

Application of Machine Learning Methods to Predict Non-Alcohol Fatty Liver Disease in Taiwanese High-Tech Industry Workers

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Abstract - *The prevalence of obesity has led the metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), to become a serious health concern during recent years. The objective of the study is to identify the potential factors of NAFLD by decision tree first and then apply machine learning methods to the health examination data to construct the learning system. The performance of several methods including k-nearest neighbor, bootstrap aggregating, random forest, and support vector machine will be compared in this work. We observed that metabolic syndrome, body mass index, triglyceride, total cholesterol, age, waist to hip ratio, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol might be the risk factors of NAFLD for males and SVM classifier gave the best performance (86.9% accuracy, 90.0% sensitivity, and 81.0% specificity). We infer from the study that a combination of decision tree and SVM have the potential to classify NAFLD in males properly. This work can bring more awareness to the importance of regular health checkups to prevent metabolic diseases and aid in the clinical decision making for decreasing NAFLD in Taiwan in the future.*

Keywords: NAFLD; decision tree; support vector machine

1 Introduction

The definition of nonalcoholic fatty liver disease (NAFLD) includes the following two criteria: (a) there exists hepatic steatosis by imaging or by histology and (b) no other factors of causing secondary hepatic fat accumulation, such as alcohol overdose, medication using or genetic diseases [1]. NAFLD has the chance to be associated with hepatocellular carcinoma (HCC) by epidemiological evidence [2]. Also, Michelotti *et al.*, mentioned that the risk of liver cancer can elevate due to NAFLD [3]. In Taiwan, the mortality rate of HCC ranks second among the top 10 death of cancer. With the government carrying out the programs such as neonatal

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vaccination and the strengthening of follow-up treatments for hepatitis B and hepatitis C patients, liver cancer caused by hepatitis B and hepatitis C are under control. Duan *et al.* further proposed that 15% to 50% of liver cancer are caused by NAFLD rather than hepatitis B, hepatitis C or alcohol assumption in the developed countries [4]. In clinical practice, abdominal echogram is the most common way to diagnose NAFLD and the fatty liver is defined by the standard of Asian Pacific Association for the Study of the Liver.

With the worldwide prevalence of obesity and diabetes, the most common liver disease, NAFLD, has gradually caught public's attention. The prevalence of NAFLD is 15% to 30% in western countries, 20% in China, 27% in Hong Kong, 15% to 45% among South Asia, South-East Asia, Korea, Japan and Taiwan [5].

Generally, NAFLD is highly related to metabolic syndrome, diabetes, hyperlipidemia, etc. NAFLD patients usually have high triglycerides (TG) and low high-density lipoprotein (HDL). In addition, high risk group gets higher prevalence. For example, the prevalence of NAFLD increases to 69% for type II diabetes mellitus patients, 57% for the overweight people and 98% for those who are non-diabetic obese [6]. Therefore, high risk groups should be highly aware of the important factors associated to NAFLD. Here, we aim to identify important NAFLD factors in the routine checkup items to aid physicians in making diagnosis and patients aware of the signs of NAFLD.

2 Literature reviews

The majority of studies focused on univariate analysis and constructed logistic regression model to find out the important factors causing NAFLD for ad hoc groups [7-10]. Birjandi *et al.* used decision tree [11], one of machine learning methods, to find relevant factors and predict NAFLD. In this section, we summarized NAFLD-related studies for reference.

In the retrospective study of Lin *et al.* [7], multinomial logistic regression was applied to the physical and biochemical examination data with four-graded NAFLD (0: none, 1: mild, 2: moderate, 3: severe) for the sake of prediction. The result indicated that older age, male gender, increased body mass index (BMI), serum glutamic-pyruvic

transaminase (SGPT), TG, and total cholesterol (TC) had influence on grade 2-3 NAFLD and the overall accuracy was 61.4% with sensitivity 70.8% and specificity 85.2%.

