Graft Survival in Liver Transplantation:

An ANN Analysis of the Impact of Comorbidities

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1. INTRODUCTION

Liver transplantation (LT) is considered the only available therapeutic option for many patients with end-stage liver failure. Still, over half of patients that undergo a liver transplant will suffer at least one significant complication during the first year upon transplantation. In this context, the criteria for assigning an organ should include the appropriate balance between benefit and utility, in which the concept of "survival benefit" plays a pivotal role.[1] Such high rates of LT complications could be attributed to the increasing use of organs from marginal donors *(older age, asystole donors, donors with expanded criteria, etc.*) and/or the clinical characteristics of the recipient *(age, disease state, comorbidities., etc.)*.

Comorbidity is a medical term coined by AR Fenstein in 1970, and subjected to several terminological proposals. More specifically, multimorbidity could be defined as the presence of different diseases or conditions that coexist with a main chronic disease[2] **(Supplementary Information e-1)**. In recent years, the indications for LT have been progressively expanded, which in addition to the admission of older patients in the transplant waiting list have resulted in an growing number of comorbidities among transplant recipients.[3]. In this manner, a myriad of studies have been devoted to determine the impact of specific comorbidities on the outcomes of liver transplant – e.g, coronary disease[4,5,6], chronic kidney disease[7], diabetes[8], and nonhepatic cancer[9]. However, most of the indicators described to adjust the donor-recipient allocation not only ignore the recipient comorbidities, but also share some common flaws such as: limited external validity when applied to populations other than those initially described[10,11]; and the use of the logistic regression as the principal statistical tool[12,13] .

In addition to conventional methods, the implementation of techniques from artificial intelligence (AI), such *as big data analysis* (BDA) *and machine learning* (ML), may significantly enhance clinical research and subsequently improve clinical practice in the close future[14]. Particularly, Artificial Neural Networks (ANNs) emerge as an alternative multivariate analysis method, which could better address the complexity found among patients with different comorbidities.
Overall, the main objective of this study was to explore and analyze the predictive value of the recipients comorbidities in liver graft survival within the first year posttransplantation by conventional and AI methods.

2. MATERIALS AND METHODS

2.1. Data sources.

The study included prospectively collected data from all the patients that received a liver transplant (first transplant) at the University Hospital Lozano Blesa (Aragón, Spain) from 2010 to 2021. The study complied with Organic Law 15/1999 on Personal Data Protection, and was approved by the **Aragon Ethics Committee (CEICA, for its acronym in Spanish)** *(Act 1/2022)* **(Supplementary Information e-2)**.

2.2. Variables and Event.

Three large groups of variables were collected **(Supplementary Information e-3)**. **Donor data**: *age, sex, cause of death, Donor after cardiac death (DCD), Donor after brain death (DBD)*. **Recipient data**: Demographic and anthropometric characteristics of the recipient: *Sex, age, weight, height...* Characteristics of liver disease: *list entry code, etiology of liver disease, MELD score, Child–Pugh score* and recipients' comorbidities. **Transplant Data**: Surgery Variables: *Time on the waiting list*; *time of cold ischemia...* Evolution variables: Patient *death*. *Survival time* and *cause of death* were collected according to the Spanish Liver Transplant Registry (RETH) categorization and the graft function in case of death: death or with/without functioning graft; *Retransplantation*.

The **event** under study was defined as the loss of the graft in the first year, either by retransplantation or death due to any cause with graft dysfunction.

2.3. Conventional Statistics.

For the quantitative variables, central tendency parameters (arithmetic, geometric and harmonic mean and mode), dispersion measures (standard deviation, standard error, coefficient of variation, range and variance) and shape measures (kurtosis coefficient or flattening and coefficient) of asymmetry), were obtained. For qualitative variables, the frequency distribution was calculated according to the included categories (responses) in each of them.

The following tests were used in the hypothesis contrast: Pearson's chi-square derived from contingency tables for qualitative variables and Student's "t" or non-parametric test for quantitative variables, depending on their normality distribution.

