Graft Risk Index After Liver Transplant: Internal and External Validation of a New Spanish Indicator

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Abstract

Objectives: **Scarcity of liver grafts has led to the use of marginal donors, consequently increasing the number of complications posttransplant. To prevent this situation, several indicators have been developed. However, important differences remain among countries. Here, we compared an early-risk liver transplant indicator based on the Spanish Liver Transplant Registry, called the Graft Risk Index, versus the US donor risk index and the Eurotransplant donor risk index.**

Materials and Methods: **The new indicator was based on prospectively collected data from 600 adult liver transplants performed in our center. We considered 2 events to compare the indexes: graft survival and rejection-free graft survival, with Cox proportional regression for analyses. Power to predict graft survival was evaluated by calculating the receiver operating characteristic area under the curve.**

Results: **We found no differences between the US and Eurotransplant donor risk indexes in prediction of patients with and without early graft failure. With regard to early survival, only the Graft Risk Index allowed better survival discrimination, in which survival progressively decreased with values ≥ 3 (with probability of graft survival at 1 month of 68%; 95% confidence interval, 46.2-82.5). This increase in risk was significant compared with the standard group (hazard ratio of 10.15; 95% confidence interval, C 3.91- 26.32; *P* < .001). We calculated powers of prediction of 0.52 (95% confidence interval, 0.43-0.62), 0.54 (95% confidence interval, 0.45-0.65), and 0.69 (95% confidence interval, 0.61-0.77) for donor risk index, Eurotransplant donor risk index, and early Graft Risk Index, respectively.**

Conclusions: **Neither the US donor risk index nor the Eurotransplant donor risk index was valid for our Spanish liver donation and transplant program. Therefore, an indicator to predict posttransplant graft survival that is adapted to our environment is necessary. This national Graft Risk Index can be a useful tool to optimize donor-recipient matching.**

Key words: *Donor Risk Index, Early complications, Eurotransplant Donor Risk index, Graft survival, Organ Procurement and Transplantation Network, Rejection-free graft survival*

Introduction

In Spain, more than 1000 transplant procedures have been performed each year in the past decade; more than half of these patients will have at least 1 significant complication during their first year posttransplant.[1] Specifically, in the immediate postoperative period, they are admitted to the intensive care unit (ICU) and may have systemic complications, including respiratory, cardiovascular, renal, and hematologic, as well as graft complications (technical and nontechnical), including primary graft failure, arterial or portal thrombosis, and rejection. These complications can lead to longer ICU and hospital stays and can result, in many cases, in graft failure (retransplant) or even patient death.

High complication rates may be associated with the use of expanded criteria donors and/or recipients with comorbidities and poor clinical conditions

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pretransplant. An important way to prevent these complications is appropriate donor-recipient matching. For this purpose, several indicators have been described: Model for End-Stage Liver Disease (MELD), Child-Turcotte-Pugh score,[2] Newly Derived Discrimination Function,[3] Score of Liver Donor,[4] the Donor Risk Index (DRI),[5] Survival Outcome Following Liver Transplantation (SOFT),[6] donor-MELD (D-MELD),[7] Balance of Risk score,[8] Eurotransplant Donor Risk Index (ET-DRI),[9] Neural Network-Correct Classification Rate, Neural Network-Minimum Sensitivity,[10] Neural Network,[11] and the Donor Liver Index.[12]

There are important differences among organ donation and transplant programs in different countries and organizations in terms of both donor characteristics and transplant results. These differences are more striking regarding donor age and ethnicity, number of donors after brain death versus donors after cardiac death, causes of brain death, controlled hepatic bipartition, and other factors. For example, for the French donation program, Winter and associates have shown that DRI and ET-DRI were not useful.[13]

All of the above factors indicate that donors and recipients can differ between countries and/or regions; therefore, a region-specific scoring system that could be used for liver selection and allocation would be appropriate. The Spanish Liver Transplant Registry (RETH; for its acronym in Spanish) was created with the cooperation of professional teams incorporated in the Spanish Liver Transplantation Society and the Spanish National Transplant Organization. The RETH records the experiences of liver transplant in Spain; the database contains structured data of all liver transplants performed in the country, thus serving as a knowledge repository of our own experience.

