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ORIGINAL ARTICLE

Prediction of the Total Liver Weight using anthropological clinical parameters: does complexity result in better accuracy?

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Abstract

Background: The performance of linear models predicting Total Liver Weight (TLW) remains moderate. The use of more complex models such as Artificial Neural Network (ANN) and Generalized Additive Model (GAM) or including the variable "steatosis" may improve TLW prediction. This study aimed to assess the value of ANN and GAM and the influence of steatosis for predicting TLW.

Methods: Basic clinical and morphological variables of 1560 cadaveric donors for liver transplantation were randomly split into a training (2/3) and validation set (1/3). Linear models, ANN and GAM were built by using the training cohort and evaluated with the validation cohort.

Results: The TLW is subject to major variations among donors with similar morphological parameters. The performance of ANN and GAM were moderate and similar to that of linear models (concordance coefficient from 0.36 to 0.44). In 28–30% of cases, TLW cannot be predicted with a margin of error ≤20%. The addition of the variable "steatosis" to each model did not improve their performance.

Conclusion: TLW prediction based on anthropological parameters carry a significant risk of error despite the use of more complex models. Others determinants of TLW need to be identified and imaging-based volumetric measurements should be preferred when feasible.

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Introduction

A correct estimation of liver volumes is crucial before liver resection or liver transplantation. Indeed, the future remnant liver volume/total functional liver volume ratio is widely used to prevent post-hepatectomy liver failure.[1,2] Likewise, in cadaveric liver transplantation (LT), an accurate prediction of the total liver volume (TLV) helps to anticipate a graft size mismatch with the recipient.[3]

Liver volumes are usually assessed by computerized tomography (CT) scan-based volumetric measurements. However, the presence of multiple tumors in the future resected liver makes impossible to accurately measure the total functional liver volume. In the setting of LT, lack of time often precludes any volumetric measurements of the future liver graft, and decisions are commonly based on morphological data of the donor.

Thus, some formula predicting TLV, by using anthropological parameters have been proposed. To date, more than fifteen formulas have been reported.[4,5] There are usually based on the linear correlation between TLV and morphological parameters, such as Body Surface Area (BSA) or body weight (BW).[6–9] However, others factors are involved such as age, sex and ethnicity[10] and variability within segment volumes in healthy liver has been well demonstrated.[11] A wide range of TLV for similar BW or BSA has been observed in all these studies, and the coefficient of correlation reported in these formula remained moderate, suggesting that linear models used for TLV prediction should be challenged.

More complex models, such as Artificial Neural Networks (ANN) and Generalized Additive Models (GAM), have shown excellent performance in scientific and medical fields.[12–16]

Moreover, liver steatosis, as being an accumulation of fat within hepatocyte cytoplasm, may potentially influence liver weight. We hypothesized that steatosis, which can be diagnosed by imaging,[17] may account for a part of the important variations observed.

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The objective of this study was to assess the value of ANN and GAM and to test whether steatosis may improve predictive models.

Methods

Study population

This study was undertaken at the Centre Hepatobiliaire, at the Paul Brousse Hospital, Villejuif, France, a high-volume *HBP* surgery and liver transplantation center. Data of donors and recipients are prospectively collected in a database by a dedicated professional (FB). The following variables were extracted from this database from January 1995 to June 2014: total weight of the graft (TLW), percentage of liver steatosis and donor's characteristics as gender, age, body height (BH), and body weight (BW). Using those variables, donor's body mass index (BMI) was calculated, as well as Body Surface Area (BSA) based on Mosteller's formula.[18] We excluded all split or reduced grafts as well as every donor in whom there was a missing data.

Measurement of Total Liver Weight

During graft preparation, the hepatic artery and the portal vein are freed from all surrounding fat and perivascular lymph nodes and cholecystectomy is systematically performed. Then, the liver weight is systematically measured with an electronic balance at the end of the "back table" before implantation.

Hepatic steatosis evaluation

Liver steatosis was evaluated by a surgical biopsy of the graft, systematically performed at the time of liver procurement before clamping. Steatosis was histologically classified as follows: absent, mild <30%, moderate 30–60%, severe >60%. For this analysis, the "steatosis" variable refers to the presence of moderate to severe macro vesicular and/or micro vesicular steatosis.

Statistical analysis

Calculations were done with R 3.1.1 software and the *rms* package, *nnet* package, *mgcv* package and *epiR* package. Plots were drawn using the *ggplot2* package. Continuous data were expressed as mean (±standard deviation) whereas categorical data were compared using the *T-test* and the *chi-square test*, respectively.

Training and validation groups

The study population was randomly split into a training group (2/3; N = 1040) and a validation group (1/3, N = 520). The training Group served to build linear models, GAM and ANN for predicting TLW. The validation cohort served to assess performances of models.

Linear models

We used simple linear regression including each single variable: age, BW, BH, BSA, BMI, gender and steatosis to derive formulas predicting TLW.

All significant variables on univariate analysis were included in a multivariate linear model. Selection of the variables for the final multivariate model was done according to a backward stepwise procedure.

Using the fact that in non-cirrhotic liver, TLW is almost similar to TLV,[19] we also added for comparisons two published linear formulas predicting TLV, established with western cohorts.[8,9]

Artificial Neural Network (ANN)

ANN belong to machine learning methods, used to estimate function of a variable, depending on variable predictors. We constructed an artificial network with a single hidden layer feed-forward with 4 input nodes, 4 neurons in the hidden layer and one output neuron, using the donors' variables "predictors" BW, BH, age and gender. The ANN was first trained using 80% of the training group (N = 832), whereas the remaining 20% served for cross validation. This step enables the ANN to learn general predictive rules rather than recognize specific case, which can lead to good performance in the training set but poor performance in the testing set.

Generalized Additive Model (GAM)

GAM aimed to maximize the accuracy of prediction of a variable Y by using a sum of non-parametric function, applied to each predictor. The smoothing spline is the most often used method used in GAM to fit the relationship between predictors and Y. Terms of the model selection and smoothness selection were performed by using the REML method, as proposed in the *mgcv* package.

Endpoints for models comparisons

The Mean Square Error ($MSE = 1/n \times \sum (\text{target value} - \text{output value})^2$), the Mean Absolute Percentage Error ($MAPE = 1/n \sum ([\text{target value} - \text{output value}]/\text{target value}) \times 100\%$) and the Lin's concordance correlation coefficient[20] were evaluated. We also provided the percentage of predictions obtained with ±10% and ±20% absolute error margin.

Results

Study population

A total of 1560 cadaveric donors were included in the analysis. The baseline characteristics of the study population, the training and validation cohorts are given in Table 1. Briefly, there were 941 (60%) men and 619 (40%) women. Donors had a mean age of 48 years (±17; range: 15–89 years). The mean BH and BW were 170 cm (±9) and 71 kg (±13) respectively. The mean TLW of the entire study population was 1485 g (±302) and ranged from 765 to 2480 g. The baseline characteristics of the training and validation groups were similar.

Simple linear model

Using the training group, we found that the age, BH, BW, BSA and BMI were all significantly associated with TLW. Their

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