2.4. Artificial Neural Network (ANN)

A predictive model was created using an artificial neural network (MLP: multilayer perceptron) that only included the statistically significant variables associated with graft survival according to the RETH report, based on data from 28 609 patients (Cox analysis)[15] **(Supplementary Information e-4)**, and the comorbidities collected with a prevalence greater than 2%.

In the exploratory ANN model, the data were randomly divided into learning (70%) and avalidation (30%) groups. The hyperbolic tangent activation function was used in the hidden layer and softmax in the output layer. The learning parameters were as follows: batch, scaled conjugate gradient as the algorithm, initial lambda 0.0000005, initial sigma 0.00005, and center of interval 0.

2.5. ANN Sensitivity Analysis.

A sensitivity analysis, also known as **variable importance (VI)** analysis, was performed to retrieve 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 greater than and > 0.1 highly predictive.

2.6. Programs.

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

3. RESULTS

3.1. General Description

The general description of the series studied 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 the transplant was cirrhosis (86.7%), and 67.4% of the patients had some associated comorbidities.

3.2. Description of Groups: *Event*

Graft loss due to retransplantation or death with dysfunction occurred in 14% of cases.
In **Table 2** the two event groups are described in terms of the variables that the RETH report considers statistically significant for liver graft survival. In our series, only the age of the donor *(52.8 ± 17.5 vs. 57.0 ± 17.1, p <0.05)* and liver infection caused by virus C *(30.7% vs. 46.4%, p <0.01)* displayed significant differences between both groups.

3.3. Description of Groups: *Comorbidities*

Table 3 shows a description of the two event groups in relation to all the comorbidities analyzed. Of all the comorbidities studied only the use of antiplatelet and/or anticoagulant agents *(4.5% vs. 11.9%, p <0.01)* and portal thrombosis *(30.7% vs. 46.4%, p <0.01)*, showed statistically significant relation with the occurrence of the event.

3.4. Artificial Neural Network: *Importance of Variables*

From the 6 variables recognized by RETH as independent predictors of graft survival and the 5 comorbidities of our series with a prevalence greater than 2% in both groups, an 11:8:2 ANN was deployed **(Supplementary Information e-5)**. The sensitivity analysis of the variables included in the network was used to estimate the parameter IV and normalized IV (IV_n), as detailed in **Table 3**. Of note, almost all the variables showed a certain predictive capacity, with the highest values for the age of the recipient *(IV: 0.159; IV_n: 100%)* and the age of the donor *(IV: 0.132; IV_n: 83.1%),* followed by 3 morbidities: antiplatelet and/or anticoagulants *(IV: 0.124; IV_n: 78.4%) treatments,* previous immunosuppression *(IV: 0.110; IV_n: 69.6%)* and portal thrombosis *(IV: 0.105; IV_n: 66.3%)*. In contrast, the presence of associated hepatocarcinoma did not show predictive value in graft survival *(IV: 0.019; IV_n: 11.8%).*

4. DISCUSSION

Many indicators have been described to predict the probability of liver graft survival; however, they typically underperform when extrapolated to the general population *(i.e., external validation)*. In this regard, a recent meta-analysis including 12 articles published in 2021[17] in Germany, reviewed the prediction capacity of the Donor Risk Index (*DRI*), Eurotransplant Donor Risk Index (*ET-DRI*) and Balance of Risk (*BAR*) scores. The authors concluded that these three scores did not discriminate well between graft loss and survival. Besides, the result of the transplant was mainly influenced by the age of the donor, the MELD score and the etiology of the liver failure.

In 2021, a retrospective cohort of 177 patients in Brazil was also published[18], evaluating the Survival Outcome Following Liver Transplantation (SOFT), BAR and DRI indices. The SOFT score, which includes recipient`s data among its variables, was the only one offering an area under the curve greater than 0.7 *(0.73),* followed by the BAR index *(0.69)*. Hence, the authors concluded that the scores that consider data from both the recipient and the donor *(SOFT and BAR)* consistently offered more accurate predictions of graft survival.