In this study, our main objective was to determine graft quality when we compared the DRI, the ET-DRI, and our region-specific Graft Risk Index (GRI).[14] We used data from 22 846 liver transplants from RETH, which included liver transplant procedures done at our center. The GRI, a new early risk indicator in liver transplant, was based on outcomes recorded in RETH. This Spanish-specific indicator, which combines donor- and recipient-related factors, could facilitate patient-specific decision-making in organ selection and allocation.

Materials and Methods

The description of the new indicator was based on data collected from the annual report from RETH,[15] which describes donor characteristics and liver transplant results in Spain. In particular, the structured data include 22 846 liver transplants, which were performed in 24 transplant centers from 1984 to 2016. This report is in the public domain and is available online.

For validation of described indicators, we included prospectively collected data of 600 adult liver transplants (recipients were older than 15 years) performed consecutively in our center. The study complied with Organic Law 15/1999 on Personal Data Protection. It was also approved by the Aragon ethics committee ($Code_{CEICA}$ PI18/0097) on April 24, 2018.

The RETH report also included a Cox proportional hazards regression analysis of the factors associated with overall graft survival. Results are expressed as Cox regression values with their 95% confidence intervals (95% CI).

Based on the Cox regression equation itself, $\ln(\lambda t) = a + b_1x_1 + b_2x_2 + \ldots + bnxn$, an indicator can be defined as the exponential (inverse logarithm) of a linear risk score. By grouping variables with statistically significant differences for multivariate analysis, 2 GRIs can be defined, one overall (global) and one early (< 1 month).

To evaluate the indicators, 2 types of events were considered. The first event was graft survival, defined as the period from date of transplant to date of retransplant or death for any reason, whichever occurred first. The second event was rejection-free graft survival, defined as the period from date of transplant to date of retransplant or death due to chronic graft dysfunction, whichever occurred first.

The Hosmer-Lemeshow goodness of fit test ($P < .05$) was used to evaluate model fit. We then obtained the values used to generate the logistic regression curve: regression coefficients (β0 and β1) with their corresponding standard errors, the Wald statistic, and odds ratio and confidence intervals.

To compare indicators, graft survival curves were calculated by indicator-related risk group using Kaplan-Meier estimations. The hazard ratio (HR) for each risk group was estimated versus a standard group using a Cox regression model.

The accuracy of DRI, ET-DRI, and GRI to predict graft survival was assessed using the area under the

curve in a receiver operating characteristic curve analysis, where 1 represents perfect discrimination and 0.5 represents discrimination not above chance level.

A Wald *P* value < .05 was considered significant. All analyses were performed with IBM SPSS Statistics version 22.0 (IBM Corporation, Chicago, IL, USA).

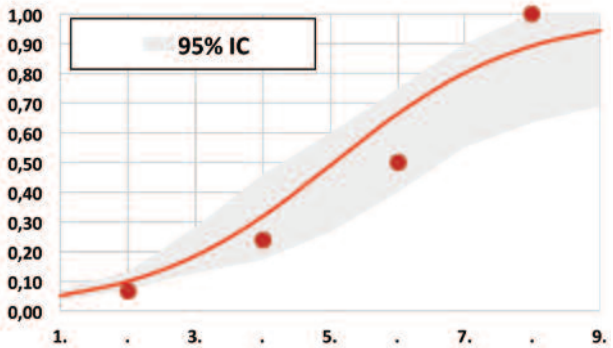
Results

To describe and calculate the GRI, global and early GRIs were obtained using Cox logistic regression analysis on global graft survival data from the RETH (Table 1). Table 1 shows an example of a global GRI with risk 1 and an example of maximum risk (GRI = 81.04); the examples shown are accompanied by DRI and ET-DRI scores.

To validate new indicators besides DRI and ET-DRI, data from 600 adult liver transplants performed at our center were included. Validation series data are described in Tables 2, 3, and 4.

