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Intuitionistic fuzzy RFE-based prognostic model for liver transplantation

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ABSTRACT

Background: Survival prediction after liver transplantation is a very challenging but complex task. LT is often the best treatment for advanced liver disease, provided no other medical conditions contraindicate it. This article explores clinical predictors, such as MELD scores and hormone levels, along with computational algorithms for forecasting post-transplant survival.

Objective: This study evaluates the performance of machine learning models for predicting survival outcomes in liver transplant recipients using UNOS data. It develops and validates a donor and recipient-based prognostic model.

Materials and methods: The UNOS database contains 65,535 donor-recipient pairs in transplants conducted in the U.S. between October 1987 and June 2021, with 421 attributes. The top 24 features, including logistic regression, random forest, artificial neural networks, XGBoost, CART, and K-nearest neighbors, were used to train the models upon feature selection. Models were compared using AUROC, accuracy, specificity, sensitivity, and precision.

Results: ANN outperformed other models for the UNOS dataset, with an AUROC of 0.98–0.99. Validated results in the KCH dataset are robust at AUROC: 0.94–0.95.

Conclusion: The model offered exceptional generalizability performance to guide clinical decisions in transplantation support, yet variability in patients' characteristics may differ significantly among the cohorts and impact the results.

Introduction

Liver disease represents a significant global health issue, causing approximately 2 million deaths annually, with conditions such as cirrhosis, viral hepatitis, and liver cancer contributing to these statistics. Despite being the eleventh leading cause of death,[1] liver-related mortality often remains underreported,[2] with notable variations in regional impact. Women comprise 34% of liver-related deaths. Liver transplantation is the primary treatment for end-stage liver disease; however, patient outcomes significantly rely on factors such as organ quality, donor availability, and illness severity.[3] Accurate pre-transplant mortality prediction is crucial in clinical decision-making and organ allocation, which currently employs the MELD score system. Nonetheless, there are inconsistencies in the MELD score's predictive efficacy[4,5] due to its variability and the exclusion of certain patient factors.[6,7] the field recognizes the need for advanced modeling techniques, such as machine learning, to enhance predictive accuracy by analyzing extensive patient data.[8,9] Integrating varied demographic and clinical information is essential for improving risk assessments and optimizing organ use.[10]

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Table 1. describes the abbreviations used in this study. Table 2. describes significant works in the field, emphasizing the need for more reliable and interpretable models.

Table 1. Nomenclature.

Abbreviation	Description
PTIME	Patient survival time in days
GSTATUS	Graft failed (1=yes)
LIST_MELD	Patient listed prior to meld/ peld?
GRF_STAT	Recipient graft status
EXTRACRANIAL_CANCER_DON	Deceased donor-extra cranial cancer
MALIG	previous malignancy
DIABETES_DON	Diabetes duration
PREV_TX_ANY	previous transplant any organ
BILIARY	biliary tract complication
HTLV2_OLD_DON	donor-antibody to htlv
HBV_CORE_DON	Donor hbv core antibody
PRETREAT_MED_DON_OLD	Deceased donor pre-recovery medications
INOTROPES	Recipient life support type
TX_MELD	Transplant occurred prior to meld/peld?
PSTATUS	Boolean Patient Status(1=Dead,0=Alive)

Table 2. Overview of existing work.

Findings	Dataset used	Limitations	Reference
ANN achieved 99.74% accuracy in survival prediction.	United Network for Organ Sharing data.	Clinical interpretability.	Raji & Chandra[6]
Neural networks outperformed for 10-year survival prediction.	62,294 patients with 97 predictors.	Handling large datasets and model interpretability.	Kantidakis *et al*.[7]
RF achieved AUROC (0.85).	Liver transplantation patients with perioperative data.	Specific to kidney injury.	Yeh *et al*.[8]
Predicted postoperative morbidity and mortality.	242 patients in Korea.	Potential for selection bias.	Jung et al.[9]
ML models outperformed in predicting survival after liver transplantation.	Multi-institutional liver transplantation.	Ethical and logistical challenges in clinical implementation.	Tran *et al*.[10]
Lasso regression identified novel biomarkers which improved the MELD score for 90-day survival predictions.	Data from a European liver transplant cohort.	External validation needed.	Gibb *et al*.[11]
Light GBM achieved AUC 0.740.	Multicenter liver transplant registry data.	No validation on external datasets.	Yanagawa *et al*.[12]

Motivation and goals of the research

The study addresses the limitations of current machine learning models in predicting liver transplant survival by developing a novel method that utilizes intuitionistic fuzzy and recursive feature elimination techniques. Key contributions include a hybrid feature extraction methodology aimed at discarding less relevant and ambiguous data and a ranking system based on entropy values to calculate feature weights effectively. This process ensures that the selected features are refined and appropriately scaled for use in machine learning classifiers, ultimately enhancing mortality risk assessment in LT based on pre-transplant data.

