TITLE PAGE

EXTERNAL VALIDATION OF ARTIFICIAL NEURAL NETWORKS AS A METHODOLOGY FOR DONOR-RECIPIENT MATCHING FOR LIVER TRANSPLANTATION

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ABBREVIATIONS

ALF, acute liver failure; ALT, alanineaminotransferase plasma level; ANN, artificial neural network; AntiHBc, Hepatitis B (core Ab positive); AST, aspartatetransaminase level; AU-ROC, Area-Under-the Receiver Operating Characteristic Curve; BAR, Balance of Risk; BMI, Body Mass Index; CCR, correct classification rate; CVA, cardiovascular accident; DCD, donation after cardiac death; DRI, donor risk index; D-R, donor-recipient; ECD, extended criteria donors; HBV, Hepatitis B; HCC, hepatocellular carcinoma; HCV, Hepatitis C; ICU, Intensive Care Unit; KCH.- King's College Hospital; LT, liver transplantation; MADR-E.- Model for the Assignment of Donor and Recipient in España; MELD, model of end-stage liver disease; MOEA, multiobjective evolutionary algorithm; MPENSGA2, memetic Pareto evolutionary approach based on the NSGA2 evolutionary algorithm MS,

Minimum Sensitivity; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SD, standard deviation; SOFT, survival outcomes following liver transplantation score.

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ABSTRACT

BACKGROUND AND AIMS. In 2014, we reported a model for Donor-Recipient matching (D-R) in liver transplantation (LT) based on artificial neural networks (ANN) from a Spanish multicentre study (**MADR-E**: **M**odel for **A**llocation of **D**onor and **R**ecipient in **E**spaña) and compared it against all previously reported scores with excellent results. The main aim is to test the ANN-based methodology in a different European healthcare system in order to validate it.

METHODS. An ANN D-R model was specifically designed for a cohort of patients selected from King's College Hospital (KCH) (N=822). The ANN was trained and tested using KCH pairs for both 3- and 12-months survival models. Two more validations were tested (MADR-E training and KCH testing; and a combined model using MADR-E and KCH for both training/testing). Endpoints were probability of graft survival (CCR) and non-survival (MS).

RESULTS. Models designed for KCH had excellent prediction capabilities for both 3-months (CCR AUROC=0,9375; MS AUROC=0,9374) and 1-year (CCR AUROC=0,78333; MS AUROC=0,81528), being almost 15% higher than the best obtained by other known scores. The pure validation of MADR-E model had much lower prediction capabilities (CCR AUROC=0,6400; MS AUROC=0,6235). A combined model grouping both populations was complex but also achieved good prediction capabilities (CCR AUROC=0,7791; MS AUROC=0,7016), almost 20% higher than other scores.

CONCLUSIONS. The use of ANN for D-R matching in LT in other healthcare systems achieved excellent prediction capabilities being clearly validated. It should

be considered as the most advanced, objective and useful tool to date for the management of waiting lists.

INTRODUCTION

Liver transplantation (LT) offers the best outcome for several end-stage liver disorders. Thanks to its wide applicability and excellent outcomes, the number of candidates continues to grow. However, this has not been matched by growth in the number or quality of the donors. As a consequence, death and drop-out from the waiting list continue to be significant. Over the last 20 years, criteria for considering a graft suitable for transplantation have extensively widened and the use of extended criteria donors (ECD) is widely accepted in the transplant community. However, the balance between waiting list, ECD and outcomes after transplantation is tenuous and care is required to maintain outcomes after LT on an intention to treat basis [1].

It is well-known that donor and recipient matching (D-R matching) is important in determining outcomes after LT and several 'scores' have been proposed to provide help [2-4]. The use of high-risk-donors in high-risk-recipients has been postulated as a complex combination which is not always advantageous [5-7]. Similarly, others have analyzed how specific factors are harmful for some recipients but not for others (i.e. donor macrosteatosis and hepatitis-C (HCV) vs non-HCV recipients) [8]. D-R matching is not important in terms of individual outcomes but best use for the overall population also has to be considered. An optimal D-R matching is the key for an allocation system that intends to be objective and equal for every patient [9].

In 2014, our groups reported the utility of artificial neural networks (ANN) as an optimal D-R matching system (MADR-E.- Model for the Assignment of Donor and Recipient in España) for LT in a large multicenter cohort of D-R pairs [10]. In

this study, ANN were superior to all other scores published to date in predicting graft survival and graft loss. The manuscript included a theoretical model in which it was possible to observe how donor livers were allocated to recipients in both standard and extended criteria groups. However, it was suggested that an external validation would be needed in order to find out if the results obtained in Spain could be duplicated elsewhere in Europe.

The aim of our study was to find out if ANN would have a similar behaviour in a different healthcare system and whether they would be a powerful tool for D-R matching in comparison to other current models. The secondary aims, were to test if the MADR-E model would be exportable to another system or if the ANN worked better being self-trained-self-tested. In addition, a combined model formed by grouping all Spanish and foreign D-R pairs was used to build a combined ANN.

PATIENTS AND METHODS

a. **Hospital selection for the validation.** From the whole spectrum of hospitals in Europe, we performed the external validation with King's College Hospital (KCH) in London-United Kingdom. The reasons for choosing this center were: first, it is the highest-volume center (>200 transplant per year) in Europe with excellent results and protocols; second, it could be obtained a similar population to that used for the Spanish model in a similar period of time, leading to similar sample sizes and avoiding biases as long time periods or lack of standardized model for end-stage liver disease (MELD) use; third, data collection seems fairly more strict, homogeneous and with less amount of missing data if validation comes

from a single Unit; and fourth, KCH belongs to a public healthcare system (similar to Spain) but with clear differences in terms of donation and distribution of transplantation centers.

b. Patient selection.

1. **Spanish dataset.-** The chosen dataset was the same as the previously 1,003 matched D-R cases in the Spanish series[10].
2. **King's College Hospital dataset.-** To obtain a similar number of patterns, only reported pairs from January 2002 to December 2010 were included. Thereby, a dataset containing 858 English D-R pairs was collected.
3. **Exclusion criteria:** Paediatric liver transplants, living donor liver transplants and hepatocellular carcinoma (HCC). These last 2 exclusion criteria were because they follow different allocation policies not strictly ruled by MELD score or random MELD score points additions according to time on waiting list or high/low risk HCC criteria.

c. Missing values. Imputation techniques. Once the data were collected (both in the Spanish and English series), it was necessary to perform some classical techniques of data imputation in order to replace all the missing values. To do so, first, when the ratio of missing values for any variable was <1%, those were substituted by the mean (in the case of a continuous and quantitative variable) and by the mode (in the case of a binary and qualitative variable). When the ratio of missing values was >1% and <10%, a linear and nonlinear regression analysis was performed for recover those missing values. Finally, patterns with a percentage of missing values >10%

were not considered for the study. Besides, It was necessary to exclude four hospitals from the study (from the eleven initial ones), because when classifying each hospital separately, those four obtained an AUC measure < 0.5, which means that a random classifier would be even better for those samples. Thus, once the patterns from those hospitals were removed, the total number of cases was 615 for the Spanish dataset.

d. Building the artificial neural networks: Models of donor-recipient matching. In order to obtain the best knowledge of D-R prognosis, a new system was developed for graft assignment. For each D-R pair, two probabilities were calculated using 2 different and non-complementary models: the positive-survival model and the negative-loss model.