With reference to the logistic function of the GRI, the Hosmer-Lemeshow test revealed that the probabilities observed were similar to those expected for the 3 indicators concerned: DRI (*P* = .20), ET-DRI (*P* = .25), global GRI (*P* = .20), and early GRI (*P* = .28). Figure 1 shows the logistic equation curve of the early GRI, together with the values observed in the early GRI intervals. An early GRI value of 1 corresponded to a probability of graft failure (5.07%), and each point of early GRI increase indicated that the probability of having a graft failure was multiplied by 2.06 (95% CI, 1.57-2.96).

Figure 1. Curve for the Predicted Event Probability for Early Graft Risk Index With 95% Confidence Interval



Probability was observed for Graft Risk Index (GRI) < 3, ≤ 3 GRI < 5, ≤ 5 GRI < 7, and ≤ 7 GRI. Values are as follows: β_0 = -3,650; β_1 = 0,721; odds ratio = e(β_1) = 2057 (95% confidence interval, 1.571 – 2,963). Dots show observed values and lines show predicted values.

Table 1. Prospective Calculation of Global and Early Graft Risk Index: Formula and Examples Compared With US Donor Risk Index and European Eurotransplant Donor Risk Index

Prospective GRI = dRI × rRI = expdonor factors × exprecipient factors

Prospective Global GRI = eg [(0.247 if > 50 donor age < 74) + (0.525 if donor age > 75) + (0.113 if DBD = CVA) + (0.122 if DBD = anoxia) + (0.365 if DBD = tumor) + (0.231 if DBD = other) + (0.174 if ABO = compatible) + (0.688 if ABO = incompatible) + (0.148 if ischemia 6-12 h) + (0.270 if ischemia > 12 h) + (0.285 if recipient child) + (0.507 if recipient age > 60) + (0.329 if positive HCV recipient) + (0.322 if No. LT = 2) + (0.519 if No. LT > 3) + (0.140 if cirrhosis) + (0.285 if cancer) + (0.457 if other, not cholestasis, neither fulminant, nor metabolic) + (0.457 if UNOS = 1) + (0.351 if UNOS = 2) + (0.077 if UNOS = 3) + (0.131 if extracorporeal bypass) + (0.278 if piggyback)]

Prospective Early GRI = eg [(0.501 if DBD = tumor) + (0.300 if DBD = other) + (0.577 if ABO = incompatible) + (0.336 if ischemia 6-12 h) + (0.501 if ischemia > 12 h) + (0.329 if adult recipient age < 60) + (0.464 if No. OLT = 2) + (0.732 if No. OLT > 3) + (-0.446 if cirrhosis) + (-0.462 if cancer) + (1.015 if UNOS = 1) + (0.668 if UNOS = 2) + (0.239 if UNOS = 3) + (0.215 if classic bypass) + (0.501 if extracorporeal bypass)]

Donor or Recipient	Factor	Reference Example	Example 1	Example 2	Example 3	Example 4
D1	Age, y	35	64	78	80	82
D2	Cause DBD	Trauma	*CVA*	*CVA*	*Anoxia*	*Tumor*
D3	ABO	Isogroup	Isogroup	Isogroup	*Compatible*	*Incompatible*
D4	Ischemia, h	< 6	< 6	6-12	> 12	> 12
R5	Age, y	45	55	62	64	64
R6	HCV	No	Yes	Yes	Yes	Yes
R7	No. LT	1	1	1	3	3
R8	Disorder	Cholestasis	*Cirrhosis*	*Cirrhosis*	*Cirrhosis*	*Other*
R9	UNOS	4	4	4	2	1
R10	Bypass	Classic	*Piggyback*	*Piggyback*	*Piggyback*	*Piggyback*
		Calculations				
Global GRI		1	3.025	7.691	24.903	81.045
Early GRI		1	0.640	0.896	2.197	10.085
DRI (Feng et al[5])		0.954	1.686	1.914	1.916	1.770
ET-DRI (Braat et al[9])		0.956	1.651	1.865	1.866	1.730

Abbreviations: CVA: cerebrovascular accident; D, donor; DBD, donor brain dead; DCD, deceased cardiac donor; DRI, US Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; GRI, Graft Risk Index; HCV, hepatitis C virus; LT, liver transplant; OLT, orthotopic liver transplant; R, recipient; UNOS: United Network for Organ Sharing

Underlined variables were included in the early GRI. Variables in italics were modified with respect to reference. For the calculation of the DRI and ET-DRI, the variables not contemplated in the GRI have been considered of to have value 0 (risk 1).