In light of the above, one of the reasons underlying the poor external validity of these indicators could be the lack of sufficient information from the recipient. In literature, we can observe the emphasis typically given to the presence of high MELD values[19] [20] or to specific pathologies that may incur a contraindication for transplantation[21], while there are only few studies reporting the impact of the recipient's multimorbidity. For example, 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 conducted in the United Kingdom, observed that there are 4 factors related to the risk of mortality at 90 days: *congestive heart failure, history of extrahepatic malignant disease, cardiovascular disease and chronic kidney disease*. However, only the cardiovascular disease was an independent risk factor for mortality in all periods studied (90 days, 1 year and 5 years).

The University of Pennsylvania published in 2020[25] a review about the selection criteria for the recipient in LT. Along the discussion, the authors raised the importance of not only considering the cause of liver failure, but also including some comorbidities of the recipient, especially those that are now considered relative contraindications for LT and were previously considered absolute. Among these pathologies, the authors stressed the importance of portal venous thrombosis, HIV and morbid obesity , which were also analyzed in our study. Furthermore, they claimed that especially in some transplant candidates (for example, patients *over 65 years)*, it should be carefully assessed whether they present a *"favorable comorbidity profile"*.

Recently, the DACOLT (*Danish Comorbidity Liver Transplant Recipient*) project was published, a prospective study initiated in Denmark in 2021.[26]. This study also considered many of the comorbidities included in ours; however, rather than analyzing the survival of the graft, the authors monitored the survival of the patient. One of the objectives was to determine whether all these comorbidity factors could be used to develop guidelines for detection, monitoring and treatment in liver transplantation.

In our particular study, the way in which comorbidities can influence graft survival is evaluated, introducing them into an ANN model with 6 independent risk factors, previously identified through the National Multicenter Registry (RETH, with more than 28,000 patients). Of the 11 variables analyzed, 10 were found to have a certain predictive capacity, and 4 of them were comorbidities. Our model showed a c-statistic of 0.745 *(95% CI 0.692-0.798, asymptotic p <0.001)*, which was higher than some. of those indicated in other works **(Supplementary Information e-6)**.

Arguably, the ANN built in this study outperforms other strategies by accounting for outliers and nonlinear interactions between the input variables, so that weak or previously unrecognized relationships between the included parameters emerge. In this manner, ANNs can reveal connections between the set of data that would not reach significance using conventional statistics, as observed in other studies.[27,28].

Nonetheless, our study has some limitations. Firstly, the data was collected retrospectively and from a single center, which can lead to a population bias. Secondly, the sample is rather small, restraining the prevalence of multimorbidity in both groups. Finally, the sensitivity analysis is based on an ANN model that provides a moderate network performance (c-statistic: 0.745; *95% CI 0.692-0.798)*, yet in line with other ANN models in literature.

In conclusion, when developing an ANN model, apart from including consistent variables (such as the ages of donors and recipients) it is also recommended to add the recipient's comorbidities. Even more considering that, as presented in this manuscript, some of them can be highly predictive clinical factors in liver graft survival during the first year.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Tables y Figures

Table 1. **Main Characteristics of the cohort.**

N = 596		
Sex:		
Female	*146 (24.5%)*	
Male	*450 (75.5%)*	
Age:		
Mean ± SD I $P_{50}(P_{25}$-$P_{75})$, y	*54.8 ± 9.6*	*56 (50 - 62)*
Cause of liver disease:		
Cholestasis	*19 (3.2%)*	
Acute hepatic faillure	*25 (4.2%)*	
Cirrhosis	*517 (86.7%)*	
Cancer *(without cirrhosis)*	*7 (1.2%)*	
Metabolic	*9 (1.5%)*	
Other	*19 (3.2%)*	
Child-Pugh class (n = 549)		
A	*102 (18.6%)*	
B	*205 (37.3%)*	
C	*242 (44.1%)*	
MELD score		
Mean ± SD I $P_{50}(P_{25}$-$P_{75})$	*15.6 ± 5.5*	*15 (12 - 19)*
UNOS status(n = 569)		
UCI admission	*35 (6.2%)*	
Hospital admission	*79 (13.9%)*	
With continuous 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:		

"Urgencia O"	*26 (4.4%)*	
"Urgencia Zona"	*9 (1.5%)*	
Elective	*561 (94.1%)*	
Time in waiting list:		
Mean ± SD I $P_{50}(P_{25}$-$P_{75})$	*89.8 ± 106.5*	*53 (16 - 129)*
Time by blood type:		
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:		
Without comorbidities	*194 (32.6%)*	
With comorbidities	*402 (67.4%)*	

