Predictors of Death in the Liver Transplantation Adult Candidates: An Artificial Neural Networks and Support Vector Machine Hybrid-Based Cohort Study

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ABSTRACT

Background: Model for end-stage liver disease (MELD) is currently used for liver transplantation (LT) allocation, however, it is not a sufficient criterion.

Objective: This current study aims to perform a hybrid neural network analysis of different data, make a decision tree and finally design a decision support system for improving LT prioritization.

Material and Methods: In this cohort follow-up-based study, baseline characteristics of 1947 adult patients, who were candidates for LT in Shiraz Organ Transplant Center, Iran, were assessed and followed for two years and those who died before LT due to the end-stage liver disease were considered as dead cases, while others considered as alive cases. A well-organized checklist was filled for each patient. Analysis of the data was performed using artificial neural networks (ANN) and support vector machines (SVM). Finally, a decision tree was illustrated and a user friendly decision support system was designed to assist physicians in LT prioritization.

Results: Between all MELD types, MELD-Na was a stronger determinant of LT candidates' survival. Both ANN and SVM showed that besides MELD-Na, age and ALP (alkaline phosphatase) are the most important factors, resulting in death in LT candidates. It was cleared that MELD-Na <23, age <53 and ALP <257 IU/L were the best predictors of survival in LT candidates. An applicable decision support system was designed in this study using the above three factors.

Conclusion: Therefore, Meld-Na, age and ALP should be used for LT allocation. The presented decision support system in this study will be helpful in LT prioritization by LT allocators.

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Keywords

Prioritization; Allocation; Artificial Neural Network; Decision Trees; MELD-Na; Liver Transplantation; Neural Network Computers

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Introduction

Liver transplantation (LT) has been known as the most effective treatment for acute or chronic end-stage liver disease [1]. However, the demand-supply imbalance in LT caused a long wait-

ing list in many centers, resulting in increasing death rate before receiving transplantation [2, 3]. Optimal allocation of organs always has been a challenging issue especially that multiple criteria have to be considered simultaneously for LT allocation. In order to attain this objective, many years ago, several countries used "sickest policy" for graft allocation. However, after 2002, several countries gradually started to use model for end-stage liver disease (MELD) score as a better allocation system [4]. Nowadays, most of countries at different continents apply MELD score although they well aware of this fact that this is not the optimal allocation system and needs the improvement [5]. In this study, we aimed to fill this gap by applying a hybrid neural network analysis of different data, making a decision tree and finally designing a decision support system to improve LT prioritization.

Material and Methods

In this cohort follow up-based study, a combination of data collection, input –output screening, pre-processing, processing and post-processing was applied in this study as seen in Figure 1.

Data Gathering Tool

A checklist, including demographic characteristics, medical background and nutritional status was filled for each patient, referred to the LT center of Shiraz University of Medical Sciences (SUMS) from 2017 to 2019. In this respect, data of more than 2500 cases was collected, however, after removing of missing data, 1947 patients were finally encompassed through further analysis. Mean age of patients was 46.4±13.3 years (median 48 years, min-max: 18-91 years). Male (n=1263) to female (n=684) ratio was 1.8 and mortality ratio was