Materials and methods

This process involves high risks that require assessment. The block diagram describes the model along with its feature selection criteria.

Study flow

Initially, data pre-processing steps such as transformation and cleaning were applied. Then, different feature extraction strategies were used to identify the key features. Finally, six machine learning models were selected for classification.

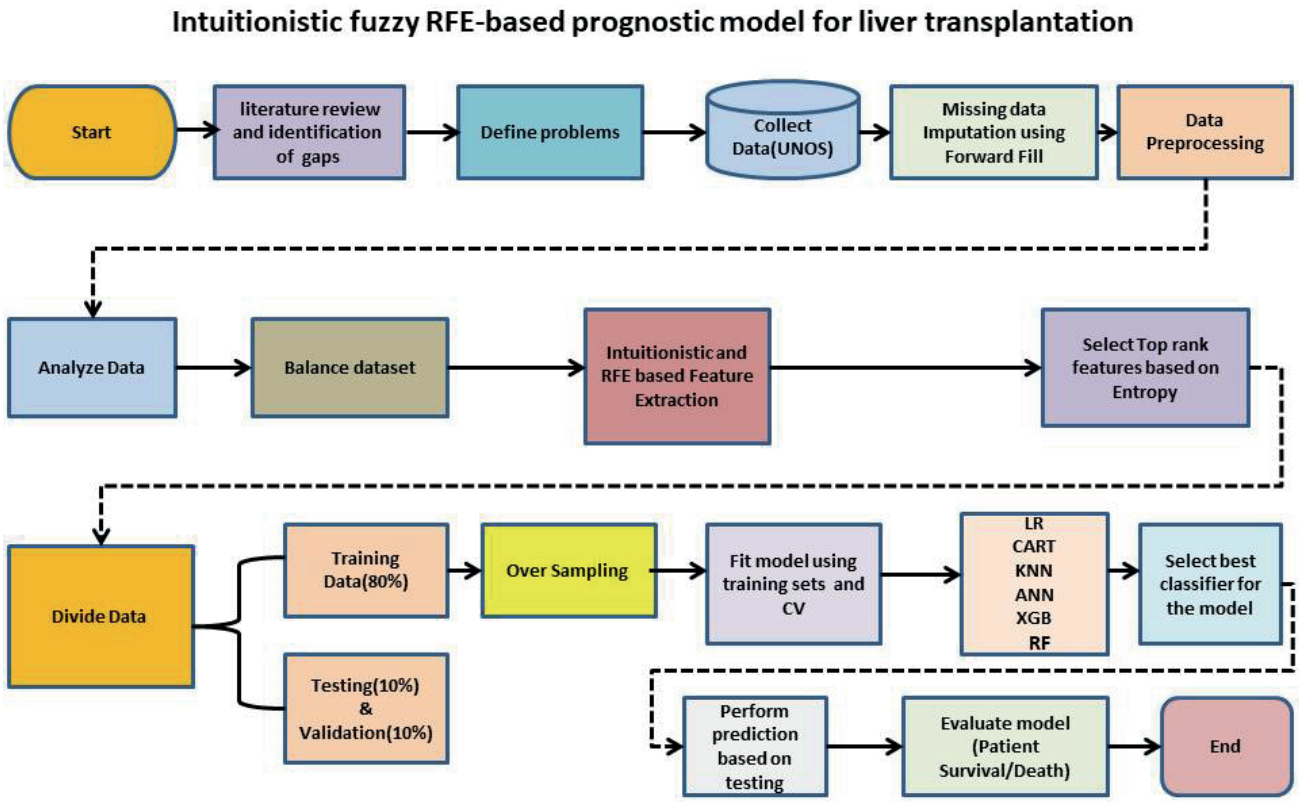

***Figure 1**. Block diagrams of the proposed model.*

Data collection

Data sources used the United Network for Organ Sharing data from 65,535 liver transplants from October 1, 1987, to June 30, 2021. The dataset included 421 variables, including 105 recipient variables, 59 donor variables, 157 clinical data points, 14 waiting list data points, 56 patient status data points, and 30 post-transplant data points.

Missing values-imputation method

This study focused on estimating missing values.[11] Missing data can be caused by the failure of laboratory devices, clinician oversight, or even patient visit cancellation. We compared several imputation methods, including forward filling, mean filling, median filling, and random filling.[12] The forward-filling method is employed as it provides the best AUROC on this dataset.

