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Analysis of the Importance of Comorbidities with RNAGraft Survival in Liver Transplantation: Analysis of the Importance of Comorbidities with ANN

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Keywords: Liver transplantation; Age; Disease status; Comorbidities; Coronary heart disease; Pathologies; Portal vein thrombosis; HIV; Morbid obesity

Abbreviations: BDA: Big Data Analysis; ML: Machine Learning; ANN: Artificial Neural Networks; MLP: Multilayer Perceptron

Introduction

More than half of the patients with a liver transplant (OLT) will present at least one significant complication during the first year, therefore the criteria for assigning an organ must have an appropriate combination of benefit and utility, in which a very important role is played. important concept of "survival benefit" [1-2]. High complication rates may be the result of using organs from more limited donors (older age, donors in asystole, with expanded criteria, etc.) and/or receiver characteristics (age, disease status, comorbidities, etc.). Comorbidity is a medical term, coined by AR Feinstein in 1970, and subjected to several terminological proposals. Multimorbidity could be defined as the presence of different diseases or conditions that accompany a main chronic disease two (Supplemental Information e-1). In recent years, the indications for OLT have been expanded, in addition to increasing the age of the patients included in the list, and with this the presence of comorbidities is increasing [3]. There are studies that analyze the impact of a certain comorbidity on the results of liver transplantation: coronary heart disease [4-6] chronic kidney disease [7], diabetes [8], non-liver cancer [9]. Most of the indicators described to adjust donor-recipient allocation share some limitations: poor external validation when applied to populations other than those described [10,11] the statistical methodology of most of them is a logistic regression [12,13] and do not include recipient comorbidities. Medicine is an ideal field for the use of known techniques such as Big Data Analysis (BDA) and machine learning (ML), which may allow us in the future to improve our clinical research capacity and more accurately target the therapies we provide to our patients [14]. Artificial Neural Networks (ANN/ANN) thus constitute an alternative multivariate analysis method. The objective of this study is to analyze the predictive value of comorbidities in liver graft survival in the first year.

Materials and Methods

Data sources

The study was carried out from the data of all patients with a liver transplant (first transplant) performed at the Hospital Clinico Universitario Lozano Blesa (Aragón, Spain) from 2010 to 2021. The study has the Approval of the Research Ethics Committee of the Autonomous Community of Aragon (CEICA) (Act 1/2022) (Supplemental Information e-2).

Supplementary Table 1: Multimorbidity model adopted.

Supplementary Online Content

e–1: Multimorbidity model adopted.