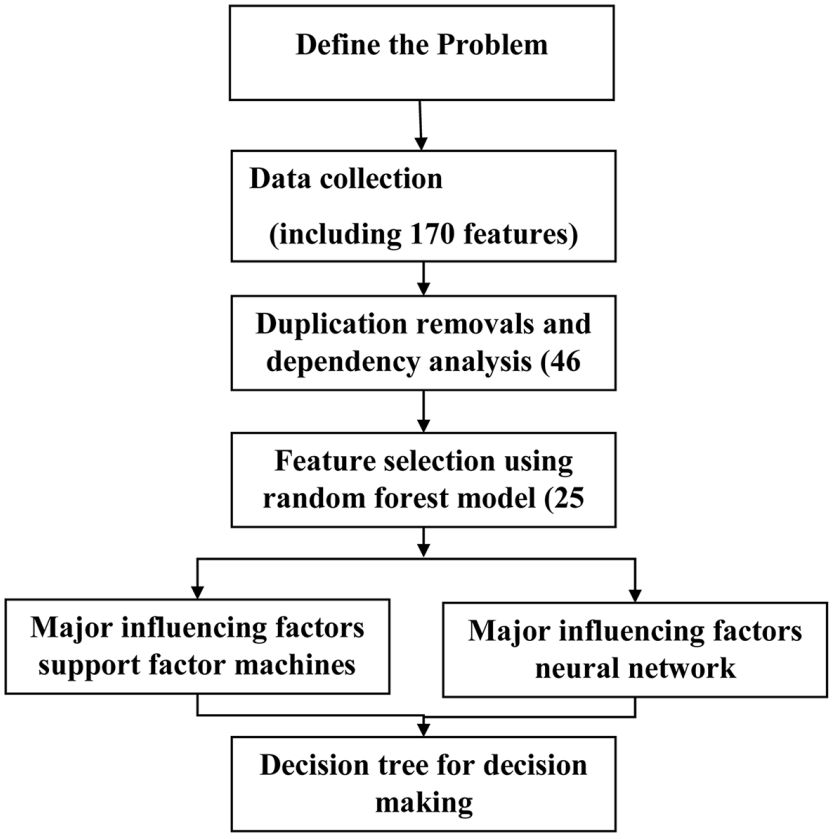

Figure 1: The proposed methodology

18.4% (360/1947). Other characteristics that were selected in the random forest model are shown in the Table 1.

Pre-processing

After definition of the problem under consideration, data collection was performed as described above. Once redundant and missing data were removed, pre-processing phase was undertaken. In this regard, 170 features were reduced to 46 features by removing duplications through dependency (correlation) test among the input variables (features). For instance, since MELD score consists of international normalized ratio (INR), creatinine (Cr) and bilirubin, consideration of MELD score and INR simultaneously will be contributed to over-fitting of the results due to the existed dependency among mentioned variables. The removal policy here was applied to maintain

Table 1: Baseline Demographic, Anthropometric and Medical Characteristics that were Selected in the Random Forest Model (n=1947).

Variable	Alive group (n=1587)	Dead group (n=360)	*P* Value
Age (years)	45.2±13.2	51.6±12.7	<0.001
Gender (male/female)	1022/565	241/119	0.36
Family dimension	3.9±1.5	4.1±2.0	0.11
BMI (kg/m²)	24.6±5.5	24.8±6.4	0.57
Mid arm circumference (cm)	27.0±6.9	25.9±8.0	0.01
Biceps fold thickness (cm)	2.8±5.0	3.2±5.2	0.22
Triceps fold thickness (cm)	5.1±7.7	5.4±8.1	0.48
Leg circumference (cm)	36.4±5.4	35.3±5.3	0.001
DM (yes/no)	210/1174	69/259	0.01
HTN (yes/no)	97/1287	23/304	0.98
Systolic Blood Pressure (mmHg)	106.5±16.5	104.1±17.0	0.01
Tobacco Smoking (yes/no)	332/1051	81/247	0.79
Opioid usage (yes/no)	87/1296	27/301	0.20
Ascites (yes/no)	1190/210	310/23	<001
AIH (yes/no)	175/1412	31/329	0.17
AIH and PSC (yes/no)	19/1429	1/333	†0.15
HCC (yes/no)	160/1240	56/277	0.007
Non-alcoholic steatohepatitis (yes/no)	71/1377	22/312	0.21
PBC (yes/no)	51/1536	16/344	0.24
ALT (u/l)	68.1±99.9	61.1±52.0	0.10
AST (u/l)	90.9±149.8	94.7±81.0	0.67
ALP (u/l)	474.3±415.4	486.9±402.6	0.65
PT (seconds)	17.3±6.1	17.9±3.9	0.12
MELD Na score	20.1±5.0	22.5±5.7	<0.001

BMI: Body Mass Index adjusted for Ascites, DM: Diabetes Mellitus, HTN: Hypertension, AIH: Autoimmune Hepatitis, PSC: Primary Sclerosing Cholangitis, HCC: Hepatocellular Carcinoma, PBC: Primary Biliary Cirrhosis, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, MELD Na: Model for End-Stage Liver Disease Sodium, †: Fisher's Exact Test

the variables, which had a better correlation with the output variable (probability of death). Then random forest algorithm was adopted in order to reduce the number of variables which have to encompass into the processing step.

Processing

As shown in the Figure 1, computational engine of the proposed model consists of three major algorithms.

Random forest algorithm

Random forest is used for feature selection, consisting of two steps as follows: 1) random forest creation, 2) making a prediction from the random forest classifier developed at the earlier stage [6].