Pre-processing

Firstly, irrelevant features were removed based on the hepatologist's judgment, reducing the dataset from 421 to 396 characteristics. Features irrelevant to graft survival, such as patient code and admission date, were excluded. Transplants performed after 2016 were retained to ensure a 5-year follow-up period for all LT cases used to build our models. The number of patients with LT was reduced from 65,535 to 64,635. The dataset contained continuous and categorical data. The categorical data were transformed into constant data using label encoding.

The feature extraction method

The proposed method enhances ML algorithm performance in predicting LT mortality risk by using Recursive Feature Elimination (RFE) with Intuitionistic Fuzzy Logic (IFL) for feature extraction. RFE removes irrelevant and poor features but preserves strong features. IFL assigns weights based on belongingness, non-belongingness, and hesitancy and introduces information about the importance of features. The entropy metric ranks the features. Lower entropy means higher relevance, whereas intuitionistic fuzzy sets create thresholds for feature inclusion. This results in better accuracy and interpretability of the model.[13,14]

Intuitionistic fuzzy concept

Non-belongingness and reluctance grades are included with intuitionistic fuzzy logic, which is quite beneficial for inconsistent, ambiguous, and uncertain datasets.[14]

Definition 1: An IFS F over a universal set $X = \{x_1, x_2, ..., x_n\}$ is defined as:

$$F = \{[x,\mu_F(x),v_F(x)] \mid x \in X\}, \quad (1)$$

Where $\mu_F(x):X \rightarrow [0,1]$ the membership degree is $v_F(x):X \rightarrow [0,1]$ is the nonmembership degree, and they satisfy:

$$0 \leq \mu_F(x) + v_F(x) \leq 1 \quad (2)$$

The hesitation degree is given by:

$$\pi_F(x)=1-\mu_F(x)-v_F(x) \quad (3)$$

Definition 2: Entropy for IFS

Its entropy $E(x_i)$ quantifies the uncertainty within the intuitionistic fuzzy framework for a feature. RFE iteratively fits a model using progressively smaller feature sets until the termination condition is met. Each iteration ranks the attributes according to their relevance.[14] The feature selection algorithm is shown in Figure 2

Require: Dataset $D = \{(x_{ij}, y_i) \mid i = 1, 2 \ldots m; j = 1, 2 \ldots n\}$
1: **Initialization:** Set $F = \{x_1, x_2 \ldots x_n\}$.
2: Define weights α, β, and γ for membership, non-membership, and hesitation components.
3: **function** COMPUTEENTROPY (F)
4: **for** each feature $x_j \in F$ **do**
5: **for** each sample $i = 1$ to m **do**
6: Compute membership: $\left(\mu_{F_j}(x_{ij})\right) = e^{-\frac{|x_{ij} - \text{mean}_j|}{\sigma_j}}$
7: Compute non-membership: $\left(\nu_{F_j}(x_{ij})\right) = 1 - \mu_{F_j}(x_{ij})^{\gamma}$
8: Compute hesitation: $\left(\pi_{F_j}(x_{ij})\right) = 1 - \mu_{F_j}(x_{ij}) - \nu_{F_j}(x_{ij})$
9. **end for**
10: Compute intuitionistic fuzzy entropy for feature x_j:

$$E_{F_j} = \frac{1}{m}\sum_{i=1}^{m}\left[\alpha\mu_{F_j}(x_{ij})\ln\left(\mu_{F_j}(x_{ij})\right) + \beta\nu_{F_j}(x_{ij})\ln\left(\nu_{F_j}(x_{ij})\right) + \gamma\pi_{F_j}(x_{ij})\ln\left(\pi_{F_j}(x_{ij})\right)\right]$$

11: **end for**
12: **return** $E_F = \{E_{F_1}, E_{F_2}, E_{F_n}\}$
13: **end function**
14: **function** RECURSIVEFEATUREELIMINATION (F, E_F)
15: **while** $|F| > k$ **do**
16: Rank feature: Rank (F) = sort (E_F)
17: $F \leftarrow F \setminus \{x \arg\max E_F\}$
18: Recompute E_F using COMPUTEENTROPY (F).
19: **end while**
20: **return** F
21: **end function**
22: Compute E_F = COMPUTEENTROPY (F)
23: Perform $F_{selected}$= RECURSIVEFEATUREELIMINATION (F, E_F)
24: **return** Ranked features and selected subset $F_{selected}$.

Figure 2*. Algorithm showing feature selection.*

Terminal classification of the model

Death within 90 days post-transplantation is a binary event represented as [0,1]. "PTIME" measures the time from transplantation to death or censoring, with PSTATUS = 1 being death post-transplantation.