1. The *positive-survival model* consists of a neural network, which predicts the probability of 3-months graft survival after LT. This model uses the mathematical concept of Correct Classification Rate (CCR), or Accuracy, defined as the percentage of correctly classified training patterns. This model tries to maximize the probability that a D-R pair has of belonging to the "graft survival" class.

2. The *negative-loss model* consists of a neural network giving the probability of non-survival of the graft 3 months following the transplant. This model uses the mathematical concept of Minimum Sensitivity (MS), defined as the minimum value of the sensitivities of each of the classes. This model tries to maximize the probability that a D-R pair has of belonging to the “non-graft-survival” class.

e. Building the artificial neural networks: the training/testing process. The values of the connections and the structure of the models are

determined by an evolutionary algorithm. To verify that the individuals obtained by the evolutionary algorithm are efficient, the coefficients of individual neural network models are trained with a subset of the database (training set) and tested with the rest of the database (generalization set) [11]. For this purpose, experts in computational analysis used the 10-fold cross-validation methodology. Briefly, the whole dataset is randomly divided, and 90% of the patients are used for the training step, leaving 10% for the final testing. This process is performed 10 times, so that all patterns participate in the testing phase. After these 10 randomizations, the best CCR and MS models are chosen. The two "best models" are those that correctly classifies the highest number of pairs in both categories of graft survival and graft loss.

f. **Building the artificial neural networks: Algorithms used.** The positive-survival and negative-loss models are models of ANN. In this manuscript, a Multiobjective Evolutionary Algorithm (MOEA) was used to train artificial neural networks models. An ANN is a mathematical model inspired by biological neural networks used to learn and predict the end-point variable from a given set of input data (in this case, characteristics of recipients, donors and other operative factors were considered). The weights of the ANNs were adjusted by operators employed by the MOEA during the evolutionary process. Both operators, as well as the MOEA, are inspired by biological evolution, performing methodologies such as reproduction, mutation or selection. In our work, the evolutionary process of the MOEA was guided by two different competing objective functions. The former function considered was the accuracy or CCR and the latter was the MS,

which reports the minimum classification rate per class of all of the classes in the problem. In this sense, the CCR metric will be focused on overall classification, whereas MS will focused on the minority class classification (in our cases, non-survival class) [12]. The MPENSGA2 algorithm (Memetic Pareto Evolutionary approach based on the NSGA2 evolutionary algorithm) was selected as MOEA in this paper in order to train ANNs, since it has been shown to achieve competitive performance with a limited computational cost [12]. Once the evolutionary process of the algorithm has been completed, both best models (the one for CCR and the one for MS) have been selected as potential solutions to the problem

g. **Validation process.** Our previously reported MADR-E (**M**odel for the **A**llocation of **D**onor and **R**ecipient in **E**spaña) was validated in an European high-volume liver transplant Unit (King's College Hospital-London). Three different validation processes were performed to fulfill three different aims:

   1. **Training KCH → testing KCH.** In this model, the methodology is entirely new performed with KCH. Thus, a theoretical new D-R matching model is created for KCH (MADR-KCH). With this model, the aim is to find out if ANN work well in a different population within Europe. According to previous suggestions, 3-months and 1-year graft survival models were obtained.
   2. **Training MADR-E → testing KCH.** This would be the "pure" validation process in which the MADRE model is directly tested on KCH population. According to the original MADRE model, 3-months graft probability of survival and non-survival were the endpoint variables.

3. **Grouping MADR-E + KCH (training MADR-E + KCH → testing MADR-E + KCH).** The main aim of this model was to find out if a larger model would improve every result obtained to date and to test if a unique MADR-Eu (**M**odel for the **A**llocation of **D**onor and **R**ecipient in **Eu**rope) could be potentially suggested.

h. **The Rule-based system.** With the two models obtained, a very simple rule-based-for-decision system was designed: first, MELD score is the cornerstone, so in case of draw when the ANN is not capable to determine differences, the D-R matching is allocated by MELD; second, the D-R pair is chosen in cases of real biological, and not mathematical differences, defined by, at least, 3% and 5% in the NN-CCR and NN-MS models respectively. These probabilities were chosen from the standard deviations from the probabilities of belonging to the class of graft survival (SD=2.86%) or not-survival (SD=5.56%).

i. **Comparisons against other scores.** To test the accuracy of ANN in predicting both graft-survival and –loss, comparisons with other current validated scores were performed. Receiver-operating-characteristics (ROC) curves were obtained for every score to predict both end-points and compared against CCR and MS models. According to current literature, MELD[13], D-MELD[14], DRI[2], P-SOFT, SOFT[3] and BAR[4] scores were calculated.

j. **Ethical and humanae considerations.** Every procedure, including obtaining informed consent, was conducted in accord with the ethical standards of the Committee on Human of the Helsinki Declaration of 1975.

RESULTS

a. **Descriptive analysis.** Considering the surviving/non-surviving graft classes, there were 548/67 pairs, in the Spanish and 739/83 in the KCH database. A total number of 1287/150 D-R pairs was collected. **Thus, this is an unbalanced database, and therefore the usual models of binary classification that try to optimize the CCR, present the difficulty to optimize the classification of the majority class (graft survival) to the detriment of the classification of the minority class (graft not survival).** For each pair, several variables were selected, more specifically, 16 variables concerning the recipient, 17 concerning the donor and finally, 5 related to the surgery. **Some of these variables such as Aetiology are encoded in nominal scale (7 modalities) so for each modality we generate a binary variable. In this way the total number of variables is 55 (see Table 1 and the best models for CCR and MS in Supplemental Digital Content 1 and 2)**

b. Independent baseline results, comparisons between MADR-E and KCH and global data from the 1437 pairs are depicted in **Table 1**.

c. **ANN for KCH (3-months graft survival model). Training KCH → Testing KCH (Supplemental Digital Content 1).** The ANN models clearly improved the potential prediction of graft survival and graft non-survival 3-months after the transplant. The CCR (AUROC=0,9375) and MS (AUROC=0,9374) models increased up to 10% respect to the second best score (BAR score; AUROC=0,8446) **(Figure 1)**. As observed, the prediction capability was excellent and clearly better (increase >11%) than in the previous original

MADR-E model in which CCR and MS models predicted AUROC=0,8060 and AUROC=0,8215, respectively.