The corresponding steps for implementation of random forest algorithm are given as below:

1. Receiving and normalizing input data and then categorizing whole data into training and testing sets.
2. Using under sampling method for balancing data.
3. Selecting "K" features from all "m" features randomly.
4. Calculating the best node, among the selected features.
5. Breaking down the node into the daughter nodes.
6. Repeating the procedure until the desired number of nodes is found.
7. Building forest by echoing steps given above.
8. Considering the test features to predict the outcome.
9. Computing the votes for each predicted target.
10. Considering predicted target as the final prediction.

Neural network

In this study, after examining several possible neural networks, a fully connected Multi-Layer Perceptron (MLP) was fitted. The network was trained and tested using 70% and 30% of total data respectively. In all cases, at least an overall fitting of 82 percent was found and cross-validation for alive LT candidates was 95 percent. The best fitted algorithm was tuned by incurring 25 inputs (as described above), 6 neurons in a hidden layer and single output which can be expressed in two modes (alive and death conditions). Here, a procedure for implementation of MLP [7] is given through a step by step mechanism as following:

1. Receiving input data, standardizing them and break downing all data into test and training sets.
2. Initializing all weights related to each interconnecting arrow randomly.
3. Creating network architecture, including number of hidden layers and neurons associated in each individual layer, type of activation function (softmax).
4. Training the network.
5. Calculating the difference between output of the network and actual data and constructing the error function (cross entropy).
6. Setting a learning rate, continuing until minimizing error function and optimizing the algorithm using gradient descent function (Learning rate of 0.4, momentum: 0.9).
7. Continuing until stopping condition is reached.

However, training might be stopped according to some pre-determined criteria, we considered, when there is no decrease in the error function after 50 steps, then training procedure stops.

Support vector machines

In order to examine the validity of the results obtained by MLP, a SVM has been employed in parallel with the neural network to validate the best known affecting parameters on LT prioritization because Support Vector Machine (SVM) is a strong supervised machine learning algorithm [8]. The structure of the proposed SVM is given below:

1. Receiving input data, normalizing them with breakdown all data into training and test sets.
2. Considering under-sampling method in

order to balance the cleaned data.

3. Choosing kernel function (like RBF kernel).

4. Training SVM, and calculating the fitness value.

5. Checking the requirements for the fitness value.

6. Reaching the optimal kernel parameters and penalty parameters.

7. Examining the obtained SVM model.

Ethics

All subjects provided written informed consent, while voluntarily participation in all stages of this study was respected. Privacy was assured in all steps of study, including interview and data gathering, recording, analysis and reporting.

Results

After running the proposed methodology, the following results were ensued at the post processing stage.

Main Determinants of Mortality in LT Candidates

After running the modeling procedure, both MLP and SVM confirmed that MELD-Na, age and ALP are the major important factors, affecting mortality of LT candidates, respectively. The extent of normalized importance in MLP was 100%, 84% and 65% for these variables, respectively.

Decision tree

Once the above results have been found through MLP optimization, it became possible to construct a decision tree as illustrated in Figure 2. In Figure 2, at the first, second and third layers, Meld-Na, age and ALP have been considered, respectively, while the probability of being alive and dead were also reported at each node.

Other Findings

This study revealed other important findings as below:

