

ORIGINAL ARTICLE

Identification of hepatic steatosis in living liver donors by machine learning models

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Abstract

Selecting an optimal donor for living donor liver transplantation is crucial for the safety of both the donor and recipient, and hepatic steatosis is an important consideration. We aimed to build a prediction model with noninvasive variables to evaluate macrovesicular steatosis in potential donors by using various prediction models. The study population comprised potential living donors who had undergone donation workup, including percutaneous liver biopsy, in the Republic of Korea between 2016 and 2019. Meaningful macrovesicular hepatic steatosis was defined as >5%. Whole data were divided into training (70.5%) and test (29.5%) data sets based on the date of liver biopsy. Random forest, support vector machine, regularized discriminant analysis, mixture discriminant analysis, flexible discriminant analysis, and deep neural network machine learning methods as well as traditional logistic regression were employed. The mean patient age was 31.4 years, and 66.3% of the patients were men. Of the 1652 patients, 518 (31.4%) had >5% macrovesicular steatosis on the liver biopsy specimen. The logistic model had the best prediction power and prediction performances with an accuracy of 80.0% and 80.9% in the training and test data sets, respectively. A cut-off value of 31.1% for the predicted risk of hepatic steatosis was selected with a sensitivity of 77.7% and specificity of 81.0%. We have provided our model on the website (https://hanseungbong.shinyapps.io/shiny_app_up/) under the name DONATION Model. Our algorithm to predict macrovesicular steatosis using routine parameters is beneficial for identifying optimal potential living donors by avoiding superfluous liver biopsy results.

Jihye Lim and Seungbong Han contributed equally to this work.

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INTRODUCTION

Because living donor liver transplantation (LDLT) was confirmed to be as efficacious as deceased donor liver transplantation in patients with end-stage liver diseases,^[1] the number of LDLTs has been increasing, particularly in Asian countries where deceased donors are significantly limited.^[2,3] Selection of the optimal donor is paramount to the success of an LDLT and to assure donor safety and achieve the best operative outcomes in both donors and recipients. Hepatic steatosis in the living donor adversely affects the LDLT outcome. In donors, fatty parenchyma delays the recovery of the remnant liver and can even cause hepatic failure following donor hepatectomy.^[4,5] When a liver with steatosis is transplanted, the risk of complications, including graft failure or even death, is increased.^[6-8] Although there is no consensus on the threshold of hepatic steatosis in a living liver donor, the acceptable limit of hepatic steatosis at many transplant centers ranges from 10% to 30%.^[9,10]

Potential liver donors are considered to be relatively young and generally healthy. However, the prevalence of hepatic steatosis has been increasing recently, even in the general population, due to the increased prevalence of obesity.^[11] Indeed, hepatic steatosis is the most common cause of rejection of potential liver donors.^[12] Therefore, accurate preoperative assessment of hepatic steatosis in potential liver donors is crucial.

Percutaneous liver biopsy is the standard method of quantitative assessment for hepatic steatosis despite its invasiveness and limitations, such as sampling variability.^[13] Many noninvasive methods, including biochemical, clinical, and radiologic modalities, have been extensively evaluated to accurately predict hepatic steatosis over the past 2 decades.^[14-18]

Indeed, selective predonation liver biopsy has been acknowledged, although the criteria remain controversial.^[19] Noninvasive assessments of hepatic steatosis for this donor selection process include body mass index (BMI),^[14] computed tomography (CT),^[15] ultrasonography (US), magnetic resonance imaging (MRI),^[16] scoring systems with combination of biochemical factors,^[17] and controlled attenuation parameters.^[18] However, the performance of each of these noninvasive methods was insufficient to minimize predonation liver biopsy or to safely replace the role of liver biopsy in those with a high probability of hepatic steatosis.

In this study, we aimed to build a model for the identification of hepatic steatosis in potential liver donors by using machine learning algorithms, discrimination analysis, and classical logistic regression with various noninvasive variables, mostly focusing on identifying potential donors with a high probability of hepatic steatosis.

PATIENTS AND METHODS

Study population

Between January 2016 and December 2019, 1662 individuals who had undergone percutaneous liver biopsy as a potential living liver donor at Asan Medical Center, a tertiary referral and transplant center in Seoul, Republic of Korea, were included in this study (Figure 1). Of these donors, 10 were excluded due to missing clinical information, mostly owing to nonenhanced CT images. This study was approved by the Institutional Review Board (IRB) of our center (IRB No. 2020-1181), and the need for informed consent was waived owing to the study's retrospective nature.