Table 2. Main Characteristics of the Cohort

Variable	Transplant Recipient (N = 600)
Mean age ± SD, y	54.2 ± 9.7
Median age (interquartile range), y	55 (48-61)
Range, y	15-69
Male sex (% vs female)	447 (74.6)
Blood type, No. (%)	
O	252 (41.9)
A	283 (47.2)
B	49 (8.2)
AB	16 (2.7)
Mean MELD score ± SD	16.2 ± 5.9
Child-Pugh class (N = 464), No. (%)	
A	78 (16.8)
B	165 (35.6)
C	221 (47.6)
UNOS status, No. (%)	
ICU admission	50 (8.3)
Hospital admission	102 (17.0)
With continuous care	277 (46.2)
At home	17 (28.5)
Cause of liver disease, No. (%)	
Cholestasis	6 (1.0)
Metabolic	10 (1.7)
Cancer	16 (2.7)
Fulminant	20 (3.4)
Other	84 (14.0)
Retransplant	78
Cirrhosis	464 (77.3)
Alcohol	234 (39.0)
Virus	181 (30.2)
HBV	27 (4.5)
HCV	154 (25.7)
HCV + HBV coinfection	3
HCV + HIV coinfection	10
Cryptogenetic	22 (3.7)
Autoimmune	15 (2.5)
Biliary	12 (2.0)
Total cirrhosis with HCC	120
Mean time on wait list ± SD, mo	80.4 ± 103
Median wait time by blood type (interquartile range), mo	
O	47 (13-122)
A	49 (11-112)
B	36 (9-109)
AB	26 (6-73)

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; SD, standard deviation; UNOS, United Network for Organ Sharing

In our comparison of indicators, no statistically significant differences in mean DRI results were seen between groups with and without graft survival. However, the GRI (global and early) results showed significant differences between both groups (Table 5).

Regarding early survival, risk group stratification of the DRI and ET-DRI values did not show significant differences in early graft survival between these indicators and global GRI, except for the group with extreme values. Only early GRI showed better survival discrimination, with an observation of a progressive decrease in survival in which an early GRI value ≥ 3 indicated a probability of graft survival at 1 month of 68.0% (95% CI, 46.2-82.5) and a significant increase in risk compared with the standard group (HR = 10.15, 95% CI, 3.91-26.32; $P < .001$) (Table 6). With regard to global survival, all indexes showed differences between extreme groups, with GRI having the best discrimination.

Our power of prediction calculation using receiver operating characteristic area under the curve showed values of 0.52 (95% CI, 0.43-0.62) and