d. **ANN for KCH (1-year graft survival model). Training KCH → Testing KCH (Supplemental Digital Content 2).** The impact of D-R matching on graft survival was also analyzed in the long-term setting. One-year probability of graft (AUROC=0,78333) and non-graft (AUROC=0,81528) survival were better predicted by ANN compared to the best prediction achieved by other scores (BAR score; AUROC=0,70972) **(Figure 2)**.

e. **The exportation model. Training MADR-E → Testing KCH.** The statistical analysis performed by using MADR-E for the training and testing with the KCH showed that both CCR (AUROC=0,6400) and MS (AUROC=0,6235) models worked slightly better than the best score (BAR score; AUROC=0,6034) **(Figure 3)**.

f. **Global ANN using combined data. Training MADR-E + KCH → Testing MADR-E + KCH (The potential MADR-Eu) (Supplemental Digital Content 3).** By grouping both Spanish and KCH population, 1470 D-R pairs were analyzed (by the 10-fold technique, 147 pairs were randomly selected 10 times and 1323 were validated 10 times). Both CCR (AUROC=0,7791) and MS (AUROC=0,7016) achieved excellent prediction probabilities almost 20% higher than the best current score (BAR score; AUROC=0,5973) **(Figure 4)**. These results were slightly worse than those obtained in our previous MADR-E only manuscript (CCR AUROC=0,8060; MS AUROC=0,8215).

g. **A theoretical D-R selection model using the rule-based model in the KCH model.** By the application of the rule-based model, 5 random real

recipients and 10 random potential donors were selected. The ANN calculated the highest probability of graft survival (CCR model) and the lowest probability of graft non-survival (MS model). By combining both of them and using the rule-based system, a recipient was chosen for a specific donor. In our theoretical model, R1 was the preferential selection for donors 2, 8 and 10. For example, when donor 10 was selected, R1 and R3 had equal survival and non-survival probabilities, but highest MELD score (and thus, highest probability of death on waiting list) ruled the decision from the ANN. For example, when donor 6 was selected, R1 and R3 had similar graft surviving rates but R3 had the lowest probability of non-survival and then, it was selected by the **rule-based system (see Table 2).**

DISCUSSION.

The management of waiting lists for liver transplantation is not an easy task. The number of candidates continues to increase and could be even higher if expanded indications such as colorectal liver metastases and extended criteria for HCC and cholangiocarcinoma were accepted for inclusion on the waiting list. The medical community needs a tool that could combine three features: objectivity (to avoid human subjectivity in the management of waiting list), optimization (to achieve highest post-transplant survival rates) and justice (to give the chance to be transplanted with advanced disease). Besides, this tool should be flexible and adapt to most of the allocation systems in all countries with their own peculiarities. We developed models entitled MADR ("madre" in Spanish means "mother", that helps conceive these models as a creative tool that generates

multiple individual and unique models). Our findings confirm that the best D-R matching system to date would be an ANN-guided system trained, tested and optimized for each healthcare system.

Several systems have been proposed for D-R matching in LT. All of them have been built using regression models or statistical findings. They work well and highlight the complexity of donor and recipient matching. None have emerged as of value in healthcare systems worldwide. Reasons for this include their heterogeneity, the different variables used and that some of them are all-or-none systems in which only a small number of patients can be discriminated. Further disadvantage is that access to transplant may not be equally guaranteed in special indications such as recurrent encephalopathy or refractory as cites [9].

Our MADR-E worked well in the Spanish database grouping data from several centres. The development of an ANN for KCH (MADR-KCH) had excellent prediction capabilities which was even better than the original MADR-E. Validation of ANN as a tool for optimal D-R matching is supported by our findings. However, exporting the MADR-E ANN to KCH was unsatisfactory. The explanation for this would include that ANN is built for a different healthcare system and that input variables are absolutely different (different donors, indications, race proportions, …). Therefore each ANN model utilised worldwide is trained for a specific purpose in a single distinctive population. The 1-year MADR-KCH ANN was also notable. In that, the model was useful, but was less accurate than the 3-months model. This is probably because D-R interactions may not have such a direct impact on mid-term survival as they do on short-term outcomes.

The development of a preliminary MADR-Eu is interesting and the results are promising. By grouping all the populations and training/testing them, excellent prediction rates for graft survival and non-survival were achieved, which were higher than with other scores. This potential utility needs to be evaluated with a much larger population using large multinational databases. It is an attractive prospect to think that it may be possible to find a unique ANN that may be exportable to liver transplant programs in every country. However, it should be possible for each transplant program to analyse their data by building their own ANN and generating specific D-R matching software. Unfortunately, medical records are not as accurate as they should be and databases do not equally work in every hospital. ANN could potentially work better if they could be developed using previously recorded data with no missing values. A potential area of research would be to prospectively build an ANN using hundreds of pre-transplant variables and hundreds of post-transplant variables.

Conventional regression analyses use historical data and try to fit them to some function. The drawback here is the difficulty of selecting an appropriate function capable of capturing all forms of data relationships as well as automatically modifying output in case of additional information, because the performance of a candidate is influenced by a number of factors, and this influence/relationship is not likely to be represented by a simple known regression model. An ANN, which imitates the human brain in problem solving, is a more general approach that can handle this type of problem by adapting itself, learning from every candidate and modifying with every situation.

Artificial neural networks are complex tools. They can predict several important situations from which the life of human populations is decided. For example, during emergencies such as flood and drought seasons, reservoirs act as defence mechanisms to reduce the risk of flooding and to maintain water supply. During this period, decision regarding water release is critical [15]. Another example is the prediction of water levels at Kainji Dam, which supplies water to Nigeria's largest hydropower generation station in which ANN were built to generate a more efficient power supply [16]. All the models used hundreds of variables recorded daily for several years to build extremely accurate tools that have led to excellent prediction capabilities not reachable by the human mind and far from simplistic common statistical models. Nowadays, a huge number of processes worldwide are predicted, controlled and guided by ANN. All are specifically designed for each individual process. For example, the ANN designed for the forecast prediction of one is not the same for another, or the one that controls variables affecting flight status of one type of plane is not usable for another.

It is extremely difficult to predict every human behaviour and every human medical process. But it is more complex to modify human feelings and to adapt them to artificial intelligence. Even the most sophisticated robot may not accurately consider individual factors and ethical issues are unlikely to be accurately modelled. For example, an ANN would be unlikely to consider an adequate donor for a third-graft recipient that developed a primary graft non-function in his first transplant and a late arterial thrombosis after his second transplant. The likelihood is that this recipient would never be allocated a donor,

due to the poor outcomes. The solution would be to create a specific ANN for retransplants or to bypass the ANN solution generating a mixed model in which artificial intelligence and human factors would coexist.