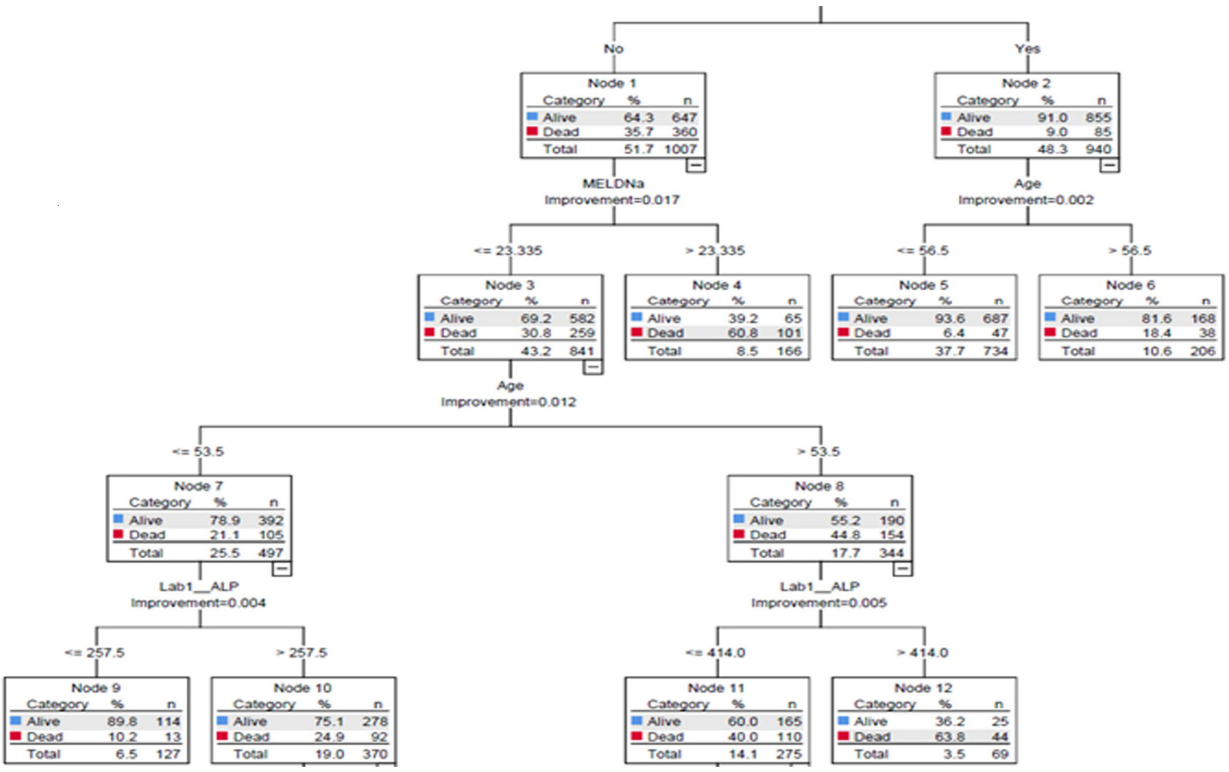

Figure 2: Decision tree for liver transplantation prioritization.

1. Among MELD types (MELD, adjusted MELD, UK MELD, and MELD-Na), MELD-Na has a better performance in predicting mortality in LT candidates. Indeed, the best fitting functions and validations were found when MELD-Na was adopted during the modeling procedure. This finding revealed that in addition to INR, Cr and bilirubin, Na also has an important association with LT candidate's survival.

2. Critical points for MELD-Na and age before LT, are 23 and 53 years, respectively. Indeed, in order to make a proper decision for LT allocation, patients with MELD-Na <23 and Age <53 years significantly had a higher chance of being alive, while are on the waiting list for LT.

3. In equal conditions, patients with MELD-Na <23 have a 30 percent more chance of being alive compared to those that have MELD-Na higher than 23 (level 2 in Figure 2).

4. In equal conditions, patients with age <53 years have a 23 percent more chance of being alive compared to those aged above 53 years (level 3 in Figure 2).

5. The best result is found in this category: Meld-Na <23 and Age <53 years and ALP <257 IU/L, where, in this case, the probability of remaining alive in the LT waiting time is about 90% (level 4 in Figure 2).

6. In order to adopt the results into practice for decision makers, a decision support system was designed as its one sample was shown in Figure 3. Here, in order to develop the decision support system, whole the influencing factors affecting on LT prioritization in the decision tree have to be considered. Therefore, through a combo box, decision makers are able to discover the probability of being alive for numerous patients who are waiting for LT. One important advantage of this decision support system is that once MELD-Na, ALP and age change over time, the probability of being alive can be periodically updated. Therefore, dynamic allocation for LT prioritization can be developed according to the updates done.

7. Sensitivity analysis of Meld-Na, showed that decreasing serum creatinine level by 5% or 10% will equally decrease the Meld-Na from the baseline of 23 to 22, while increasing the same amount of serum Na will decrease the baseline MELD-Na from 23 to 22 and 21, respectively. If serum creatinine decreases by 5% and simultaneously serum level of Na increases by 5%, the baseline MELD Na will drop by 3 units, i.e. from 23 to 20. These findings show that, to decrease MELD-Na, changing the serum Na level is more effective than changing in the serum creatinine level.