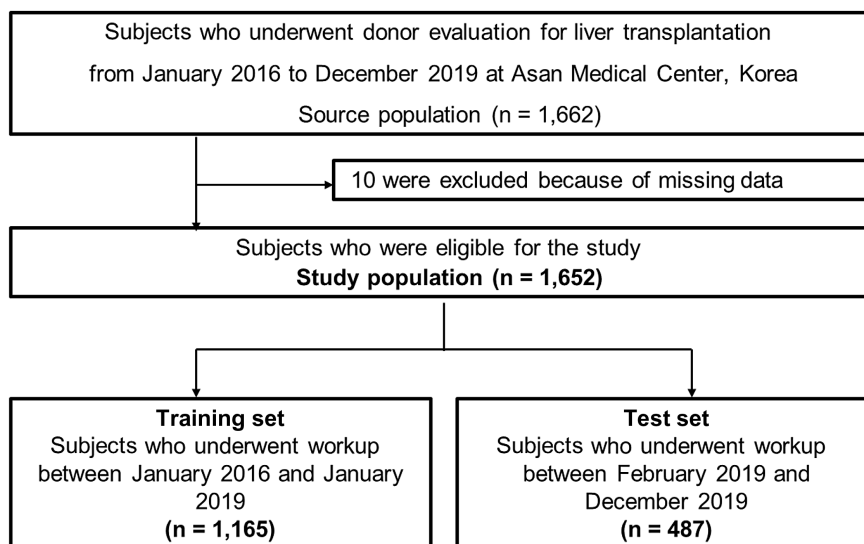


FIGURE 1 Study flow diagram

Clinical, biochemical, and radiologic information

Data were obtained from the electronic medical records. Baseline demographic variables included age, sex, and BMI. All potential liver donors were examined based on biochemical tests, including hemoglobin, platelet, prothrombin time, activated partial thromboplastin time, aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyltransferase, total bilirubin, direct bilirubin, albumin, protein, creatinine, cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, calcium, phosphorus, and fasting glucose. Additionally, CT scans of the abdomen and pelvis were obtained in all potential liver donors as a routine predonation evaluation. To estimate the radiologic assessment of hepatic steatosis, we measured the Hounsfield units (HUs) of the liver 5 times (3 times in the right lobe and 2 times in the left lobe), avoiding vessels, cysts, calcifications, or masses, and of the spleen 3 times by using the region-of-interest measurement of CT attenuation on the nonenhanced phase CT scans.

Histologic information

US-guided percutaneous liver biopsy was routinely performed as a predonation evaluation after obtaining written informed consent.^[13] The degree of total hepatic steatosis was also described separately as macrovesicular and microvesicular steatoses expressed as a percentage. Hepatic steatosis was histologically diagnosed when the macrovesicular fatty changes affected >5% of the biopsied liver parenchyma.

Outcomes

The primary outcome of interest in this study was the identification of potential donors with macrovesicular hepatic steatosis because microvesicular steatosis has not been reported to be associated with graft outcomes.^[20,21]

We aimed to develop a model that can discriminate between potential donors of two categories using the baseline variables: (1) donors with macrovascular steatosis $\leq 5\%$ who can safely donate their liver without liver biopsy and (2) those with macrovascular steatosis >5% who require further investigation to ascertain donation adequacy.

Statistical analyses and construction of a prediction model

The data are expressed as means \pm SDs for continuous variables and numbers with percentages for categorical

variables. We applied a complete case analysis to develop prediction models such that 1652 observations were used for the development. The data were divided into two sets, the training and test sets, depending on the date of liver biopsy; the training data set comprised those who underwent workup between January 2016 and January 2019, and the test data set comprised those who underwent workup between February 2019 and December 2019 (Figure 1). We used the training data set for the learning process and the test data set for evaluating model performance. For the binary outcome variable, we employed three discrimination-based algorithms, regularized discriminant analysis (RDA), flexible discriminant analysis (FDA), and mixture discriminant analysis (MDA).^[22-24] The RDA depends on a classification rule based on regularized group covariance matrices that are said to be more robust against multicollinearity among covariates. It is known that the RDA performs well in settings for which the sample sizes are small and the number of variables is large. In contrast, the FDA uses multivariate nonparametric regression for discriminant analysis to address nonlinear classification schemes. The MDA models the classes as mixtures of Gaussian distributions to facilitate better classification, particularly in clustered non-normal settings. This method produces nonlinear decision boundaries. We also used the traditional logistic regression as well as three different machine learning algorithms comprising random forest (RF), support vector machine (SVM), and deep neural network (DNN). The RF is based on ensemble learning theory, and it constructs many decision trees in the training time. The predicted class is derived from the mode of predicted classes in each individual decision tree. The RF allows us to learn both simple and complex classification functions by incorporating interactions between predictors; the default parameterization of the RF often produces excellent performance.^[25] However, the SVM aims to find a hyperplane in a high-dimensional space, which clearly separates individual data points. It attempts to find a plane that has the maximum margin or maximum distance between the data points of classes. The SVM is robust to the high-dimensional data and can efficiently learn complex classification functions. Because it employs a powerful regularization approach, it helps to protect models from overfitting.^[26] Finally, a DNN algorithm was employed because it is highly flexible and shows success in many areas (e.g., analyses of text, images, voices, and videos). In particular, we used the multilayer perceptron network, which comprises a series of connected layers of input, hidden, and output layers. Essentially, it minimizes a cost function or maximizes the predictive ability. The keras and tensorflow R packages were used for both model training and prediction. The selected neural network had one input layer, two hidden layers, and one output layer, such that our multilayer perceptron comprised a three-layer

architecture. We considered 50 nodes in the hidden layers, and the multilayer perceptron can be summarized as 15/50/50/1. The learning process was configured by specifying rmsprop as the gradient decent method (optimizer), binary cross entropy as the loss function (loss), and classification accuracy as the metrics. We considered relu or sigmoid for the activation function in the hidden layers or output layer. The batch size for the minibatch and epoch sizes were selected based on the grid search. $p < 0.05$ was considered statistically significant (two tailed). All data analyses were performed using R software, version 4.0.4. In particular, the mda and klaR R packages were used for the FDA, MDA, and RDA methods. Furthermore, the SVM and RF were fitted using the e1071 and randomForest R packages.