The research field that our group has started is at the very beginning. Leaving the decision of who will get a graft and who will not and thus, who will die to software will not satisfy everyone. But there are now many examples such as plague control, flight behaviour, water level controls, dock openings or weather forecasting that are ANN-controlled and may lead to the survival of thousands of people everyday. The medical community has to explore the interface between human decisions and software-guided analyses which is moving in favour of complex computational tools. A prospective trial may be the next step to make the transplant community consider these tools and to further apply the results of our analysis that shows that ANN may accurately predict graft outcomes and guide donor-recipient matching decisions in different healthcare systems.

TABLE 1. Baseline characteristics of the Spanish (MADR-E) and British (KCH) populations.

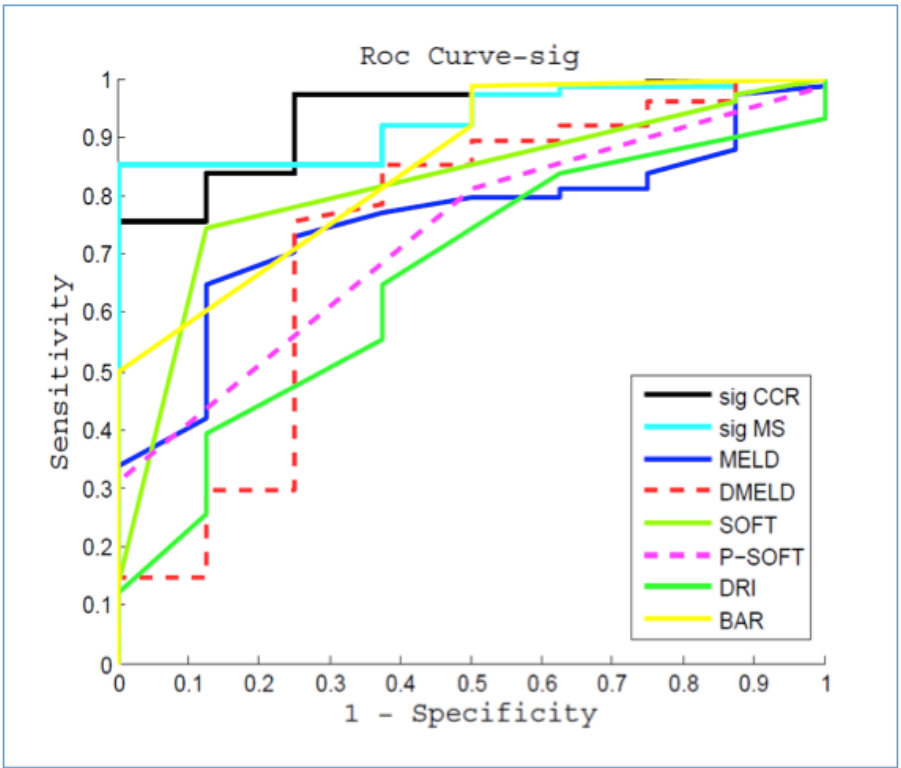
VARIABLES	GLOBAL N=1437	MADR-E N=615	KCH N=822	P
RECIPIENT VARIABLES				
Age (x1)	49.6 ±12.0	50.5 ± 11.0	49.0 ± 12.0	0.05
Gender (x2)	64.6%	65.9%	63.6%	0.36
BMI (x3)	31.4 ±6.0	29.9 ± 6.0	32.6 ± 5.0	**0.02**
Diabetes (x4)	15.8%	14.8%	16.6%	0.35
Hypertension (x5)	16.6%	14.1%	18.5%	**0.03**
Pre-transplant dialysis (x6)	2.7%	2.4%	2.9%	0.57
Aetiology				**0.02**
• **HCV (x7)**	21.4%	24.7%	18.9%	
• **ALCOHOL (x8)**	25.0%	25.6%	24.5%	
• **HBV (x9)**	5.2%	5.2%	5.2%	
• **ALF (x10)**	13.6%	11.9%	15.0%	
• **PBC (x11)**	5.6%	3.7%	7.1%	
• **PSC (x12)**	7.7%	8.1%	7.4%	
• **Others (x13)**	21.4%	20.8%	21.9%	
Portal vein thrombosis				0.35
• **Absent (x14)**	88.0%	87.7%	87.6%	
• **Partial (x15)**	11.6%	11.2%	11.9%	
• **Complete (x16)**	0.8%	1.1%	0.5%	
Days on waiting list (x17)	165 ± 200	167 ± 211	164 ± 192	0.56
MELD (at inclusion) (x18)	17.5 ± 7.8	18 ± 7.4	17.1 ± 8.0	**0.03**
MELD (at transplant) (x19)	18.9 ± 8.2	19.2 ± 7.4	18 .6 ± 8.5	**0.002**
TIPS (x20)	3.8%	4.4%	3.3%	0.28
Hepatorenal syndrome (x21)	10.4%	10.6%	10.4%	0.90
Abdominal surgery (x22)	11.0%	12.8%	9.6%	0.06
Pre-transplant status				**0.04**
• **Ambulatory (x23)**	65.6%	66.9%	64.7%	
• **Admitted ward (x24)**	18.3%	18.8%	17.9%	
• **ITU (x25)**	4.0%	4.9%	3.4%	
• **ITU + ventilator (x26)**	12.0%	9.4%	14.0%	
CMV status (x27)	71.5%	74.2%	69.4%	**0.05**

DONOR VARIABLES				
Age (x28)	49.8 ± 16.0	52.6 ± 16.0	47.8 ± 15.0	0.12
Gender (Male) (x29)	53.3%	54.1%	52.7%	0.62
BMI (x30)	26.2 ± 4.0	26.5 ± 4.0	25.8 ± 4.0	0.05
Diabetes (x31)	7.7%	8.3%	7.3%	0.49
Hypertension (x32)	22.0%	25.3%	19.5%	0.08
Cause of death				**0.005**
• **Trauma (x33)**	17.5%	19.2%	16.2%	
• **CVA (x34)**	68.1%	68.5%	67.8%	
• **Anoxia (x35)**	7.1%	4.4%	9.1%	
• **DCD (x36)**	1.7%	1.5%	1.8%	
• **Others (x37)**	12.7%	10.9%	14.1%	
Days on ICU (x38)	2.8 ± 3.9	2.9 ± 3.6	2.8 ± 4.1	0.85
Hypotensive episode (x39)	15.9%	17.7%	14.6%	0.11
Inotropes (x40)	76.5%	77.4%	75.9%	0.49
Creatinine (x41)	1.02 ± 0.60	1.04 ± 0.60	1.00 ± 0.60	0.12
Sodium (x42)	147.1 ± 8.0	147.4 ± 8.0	146.9 ± 8.0	0.65
AST (x43)	60.2 ± 91.0	55.4 ± 71.0	63.8 ± 103.0	**0.04**
ALT (x44)	51.9 ± 91.0	52.3 ± 87.0	51.7 ± 93.0	0.87
Bilirubin (x45)	0.70± 0.48	0.70 ± 0.40	0.69 ± 0.40	0.95
Hepatitis B (HBcAb +) (x46)	5.6%	5.7%	5.5%	0.87
Hepatitis C (HCV +) (x47)	1.0%	1.5%	0.6%	0.10
CMV status (x48)	60.3%	63.3%	58.0%	**0.04**
PERI-TRANSPLANT VARIABLES				
Multiorgan donor (x49)	48.3%	58.1%	40.9%	**0.001**
Combined transplant (x50)	3.1%	4.1%	2.3%	0.06
Partial graft (x51)	6.9%	3.9%	9.1%	**0.001**
Cold ischaemia (h) (x52-54)	8.1	7.4	8.8	**0.002**
• **<6h**	26.7%	58.7%	28.0%	
• **6-12h**	44.3%	39.7%	47.8%	
• **>12h**	28.9%	16.0%	49.4%	
ABO compatibility (x55)	94.2%	94.8%	93.8%	0.41