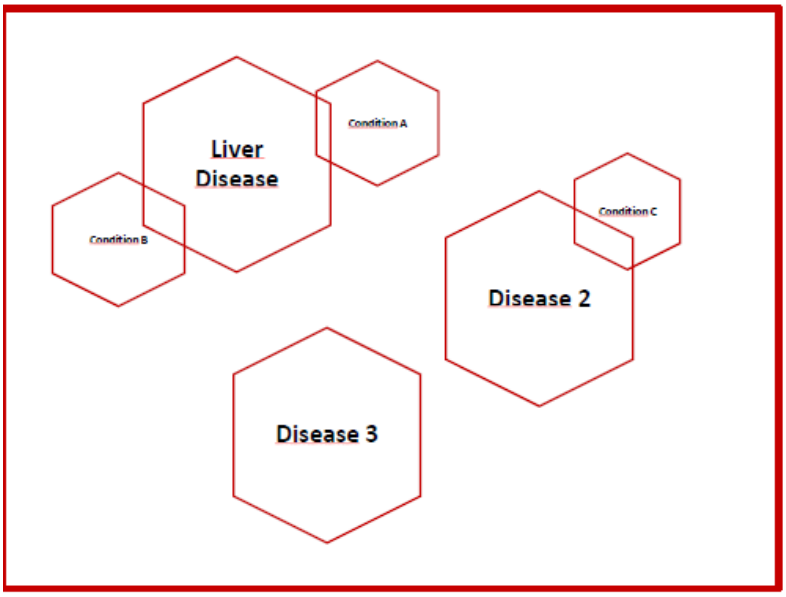
e–2: CEICA approval

e–3: Variables

e–4: Multivariate Analysis of the RETH

e–5: Network Results: architecture, weights and biases

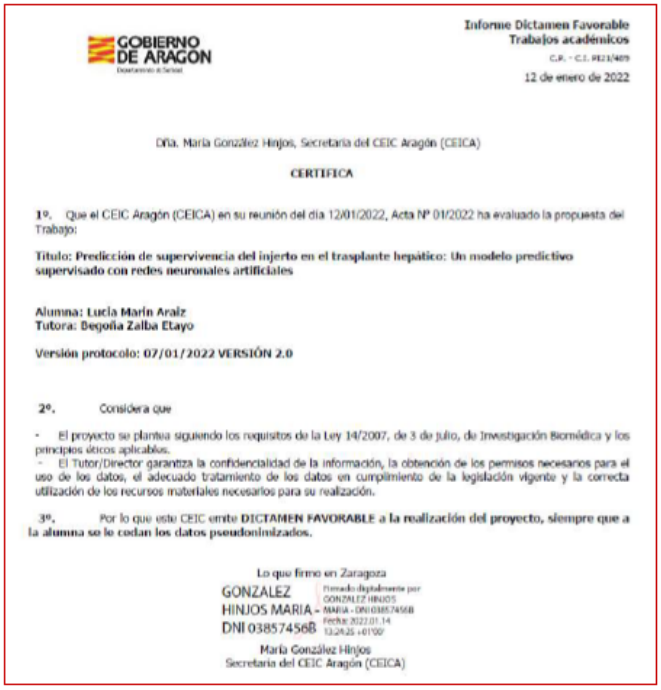
e–6: ROC Area of the Model



Uhlig K, Leff B, Kent D, Dy S, Brunnhuber K, Burgers JS, et al. (2014) A framework for crafting clinical practice guidelines that are relevant to the care and management of people with multimorbidity.

J Gen Intern Med 29(4): 670-679/

Supplementary Table 2: CEICA Approval.



GOBIERNO DE ARAGON

Informe Dictamen Favorable
Trabajos académicos

12 de enero de 2022

Dña. María González Hinjos, Secretaria del CEIC Aragón (CEICA)

CERTIFICA

1º. Que el CEIC Aragón (CEICA) en su reunión del día 12/01/2022, Acta Nº 01/2022 ha evaluado la propuesta del Trabajo:

Título: **Predicción de supervivencia del injerto en el trasplante hepático: Un modelo predictivo supervisado con redes neuronales artificiales**

Alumna: **Lucía Marín Araiz**
Tutora: **Begoña Zalba Etayo**

Versión protocolo: **07/01/2022 VERSIÓN 2.0**

2º. Considera que

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y los principios éticos aplicables.
- El Tutor/Director garantiza la confidencialidad de la información, la obtención de los permisos necesarios para el uso de los datos, el adecuado tratamiento de los datos en cumplimiento de la legislación vigente y la correcta utilización de los recursos materiales necesarios para su realización.

3º. Por lo que este CEIC emite **DICTAMEN FAVORABLE a la realización del proyecto, siempre que a la alumna se le cedan los datos pseudonimizados.**

Lo que firmo en Zaragoza

GONZALEZ HINJOS MARIA - DNI 03857456B

María González Hinjos
Secretaria del CEIC Aragón (CEICA)

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Variables and event

Thus, 3 large groups of variables were collected (Supplementary Information e-3): Donor Data: age, sex, cause of death, DBD, DCD; Receiver Data: Demographic and anthropometric factors of the recipient: Sex, age, weight, height...Characteristics of liver disease: code entry list, etiology of liver disease, MELD, Child-Pugh, comorbidities; Y Transplant Data: Surgery Variables: time on list Stand by; cold ischemia time Evolution variables: Death of the patient. Survival time and cause of death will be collected according to RETH categorization and graft function in case of death: death with/without a functioning graft; Re-transplantation. The Event object of study is defined as graft loss in the first year, either due to re-transplantation or death due to any cause with graft dysfunction.

Supplementary Table 3: Variables and definition of comorbidities.