UNOS: United Network for Organ Sharing

Table 2. **Description of the event groups in terms of the RETH variables.**

	Total	Event *(Perdida del Injerto < 1 año)*		
	N = 596	NO n = 512	P value	YES n = 84
Donor's characteristics				
Age:				
Cuantitative				
Mean ± SD, y	*53.4 ± 17.5*	*52.8 ± 17.5*	***0.0407***	*57.0 ± 17.1*
Median (IQR), y	*56 (41 - 67)*	*55 (40 - 67)*		*60 (46 - 71)*
Cualitative				
≤ 49 years	*228 (38.3%)*	*203 (39.6%)*		*25 (29.8%)*
50 – 74 years	*306 (51.3%)*	*260 (50.8%)*	*0.1061*	*46 (54.7%)*
≥ 75 years	*62 (10.4%)*	*49 (9.6%)*		*13 (15.5%)*
Cause of death				
Trauma	*140 (23.5%)*	*119 (23.2%)*		*21 (25.0%)*
CVA	*392 (65.8%)*	*339 (66.2%)*	*0.9550*	*53 (63.1%)*
Anoxia	*51 (8.6%)*	*43 (8.4%)*		*8 (9.5%)*
Others	*13 (2.9%)*	*11 (2.1%)*		*2 (2.4%)*
Recipient's characteristics				
Virus C:				
No	*400 (67.1%)*	*355 (69.3%)*	***0.0044***	*45 (53.6%)*
Yes	*196 (32.9%)*	*157 (30.7%)*		*39 (46.4%)*
Age of the recipient:				
Cuantitative				
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)*
Cualitative				
< 60 years	*383 (64.3%)*	*324 (63.3%)*	*0.2175*	*59 (70.2%)*
≥ 60 years	*213 (35.7%)*	*188 (36.7%)*		*25 (29.8%)*

Cause of liver disease:				
Cholestasis	*19 (3.2%)*	*19 (3.7%)*		*0*
Acute hepatic faillure	*25 (4.2%)*	*20 (3.9%)*		*5 (20.0%)*
Chirrosis	*517 (86.7%)*	*440 (85.9%)*		*77 (91.7%)*
Cáncer *(without chirrosis)*	*7 (1.2%)*	*6 (1.2%)*	*0.2351*	*1 (1.2%)*
Metabolic	*9 (1.5%)*	*9 (1.8%)*		*0*
Other	*19 (3.2%)*	*18 (3.5%)*		*1 (1.2%)*
Technical variables				
Transplant date:				
≥ 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%)*

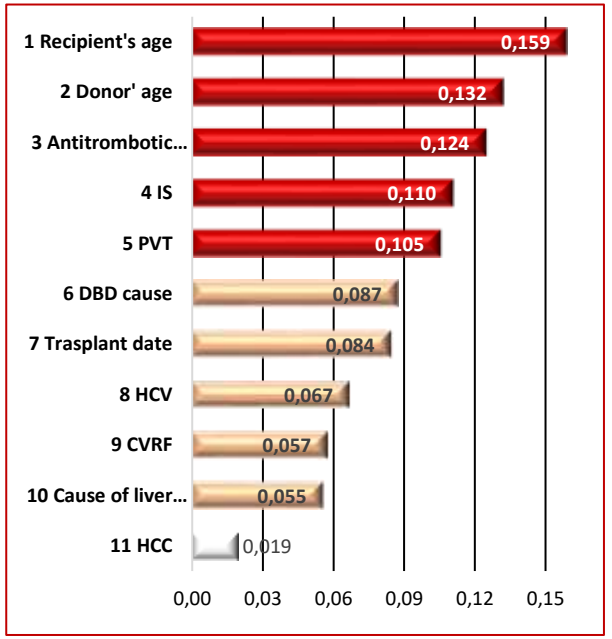
Table 3. Description of the event groups in relation to the comorbidities studied.