Table 2. A simulation of D-R allocation by the ANN. By randomly choosing 5 potential recipients with MELD score 23-27 and 10 random donors, probability of survival (CCR) and non-survival (MS) were calculated. After that, and using the "rule-based system", a D-R pair is selected.

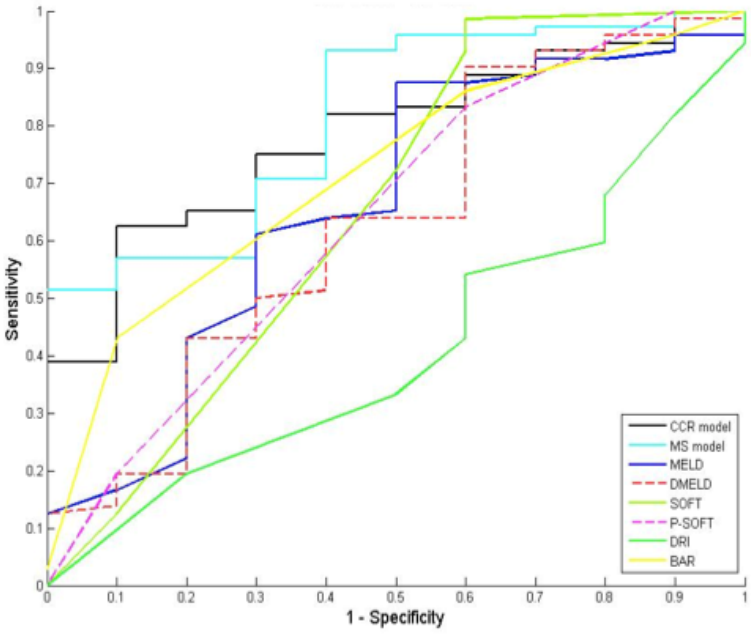
CCR MODEL.- 3-MONTHS PROBABILITY OF GRAFT SURVIVAL										
Recipient (MELD)	Don1	Don2	Don3	Don4	Don5	Don6	Don7	Don8	Don9	Don10
Recipient 1(27)	**93.19**	**91.43**	**93.19**	**94.26**	**94.13**	**93.19**	**94.26**	**94.13**	**94.26**	**94.27**
Recipient 2(26)	84.37	84.30	84.37	94.25	85.28	84.37	92.95	85.28	92.95	94.26
Recipient 3(23)	92.95	90.95	92.95	**94.26**	94.10	92.95	**94.26**	94.10	**94.26**	**94.27**
Recipient 4(23)	84.35	84.30	84.35	94.24	85.28	84.35	92.95	85.28	92.95	94.26
Recipient 5(23)	84.18	84.27	84.18	94.09	84.33	84.18	87.05	84.33	87.05	94.13
MS MODEL.- 3-MONTHS PROBABILITY OF NON-GRAFT SURVIVAL										
	Don1	Don2	Don3	Don4	Don5	Don6	Don7	Don8	Don9	Don10
Recipient 1(27)	74.85	76.37	75.60	19.69	25.31	74.16	18.91	76.36	73.31	13.75
Recipient 2(26)	75.83	76.39	76.11	30.29	41.08	75.58	28.50	76.38	75.24	15.13
Recipient 3(23)	**49.29**	**75.74**	**60.16**	**13.26**	**13.52**	**42.41**	**13.23**	**75.60**	**36.03**	**13.00**
Recipient 4(23)	68.76	76.25	72.39	14.29	15.46	65.63	14.13	76.22	61.67	13.12
Recipient 5(23)	76.40	76.40	76.40	74.95	75.61	76.40	74.73	76.40	76.38	64.57
Allocation:	R3	R1	R3	R3	R3	R3	R3	R1	R3	R1

Figure 1. Artificial neural network model to predict 3-months graft survival developed using the KCH population for both training and testing and comparisons against other scores. CCR: correct classification rate; MS: minimum sensitivity.



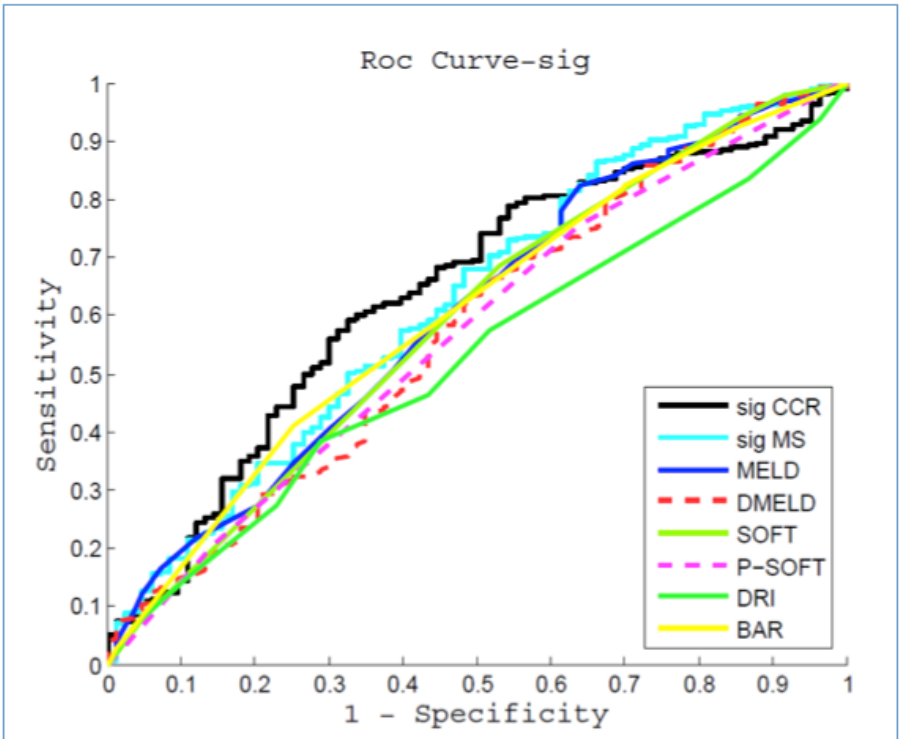
KCH(train) → KCH(test) 3-month	CCR gener.	MS gener.	AUC gener.
MELD	0.7683	0.5000	0.7517
DMELD	0.8659	0.3750	0.7297
SOFT	0.8902	0.1250	0.8159
P-SOFT	0.9024	0.0000	0.7230
DRI	0.9024	0.0000	0.6571
BAR	0.8780	0.5000	0.8446
sig_CCR	0.9024	0.0000	0.9375
sig_MS	0.6585	0.6216	0.9274

Figure 2. Artificial neural network model to predict 1-year graft survival developed using the KCH population for both training and testing and comparisons against other scores. CCR: correct classification rate; MS: minimum sensitivity.