Groups of Variables			Variables
Donor Data			Age, sex, cause of death, brain death (DBD) vs asystole (DCD)
Data from Receiver	Demographic factors and anthropometrics of receiver		Age, sex, weight, height...
	Features of the liver disease		List entry code, UNOS, etiology of liver disease, MELD, Child-Pugh (A, B, C) ...
	Comorbidities Per chart review retrospective review systemic	systemic	• FRCV: 2 or more of Arterial Hypertension (HTA): Confirmed in clinical history. and/or Insulin-Dependent Diabetes Mellitus (DMID): With a diagnosis of DM (I or II) and whose treatment requires insulin and/or tobacco: Active smokers or a history of smoking collected in the medical history and/or Hyperlipoproteinemia.
			• Anticoagulation (AC) and/or Antiaggregation (AG): need for treatment before and after anticoagulation and/or antiplatelet OLT.
			• Chronic Renal Insufficiency (CRF)/ Hepato-Renal Syndrome (HRS)
			• Malnutrition: Indicated in the medical history in the context of illness chronicle.
			• Immunosuppression: indifferently due to the pathology itself or to Pharmacotherapy.
		Cardiopulmonares	• Chronic obstructive pulmonary disease (COPD)
			• Pulmonary hypertension (PHT)
			• Hepato-Pulmonary Syndrome (HPS).
			• Valvulopathies.
			• Ischemic Heart Disease: Understood as Acute Myocardial Infarction (AMI), Acute Coronary Syndrome (ACS), need for revascularization surgery coronary.
		Infectious	• Human Immunodeficiency Virus (HIV)
			• Hepatitis B virus (HBV)
			• Tuberculosis (TBC)
		Surgical	Portal Thrombosis (PT): Verification in the Clinical History by Eco-Doppler and/or AngioCT.
			• Spleno-portal shunt
			• Transjugular Intrahepatic Portosystemic Shunt. (TIPS)
			• Gastrointestinal Surgery: Surgical history without considering the type or etiology.
			• Simultaneous double transplant: kidney and liver.
		Oncological	• Hepatocarcinoma (HCA)
			• Extrahepatic
Data from Transplant	Surgery Variables		Time on the waiting list; cold ischemia time...
	Evolution variables		Death of the patient. Survival time and cause of the death and graft function in case of death: death with/without graft functional.
			Retransplant. The date and cause of the re transplantation will be collected

They will be collected according to the categorization of the Spanish Liver Transplant Registry (RETH). http://www.ont.es/infesp/Paginas/Registro-Hepatico.aspx

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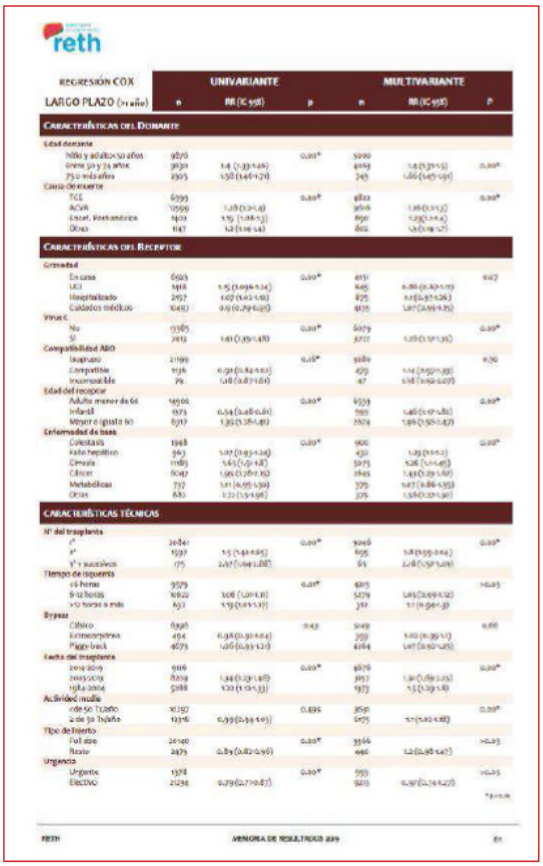
Conventional statistics

For the quantitative variables, central tendency parameters will be obtained (arithmetic, geometric and harmonic mean, and mode), measures of dispersion (standard deviation, standard error, coefficient of variation, range, and variance) and measures of shape (Coefficient of kurtosis or flattening and coefficient of asymmetry). For qualitative variables, the frequency distribution will be calculated according to the categories (responses) existing in each of them. The following tests will be used in the hypothesis contrast: Pearson's Chi-square derived from contingency tables for qualitative variables; Student's "t" or Non-Parametric Test for quantitative variables, depending on their normal distribution.