RESULTS

Baseline characteristics of the study participants

Of a total of 1652 participants, 1165 (70.5%) were assigned to the training data set and 487 (29.5%) to the test data set. The baseline characteristics are shown in Table 1. The mean \pm SD age was 31.4 ± 9.4 years, and 66.3% were men. The mean \pm SD BMI was 24.2 ± 3.4 kg/m². Less than 1% of the study population had diabetes, and 2.8% had hypertension. The fasting serum cholesterol and glucose levels (mean \pm SD) were 174.2 ± 33.0 mg/dL and 95.7 ± 14.6 mg/dL, respectively.

The mean ALT level of the study participants was 20.2 IU/L, and 110 (6.7%) had an elevated ALT level at the predonation evaluation. Aside from blood pressure, prothrombin time, and direct bilirubin, creatinine, and calcium levels, the baseline characteristics did not significantly differ between the training and test data sets. Despite these characteristics showing a statistically significant difference, the small numerical differences did not have clinically significant differences. The mean \pm SD liver HU was 54.4 ± 10.0 . The pathology results indicated that 68.6% of participants had macrovesicular steatosis $\leq 5\%$ whereas 31.4% had steatosis $>5\%$. The distributions of macrovesicular steatosis $>10\%$, $>20\%$, and $>30\%$ were 12.2%, 5.8%, and 2.2% of study participants, respectively.

Among participants with macrovesicular steatosis $>5\%$, 75.5% were men, while 62.2% of subjects without hepatic steatosis were men (Table S1). Potential donors with hepatic steatosis were more likely to be older (mean \pm SD, 32.8 ± 9.7 vs. 30.8 ± 9.2 years; $p < 0.01$) and have higher BMIs than their counterparts (mean \pm SD, 25.9 ± 3.3 vs. 23.5 ± 3.2 kg/m²; $p < 0.01$). The ALT (mean \pm SD, 26.1 ± 14.5 vs. 17.5 ± 10.8 ; $p < 0.01$) total cholesterol (mean \pm SD, 180.1 ± 37.1 vs. 171.5 ± 30.5 mg/dL; $p < 0.01$), and glucose (mean \pm SD, 98.0 ± 15.5 vs. 94.7 ± 14.1 mg/dL; $p < 0.01$) levels were

also higher in the steatosis group than in the nonsteatosis group, while the HDL cholesterol level (mean \pm SD, 48.6 ± 11.1 vs. 57.4 ± 13.5 mg/dL; $p < 0.01$) was lower in the steatosis group than in the nonsteatosis group. The mean HU of the liver was lower in the steatosis group than in the nonsteatosis group (mean \pm SD, 46.7 ± 11.8 vs. 57.9 ± 6.6 ; $p < 0.01$).

Identification of subjects with hepatic steatosis by the various models

The performances of each model in the training and test data sets are summarized in Table 2. In the training data set, the RF model (100.0%) showed the highest performance, followed by the SVM (84.7%), RDA (81.8%), MDA (81.7%), FDA (81.4%), logistic (80.0%), and DNN (77.6%) models, based on accuracy. Most models had a high accuracy rate $>75\%$. The area under the receiver operating curve (AUROC) was highest for the RF model (1.00; 95% confidence interval [CI], 1.00-1.00), whereas the RDA model had the lowest AUROC (0.86; 95% CI, 0.83-0.88) (Figures S1-S6).

In the test data set, the logistic and RDA (80.9%) models showed the highest accuracy, followed by the MDA (79.9%), SVM (79.5%), RF (79.3%), FDA (79.1%), and DNN (77.6%) models. The AUROC of the logistic (0.87; 95% CI, 0.83-0.90; Figure 2A) and FDA (0.87; 95% CI, 0.83-0.90) models were the highest, followed by those of the RDA, MDA, RF, SVM, and DNN models (Figures S1-S6). The calibration chart, depicted in Figure 2B, indicates favorable agreement between the risk predicted by the model and the observed risk. The Hosmer-Lemeshow test results also suggested adequate agreement in the training and test cohorts with $p = 0.50$ and $p = 0.19$, respectively (Table 2).

Variable of importance and final model selection

We obtained importance scores of predictive variables using the RF model (Figure S7). Among the patients' demographic, laboratory, and imaging variables, the liver HU had the largest contribution to the prediction of the steatosis group, followed by the ALT level, BMI, serum HDL cholesterol level, cholesterol, age, and glucose level. Machine learning algorithms, such as the RF and DNN, exhibited reduced performance in terms of calibration abilities, although their discriminative abilities were high. In addition, discrimination analyses led to poor calibration metrics in the test data set. The SVM and logistic regression models produced comparable prediction results, although difficulties were encountered in the final model interpretation when we used the SVM as the final predictor model. Therefore, we adopted the traditional logistic regression model for