Overview of methods

Different methods were used to develop the classification models. Logistic regression was first used due to its simplicity and interpretability, assuming linearity and no interactions. Random forests and ANN models were then used to model nonlinear relationships.

Logistic regression

Logistic regression, a type of generalized linear model (GLM), is described by[15]

$$g(y) = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n \quad (4)$$

Where y is the dependent variable, x_i are predictors, and i's are coefficients.

$$g(y) = 0 + 1x_1 + \ldots nx_n \quad (5)$$

Random forest classifier

Random forests capture interactions and nonlinearity, often outperforming simpler models, though they lack interpretability.[16]

$$y = f(x_1, \ldots, x_n) \quad (6)$$

CART classification

CART creates decision trees based on the Gini impurity index. Nodes split according to attribute thresholds and result in homogeneous sub-nodes. The process is called tree pruning, and it continues until pure subsets or leaves are produced.[17]

XGBoost classification

XGBoost is a gradient-boosting technique. It is used to improve the performance of the weak model predictions. At iteration, it minimizes the regularization and loss functions t:

XGBoost is efficient, scalable, and good for large datasets.[18,19]

$$L^{(t)} = \sum_{i=1}^{n} l(\dot{y}_i, \dot{y}_i^{(t-1)} + f_t(x_i)) + (f_t) \quad (7)$$

ANN classifier

A fully connected multilayer perceptron (MLP) with ReLU activation functions was used. Dropout and batch normalization were used to prevent overfitting, while training was performed using backpropagation with a cross-entropy loss function.[20] Features were standardized, missing values imputed, and training performed over 50 epochs with 5-fold cross-validation. The best model, selected based on validation loss, was compared using average AUROC scores.[21] Mini-batch gradient descent with the Adam optimizer was used.

K nearest neighbor (KNN)

KNN classifies new instances based on similarity to previous cases. It offers quick and accurate results after capturing existing data.[22]

K-fold cross-validation

In k-fold CV, the dataset is divided into k equal-sized, mutually exclusive folds (DS_1, DS_2, and DSk). CV accuracy is calculated using the following formula.[23]

$$CV = \frac{1}{k} \sum_{1}^{k} A_i \quad (8)$$

Where A_i is the accuracy of each fold, and k denotes the number of folds. Tenfold CV was adopted in the present research. It distributed the data into 10 equally sized folds. Stratified CV maintained that the percentage distribution of predictor labels in all folds would be identical to that in the original data.

Results and discussion

Classifier's ability to classify the patient survival: Class "1" or "0" was checked using the area under the receiver operating characteristic curve, AUROC.

The following are the formulas adopted to check performance:

$$\text{Sensitivity} = \frac{TP}{TP+FN} \quad (9)$$

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} \quad (10)$$

$$\text{Precision} = \frac{TP}{TP+FP} \quad (11)$$

$$\text{F1 Score} = 2* \frac{\text{Precision}*\text{Recall}}{\text{Precision}+\text{Recall}} \quad (12)$$

$$\text{Specifity} = \frac{TN}{TN+FP} \quad (13)$$

The above expressions represent the equations for true positive, false negative, true negative, and false positive, respectively. Feature selection employed RFE and intuitionistic fuzzy set. The key features were established by LR, KNN, RF, CART, ANN, and XGBoost classifiers.[24] The crucial features, GSTATUS and GRF_STAT, are in Figures 3A-3G. For example, RF-Intuitionistic Fuzzy and ANN ranked PTIME, GSTATUS, and GRF_STAT as the top rank. In contrast, RFE-Intuitionistic Fuzzy, as well as CART, ranked the features as GSTATUS, followed by PTIME, and finally GRF_STAT. Features concerning entropy are present in Figure 3G.