Artificial neural network (ANN/ANN)

With the variables with statistical significance in graft survival described in the RETH based on data from 28,609 patients (Cox Analysis) fifteen (Supplementary Information e-4) and the comorbidities collected with a prevalence greater than 2%, a predictive model was created using an Artificial Neural Network (MLP: Multilayer Perceptron). In the exploratory ANN model, the data was randomly divided into a learning sample (70%) and a validation sample (30%). The hyperbolic tangent activation function was used in the hidden layer and SoftMax in the output layer. The learning parameters were Batches, Scaled Conjugate Gradient as algorithm, Initial Lambda 0.0000005, Initial Sigma 0.00005, Interval center 0.

Supplementary Table 4: Multivariate analysis of the RETH.



Available at: http://www.ont.es/infesp/Paginas/RegistroHepatico.aspx

ANN sensitivity analysis

A sensitivity analysis, also known as an analysis of the importance of Variable (IV) to determine the optimal variables in the construction of the ANN model [16]. An IV value greater than 0.03 was considered clinically important (predictive): between 0.03-0.1 somewhat predictive and > 0.1 highly predictive.

Programs

For data treatment, the statistical package IBM® was used. -SPSS® -Statistics version 26.0. (©Copyright IBM Corporation 1989 to 2013, Chicago, IL, USA). For the design and validation of the Artificial Neural Network, the IBM® program will be used. -Neural Network version 25.0. A Wald p-value of $p < 0.05$ was considered significant.

Results

General description

The general description of the studied series is shown in table 1. The majority were male (75.5%), the mean age of the patients was 54.8±9.6 years, the main cause of transplantation was cirrhosis (86.7%) and 67.4% of patients had some associated comorbidity.

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Table 1: Description of the global population.

Global Population		
Sex		
Women	146 (24.5%)	
Men	450 (75.5%)	
Age:		
Media±SD I P_{50}(P_{25}-P_{75})	54.8±9.6	56 (50 - 62)
Primary Diagnosis:	19 (3.2%)	
Cholestasis	19 (3.2%)	
Liver failure	25 (4.2%)	
Cirrhosis	517 (86.7%)	
Cancer (without cirrhosis)	7 (1.2%)	
Metabolic	9 (1.5%)	
Other	19 (3.2%)	
Child-Pugh $_{(n = 549)}$		
A	102 (18.6%)	
B	205 (37.3%)	
C	242 (44.1%)	
MELD		
Media ± SD I P_{50}(P_{25}-P_{75})	15.6±5.5	15 (12 - 19)
SOME $_{(n = 569)}$		
ICU	35 (6.2%)	
Hospital	79 (13.9%)	
Continuing Care	261 (45.9%)	
At home	194 (34.1%)	
ABO Compatibility:		
Isogroup	577 (96.8%)	
Compatible	15 (2.5%)	
Incompatible	4 (0.7%)	
Transplant Code:		
Urgency OR	26 (4.4%)	
Urgency Zone	9 (1.5%)	
Elective	561 (94.1%)	
Waiting List Time:		
Mean ± SD I P50(P25-P75)	89.8±106.5	53 (16 - 129)
Time for Blood G.:		
O $_{(n = 249)}$	97.0±123.2	
A $_{(n = 287)}$	88.4±96.3	
B $_{(n = 47)}$	70.7±71.6	
AB $_{(n = 13)}$	48.3±55.9	
Comorbidities:		
No Comorbidities	194 (32.6%)	
With Comorbidities	402 (67.4%)	

UNOS: United Network for Organ Sharing.

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Groups description

Graft loss due to transplantation or death with dysfunction occurred in 14% of cases. In table 2 These groups are described with respect to the variables that the RETH considers to be statistically significant. In our series, only the age of the donor (52.8±17.5 vs. 57.0±17.1, p<0.05) and liver disease caused by Virus C (30.7% vs. 46.4%, p<0.01) showed statistically significant differences between both groups.

Table 2: Description of Events according to RETH variables.