TABLE 1 Baseline characteristics of the study participants

	Entire Data Set (n = 1652)	Training Data Set ^a (n = 1165)	Test Data Set ^a (n = 487)	p Value
Demographic findings				
Sex, male, n (%)	1096 (66.3)	780 (67.0)	316 (64.9)	0.45
Age (years)	31.4 ± 9.4	31.2 ± 9.4	31.9 ± 9.4	0.21
Diabetes, n (%)	15 (0.9)	10 (0.9)	5 (1.0)	0.97
Hypertension, n (%)	47 (2.8)	31 (2.7)	16 (3.3)	0.59
Hepatitis, n (%)	3 (0.2)	1 (0.1)	2 (0.4)	0.44
Hypothyroidism, n (%)	3 (0.2)	3 (0.3)	0 (0.0)	0.63
Hyperthyroidism, n (%)	4 (0.2)	4 (0.3)	0 (0.0)	0.46
Height (cm)	170.0 ± 8.5	170.2 ± 8.7	169.6 ± 8.1	0.23
Weight (kg)	70.3 ± 12.7	70.4 ± 12.5	70.0 ± 13.2	0.57
BMI (kg/m ²)	24.2 ± 3.4	24.2 ± 3.4	24.2 ± 3.6	0.99
Systolic blood pressure (mm Hg)	123.4 ± 14.9	122.7 ± 15.0	125.0 ± 14.6	0.01
Diastolic blood pressure (mm Hg)	77.8 ± 10.8	77.4 ± 11.1	78.9 ± 10.0	0.01
Laboratory findings				
Hemoglobin (g/dL)	14.4 ± 1.6	14.4 ± 1.6	14.4 ± 1.5	0.35
Platelet (×10 ³ /μL)	259.9 ± 54.9	261.4 ± 55.1	256.5 ± 54.4	0.10
PT (seconds)	11.9 ± 0.8	11.8 ± 0.8	12.1 ± 0.7	<0.01
aPTT (seconds)	28.0 ± 2.4	28.0 ± 2.4	28.1 ± 2.4	0.24
AST (IU/L)	20.4 ± 7.9	20.3 ± 7.7	20.7 ± 8.1	0.38
ALT (IU/L)	20.2 ± 12.7	20.2 ± 11.6	20.2 ± 15.0	0.99
Alkaline phosphatase (IU/L)	64.0 ± 18.7	63.7 ± 19.1	64.6 ± 17.9	0.38
GGT (IU/L)	23.4 ± 24.0	24.0 ± 25.2	22.1 ± 20.9	0.12
Total bilirubin (mg/dL)	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.72
Direct bilirubin (mg/dL)	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.02
Albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	0.39
Total protein (g/dL)	7.3 ± 0.4	7.3 ± 0.4	7.3 ± 0.4	0.27
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.01
Total cholesterol (mg/dL)	174.2 ± 33.0	174.6 ± 32.1	173.1 ± 34.9	0.41
Triglyceride (mg/dL)	113.0 ± 86.6	111.7 ± 73.0	116.2 ± 112.6	0.42
HDL cholesterol (mg/dL)	54.6 ± 13.5	55.0 ± 13.7	53.8 ± 12.8	0.10
Uric acid (mg/dL)	5.5 ± 1.5	5.5 ± 1.5	5.5 ± 1.5	0.94
Total calcium (mg/dL)	9.3 ± 0.5	9.4 ± 0.5	9.3 ± 0.6	<0.01
Phosphorus (mg/dL)	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	0.37
Glucose (mg/dL)	95.7 ± 14.6	95.9 ± 15.3	95.3 ± 13.0	0.46
Image findings				
Liver (HU)	54.4 ± 10.0	54.4 ± 9.5	54.4 ± 11.2	0.99
Liver/spleen (HU)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.92
Pathologic findings				
Macrovesicular steatosis	4.9 ± 8.6	4.6 ± 7.9	5.7 ± 10.0	0.02

Note: Values are presented as mean ± SD or frequency (percentage).

Abbreviations: aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; PT, prothrombin time; GGT, gamma-glutamyltransferase.

^aThe training data set comprised subjects who underwent predonation evaluation between January 2016 and January 2019; the test data set comprised those who underwent evaluation between February 2019 and December 2019.

the final prediction model in light of high discrimination and calibration abilities. Logistic regression analysis in the training cohort also identified liver HU, ALT level,

BMI, HDL cholesterol, total cholesterol, age, and glucose levels as predictive factors for hepatic steatosis (Table 3). Based on the receiver operating characteristic

TABLE 2 Summary of the classification model performance for the identification of hepatic steatosis

	Training Data Set ^a				Test Data Set ^a					
	Discrimination		Calibration ^a		Discrimination		Calibration			
	Accuracy	AUROC (95% CI)	Chi-Squared	DF	p Value	Accuracy	AUROC (95% CI)	Chi-Squared ^b	DF ^b	p Value ^b
Logistic model	0.800	0.862 (0.839-0.885)	7.3	8	0.50	0.809	0.865 (0.830-0.900)	11.3	8	0.19
Random forest	1.000	1.000 (1.000-1.000)	136.5	8	<0.01	0.793	0.851 (0.814-0.888)	17.2	8	0.03
Support vector machine	0.847	0.890 (0.867-0.912)	36.1	8	<0.01	0.795	0.831 (0.790-0.872)	9.1	8	0.34
Regularized discriminant analysis	0.818	0.858 (0.834-0.882)	17.2	8	0.03	0.791	0.862 (0.827-0.897)	26.4	8	<0.01
Mixture discriminant analysis	0.817	0.862 (0.838-0.885)	17.4	8	0.03	0.799	0.854 (0.818-0.890)	29.7	8	<0.01
Flexible discriminant analysis	0.814	0.862 (0.839-0.885)	10.8	8	0.21	0.809	0.865 (0.830-0.900)	22.6	8	<0.01
Deep neural network	0.776	0.953 (0.938-0.968)	2.5 × 10 ⁶	8	<0.01	0.776	0.830 (0.791-0.869)	3.4 × 10 ⁸	8	<0.01

Abbreviation: DF, degrees of freedom.

^aThe training data set comprised subjects who underwent predonation evaluation between January 2016 and January 2019; the test data set comprised those who underwent evaluation between February 2019 and December 2019.^bChi-squared, DF, and p value were the results of the Hosmer-Lemeshow test.

curve analysis, we maximized the Youden index to select a cut-off value classifying a patient into the hepatic steatosis group. A cut-off value of 31.1% was selected, which resulted in high sensitivity (77.7%) and specificity (81.0%).