In the study of Felix *et al.* [8], Chen *et al.* [9], and Tung *et al.* [10], binary logistic regression was implemented on the datasets for Brazilian obese children, Taiwanese adult population and Taiwanese taxi drivers, respectively. Felix *et al.* indicated that predictive factors for NAFLD were related to male gender, high consumption of refined carbohydrates, and sedentary lifestyle [8]. Chen *et al.* revealed that the risk factors for NAFLD in the general population were male gender, elevated SGPT, obesity, blood glucose ante cibum (GLU-AC), TC, triglyceride (TG), and hyperuricemia [9]. In the group of Taiwanese male taxi drivers, their risk factors contained hypertension, hyperuricemia, higher serum glutamic-oxaloacetic transaminase (SGOT), higher SGPT, hypertriglyceridemia, and higher GLU-AC [10]. From the above studies, male gender might be a common factor for NAFLD in different races. We can also notice that some risk factors vary from person to person of assorted community in Taiwan.

It was not until 2015 that M.Birjandi *et al.* [11] made use of classification tree, a non-parametric statistical learning approach, to diagnose NAFLD and identify its associated factors in the area of Iran. The output of tree showed 6 vital attributes for NAFLD: BMI, waist-hip ratio (WHR), TG, GLU-AC, systolic blood pressure (SP) and SGPT. The prediction accuracy attained 75% with sensitivity 73% and specificity 77%. Another remarkable point was the finding of great association between metabolic syndrome and NAFLD.

In our study, we have tried both binary logistic regression and classification tree to reduce the number of predictor variables for the purpose of dimension reduction. However, we preferred tree method because it is straightforward to interpret. Furthermore, we also investigated several machine learning methods, including k-nearest neighbor, bootstrap aggregating, random forest, and support vector machine to predict the incidence of NAFLD.

3 Research design and methods

3.1 Study materials

Our investigations focus on the health checkup data for 5 years (from Year 2010 to 2014) to diagnose NAFLD. The data were taken from the staff health check-up of a company in Hsinchu Science Park and were stored in Health Evaluation Center in MacKay Memorial Hospital.

There were 2,110 observations in total before data cleaning. In this work, the diagnosis of NAFLD was based on abdominal ultrasonography. Because supervised learning required labeled data for training and testing, those samples without taking abdominal ultrasonography were deleted, leaving 1,202 results for further analysis. Each check-up item was viewed as a variable. We removed variables that satisfy any of the following three criteria: i) the number of missing data is greater than 1055, which is about half of sample size

2,110; ii) the proportion of observations diagnosed as normal is equal or greater than 90 percent and iii) some data were removed based on clinical expert opinions. After filtering, we pre-selected 17 explanatory variables for subsequent analysis. Our data processing workflow is summarized in Fig. 1.

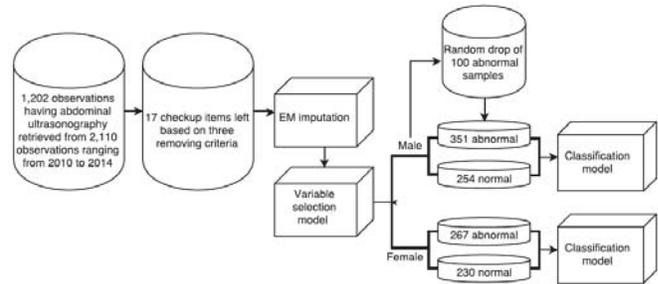


Fig. 1. A classification framework to distinguish observations with or without NAFLD. The abnormal and normal refer to NAFLD and non-NAFLD observations respectively.

Our study was based on classification framework to predict the label of unlabeled data (i.e., testing data) by training the algorithm with the known labeled data (i.e., training data). Our response variable, i.e., label variable was defined as

$$FL = \begin{cases} 1, & \text{if the observation has NAFLD} \\ 0, & \text{otherwise} \end{cases}$$

It should be noted that the diagnosis of NAFLD was rendered by doctors according to the subject's abdominal echogram. In accordance with the standard of Asian Pacific Association for the Study of the Liver, the definition of fatty liver satisfies at least two of the following three guidelines on abdominal echogram [12, 13]: (1) the pattern of liver is brighter than that of renal parenchyma, (2) blurred vascular, and (3) deep attenuation.

Missing data is common in clinical and epidemiological research. However, the incompleteness of dataset may cause some problems such as the lack of representativeness of samples and biased estimation of parameters, making the process of analysis more complicated [14]. Thus, we need to make sure that there is no missing value in the dataset before data analysis is conducted. Now we have 1,202 samples and 17 variables. About 1.6% of data were missing in the dataset and their values were estimated by EM (expectation maximization) imputation [15].