	Total	Event (Graft Loss < 1 year)		
	N = 596	NO n = 512	P Value	Si n = 84
Donor Characteristics				
Age:				
Quantitative				
Mean±SD	53.4±17.5	52.8±17.5	0.0407	57.0±17.1
Median (IQR)	56 (41 - 67)	55 (40 - 67)		60 (46 - 71)
Qualitative				
< 49 years	228 (38.3%)	203 (39.6%)	0.1061	25 (29.8%)
50 - 74	306 (51.3%)	260 (50.8%)		46 (54.7%)
> 75	62 (10.4%)	49 (9.6%)		13 (15.5%)
Cause of Death:				
TBI	140 (23.5%)	119 (23.2%)	0.955	21 (25.0%)
ACVA	392 (65.8%)	339 (66.2%)		53 (63.1%)
Enceph. Post-anoxic	51 (8.6%)	43 (8.4%)		8 (9.5%)
other	13 (2.9%)	11 (2.1%)		2 (2.4%)
Receiver Features				
Virus C:				
NO	400 (67.1%)	355 (69.3%)	0.0044	45 (53.6%)
SI	196 (32.9%)	157 (30.7%)		39 (46.4%)
Recipient Age:				
quantitative				
Mean±SD	54.8±9.6	55.1±9.6	0.1808	53.5 + 9.8
Median (IQR)	56 (50 - 62)	56 (50 - 62)		54 (47 - 61)
qualitative				
< 60	383 (64.3%)	324 (63.3%)	0.2175	59 (70.2%)
> 60	213 (35.7%)	188 (36.7%)		25 (29.8%)
Underlying Disease:				
Colestasis	19 (3.2%)	19 (3.7%)	0.2351	0
Fallo Hepático	25 (4.2%)	20 (3.9%)		5 (20.0%)
Cirrosis	517 (86.7%)	440 (85.9%)		77 (91.7%)
Cáncer (sin cirrosis)	7 (1.2%)	6 (1.2%)		1 (1.2%)
Metabólicas	9 (1.5%)	9 (1.8%)		0
Otras	19 (3.2%)	18 (3.5%)		1 (1.2%)
Technical characteristics				
Transplant Date:				

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> 2014	175 (29.4%)	151 (29.5%)		24 (28.6%)
2005 - 2013	247 (41.4%)	217 (42.4%)	0.3298	30 (35.7%)
1984 - 2004	174 (29.2%)	144 (28.1%)		30 (35.7%)

Groups description: comorbidities

In Table 3a description of the two groups is shown in relation to the event with respect to all the comorbidities analyzed. Of all the comorbidities studied, they presented statistical. significance with respect to the appearance of the event: Taking antiaggregant and/or anticoagulants (4.5% vs. 11.9%, p<0.01) and portal vein thrombosis. (30.7% vs. 46.4%, p<0.01), both with a p<0.01.

Table 3: Description of the Event Population and Comorbidities.

	Population Global	Event (Graft Loss < 1 Year)		
	No = 596	**NO n = 512**	**p-Value**	**Si n = 84**
Systemic Comorbidities:				
CVRF	69 (11.6%)	56 (10.9%)	NS	NS 13 (11.6%)
AG and/or ACO	33 (5.5%)	23 (4.5%)	0.0059	10 (11.9%)
Chronic Renal Failure	26 (4.4%)	25 (4.9%)	NS	1 (1.2%)
Malnutrition	5 (0.8%)	4 (0.8%)	NS	1 (1.2%)
Immunosuppression	13 (2.4%)	11 (2.1%)	NS	NS 2 (2.4%)
Cardiopulmonary Comorbidities:				
COPD 9	9 (1.5) %	7 (1.4%)	NS	2 (2.4%)
Pulmonary Hypertension	10 (1.7%)	9 (1.8%)	NS	1 (1.2%)
S. Hepato-Pulmonary	12 (2.0%)	10 (1.9%)	NS	2 (2.4%)
Valvulopathies	5 (0.7%)	3 (0.6%)	NS	2 (2.4%)
Ischemic heart disease	9 (1.5%)	9 (1.8%)	NS	0
Infectious Comorbidities:				
HBV	4 (0.7%)	4 (0.8%)	DK	0
HIV	11 (1.8%)	8 (1.6%)	NS	3 (3.6%)
Tuberculosis	7 (1.2%)	5 (0.9%)	NS	2 (2.4%)
Surgical Comorbidities:				
Portal thrombosis	25 (4.2%)	17 (3.3%)	0.0086	8 (9.5%)
TIPS	18 (3.0%)	17 (3.3%)	DK	1 (1.2%)
Splenoportal Shunt	6 (1.0%)	5 (1.0%)	NS	1 (1.2%)
Gastrointestinal Surgery	12 (2.0%)	11 (2.1%)	NS	1 (1.2%)
Double Transplant (+kidney)	10 (1.7%)	9 (1.8%)	NS	1 (1.2%)
Oncological Comorbidities:				
Hepatocarcinoma	147 (24.7%)	126 (24.6%)	NS	21 (25.0%)
Others	11 (1.8%)	9 (1.8%)	DK	2 (2.4%)