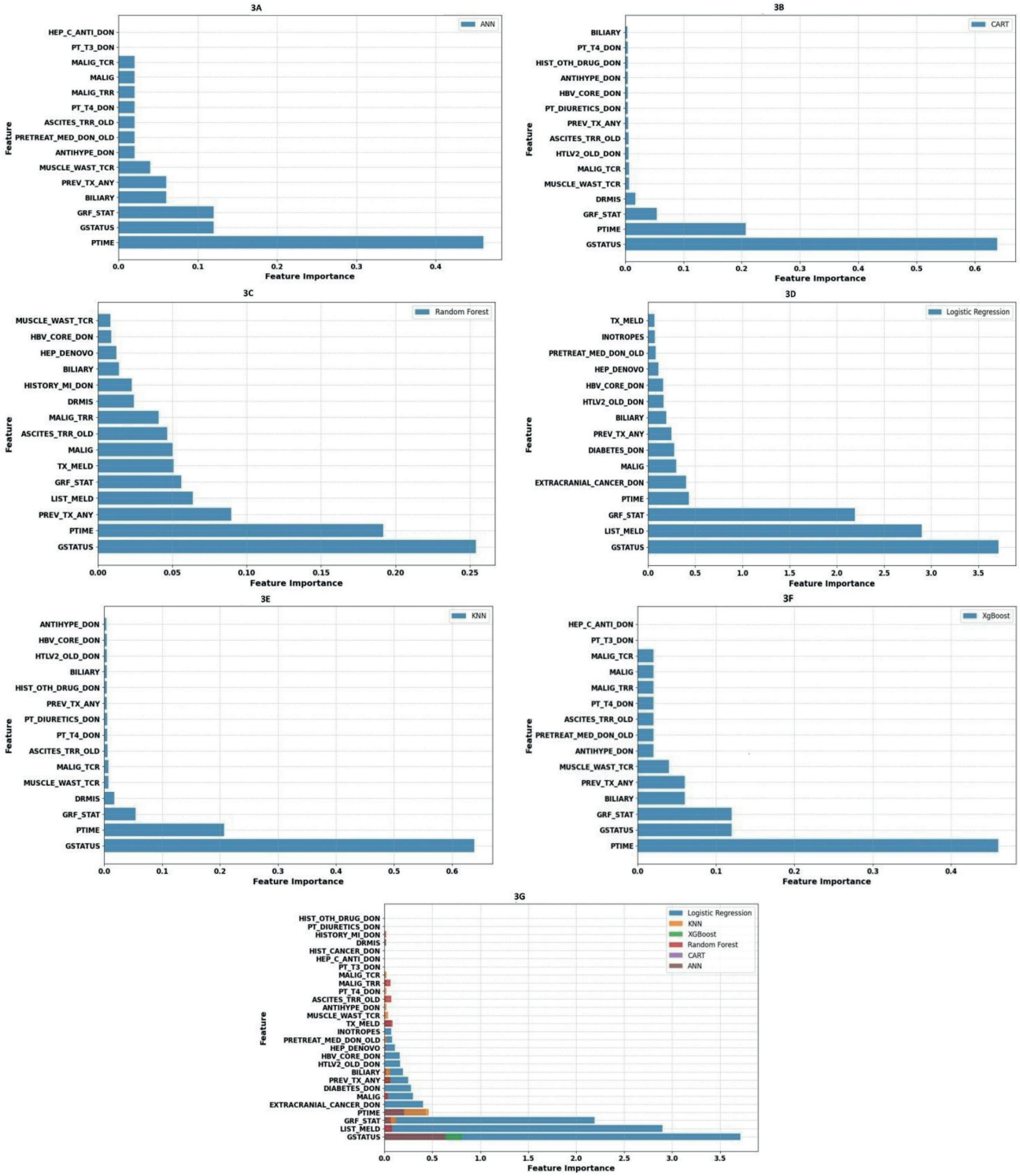

Figure 3*. Top-ranked features using different classifiers. 3A: artificial neural network (ANN), 3B: classification and regression tree (CART), 3C: random forest (RF), 3D: logistic regression (LR), 3E: K nearest neighbor (KNN), 3F: extreme gradient boosting (XGB), 3G: selected top rank features.*

ML methods' performance

Figure 4 shows a graph displaying the performance of different feature importance fed to the different classifiers and comparing different algorithms.[25] Finally, the combination of all the feature importance (24 features) is fed to different classifiers like RF, LR, KNN, XGBoost, ANN, and CART. The ANN classifier performs better than the other models.