Table 3. Characteristics of Liver Transplant Donors

Variable	Donor (N = 600)
Matching donor variables	
Mean age ± SD, y	52.9 ± 17.8
Median age (interquartile range), y	56 (40-68)
Age range, y	11-87
Male sex (% vs female)	364 (60.7)
Mean days in ICU ± SD	2.9 ± 2.1
Cause of death, No. (%)	
CVA	401 (66.8)
Trauma	144 (24.0)
Anoxia	41 (6.8)
Tumor	3 (0.5)
Others	11 (1.8)
Donor allocation, No. (%)	
Local (same city)	415 (69.2)
Regional (within < 200 km)	22 (3.7)
National (> 200 km)	163 (27.1)
Hemodynamic, No. (%)	
Noradrenaline	402 (67.0)
Cardiac arrest	82 (13.7)
Diabetes insipidus	189 (31.7)
Laboratory analysis, mean ± SD (interquartile range)	
Sodium, mmol/L	147 ± 11 (138-194)
AST, IU/L	51 ± 73 (5-920)
ALT, IU/L	40 ± 52 (4-497)
GGT, IU/L	65.8 ± 78.1
HBcAb positive, No. (%)	49 (8.2)
CMV positive, No (%)	497 (82.8)
Steatosis	
Mild	61 (10.2)
Moderate	3 (0.5)
Peritransplant variables	
Elective (% vs urgent)	544 (90.7)
Correlation (donor vs recipient)	
Blood type, No. (%)	
Isogroup	576 (96.0)
Compatible	19 (3.2)
Incompatible	5 (0.8)
Same sex	343 (57.2)
Technique	
UW preservation solution, No. (%)	362 (60.3)
Mean CIT ± SD, min	353 ± 114
Median CIT (interquartile range), min	330 (276-410)
CIT range, min	125-792
Mean surgery time ± SD, min	325 ± 64
Intraoperative event, No. (%)	
Reperfusion injury	88 (14.7)
Intraoperative mortality	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIT, cold ischemia time; CMV, cytomegalovirus; GGT, gamma glutamyl transpeptidase; HBcAb, hepatitis B virus core antibody; ICU, intensive care unit; UW, University of Wisconsin

0.54 (95% CI, 0.45-0.65) for DRI and ET-DRI, respectively, indicating that their capacity to predict graft survival was not better than chance. The receiver operating characteristic area under the curve analysis of global GRI was 0.68 (95% CI, 0.60-0.76) and that of early GRI was 0.69 (95% CI, 0.61-0.77) (Figure 2).

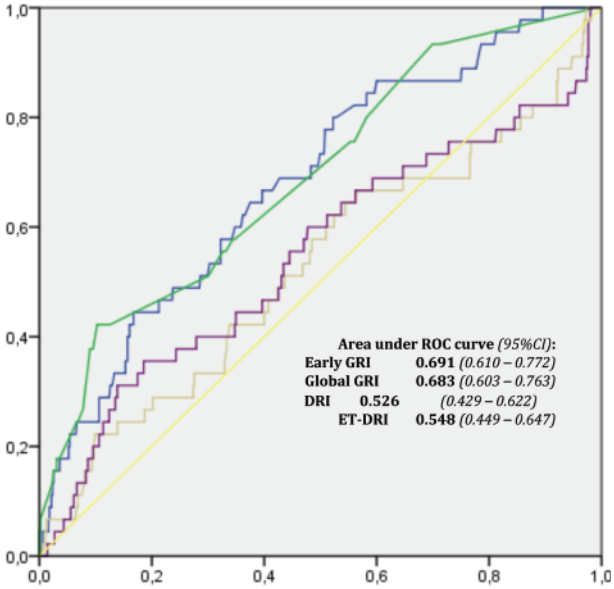
Table 4. Liver Transplant Results

Variable	Transplant Result (N = 600)
Primary non/dysfunction, No. (%)	7 (1.2)
Complication, No. (%)	
Acute rejection	46 (7.7)
Vascular	21 (3.5)
Biliary	36 (6.0)
Mean days in ICU ± SD	7.9 ± 8.2
Mean hospitalization days ± SD	15.2 ± 11.9
Mean total days ± SD	23.0 ± 15.2
Retransplant, No. (%)	74 (12.3)
Retransplant reason, No. (%)	
Primary non/dysfunction	5 (6.8)
Recurrence	14 (18.9)
Chronic rejection	18 (24.3)
Vascular complications	18 (24.3)
Biliary complications	13 (17.6)
Other	6 (8.1)
Kaplan-Meier graft survival, mean ± SD (95% CI), %	
1 year	75.3 (71.6-78.6)
3 years	66.3 (62.2-70.1)
5 years	61.4 (57.1-65.4)
Mean follow-up ± SD, d	2280.4 ± 1978.9
Median follow-up (interquartile range), d	1880.5 (452-3715)
Follow-up range, d	1-6956
Global patient death	224* (37.3)
With functioning graft	
DDG	104 (46.4)
DFG	120 (53.6)
Kaplan-Meier patient survival, mean ± SD (95% CI), %	
At 1 year	80.7 (77.3-83.6)
At 3 years	72.9 (69.0-76.4)
At 5 years	68.3 (64.2-72.0)

Abbreviations: 95% CI, 95% confidence interval; DDG, died with dysfunctional graft; DFG, died with functioning graft; ICU intensive care unit; SD, standard deviation

*21 Patients died while on retransplant wait list.