FRCV: 2 or more for hypertension, diabetes, tobacco, dyslipidemia); AG/ACO: Antiaggregants and/or Anticoagulants; COPD: Chronic Obstructive Pulmonary Disease; HBV: Hepatitis B Virus; HIV: Human Immunodeficiency Virus; TIPS: Transjugular Intrahepatic Portosystemic Shunt

In bold, variables introduced in the ANN (prevalence >2% in both groups)

Artificial neural network: importance of variables

Based on the 6 variables recognized by the RETH as independent predictors of graft survival, and the 5 comorbidities in our series with a prevalence >2% in both groups; an RNA 11:8:2 was designed (Supplemental Information e-5).The sensitivity analysis of the variables included in the network calculated the parameter IV and normalized IV (IV n), the results of which are detailed in table 3. Almost all the variables showed a certain predictive capacity, the highest being the recipient's age. (IV: 0.159;

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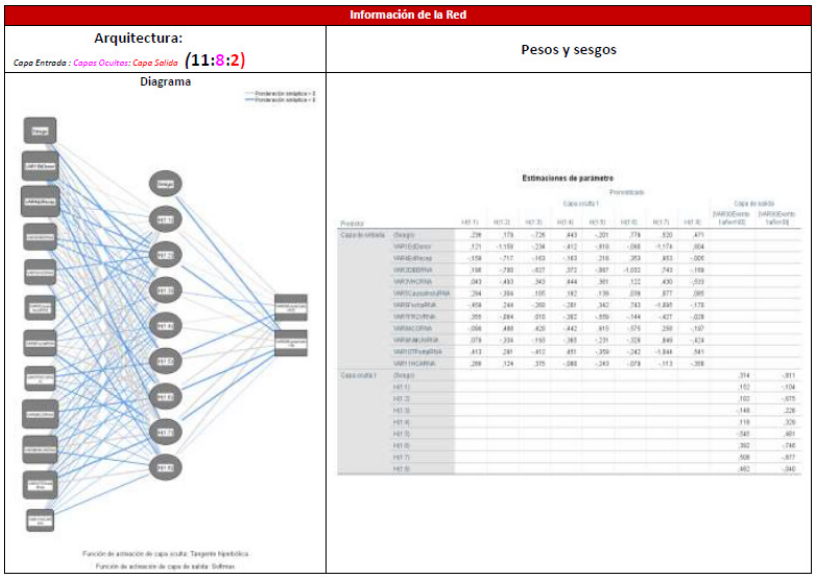
IV_n: 100%) and the age of the donor (IV: 0.132; IV_n: 83.1%), followed by 3 morbidities: taking antiaggregant and/or anticoagulants (IV: 0.124; IV_n: 78.4%), previous immunosuppression (IV: 0.110; IV_n: 69.6%) and portal vein thrombosis (IV: 0.105; IV_n: 66.3%). The presence of associated hepatocarcinoma did not show predictive value in graft survival (IV: 0.019; IV_n: 11.8%).

Supplementary Table 5: Results of the artificial neural network.



Discussion

There are many indicators that aim to predict the probability of liver graft survival, however, when extrapolating them to populations other than where they were described (external validation) show poor results. In a recent meta-analysis published in 2021 [17] in Germany, a joint review of the prediction capacity of the DRI, ET-DRIYBA Ren compassing 12 items. The authors conclude that the AUC curves were low for all and did not discriminate well between graft loss and graft survival. The outcome of the transplant was mainly influenced by the age of the donor, the MELD, and the cause of the transplant relative to the recipient. Also in 2021, a retrospective cohort of 177 patients in Brazil is published [18]. In this study, the indices SOFT, BAR and DRI and the following conclusions were reached: SOFT, which includes receiver data among its variables, was the only one capable of offering an area under the curve > 0.7 (0.73), followed by the BAR index (0.69). It is concluded that the scores with data from both the recipient and the donor (SOFT and BAR) are more accurate in predicting graft survival.