Model application

Our model was named DONATION Model from “pre-DICTION hepatic sTeatosis In dONor.” To test our model, we applied it to a real-world scenario (Figure 3). For example, a 24-year-old man with a BMI of 23.2 kg/m² was considered a donor for living liver donation. He underwent predonation evaluation, and all his result outcomes were input to our model (https://hanseungbo.ng.shinyapps.io/shiny_app_up/). Collectively, his probability of having hepatic steatosis (macrovesicular steatosis >5%) was computed as 11.0%, which was less than the predefined cut-off value of 31.1%.

DISCUSSION

We built a prediction model to identify potential living liver donors with hepatic steatosis. We used a conventional logistic model with various noninvasive predonation variables considering the high performance and convenience from a readily applicable website. With our prediction model, potential living donors who are less likely to have hepatic steatosis may be exempt from liver biopsy as a predonation evaluation before transplantation.

The optimal selection of a living liver donor is crucial for successful liver transplantation for any indication. Hepatic steatosis is a major determinant of eligibility of a living liver donor and is the main cause of rejection of a donor.^[12,27] In general, hepatic steatosis <10% in a potential living donor is considered suitable and ≤5% is considered satisfactory for living liver donation. At some transplant centers, if a potential living liver donor appears to have hepatic steatosis <10% based on various noninvasive assessments at predonation evaluation, liver biopsy may not be required for re-evaluating the degree of hepatic steatosis.^[17,28]

When building a model for living liver donor selection, two contrasting perspectives may arise. The first is that a model for predicting a high level of hepatic steatosis enables early exclusion of candidates, preventing unnecessary subsequent tests. The remaining candidates can proceed to further testing for donor eligibility. The second perspective is that a model predicting not having steatosis enables candidates to proceed to liver donation without liver biopsy. Donor eligibility of the remaining candidates will be determined by further testing, including liver biopsies. Both perspectives are reasonable. However, we believe that the second

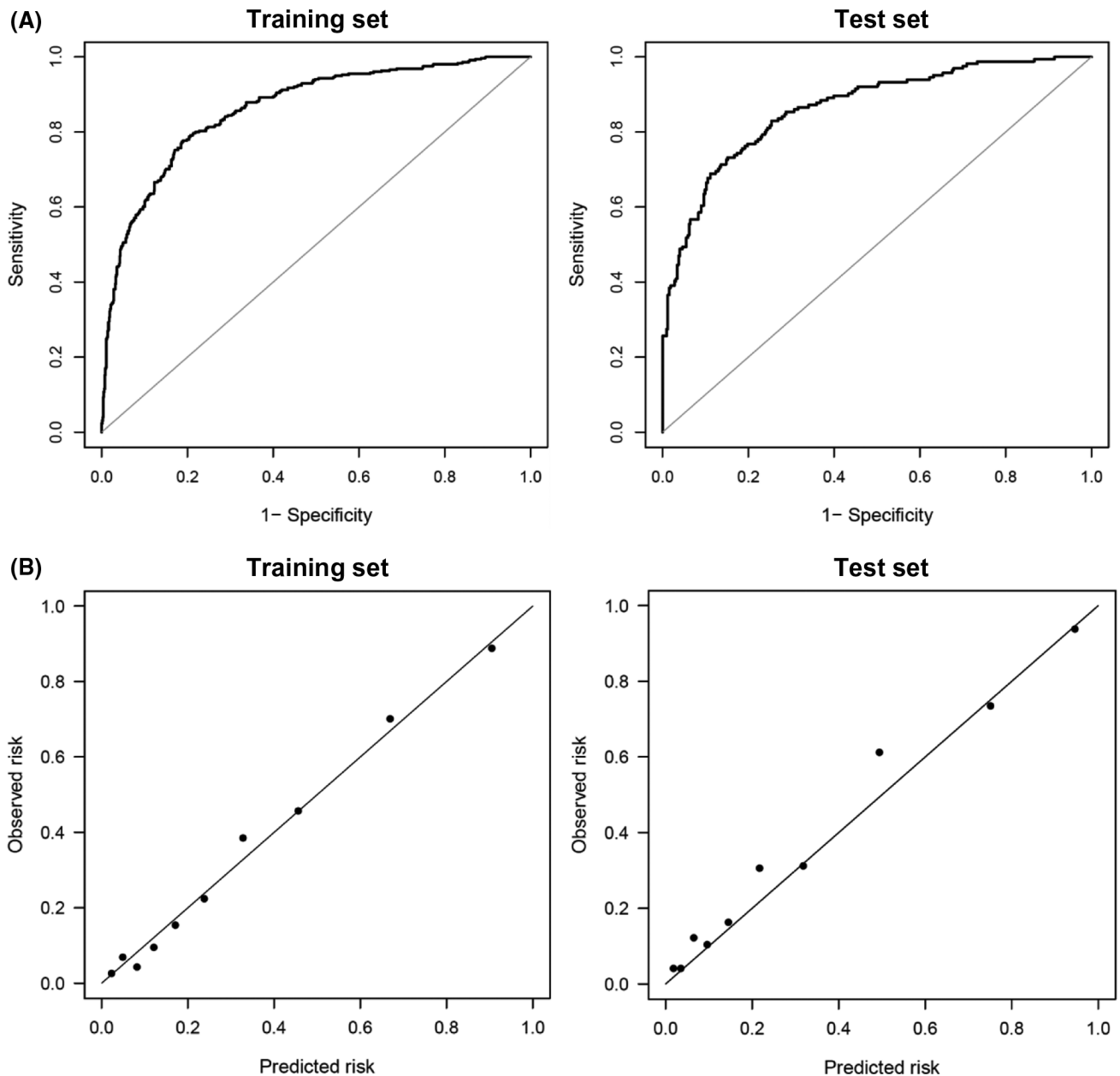


FIGURE 2 Logistic regression analysis in the training and test cohorts. (A) Receiver operating characteristic curves (B) Calibration charts

perspective may be stronger for the reasons given below.