Figure 2. Receiver Operating Characteristic Curve Analysis



Abbreviations: DRI, US Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; GRI, Graft Risk Index; ROC, receiver operating characteristic curve

Discussion

Recently, benchmark[16] indicators have been described regarding outcomes after liver transplant, including surgical outcomes, patient and graft survival, patient care in the ICU, complications, length of stay, and other factors.

Regarding length of stay in the ICU, Pedersen and associates,[17] in a study of factors associated with a longer stay in the ICU, found that pretransplant MELD was the most potent predictor of prolonged ICU stay. Stratigopoulou and colleagues[18] confirmed that MELD and transplant duration are independent predictors of prolonged ICU stay. However, Rana and associates[19] described a new index to predict the length of posttransplant hospitalization; of 22 independent risk factors associated with longer

Table 5. US Donor Risk Index and European Eurotransplant Donor Risk Versus Graft Risk Index Values With and Without Retransplant or Death

Indicator		No (n = 555)	Yes (n = 45)	*P* Value
DRI (Feng et al[5])	Mean and 95% CI	1.572 (1.541-1.604)	1.609 (1.474-1.743)	.538
	Median and interquartile range	1.555 (1.295-1.808)	1.642 (1.253-1.904)	
ET-DRI (Braat et al[9])	Mean and 95% CI	1.552 (1.523-1.581)	1.607 (1.481-1.732)	.314
	Median and interquartile range	1.557 (1.278-1.774)	1.641 (1.284-1.917)	
	Range	0.935-2.541	0.950-2.355	
Global GRI	Mean and 95% CI	5.478 (5.180-5.776)	8.046 (6.516-9.576)	< .001
	Median and interquartile range	4.627 (3.238-6.681)	6.411 (4.527-9.531)	
	Range	1.478-38.283	2.477-24.829	
Early GRI	Mean and 95% CI	1.266 (1.205-1.326)	2.094 (1.631-2.556)	< .001
	Median and interquartile range	1.146 (0.640-1.603)	1.603 (1.109-2.590)	
	Range	0.630-5.207	0.640-7.360	

Abbreviations: 95% CI, 95% confidence interval; DRI, US Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; GRI, Graft Risk Index

Table 6. Adjusted 1-Month and 1- to 5-Year Graft Survival and Hazard Ratio According to Index Stratification