One of the reasons that may justify the difficult extrapolation of these indicators to other populations is that they include few characteristics of the recipient. Analyzing previous studies, we can see how special relevance has been given to the existence of a high MELD value [19-21] or specific pathologies that could establish a contraindication twenty-one However, it is not so easy to find studies that analyze multimorbidity. Yes, there are some studies of comorbidities regarding the mortality of liver transplants. patients: Volk et al. [22] proposed a modified Charlson Index to predict mortality at 5 years; Cardoso et al. [23] found six variables related to 5-year mortality and Tovikkai et al. [24] In a study carried out in the United Kingdom, they observed that there are 4 factors related to the risk of mortality at 90 days: congestive heart failure, history of extrahepatic malignancy, cardiovascular disease, and chronic kidney disease (Table 4).

Only the presence of cardiovascular disease was a risk factor for mortality in all the periods studied (90 days, 1 year and 5 years). In our study, the way in which comorbidities can influence graft survival is assessed, introducing them into an ANN model with 6 independent factors related to it, based on a National Multicenter Registry (RETH) that includes more than 28,000 patients. Of the 11 variables analyzed, 10 turned out to have a certain predictive capacity, and 4 of them were comorbidities, in a model that showed a c-statistic of 0.745 (95% CI 0.692-0.798, asymptotic $p < 0.001$), greater than some of those indicated in other works (Supplemental Information e-6). ANNs can account for outliers and nonlinear interactions between variables and can reveal previously unrecognized or weak relationships between input variables and an outcome. Therefore, ANNs often include parameters that do not reach significance using conventional statistics, as observed in other studies [25.26].

In a University of Pennsylvania article published in 2020 [27]. A review is carried out on the criteria for selecting the recipient in liver transplantation. It exposes the importance of this selection not only including the main cause of hepatic morbidity, but also that some contraindications that were previously absolute are now relative and must be considered. Among these pathologies, portal

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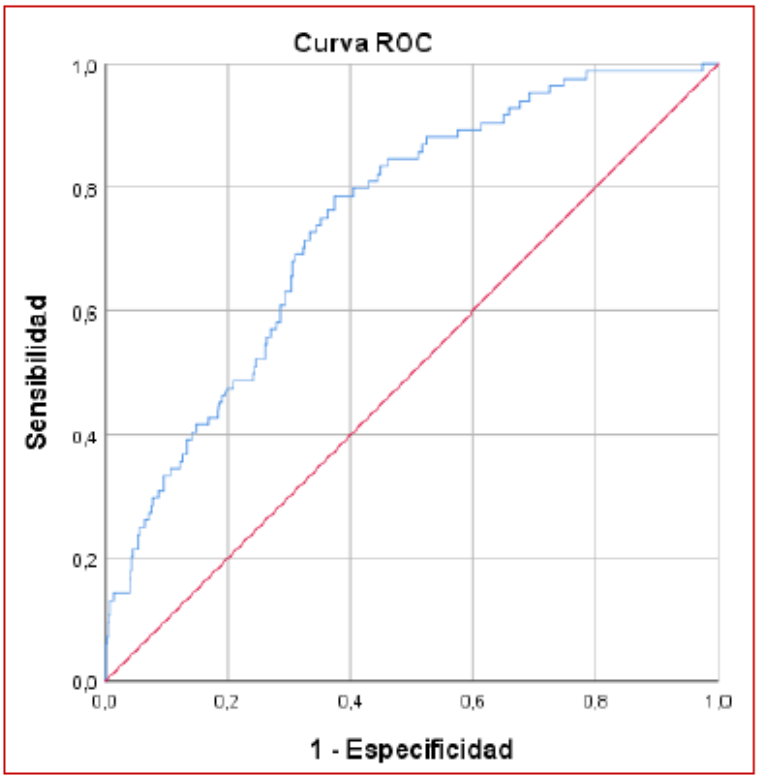
vein thrombosis, HIV, morbid obesity... and others also analyzed in our study stand out. The authors stress that especially in some transplant candidate patients "older than 65 years", it should be considered that they have a 'favorable comorbidity profile'. The DACOLT project has recently been published (Danish Comorbidity Liver Transplant Recipient), a prospective study initiated in Denmark in 2021 [28]. This study also contemplates many of the comorbidities included in ours, however, it aims to analyze. the survival of the patient and not of the graft. One of its objectives is to determine the potential of all these comorbidity factors and to what extent they can be used to develop guidelines for detection, follow-up, and treatment in liver transplantation. Our studio has several limitations. First, data was collected retrospectively and from a single center, which may lead to population bias. Second, the population sample is small, which prevents having an acceptable prevalence of multimorbidity for both groups. Finally, the described sensitivity analysis is based on an ANN model that gave moderate network performance (c-statistic: 0.745;95%CI 0.692-0.798), although not very different from other models. In conclusion, in an ANN predictive model, together with consistent variables such as donor and recipient age, it would be important to introduce recipient comorbidities, some of which may be highly predictive clinical factors in liver graft survival in the first year.