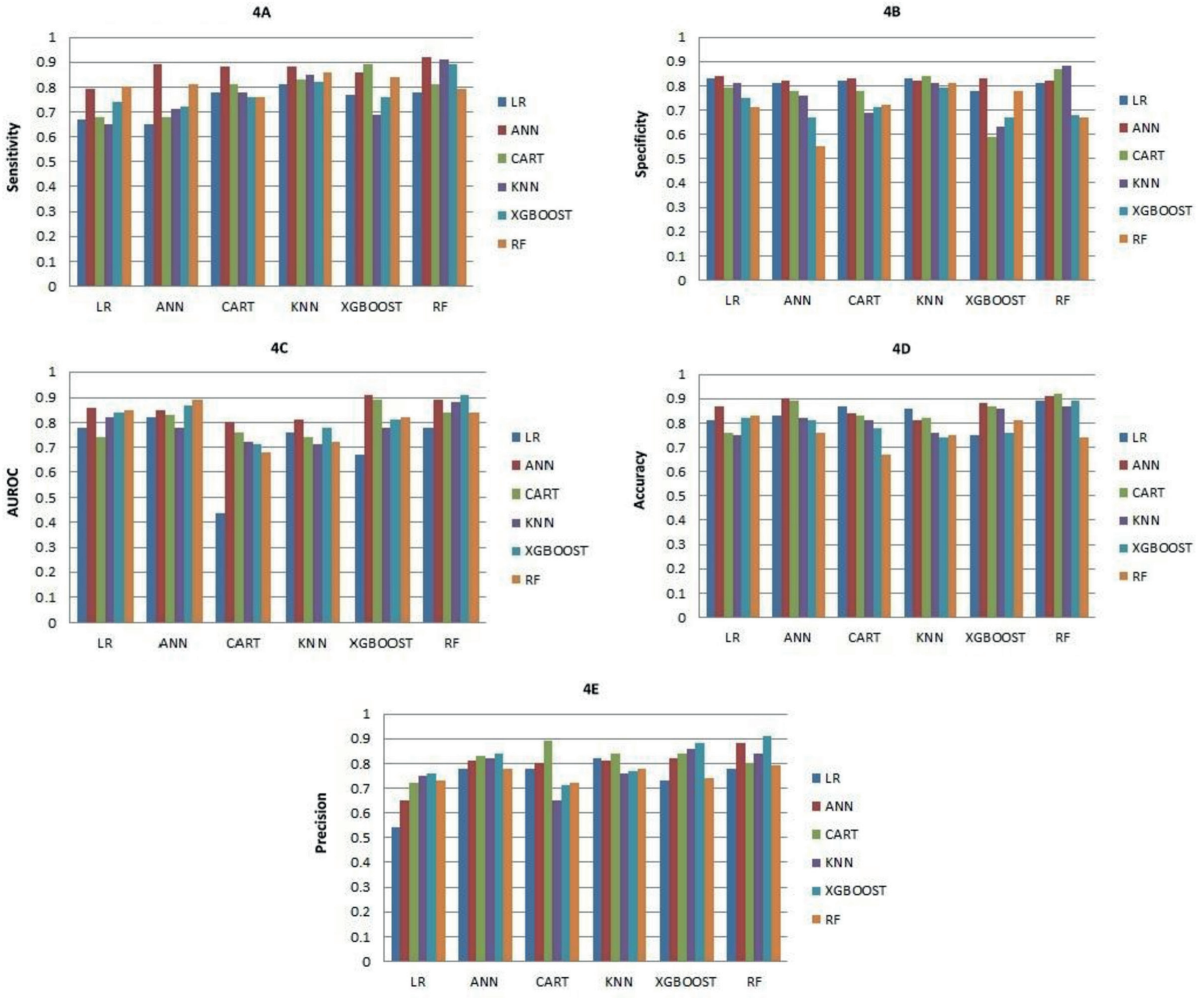

Figure 4*. Performance comparison of different feature importance applied to different classifiers. 4A: sensitivity, 4B: specificity, 4C: AUROC, 4D: accuracy, 4E: precision.*

Table 3 depicts the top-ranked variables detected in multiple studies. The predictors do not match the methods used previously; however, this will align with the indication provided by the SHAP values.

Table 3. Key variables identified in various studies.

Key variables identified	Study
Gstatus, List_MELD, frequency of graft, PTIME, Cancer condition, Diabetes of the donor.	Proposed method
MELD Score, Donor age, cold ischemia time, Liver condition.	Yanagawa *et al*.[15]
Donor age, recipient age, MELD score, cold ischemia time, donor BMI.	Kantidakis *et al*.[5]
Donor age, recipient age, MELD score, cold ischemia time, donor BMI.	Wang *et al*.[8]
Age, gender, ethnicity, BMI, blood type, MELD score, presence of HCC.	Guijo-Rubio *et al*.[24]

Comparison to previous studies

Our proposed ANN model outperformed previous studies in terms of accuracy, AUROC, specificity, precision, and sensitivity in predicting survival after LT, with an AUROC of 0.99 (Figure 5A).[26] The model's generalizability was validated by external validation using the KCH dataset, where feature importance was calculated and applied similarly to the UNOS dataset. Validation results are shown in Figure 5B.