	Total	Event *(Graft loss < 1 year)*		
	N = 596	NO n = 512	P value	YES n = 84
Systemic comorbidities:				
CVRF	*69 (11.6%)*	***56 (10.9%)***	***NS***	***13 (11.6%)***
Antithrombotic drugs	*33 (5.5%)*	***23 (4.5%)***	***0.0059***	***10 (11.9%)***
Chronic kidney disease	*26 (4.4%)*	*25 (4.9%)*	*NS*	*1 (1.2%)*
Malnutrition	*5 (0.8%)*	*4 (0.8%)*	*NS*	*1 (1.2%)*
Immunosuppresion	*13 (2.4%)*	***11 (2.1%)***	***NS***	***2 (2.4%)***
Cardiopulmonary comorbidities:				
COPD	*9 (1.5%)*	*7 (1.4%)*	*NS*	*2 (2.4%)*
Pulmonary Hypertension	*10 (1.7%)*	*9 (1.8%)*	*NS*	*1 (1.2%)*
Hepatopulmonary syndrome	*12 (2.0%)*	*10 (1.9%)*	*NS*	*2 (2.4%)*
Heart valve disease	*5 (0.7%)*	*3 (0.6%)*	*NS*	*2 (2.4%)*
Coronary Heart disease	*9 (1.5%)*	*9 (1.8%)*	*NS*	*0*
Infectious comorbidities:				
HBV	*4 (0.7%)*	*4 (0.8%)*	*NS*	*0*
HIV	*11 (1.8%)*	*8 (1.6%)*	*NS*	*3 (3.6%)*
Tuberculosis disease	*7 (1.2%)*	*5 (0.9%)*	*NS*	*2 (2.4%)*
Surgical comorbidities:				
Portal vein thrombosis	*25 (4.2%)*	***17 (3.3%)***	***0.0086***	***8 (9.5%)***
TIPS	*18 (3.0%)*	*17 (3.3%)*	*NS*	*1 (1.2%)*
Esplenoportal shunt	*6 (1.0%)*	*5 (1.0%)*	*NS*	*1 (1.2%)*
Gastrointestinal surgery	*12 (2.0%)*	*11 (2.1%)*	*NS*	*1 (1.2%)*
Kindey and Liver trasplant	*10 (1.7%)*	*9 (1.8%)*	*NS*	*1 (1.2%)*
Oncological comorbidities:				
Hepatocellular carcinoma	*147 (24.7%)*	***126 (24.6%)***	***NS***	***21 (25.0%)***
Other	*11 (1.8%)*	*9 (1.8%)*	*NS*	*2 (2.4%)*

CVRF: 2 or more of *Hypertension, diabetes, smoking, dyslipidemia*); **Antithrombotic drugs:** anticoagulants and/or antiplatelet drugs; **COPD:** Chronic obstructive pulmonary disease; **HBV:** Hepatitis B virus;
HIV: Human immunodeficiency virus; **TIPS:** Transjugular intrahepatic portosystemic shunt
In **bold** are the variables included in the ANN analysis (prevalence >2% in both groups)

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

	Variable	IV*	IV Normalized	Predictive
RETH variables	*Donor's Age*	1,32E-01	83.1%	Highly Predictive
	DBD cause	8,70E-02	55.0%	Somewhat Predictive
	HCV	6,70E-02	42.0%	Somewhat Predictive
	Recipient's Age	1,59E-01	100%	Highly Predictive
	Cause of liver disease	5,50E-02	34.8%	Somewhat Predictive
	Transplant date	8,40E-02	53.1%	Somewhat Predictive
Comorbidities	*CVRF*	5,70E-02	36.1%	Somewhat Predictive
	Antithrombotic drugs	1,24E-01	78.4%	Highly Predictive
	Immunosuppresion (IS)	1,10E-01	69.6%	Highly Predictive
	Portal vein thrombosis (PVT)	1,05E-01	66.3%	Highly Predictive
	Hepatocellular carcinoma (HCC)	1,90E-02	11.8%	Not Predictive



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

DBD: Death Brain Donor; **HCV**: Hepatitis C Virus; **CVRF:** Cardiovascular Risk Factors; **Antithrombotic drugs:** Anticoagulants and/or antiplatelet drugs
IV: Information Value

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