Index Stratification	Early (1 month)									Global (1 and 5 years)								
Index	Cases (N = 600)		Events (N = 45)		Kaplan-Meier Survival		Cox Regression			Events (N = 298)		Kaplan-Meier, 1 year		Kaplan-Meier, 5 years		Cox Regression Global		
	No.	%	No.	%*	%	95% CI	HR	95% CI	*P* Value	No.	%*	%	95% CI	%	95% CI	HR	95% CI	*P* Value
DRI (Feng et al[5])																		
DRI < 1.2	110	18.3	11	10.0	90.0	82.5-94.4				52	47.3	77.3	68.3-84.1	64.2	54.2-72.6			
1.2 ≤ DRI < 1.6	210	35.0	11	5.2	94.8	90.9-97.1	0.50	0.22-1.16	NS	100	47.6	79.8	73.6-84.7	65.7	58.6-71.9	1.07	0.77-1.49	NS
1.6 ≤ DRI < 2	213	35.5	13	6.1	93.9	88.9-96.4	0.59	0.26-1.31	NS	103	48.4	75.4	68.9-80.7	61.7	54.2-68.3	1.29	0.92-1.81	NS
2 ≤ DRI	67	11.2	10	14.9	85.1	73.9-91.8	1.55	0.66-3.64	NS	43	64.2	58.0	45.1-68.9	42.4	30.0-54.3	2.09	1.39-3.14	< .001
					Log-rank 0.0672							*Log-rank 0.0008*						
ET-DRI (Braat et al[9])																		
ET-DRI < 1.2	103	17.2	10	9.7	90.3	82.8-94.6				47	45.6	77.7	68.4-84.6	63.7	53.3-72.4			
1.2 ≤ ET-DRI < 1.6	209	34.8	9	4.3	95.7	91.9-97.7	0.43	0.17-1.04	NS	96	45.9	80.2	74.0-85.1	67.5	60.6-73.5	1.07	0.75-1.52	NS
1.6 ≤ ET-DRI < 2	227	37.8	18	7.9	92.1	87.7-95.0	0.80	0.37-1.74	NS	116	51.1	75.1	68.9-80.3	59.0	51.8-65.5	1.46	1.04-2.06	< .05
2 ≤ ET-DRI	61	10.2	8	13.1	86.9	75.6-93.2	1.39	0.54-3.51	NS	39	63.9	55.7	42.3-67.1	42.9	31.0-56.1	2.11	1.37-3.23	< .001
					Log-rank 0.0737							*Log-rank 0.0005*						
Global GRI																		
1 ≤ GRI < 3	119	19.8	5	4.2	95.0	89.2-97.7				35	29.4	83.8	75.8-89.3	73.2	63.2 - 80.9			
3 ≤ GRI < 5	240	40.0	10	4.2	96.2	93.0-98.0	0.74	0.26-2.07	NS	104	43.3	81.0	75.5-85.4	67.9	61.4 - 73.5	1.35	0.92-1.98	NS
5 ≤ GRI < 7	122	20.3	11	9.0	91.0	84.3-94.9	1.84	0.68-4.98	NS	70	57.4	72.1	63.1-79.2	55.9	46.6 - 64.2	1.77	1.17-2.65	< .01
7 ≤ GRI < 9	58	9.7	7	12.1	87.9	76.2-94.1	2.47	0.83-7.36	NS	36	62.1	70.5	56.9-80.5	54.4	40.2 - 66.6	2.06	1.29-3.29	< .01
9 ≤ GRI	61	10.2	12	19.7	80.3	67.9-88.3	4.14	1.55-11.0	.0045	53	86.9	47.5	34.6-59.3	32.8	21.5 - 44.6	4.03	2.63-6.19	< .001
					Log-rank 0.0003							*Log-rank 0.0003*						
Early GRI																		
GRI < 1	241	40.2	9	3.7	96.3	93.0-98.0				92	38.2	81.0	75.3-85.5	67.4	60.5-73.4			
1 ≤ GRI < 2	283	47.2	17	6.0	94.0	90.6-96.2	1.63	0.73-3.67	NS	152	53.7	77.3	71.9-81.8	62.5	56.5-67.9	1.17	0.89-1.52	.2505
2 ≤ GRI < 3	51	8.5	11	21.6	78.4	64.3-87.4	6.35	2.63-15.33	< .001	35	68.6	58.8	44.1-70.9	48.2	33.8-61.2	1.89	1.28-2.79	< .001
3 ≤ GRI	25	4.1	8	32.0	68.0	46.2-82.5	10.15	3.91-26.31	< .001	19	76.0	32.0	15.3-50.1	24.0	9.8-41.6	2.82	1.71-4.64	< .001
					Log-rank < 0.0001							*Log-rank < 0.0001*						

Abbreviations: 95% CI, 95% confidence interval; DRI, US Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; GRI, Graft Risk Index; NS, not significant
*% Events in "n of subgroup."

hospital stay, the 2 most significant were shown to be previous admission of the recipient to the ICU (odds ratio of 1.75; 95% CI, 1.58-1.95) and previous transplant (odds ratio of 1.60; 95% CI, 1.47-1.75).