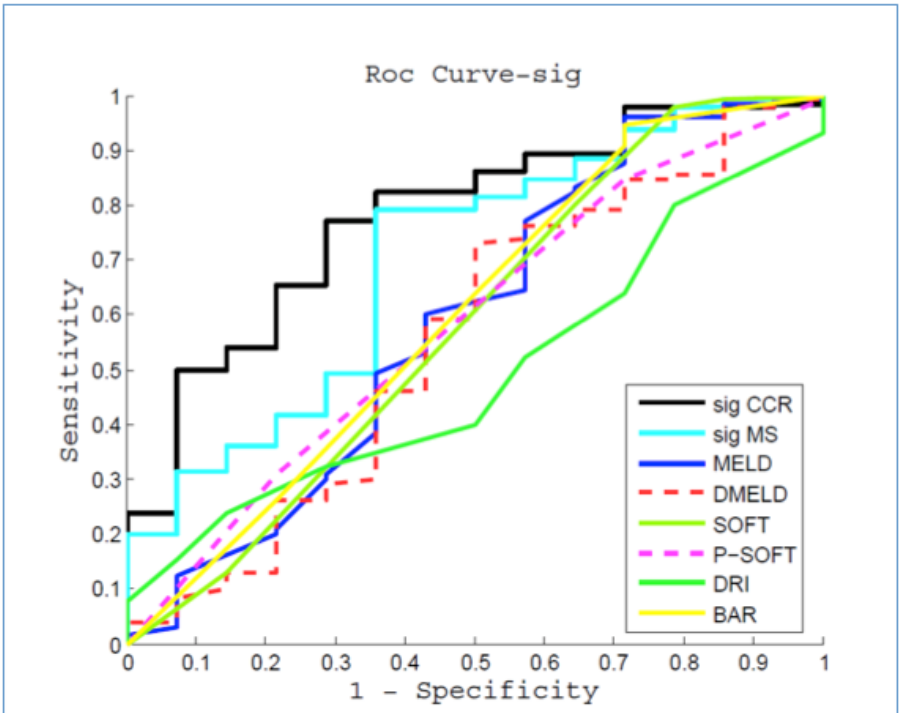
KCH(train) → KCH(test) 1-year	CCR gener.	MS gener.	AUC gener.
MELD	0.74390	0.50000	0.65972
DMELD	0.85366	0.30000	0.63056
SOFT	0.91463	0.40000	0.64861
P-SOFT	0.87805	0.00000	0.64167
DRI	0.87805	0.00000	0.41111
BAR	0.80488	0.40000	0.70972
sig_CCR	0.89024	0.10000	0.78333
sig_MS	0.57317	0.51389	0.81528

Figure 3. Artificial neural network model to predict 3-months graft survival developed using the Spanish previously reported model [10] for training and the KCH population for testing comparisons against other scores. CCR: correct classification rate; MS: minimum sensitivity.



MADRE(train) → KCH(test)	CCR gener.	MS gener.	AUC gener.
MELD	0.7384	0.3855	0.6029
DMELD	0.8406	0.1807	0.5765
SOFT	0.8880	0.0843	0.5903
P-SOFT	0.8990	0.0001	0.5700
DRI	0.8990	0.0001	0.5259
BAR	0.7700	0.3012	0.6034
sig_CCR	0.8905	0.0001	0.6400
sig_MS	0.6301	0.5301	0.6235

Figure 4. Artificial neural network model to predict 3-months graft survival developed using the combined population of MADR-E and KCH both for training and testing and comparisons against other scores. CCR: correct classification rate; MS: minimum sensitivity.



MADRE + KCH(train) → MADRE + KCH(test)	CCR gener.	MS gener.	AUC gener.
MELD	0.8403	0.2857	0.5885
DMELD	0.8264	0.1429	0.5588
SOFT	0.9097	0.1429	0.5780
P-SOFT	0.9028	0.0000	0.5830
DRI	0.9028	0.0000	0.4901
BAR	0.8819	0.2857	0.5973
sig_CCR	0.9028	0.0000	0.7791
sig_MS	0.5486	0.5385	0.7016

Supplemental Digital Content 1. Formulae obtained from the artificial neural network model to predict 3-months graft survival developed using the KCH population for both training and testing and comparisons against other scores. C: correct classification rate; MS: minimum sensitivity.

The probability that a pair (D-R) designed by **x** belongs to 3 months survival class $S_{C,3M,KC}$ is (all variables Xi are normalized between 0.1 and 0.9):

$$P(\mathbf{x} \in S_{C,3M,KC}) = \frac{1}{1+e^{-f_{C,3M,KC}(\mathbf{x})}},$$

$$\textit{where } f_{C,3M,KC}(\mathbf{x}) = 1.39 + 1.40 * B_{1,C,3M,KC}(\mathbf{x}, \mathbf{w_1}) - 1.12 * B_{2,C,3M,KC}(\mathbf{x}, \mathbf{w_2}) - 13.75 * B_{3,C,3M,KC}(\mathbf{x}, \mathbf{w_3})$$

$B_{1,C,3M,KC}(\mathbf{x},\mathbf{w_1})$= 1/(1+EXP{-9.06 -0.17 * (X6) +1.78 * (X7) -7.25 * (X8) -16.99 * (X10)-5.14 * (X11) -5.25 * (X15) -3.92 * (X21) -0.31 * (X22) -10.46 * (X24) -3.77 * (X30) +15.82 * (X32) +10.65 * (X33) -5.15 * (X34) -6.28 * (X35)-11.23 * (X43) -5.25 * (X44) -0.28 * (X48) +2.74 * (X50) -6.30 * (X51)})

$B_{2,C,3M,KC}(\mathbf{x},\mathbf{w_2})$= 1/(1+EXP{-6.05 -7.72 * (X2) -3.47 * (X10) +7.99 * (X20) -1.17 * (X31) -4.98 * (X48) -6.44 * (X49) +9.17 * (X53)})