In order to find out important factors related to NAFLD, we constructed variable selection models by the imputed dataset. Here we chose decision tree (DT) as our variable selection models since it is easy to interpret. We used "rpart" package, a classical decision tree algorithm in R to realize our goal. In the recursive binary splitting procedure, the lowest Gini cost was selected and minimum count on the number of training observations assigned to each leaf node as stopping criterion was used. Taking physiological difference between genders into consideration, we built separate models for males and

females. Besides, gender-based factors for NAFLD exist among Taiwanese taxi drivers in Taipei [10].

In the male model, 100 NAFLD male observations were randomly taken off to avoid disproportion between having and not having NAFLD. C. Drummond and R. C. Holte summarized that under-sampling (i.e. remove number of instances from the dataset) was cost sensitive for the case of C4.5 algorithm [16]. Among the rest of 605 male samples, 351 of them were found having NAFLD while the other 254 were normal. These 605 samples were then put into our classification model. As for the female model, we directly put 267 abnormal cases and 230 normal cases into classification model since the proportion between abnormal and normal cases were pretty close.

Since there is no certain algorithm that is always the best [17], we tried several common classifiers such as *k*-nearest neighbor (KNN), bootstrap aggregating (Bagging), random forest (RF) [18], and support vector machine (SVM) [19] to construct classification model with preselected variables for the male and female population separately. In addition to linear SVM, we also tried SVM with radial basis function (RBF) kernel [20]. The implementation of our work was all based on R package.

3.2 Variable description

As mentioned above, we kept 17 explanatory variables, which were sex (SEX), age (AGE), waistline (WAIST), serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), waist to hip ratio (WHR), hyperlipidemia (HPL), total cholesterol (TC), diastolic pressure (DP), systolic pressure (SP), body mass index (BMI), triglyceride (TG), blood glucose ante cibum (GLU-AC), alpha fetoprotein (AFP), and metabolic syndrome (MS). Generally, we set 0 and 1 as normal and abnormal for each check-up item respectively. The glossary of the variables and their medical normal ranges are listed in Table 1. Noted that AGE is a quantitative variable ranging from 18 to 79 years old and is not listed in the Table 1.

Table 1: Variable representation and its medical normal range.

Variable Name	Glossary	Normal Range
SEX	sex	Male: 1 Female: 0
WAIST	waistline	Male: 0~90 cm Female: 0~80 cm
SGPT	serum glutamic-pyruvic transaminase	14~40 IU/L
SGOT	serum glutamic-oxaloacetic transaminase	15~41 IU/L
LDL	low-density lipoprotein cholesterol	<130 mg/dL

HDL	high-density lipoprotein cholesterol	Male: >40 mg/dL Female: >50 mg/dL
WHR	waist to hip ratio	Male: <0.9 Female: <0.85
HPL	hyperlipidemia	TG: 35~150 mg/dL TC: 130~200 mg/dL LDL: <130 mg/dL HDL: >40 mg/dL
TC	total cholesterol	130~200 mg/dL
TG	triglyceride	35~150 mg/dL
DP	diastolic pressure	60~90 mmHg
SP	systolic pressure	90~140 mmHg
group_BMI	body mass index	1: underweight and normal (<24) 2: overweight (24~27) 3: moderately obese (27~30) 4: severely obese (30~35) 5: very severely obese (≥ 35)
GLU-AC	blood glucose ante cibum	70~99 mg/dL
AFP	alpha fetoprotein	<10 ng/mL
MS	metabolic syndrome	1. GLU-AC: ≥ 100 mg/dL 2. SP ≥ 130 mmHg, DP ≥ 85 mmHg 3. TG: ≥ 150 mg/dL 4. HDL: Male <40 mg/dl, Female <50 mg/dL 5. WAIST: Male ≥ 90 cm, Female ≥ 80 cm If three or more of the above satisfy, then identify the observation as having metabolic syndrome.

4 Results

The results presented here is the realization of the framework in Fig. 1. It is worth noting that what we demonstrated may only be applicable to some specific group or community, which in our case is Taiwanese high-tech industry workers.

