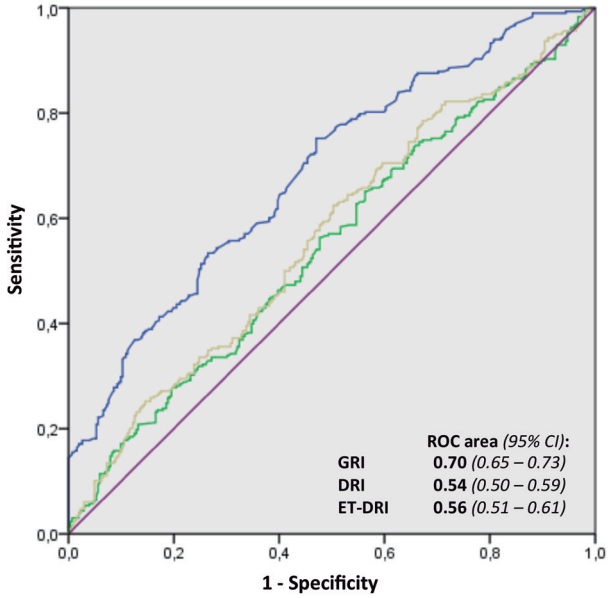

Fig. 2. *ROC curves for GRI, DRI and ET-DRI.*

All the results obtained for event 2 (ffGS) are superimposable on those described for event 1 (GS) (unpublished data).

DISCUSSION

Classic indicators to assess cirrhosis prognosis (Child-Pugh) or transplant waiting list mortality (MELD) are not suitable to predict post-transplant patient survival (1,2). The latest indicators based on neural networks are complex, rely on limited experience, are scarcely generalizable and are also difficult to extrapolate to the daily clinical practice (9,10). Finally, external validations for some indicators (DRI, MELD, D-MELD and SOFT [7], DRI and ET-DRI [13], DRI and SOFT [10]) do not confirm their validity when applied to scenarios different to their principal intended use, as is the case in our study. The latter point likely results from large differences between countries and programs, in terms of donor population and donation-transplantation process characteristics and not so much with recipient characteristics.

Donor-related variables may be linked to specific graft features and general donor characteristics. Most indicators described thus far share a number of variables including age, cause of brain death, etc. Furthermore, there are some variables where the justification or relation to graft or

patient survival does not seem to be based on clear scientific grounds, such as smoking, height, etc. However, even though steatosis is a primary determinant of post-transplant liver function (14) (particularly within the first year), none of the established indicators include this variable, either directly or indirectly. Kulik et al. (15) highlighted in a recent study that allografts with a fatty liver are a significant cause of primary graft failure and an excessive mortality after transplantation. Traditionally, high donor sodium levels have been associated with graft failure and primary non-function (PNF) (16). A study by Sirivatanauksorn et al. (17) showed that high donor sodium was associated with marginal liver grafts, but only ALT > 65 IU/l was associated with higher PNF rates. More recently, Al-Freah et al. (18) did not find any donor variables that were associated with PNF, except for donor-recipient ABO mismatch. Finally, these indicators should contemplate specific donor variables. Some of these are considered on an international level under the expanded criteria donor concept. These are also included in Spain in the non-standard risk donor (Donantes de Riesgo no Estándar [DRNE]) category and may include drug abuse, intoxications, tumors, infections, hepatitis B or C, age above 65 years, etc.

With regard to recipient-related variables, allocating a specific organ to its most appropriate recipient is a difficult decision, particularly in certain situations. We agree with Feng et al. (4) that grafts are ideally a highly homogeneous group and thus an optimal organ may be allocated to any person, whereas non-ideal grafts make up a highly heterogeneous group with a high risk spectrum. In the latter case, allocating a suboptimal organ to a high-MELD recipient (19,20) with certain conditions (21) or with a higher waiting-list mortality rate (22) gambles with the risks of post-transplant survival *versus* wait-list mortality.

Finally, with regard to variables related with the donation-transplantation process, the most established indicators include cold ischemic time (CIT) in their design. CIT may in turn be dependent on donor location, available transportation means, surgeon skill and unforeseeable events associated with the surgical technique, etc. A good indicator should already be available at the time that an organ is offered and should not include variables that measure equal or similar factors (e.g., donor location or CIT). Perhaps decision making in medicine in the future, particularly in transplant medicine, will be based on complex artificial neural networks (23). The analysis of countless variables (big data) and numerous interdependent networks means that we will learn, decide and maybe even get it right or wrong. In the meantime, we still believe that a solution to the donor-recipient matching problem may be facilitated by these types of tools and it will not entail expunging the human component of awareness, conscience and sensitivity.

The present study has a number of limitations: the above indicator is based on a non-predictive analysis of a national registry with over 22,000 transplants; it was validated with a limited series in only one center; the actual weight of certain variables in graft survival will have to be refined and updated (HCV is the most significant instance) and these indices are intended to simplify complex situations dependent on multiple factors, which often reduces quantitative variables to categorical variables.

To conclude, our study highlights that neither DRI nor ET-DRI seem to adequately predict graft risks in our setting. A national GRI might be a very useful tool to categorize graft-recipient matching. Hence, a national study is needed to regularly streamline and update this indicator and to provide a wider validation thereof.

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