Regarding morbidity and mortality in the ICU, preventing complications is a key factor in the evolution of these patients and begins with appropriate donor-recipient matching. Traditional indicators used to assess the prognosis of cirrhosis (Child-Pugh) or mortality on the liver transplant wait list (MELD) are not valid to predict posttransplant patient survival. Recent indicators based on neural networks are complex, based on limited experience, have low generalization capacity, and are difficult to extrapolate to daily clinical practice. Finally, the external validations of some indicators (DRI, MELD, vs D-MELD; SOFT, DRI, vs ET-DRI; and DRI vs SOFT)[20] could not be confirmed when applied in different scenarios from the one originally described, such as in our study. The latter is likely because of the large differences between countries and regions regarding donor population characteristics and the donation-transplant process and less to recipient characteristics.

With regard to indicators, donor-related variables may be associated with specific graft characteristics and general characteristics of the "donor per se." Most described indicators share some common variables, such as age and cause of brain death, among others. However, some indicators are those whose use is not based on a solid scientific basis, such as height. Although steatosis is a main determinant of posttransplant liver function (especially in the first year), as described by Kulik and associates[21] in a recent study, it is striking that it has not been included in any of the indicators described.

Donor age has been included in many indicators.[22] However, in RETH, it is an independent risk factor regarding overall graft survival but not with respect to short-term graft survival (< 1 mo), which has been previously concurred by an international group[23] and by our group.[24,25]

Risk factors include advanced age, and, traditionally, donor hypernatremia has been associated with primary graft dysfunction or initial poor graft function.[26] Subsequent studies have not confirmed these findings; however, donor hypernatremia may be associated with marginal livers, but only alanine aminotransferase levels (> 65 IU/L) were associated with a higher incidence of primary graft dysfunction.[27]

Variables associated with the donor per se should be included as indicators of graft survival. Some of these variables have been grouped internationally under the concept of expanded criteria donors. These include drug abuse, tumors, infections, hepatitis B/C,

age > 65 years, and high transaminase/bilirubin levels.

Regarding recipient-related variables, we have already stated how the previous clinical condition of the recipient could affect length of stay in the ICU (these include high MELD score and United Network for Organ Sharing status). Allocating an organ to the most appropriate recipient is one of the most difficult decisions. We agree with Feng and associates[5] that an ideal graft is homogeneous, allowing allocation of an optimal organ to anyone; however, nonideal grafts are heterogeneous, covering a wide spectrum of risk. In the latter case, allocating a suboptimal organ to a recipient with high MELD,[28,29] specific conditions,[30] or conditions with higher wait list mortality could interfere with the risk of patient survival against wait list mortality.[31] Therefore, an indicator should include this aspect in its design.

With regard to process-related variables, most indicators have included cold ischemia time in their design. Cold ischemia time may depend in turn on donor location, available means of transportation, surgical variables, and other factors. We believe a good indicator should be known at the time of organ donation and should not include other added variables (eg, donor location and cold ischemia time).

Another much debated issue is the influence of the number of transplants performed at the center on morbidity and mortality rates. Muller and associates[16] analyzed this effect, concluding that centers with a higher proportion of reference transplants had more biliary complications. However, in our RETH analyses, the number of transplants performed at the center did not constitute an independent risk factor for graft survival.

The present study has some limitations. Although the indicator described is based on a national registry of more than 22 000 transplants, it has been validated with a limited series of a single center. These indexes aim to predict and simplify complex situations depending on many factors and, in many cases, simplify quantitative variables (eg, time of cardiac arrest, cold ischemia time) to categorical ones.

In the future, decision-making should be based on complex artificial neural networks[32] that will eventually replace medical doctors. However, until then, we will continue the search for tools that decrease errors in our donor-recipient matching decisions.

Conclusions

We found that neither DRI nor ET-DRI adequately predicted graft risks in our setting. Therefore, it is necessary to have an indicator to predict post-transplant graft survival that is adapted to the environment in which it will be used. A national GRI can be a useful tool to optimize donor-recipient matching. Therefore, a national study would allow delineation of indicators and a more extensive validation to be performed.

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