Eastern countries, including Korea, have a shortage of cadaveric liver donors owing to the cultural background. Therefore, $\geq 75\%$ of liver transplantations in Korea are LDLTs. In this situation, the early exclusion of donor candidates using the model may reduce the pool of living liver donors. For example, a candidate predicted to have a high level of hepatic steatosis by the model (e.g., $>20\%$ or $>30\%$) may show a lesser degree of hepatic steatosis on liver biopsy than initially thought. This candidate may thus be eligible for living liver donation but may be excluded by the model considering

that no model has perfect performance. Therefore, our approach is more important in our situation to secure the pool of donor candidates without losing potential candidates.

In addition, there has been a trend of expanding the threshold of hepatic steatosis for donor eligibility because a relatively high degree of hepatic steatosis may be compensated by sufficiently large liver volume. If a candidate is excluded by a prediction model owing to a high level of hepatic steatosis, the candidate could be excluded from liver donation despite being selectively eligible if the candidate has a sufficient remnant liver volume.

Potential living donor candidates are generally young and healthy. Therefore, the number of patients with a high degree of hepatic steatosis is very low. Indeed, only 2% of our study population showed >30% hepatic steatosis (approximately 30 of 1600 patients). Thus, building the model for identifying a high level of hepatic steatosis was difficult due to the very small number of outcomes, including multicollinearity and low performance. Therefore, our most important goal was to secure as many donor candidates as possible given our current situation. Thus, we could safely omit unnecessary liver biopsies in selected candidates with the use of our model. In addition, we need a model that is statistically stable and justifiable.

We set a stricter cutoff for hepatic steatosis >5% to minimize as many false negatives as possible. Therefore, our model may render a false-positive assessment of hepatic steatosis, whereby liver biopsy will be considered as usual. However, based on our model, if a potential living liver donor is determined not to proceed for liver biopsy by showing a very low likelihood of hepatic steatosis, the actual probability of hepatic steatosis would have to be extremely low for the safety of the living donor and recipient. Using a logistic model, the false-negative rates of hepatic steatosis were 13.2% (154/1165) and 10.1% (49/487) in the training and test data sets, respectively. However, only 1 potential donor showed hepatic steatosis ≥30%, which was not eligible for living liver donation, despite our model predicting this subject did not have hepatic steatosis. This clinically significant false negative by our prediction model was about 0.1%.

TABLE 3 Summary of logistic regression analysis

	Odds Ratio	95% CI	p Value
(Intercept)	0.31	0.27-0.37	<0.01
Age (years)	1.23	1.05-1.45	0.01
BMI (kg/m ²)	1.30	1.09-1.55	<0.01
ALT (IU/L) ^a	1.61	1.35-1.91	<0.01
Total cholesterol (mg/dL)	1.40	1.19-1.66	<0.01
HDL cholesterol (mg/dL)	0.68	0.56-0.82	<0.01
Glucose (mg/dL) ^a	1.16	1.00-1.36	<0.01
Liver (HU)	0.28	0.23-0.37	<0.01

Note: All included variables in the above table were standardized.

^aLog-transformed variables.

Previous studies suggested several noninvasive indices and models to assess hepatic steatosis, including the fatty liver index, hepatic steatosis index, SteatoTest, and nonalcoholic fatty liver disease ridge score.^[29-32] However, these metrics were essentially developed from a small number of patients or populations who were at risk of having hepatic steatosis. The purpose of the previous metrics was a potential diagnosis of clinically meaningful hepatic steatosis or early identification of populations at higher risk of advanced fibrosis or cirrhosis due to hepatic steatosis. In contrast, the target population of the current study included generally young