Supplementary Table 6: ROC Area of the Model obtained.



Área bajo la curva

Variables de resultado de prueba: Pseudoprobabilidad pronosticada para VAR0

Área	Desv. Error[a]	Significación asintótica[b]	95% de intervalo de confianza asintótico	
			Límite inferior	Límite superior
,745	,027	,000	,692	,798

Las variables de resultado de prueba: Pseudoprobabilidad pronosticada para VAR00Evento1año = Si tienen, como mínimo, un empate entre el grupo de estado real positivo y el grupo de estado real negativo. Las estadísticas podrían estar sesgadas.

a. Bajo el supuesto no paramétrico

b. Hipótesis nula: área verdadera = 0,5

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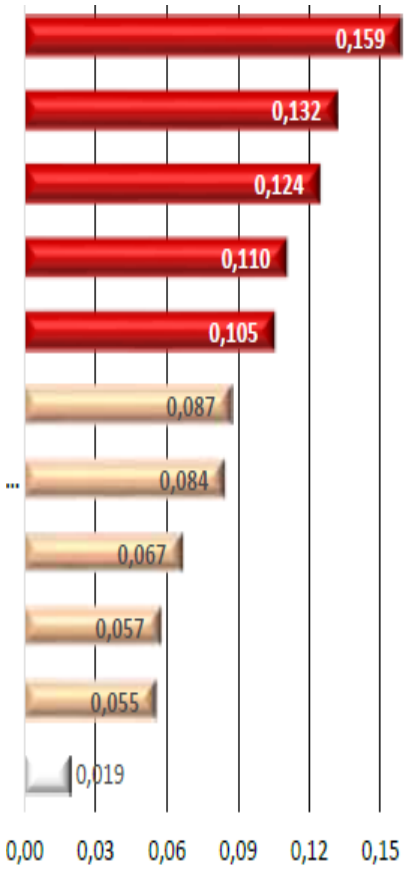
Table 4: Sensitivity Analysis: Ranking variables according to the Information Value (IV) of the RNA.

Variable		IV*	IV Normalized	Predictive	
Variables del RETH	Donor Age	1,32E-01	83.10%	Highly Predictive	1 Recipient Age
	Cause DBD	8,70E-02	55.00%	Somewhat Predictive	2 Donor Age
	HCV	6,70E-02	42.00%	Somewhat Predictive	3 AG/ACO
	Recipient Age	1,59E-01	100%	Highly Predictive	4 IDs
	enf. Base	5,50E-02	34.80%	Somewhat Predictive	5 TP
	Transplant Date	8,40E-02	53.10%	Somewhat Predictive	6 Cause DBD
Comorbilidades	CVRF	5,70E-02	36.10%	Somewhat Predictive	7 Date...
	AG/ACO	1,24E-01	78.40%	Highly Predictive	8 HCV
	Immunosuppression	1,10E-01	69.60%	Highly Predictive	9 CVRF
	Portal thrombosis	1,05E-01	66.30%	Highly Predictive	10 Sick Base
	hepatocellular carcinoma	1,90E-02	11.80%	Not Predictive	11. HCA



(*) ≤ 0.03 Not predictive; 0.03-0.1 Somewhat predictive; > 0.1 Highly predictive

DBD: Death Brain Donor; VHC: Virus Hepatitis C; FRCV: Factores Riesgo Cardiovascular; AG/ACO: Antiagregación y/o Anticoagulación

IV: Information Value

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