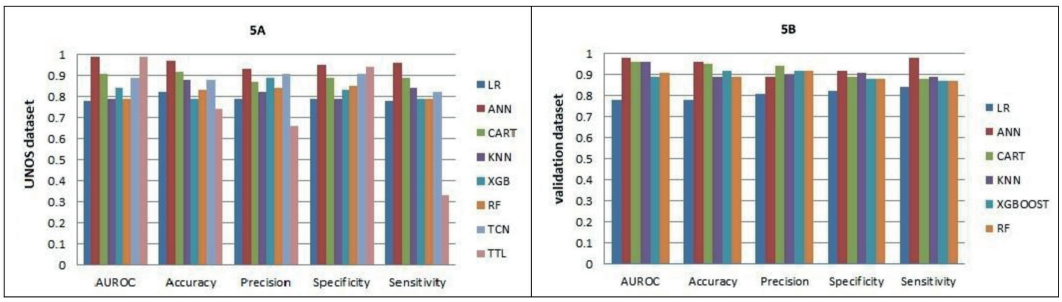

Figure 5. *Proposed model training, testing, and validation. 5A: UNOS Dataset, 5B: KCH dataset.*

SHAP values

Figure 6. Illustrates feature importance using SHAP values. Positive values increase the target prediction, while negative values decrease it. The x-axis indicates feature influence, with warmer dot colors for higher amplitudes and more remarkable for lower. The y-axis ranks features by importance, with higher positions indicating a more significant impact.[27] The algorithm performance can be measured using two parameters.

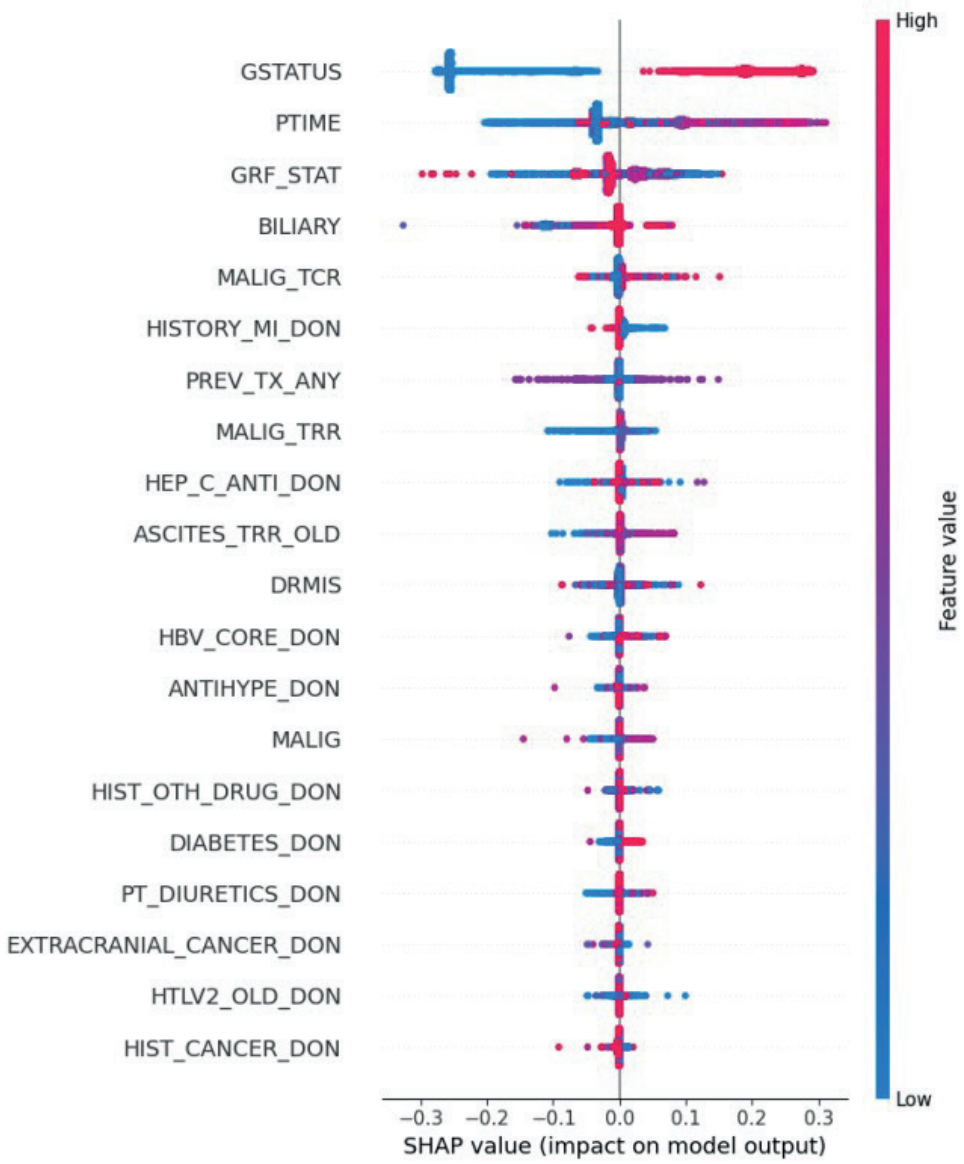

Figure 6*. Feature importance among different classes.*

Calibration curve

In machine learning and predictive modeling, a calibration curve is a helpful tool for better understanding and adjusting the projected probabilities from classification models. Figure 7A shows the calibration curve for the different algorithms used in this study.[28] It can be seen that KNN, ANN, and logistic regression are overconfident, whereas CART is underconfident in this study.