$B_{3,C,3M,KC}(\mathbf{x},\mathbf{w_3})$= 1/(1+EXP{-9.12-2.66 * (X9) +11.41 * (X17) +6.02 * (X18) -9.84 * (X19) +3.32 * (X20) +1.68 * (X24) -2.81 * (X27)-1.02 * (X33) -6.24 * (X34) +7.77 * (X36) -0.36 * (X38) +6.83 * (X49) +5.49 * (X55)})

The probability that a pair (D-R) designed by **x** belongs to 3 months survival class $S_{MS,3M,KC}$ is (all variables Xi are normalized between 0.1 and 0.9):

$$P(\mathbf{x} \in S_{MS,3M,KC}) = \frac{1}{1+e^{-f_{MS,3M,KC}(\mathbf{x})}},$$

$$\textit{where } f_{MS,3M,KC}(\mathbf{x}) = 1.42 + 0.48 * B_{1,MS,3M,KC}(\mathbf{x}, \mathbf{w_1}) - 16.34 * B_{2,MS,3M,KC}(\mathbf{x}, \mathbf{w_2}) - 3.07 * B_{3,MS,3M,KC}(\mathbf{x}, \mathbf{w_3})$$

$B_{1,MS,3M,KC}(\mathbf{x},\mathbf{w_1})$= 1/(1+EXP{10.07 -0.36 * (x6) -3.20 * (x7) -7.49 * (x8) -7.39 * (x9) -17.18 * (x10) -5.61 * (x11) -7.57 * (x15) -6.20 * (x21) -0.66 * (x22) -9.32 * (x24) +0.82 * (x29) -3.97 * (x30) +17.83 * (x32) +0.52 * (x33) -1.05 * (x34) -8.58 * (x35) -7.83 * (x43) -1.92 * (x44) -3.25 * (x47) +1.26 * (x48) -0.69 * (x49) +1.66 * (x50) -0.96 * (x51)})

$B_{2,MS,3M,KC}(\mathbf{x},\mathbf{w_2})$= 1/(1+EXP{-12.31 -0.20 * (x2) -0.59 * (x3) +2.27 * (x9) +17.57 * (x17)+6.46 * (x18) -11.40 * (x19) +4.07 * (x20) -0.77 * (x24) -3.55 * (x27) -0.70 * (x32) -0.09 * (x33) -0.50 * (x35) +6.75 * (x36) -4.50 * (x38) -0.08 * (x42) -0.97 * (x43) -0.86 * (x44) -1.84 * (x47) +6.88 * (x49) +0.53 * (x55)})

$B_{3,MS,3M,KC}(\mathbf{x},\mathbf{w_3})$= 1/(1+EXP{-8.84 +6.20 * (x4) -1.55 * (x6) -1.44 * (x8) +9.43 * (x9) -3.64 * (x10) +2.57 * (x11)+0.85 * (x12) -0.87 * (x13) +1.57 * (x14) +1.57 * (x17) -6.80 * (x18) -7.52 * (x19) -0.82 * (x20) -4.63 * (x21) -9.82 * (x22) -0.16 * (x24) -1.28 * (x25) -5.92 * (x26) -2.50 * (x27)-5.35 * (x29)+7.24 * (x31) +4.61 * (x32) +5.26 * (x33) +8.30 * (x36) -0.90 * (x38) +3.00 * (x40) -0.22 * (x42) +3.97 * (x43) -8.94 * (x45) -6.60 * (x46) -0.75 * (x47) -0.14 * (x48) -6.68 * (x49) -0.73 * (x51) +0.16 * (x52) -4.95 * (x54) +4.89 * (x55)})

Supplemental Digital Content 2. Formulae obtained from the artificial neural network model to predict 1-year graft survival developed using the KCH population for both training and testing and comparisons against other scores. C: correct classification rate; MS: minimum sensitivity.

The probability that a pair (D-R) designed by **x** belongs to 1 year survival class $S_{C,1Y,KC}$ is (all variables Xi are normalized between 0.1 and 0.9):

$$P(\mathbf{x} \in S_{C,1Y,KC}) = \frac{1}{1+e^{-f_{C,1Y,KC}(\mathbf{x})}},$$

$$where\ f_{C,1Y,KC}(\mathbf{x}) = 2.05 - 3.85 * B_{1,C,1Y,KC}(\mathbf{x}, \mathbf{w}_1) + 2.94 * B_{2,C,1Y,KC}(\mathbf{x}, \mathbf{w}_2)$$

$B_{1,C,1Y,KC}(\mathbf{x},\mathbf{w_1})$= 1/(1+EXP{-7.25+9.91 * (x1) -9.12 * (x2) -3.56 * (X3) +11.50 * (X4) +10.75 * (x5) -1.42 * (x6) -5.43 * (X10) -0.64 * (X11) +4.60 * (X14) -7.69 * (X15) -12.71 * (X17) +2.69 * (X20) -19.91 * (X22)+2.88 * (X23) +1.92 * (X25) +18.65 * (X27) +17.36 * (X29) -1.02 * (X30) +8.68 * (X31)+5.40 * (X32) -7.17 * (X33)-2.09 * (X36) -5.13 * (X37) +7.32 * (X38) +1.09 * (X40) +11.29 * (X41) +0.78 * (X46) +3.05 * (X48) -2.52 * (X49) +11.77 * (X50) +8.08 * (X52) +3.56 * (X53) -0.62 * (X54) -7.46 * (X55)})

$B_{1,C,1Y,KC}(\mathbf{x},\mathbf{w_2})$= 1/(1+EXP{-6.28 +5.47 * (x2) +12.22 * (X3) -10.72 * (X4) +3.46 * (X7) -7.26 * (X9) +16.46 * (X11) +5.15 * (x12) -0.29 * (X13) +0.20 * (X14) +13.09 * (X15) -0.07 * (X17) +6.02 * (X18) +4.79 * (X19) -26.00 * (X20) +10.24 * (X21) -11.58 * (X22) -5.55 * (X23) +5.67 * (X26) -4.93 * (X29) -0.10 * (X32)-32.80 * (X36) +16.27 * (X37) -7.34 * (X38) +2.31 * (X39) -7.76 * (X40) +7.86 * (X41) +6.79 * (X42) -8.42 * (X45) -17.47 * (X46) +7.49 * (X47) +5.43 * (X49) -2.49 * (X50) -8.57 * (X52)})

The probability that a pair (D-R) designed by **x** belongs to 1 year survival class $S_{MS,1Y,KC}$ is (all variables Xi are normalized between 0.1 and 0.9):

$$P(\mathbf{x} \in S_{MS,1Y,KC}) = \frac{1}{1+e^{-f_{MS,1Y,KC}(\mathbf{x})}},\ where\ f_{MS,1Y,KC}(\mathbf{x}) = -7.12 + 8.98 * B_{1,MS,1Y,KC}(\mathbf{x}, \mathbf{w}_1)$$