DONATION Model

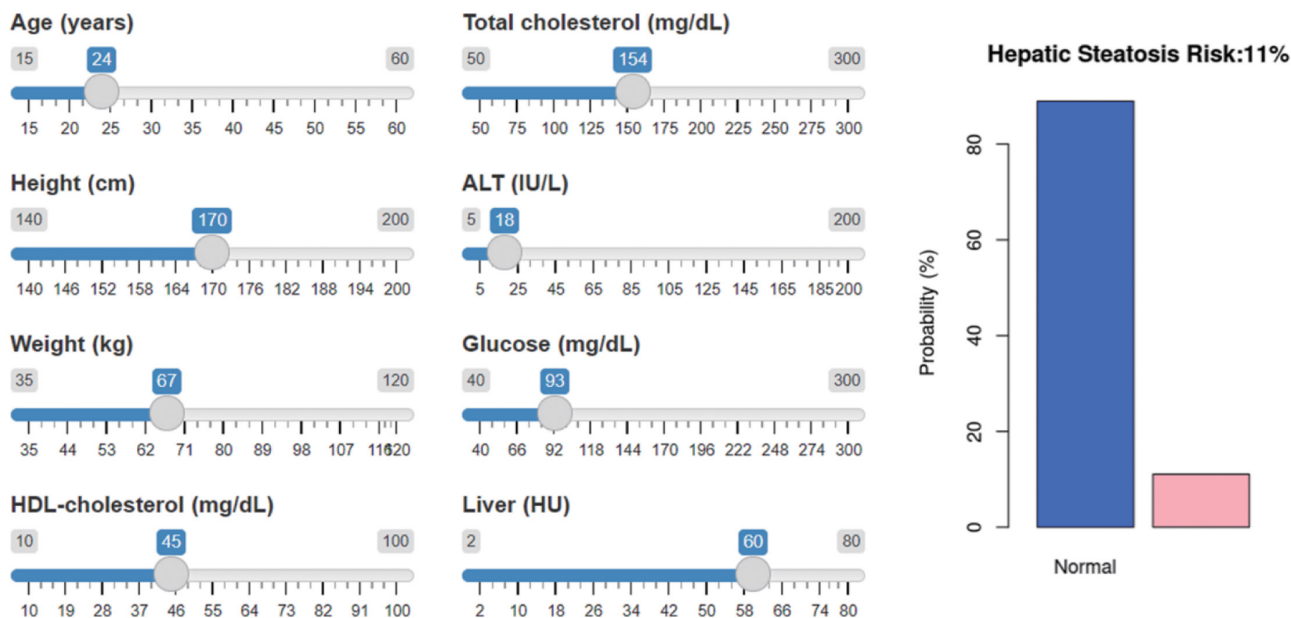


FIGURE 3 An example of applying the DONATION Model. The probability of hepatic steatosis (≥5% of macrovesicular steatosis) by the logistic model is 11.0%

and healthy individuals with a very low prevalence of hepatic steatosis.

The strength of our study was the sufficient sample size for analysis. Over 1600 potential living liver donors were biopsied and assessed for the presence of hepatic steatosis, thus enabling the construction and validation of various machine learning models. We also incorporated radiologic information as measured by HU on the noncontrast CT scan together with demographic and laboratory variables in our model. Indeed, radiologic information had the highest variable importance score in the logistic model, suggesting that liver HU may play an important role in our model. As all variables in our model were routinely collected in the predonation evaluation, no additional examinations or tests were required. We built a readily available website to apply our model in the real-world setting. The probability of having hepatic steatosis could then be calculated by simply including several variables for a potential donor.

Our study has some limitations. Our study results, gathered retrospectively from a single transplant center in the Republic of Korea, have some unavoidable biases. However, we included consecutive participants over a period of 3 years, and our models were built and validated with >25 variables from the predonation evaluation. Although we have conducted internal validation, the generalizability of our model may be limited by the lack of external validation, particularly in a population with different demographic characteristics, including a higher average BMI. In addition, our model should undergo further prospective validation. Indeed, we plan to prospectively validate and continuously upgrade our model by adding additional imaging modalities, such as transient elastography. From a statistical perspective, RF counts on the bagging algorithm as well as an ensemble learning technique. It combines the outputs of many trees on a subset of the data and may reduce the overfitting problem in the prediction. Additionally, as a retrospective cohort study, we were unable to obtain data on alcohol or drug consumption, both of which affects macrovesicular steatosis. Significant alcohol use is related to macrovesicular steatosis,^[33] although the chance of binge drinking would be lower than that in the general population. Lastly, our center has not adopted newly developed imaging modalities, such as MRI-derived proton density–fat fraction (MRI-PDFF) to assess hepatic steatosis owing to its high cost and limited availability. Considering the excellent performance of this modality in the quantitative assessment of hepatic steatosis, MRI-PDFF could be widely used in the process of living liver donor selection in the near future.

In conclusion, we developed a model to identify hepatic steatosis in potential living liver donors by using a logistic model. Our model comprised only noninvasive variables routinely collected in the predonation

evaluation. Using our model, unnecessary liver biopsies can be safely omitted in the selection of living donor candidates.

CONFLICT OF INTEREST

Nothing to report.

AUTHOR CONTRIBUTIONS

Study concept and design: J. Lim, J. Choi; Data acquisition: J. Lim, D. Lee, JH Shim, KM Kim, Y-S Lim, HC Lee, K-H Kim, S-G Lee; Data analysis and interpretation: J. Lim, S. Han, J. Choi; Manuscript drafting: J. Lim, S. Han, J. Choi; Critical revision of the manuscript for important intellectual content: D-H. Jung, S. Han, J. Choi All authors approved the final version of the manuscript.

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REFERENCES

1. Maluf DG, Stravitz RT, Cotterell AH, Posner MP, Nakatsuka M, Sterling RK, et al. Adult living donor versus deceased donor liver transplantation: a 6-year single center experience. *Am J Transplant*. 2005;5:149–56.
2. Lee S-G, Song G-W, Yoon Y-I. An exceptional series: 5000 living donor liver transplantations at Asan Medical Center, Seoul, Korea. *Transplantation*. 2019;103:1739–41.
3. Petrowsky H, Kim K-H, Tokat Y. Editorial: Living-donor liver transplantation: why the Sun rises in the East and sets in the West? *Curr Opin Organ Transpl*. 2019;24:620–2.
4. Murata H, Yagi T, Iwagaki H, Ogino T, Sadamori H, Matsukawa H, et al. Mechanism of impaired regeneration of fatty liver in mouse partial hepatectomy model. *J Gastroenterol Hepatol*. 2007;22:2173–80.
5. Fagenson AM, Pitt HA, Moten AS, Karhadkar SS, Di Carlo A, Lau KN. Fatty liver: the metabolic syndrome increases major hepatectomy mortality. *Surgery*. 2021;169:1054–60.
6. Ploeg RJ, D'alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, et al. Risk factors for primary dysfunction after liver transplantation—a multivariate analysis. *Transplantation*. 1993;55:807–13.
7. Strasberg SM, Howard TK, Molmenti EP, Hertl M. Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation. *Hepatology*. 1994;20:829–38.
8. Selzner M, Clavien PA. Fatty liver in liver transplantation and surgery. *Semin Liver Dis*. 2001;21:105–13.
9. European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation. *J Hepatol*. 2016;64:433–85.
10. Miller CM, Durand F, Heimbach JK, Kim-Schluger L, Lee S-G, Lerut J, et al. the International Liver Transplant Society guideline on living liver donation. *Transplantation*. 2016;100:1238–43.