Discussion

This study revealed that MELD-Na score, age and serum level of ALP are the most influencing factors affecting LT candidates' outcome. We also showed that among different types of MELD, MELD-Na is a stronger determinant of the survival in patients. Moreover, dropping of MELD-Na is more sensitive to increase in level of serum Na compared to the serum creatinine decline. Furthermore, by

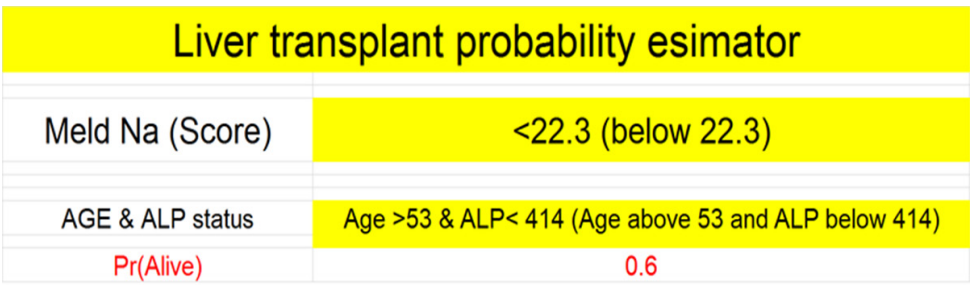

Figure 3: Decision support system for Liver Transplantation.

decreasing the level of serum ALP using appropriate interventions, a better outcome for LT candidates will be provided.

Long waiting list and prolonged waiting time for LT has become a growing challenge despite the increasing number of LT centers and facilities around the world. MELD and different variations of it were proposed for prediction of death in liver transplant candidates or post-transplant survival, while some of these scores suffer from lack of statistical validity and model evaluation [9, 10]. Therefore, survival of LT candidates till obtaining LT and finding a more applicable strategy for LT allocation than only using MELD has been regarded by others [11]. This strategy should incorporate donor and recipient factors, predicting probability of death on the waiting list, post-transplant survival and morbidity, and perhaps costs [5]. So far, different studies have been conducted to adjust LT allocation system. However, a few of these studies were conducted using non-linear models for analysis of data. Higher accuracy of artificial neural network (ANN) than MELD score in prediction of 3-month survival in patients listed for LT was shown in one study [9]. Pérez-Ortiz, et al. proposed a new allocation system which applies machine learning to forecast graft survival after transplantation using a dataset in UK [12]. The main novelty of this system is that it tackles the imbalanced nature of the dataset by considering semi-supervised learning, and analyzing its potentials for obtaining more robust models in LT [12]. Another study by Lan Q et al. focused on the liver quality evaluation as it is also a vital step for estimating the success rate of LT. Therefore, they applied a multi-task learning logistic regression in order to assess the cross-liver quality evaluation [13]. As a limitation, in this study due to administrative problems, we could not consider the amount of changes in continuous variables over the period of this study for analysis and we only considered the baseline data as the predictors of survival. However, as a strength point, this study is among scarce studies that focused on LT candidates' survival and presented an applicable allocating system that can be easily used by LT allocating team in different centers. We recommend to conduct similar studies in several LT centers and integrate the data to provide a more representative results at the nationwide and global level.

Conclusion

In this paper, the major affecting factors on LT prioritization were investigated. After running the data mining models, it is revealed that MELD-Na, age and ALP are significant determinants of death in patients who are on waiting list of LT. It is also found that MELD-Na is the best known attribute of LT candidates' death compared to other MELD types. Therefore, LT allocators should take these three factors in consideration when make decision about LT prioritization. To provide a more applicability of these findings, the decision support system was constructed in this study. Moreover, by adjusting the serum level of Na and creatinine in LT candidates, the probability of death when they are on waiting list of LT may decrease.

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Authors' Contribution

K. Bagheri Lankarani, B. Honarvar and M. Bagherpour conceived the idea. Introduction of the paper was written by F. Shafi Pour, M. Bagherpour, A. Erjaee, V. Seifi and B. Geramizadeh. M. Khorrami, S. Amiri Zadeh Fard, V. Seifi and S. Shirzadi gathered the related literature and also helped with writing of the related works. The method implementation was carried out by MR. Rouhezamin, M. Khorrami, S. Amiri Zadeh Fard, V. Seifi, B. Geramizadeh, H. Salahi, S. Nikeghbalian, AR. Shamsaeefar and SA. Malek-hosseini. Results and Analysis was carried out by B. Honarvar, F. Shafi Pour, M. Bagherpour and A. Erjaee. The research work was proofread and supervised by K. Bagheri

Lankarani, B. Honarvar, F. Shafi Pour and M. Bagherpour. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

The protocol of this study was approved by the SUMS Ethics Committee with registration number: IR.SUMS.REC.1396.S1000.

Informed consent

Written informed consent was obtained from each participant in this study.

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Conflict of Interest

None

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