Discrimination

The best measure for evaluation is the concordance statistic, the c-index. For a prediction model to be helpful in medical decision-making, it must be able to distinguish between those who experience the outcome and those who do not.[28] Figure 7B presents the discrimination analysis of the proposed model.

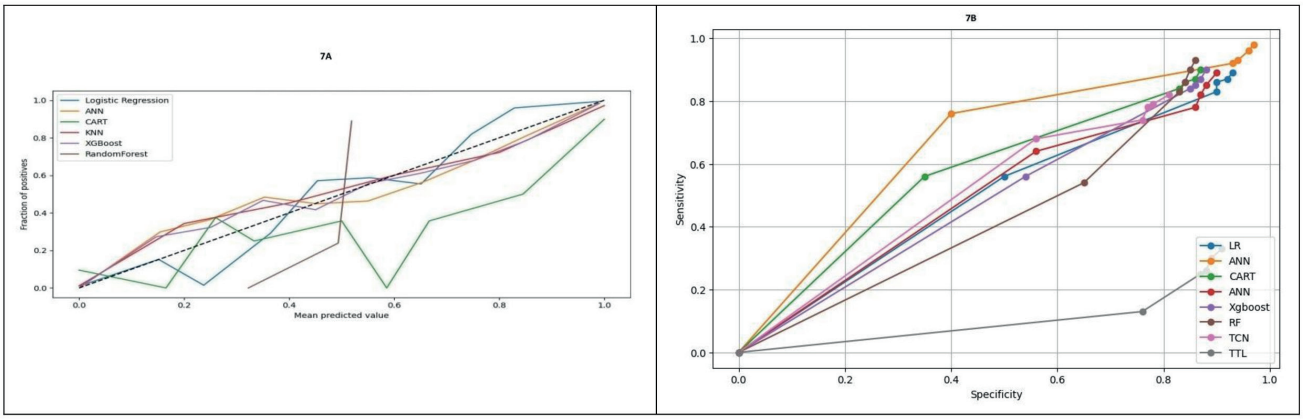

Figure 7*. Proposed model's performance. 7A: calibration plot, 7B: discrimination plot.*

Ablation analysis

Ablation analysis is performed to determine the effect of a component in a system. The result of this proposed model is compared with the performance of the model when the meld score was used for survival prediction. Figure 8 presents the comparison of the ablation study.

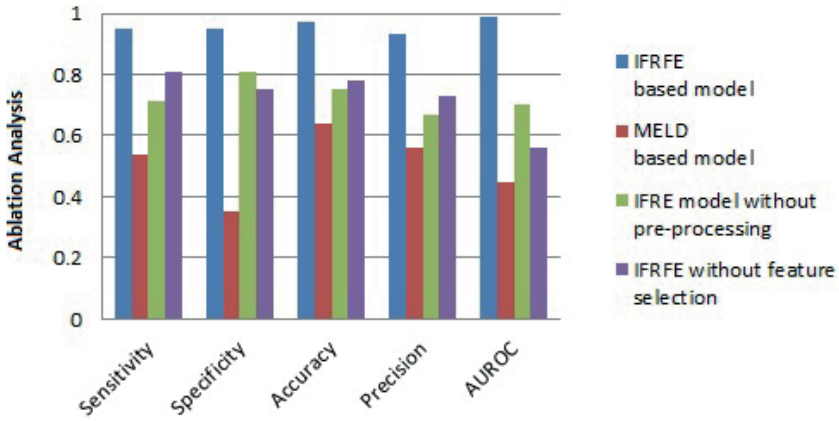

Figure 8*. Ablation analysis results.*

Strengths and limitations

This study has the advantage of a large dataset with many patients and attributes, advanced machine-learning techniques, and SHAP values for model interpretation. However, it relies on potentially biased and error-prone UNOS database data.

Conclusions

Machine learning is increasingly used in healthcare to identify patterns, though many algorithms lack interpretability. This study's main contribution is applying interpretable machine learning for prediction. Among the six models, ANN best predicts mortality after liver transplantation, supporting the development of early warning systems. Future research could focus on survival prediction for other transplants with improved optimization methods.

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Conflict of interest

There are no conflicts of interest.

Funding Statement

Nil

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