11. Im HJ, Ahn YC, Wang J-H, Lee MM, Son CG. Systematic review on the prevalence of nonalcoholic fatty liver disease in South Korea. *Clin Res Hepatol Gastroenterol*. 2021;45:101526.
12. Tsang L-C, Chen C-L, Huang T-L, Chen T-Y, Wang C-C, Ou H-Y, et al. Preoperative imaging evaluation of potential living liver donors: reasons for exclusion from donation in adult living donor liver transplantation. *Transplant Proc*. 2008;40:2460–2.
13. Jun M-J, Shim JH, Kim SY, Seo N, Kim KM, Lim Y-S, et al. Clinical implications of preoperative and intraoperative liver biopsies for evaluating donor steatosis in living related liver transplantation. *Liver Transpl*. 2014;20:437–45.
14. Peng CJ, Yuan D, Li B, Wei YG, Yan LN, Wen TF, et al. Body mass index evaluating donor hepatic steatosis in living donor liver transplantation. *Transplant Proc*. 2009;41:3556–9.
15. Şeker M, Erol C, Sevmiş Ş, Saka B, Durur Karakaya A. Comparison of CT methods for determining graft steatosis in living donor liver transplantation. *Abdom Radiol (NY)*. 2019;44:2418–29.
16. Zheng D, Guo Z, Schroder PM, Zheng Z, Lu Y, Gu J, et al. Accuracy of MR imaging and MR spectroscopy for detection and quantification of hepatic steatosis in living liver donors: a meta-analysis. *Radiology*. 2017;282:92–102.
17. Kim JM, Ha SY, Joh J-W, Sinn DH, Jeong WK, Choi G-S, et al. Predicting hepatic steatosis in living liver donors via noninvasive methods. *Medicine (Baltimore)*. 2016;95:e2718.
18. Hong YM, Yoon KT, Cho M, Chu CW, Rhu JH, Yang KH, et al. Clinical usefulness of controlled attenuation parameter to screen hepatic steatosis for potential donor of living donor liver transplant. *Eur J Gastroenterol Hepatol*. 2017;29:805–10.
19. Soin AS, Chaudhary RJ, Pahari H, Pomfret EA. A worldwide survey of live liver donor selection policies at 24 centers with a combined experience of 19 009 adult living donor liver transplants. *Transplantation*. 2019;103:e39–47.
20. Han S, Ko JS, Kwon G, Park C, Lee S, Kim J, et al. Effect of pure microsteatosis on transplant outcomes after living donor liver transplantation: a matched case-control study. *Liver Transpl*. 2014;20:473–82.
21. Spitzer AL, Lao OB, Dick AAS, Bakthavatsalam R, Halldorson JB, Yeh MM, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. *Liver Transpl*. 2010;16:874–84.
22. Friedman JH. Regularized discriminant analysis. *J Am Stat Assoc*. 1989;84:165–75.
23. Hastie T, Tibshirani R, Buja A. Flexible discriminant analysis by optimal scoring. *J Am Stat Assoc*. 1994;89:1255–70.
24. Hastie T, Tibshirani R. Discriminant analysis by Gaussian mixtures. *J Roy Stat Soc Ser B Met*. 1996;58:155–76.
25. Breiman L. Random forests. *Mach Learn*. 2001;45:5–32.
26. Statnikov A, Wang L, Aliferis CF. A comprehensive comparison of random forests and support vector machines for microarray-based cancer classification. *BMC Bioinformatics*. 2008;9:319.
27. Angulo P. Nonalcoholic fatty liver disease and liver transplantation. *Liver Transpl*. 2006;12:523–34.
28. Hwang I, Lee JM, Lee KB, Yoon JH, Kiefer B, Han JK, et al. Hepatic steatosis in living liver donor candidates: preoperative assessment by using breath-hold triple-echo MR imaging and 1H MR spectroscopy. *Radiology*. 2014;271:730–8.
29. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006;6:33.
30. Lee J-H, Kim D, Kim HJ, Lee C-H, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis*. 2010;42:503–8.
31. Poynard T, Ratzu V, Naveau S, Thabut D, Charlotte F, Messous D, et al. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. *Comp Hepatol*. 2005;4:10.
32. Yip TC-F, Ma AJ, Wong VW-S, Tse Y-K, Chan HL-Y, Yuen P-C, et al. Laboratory parameter-based machine learning model for excluding non-alcoholic fatty liver disease (NAFLD) in the general population. *Aliment Pharmacol Ther*. 2017;46:447–56.
33. Yerian L. Histopathological evaluation of fatty and alcoholic liver diseases. *J Dig Dis*. 2011;12:17–24.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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