$B_{1,MS,1Y,KC}(\mathbf{x},\mathbf{w_1})$= 1/(1+EXP{-1.83 -1.03 * (X2) -0.84 * (X3) -3.29 * (X4) -3.59 * (x5) -0.96 * (X6) +7.10 * (X7) +4.67 * (X9)+0.51 * (X10) +0.92 * (X11) -0.62 * (x12) +2.40 * (X14) +5.83 * (X15) -0.58 * (X17) -7.36 * (X18) +8.72 * (X19) -0.48 * (X22) -6.53 * (X23) +0.50 * (X24) -1.93 * (X25) -0.31 * (X26) +0.90 * (X29) +1.50 * (X31) +0.45 * (X33) +1.24 * (X37) +3.34 * (X38) +0.03 * (X39) -1.37 * (X41) +0.60 * (X42) -7.17 * (X43) -8.36 * (X44) +0.59 * (X48) -0.22 * (X49) -8.76 * (X52) -1.64 * (X53) +0.91 * (X54)})

Supplemental Digital Content 3. Formulae obtained fro the artificial neural network model to predict 3-months graft survival developed using the combined population of MADR-E and KCH both for training and testing and comparisons against other scores. C: correct classification rate; MS: minimum sensitivity.

The probability that a pair (D-R) designed by **x** belongs to 3 months survival class $S_{C,3M,MKC}$ is (all variables Xi are normalized between 0.1 and 0.9):

$$P(\mathbf{x} \in S_{C,3M,MKC}) = \frac{1}{1+e^{-f_{C,3M,MKC}(\mathbf{x})}},$$

$$\textit{where } f_{C,3M,MKC}(\mathbf{x}) = 0.43 + 3.09 * B_{1,C,3M,MKC}(\mathbf{x}, \mathbf{w_1}) + 5.21 * B_{2,C,3M,MKC}(\mathbf{x}, \mathbf{w_2}) - 1.75 * B_{3,C,3M,MKC}(\mathbf{x}, \mathbf{w_3})$$

$B_{1,C,3M,MKC}(\mathbf{x},\mathbf{w_1})$= 1/(1+EXP{-8.79-2.84 * (x3) +5.86 * (x6) +4.02 * (x7) +7.83 * (x8)-0.53 * (x9) +3.18 * (x10) -1.87 * (x11) +3.42 * (x15) +3.29 * (x17) +8.72 * (x19) -4.65 * (x20) -8.48 * (x21) -9.32 * (x23) -2.62 * (x24) +0.53 * (x25) +1.80 * (x26) +5.97 * (x28) +7.76 * (x30) +6.23 * (x31) +1.02 * (x32) +1.07 * (x33) -2.51 * (x34) -8.31 * (x37)-0.50 * (x38) -1.13 * (x40)-0.94 * (x45)-4.42 * (x46) +9.43 * (x49) -0.92 * (x50) +2.20 * (x51) })

$B_{2,C,3M,MKC}(\mathbf{x},\mathbf{w_2})$= 1/(1+EXP{- 3.45+6.46 * (x2)+3.98 * (x4) +5.57 * (x5) -2.24 * (x7) -2.73 * (x8) +2.81 * (x11) -6.87 * (x12) -6.76 * (x13) -5.67 * (x15) -6.38 * (x16) +4.48 * (x18) -1.73 * (x19)+8.97 * (x20) +9.43 * (x21) +6.49 * (x23)+9.16 * (x24) -4.91 * (x25) -4.52 * (x26) -0.99 * (x27) +10.12 * (x28) +6.15 * (x29) +11.03 * (x30) +7.02 * (x31) -7.38 * (x34) +4.25 * (x35) +6.50 * (x36) -3.18 * (x37) +1.01 * (x39) -6.08 * (x41) +4.85 * (x42) -6.28 * (x43) +5.46 * (x47) +2.45 * (x48) +7.67 * (x49) +3.60 * (x50) +7.78 * (x51) -6.48 * (x52) -5.42 * (x53) +11.33 * (x55)})

$B_{3,C,3M,MKC}(\mathbf{x},\mathbf{w_3})$= 1/(1+EXP{4.82 +4.74 * (x10) +3.99 * (x14) +1.84 * (x15) -1.11 * (x16) -0.15 * (x17) -3.64 * (x25) +6.57 * (x29) +1.08 * (x31) +0.83 * (x32) +7.36 * (x34) +1.06 * (x36) -8.70 * (x37) +2.95 * (x38) +7.11 * (x42) -3.49 * (x45) -6.90 * (x46) +10.59 * (x48) -4.40 * (x50) -0.06 * (x51) -6.33 * (x52) -4.87 * (x55)})

The probability that a pair (D-R) designed by **x** belongs to 3 months survival class $S_{MS,3M,MKC}$ is (all variables Xi are normalized between 0.1 and 0.9):

$$P(\mathbf{x} \in S_{MS,3M,MKC}) = \frac{1}{1+e^{-f_{MS,3M,MKC}(\mathbf{x})}},$$

$$where\ f_{MS,3M,MKC}(\mathbf{x}) = -9.73 + 4.40 * B_{1,MS,3M,MKC}(\mathbf{x},\mathbf{w_1}) + 8.03 * B_{2,MS,3M,MKC}(\mathbf{x},\mathbf{w_2})$$

$B_{1,MS,3M,MKC}(\mathbf{x},\mathbf{w_1})$= 1/(1+EXP{0.05+5.60 * (x1) +3.71 * (x2) +2.32 * (x3) -9.95 * (x6)-6.64 * (x8) -2.24 * (x9)-1.86 * (x10) -7.46 * (x11) -3.90 * (x12)-2.62 * (x14)-5.99 * (x15)-8.68 * (x17) +8.72 * (x18) -10.37 * (x20) +2.35 * (x22) -1.67 * (x23) -0.57 * (x24)+1.35 * (x25) -3.30 * (x26)-2.43 * (x27)+4.23 * (x28)+6.03 * (x30) +5.54 * (x31) -2.94 * (x32) +2.41 * (x34) -7.68 * (x36) +9.91 * (x37) -5.11 * (x38)-2.37 * (x40) -5.63 * (x41) -6.52 * (x42) +1.77 * (x43) +3.99 * (x44) +10.29 * (x46) -1.46 * (x47) -1.37 * (x51) -7.54 * (x52) +7.43 * (x53) -5.03 * (x55) })

$B_{2,MS,3M,MKC}(\mathbf{x},\mathbf{w_2})$= 1/(1+EXP{-3.84 +10.41 * (x3) +1.18 * (x6) +8.28 * (x7) +3.93 * (x13) +2.27 * (x14) -4.71 * (x15) -9.02 * (x20) -11.36 * (x22) -9.32 * (x23) -2.48 * (x28) +3.40 * (x29) +1.94 * (x31) +9.08 * (x38) +2.60 * (x39)+0.71 * (x43) -1.53 * (x44) +0.11 * (x46) -4.14 * (x47) +1.58 * (x49) +6.55 * (x51) -1.54 * (x54) }))

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