4.1 Male model

We first input 605 male observations with 16 variables to decision tree for the sake of variable selection. The minimum count on the number of training observations to each leaf node was assigned to be 20. The output is shown in Fig. 2. From the plot, we can see that 8 variables: MS, group_BMI, TG, TC,

AGE, WHR, HDL, LDL were selected by the decision tree, indicating that they might be the risk factors of NAFLD. To verify our results, Lin *et al.*, mentioned that male gender, older age, BMI, TG, and TC were found to be significantly associated with NAFLD in Taiwan [7]. Hsu *et al.*, observed that the growth of NAFLD in Taiwan had something to do with metabolic disorders [21]. Fu *et al.*, concluded that the weight problem and elevated non-HDL-cholesterol might lead the adolescent students in Hualien City, Taiwan to NAFLD [22]. In China, Shi *et al.*, also mentioned that MS was regarded as a sufficient factor for NAFLD [23].

In the decision tree, the earlier the variable is split, the more vital the variable is, and the values in the bottom suggest the likelihood of one getting NAFLD.

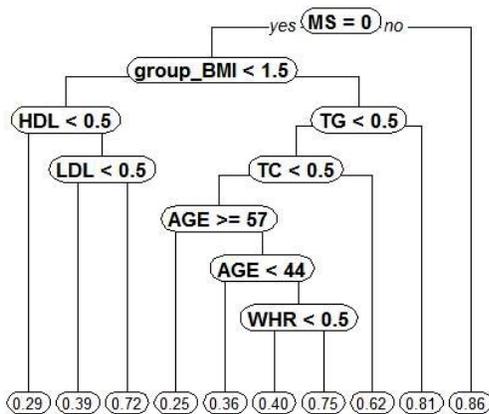


Fig. 2. A decision tree for the male samples. The values at the end node are the probability of getting NAFLD and are calculated by the number of correct classifications divided by the number of observations in that node.

The variables selected by the DT was subsequently fed into the classification model. Here, 90% of 605 samples, i.e., 544 random observations were employed as the training set with the rest 10% as the testing set (61 observations). We input with selected 8 variables into the classification models KNN, Bagging, RF, linear SVM, RBF SVM, to the observations and evaluated their performance. The classification system learned from the training set and made prediction for testing data. For each classifier, we set 10-fold cross-validation and computed their average performance. To evaluate the model with the selected 8 variables, the performance of each model was measured in terms of accuracy, sensitivity, and specificity.

Table 2 shows the classification results using the 8 variables selected by decision tree (DT). In order to optimize our machine learning models, the parameters were tuned to minimize the cost function. Taking the DT model as an example, the parameter *k* in the KNN process was tuned, ranging from 1 to 20, and *k*=4 was found to yield the best result. The number of trees (ntree) was tuned among 500, 1000, and 2000 for tree methods (Bagging and RF). The best results were ntree=1000 for Bagging and ntree=2000 for RF, respectively. Noted that the number of variables tried at each

split in RF was 2, which was calculated by rounding down (number of input variables)/3. In SVM, *c*-parameter and gamma-parameter for kernel were tuned as $2^{-6}, 2^{-5}, \dots, 2^6$. The best outcome for linear SVM was *c*=2 while *c*=0.5 and gamma=0.125 for RBF SVM. We summarize each classifier performance on DT model in Table 2.

Based on the results below, KNN was the simplest method but had the worst accuracy. On the other hand, RBF SVM had highest accuracy for our NAFLD dataset. The sensitivity of RBF SVM was quite high compared to other four methods. However, the tradeoff was a decrease in specificity. Besides, the results of RF attained an acceptable level although the performance was not the best.

Table 2. Male classifier performances on different models.

	Accuracy (%)	Sensitivity (%)	Specificity (%)
KNN	77.0	80.0	71.4
Bagging	78.7	85.0	66.7
RF	83.6	85.0	81.0
SVM (Linear)	82.0	82.5	81.0
SVM (RBF)	86.9	90.0	81.0

4.2 Female model

We dealt with female dataset in the same way. In the step of the variable selection, we built the decision tree shown in Fig. 3 with 497 female samples. The important factors turned out to be MS, group_BMI, AGE, WAIST, HDL, LDL (6 variables). MS played an important role in the decision tree for both male and female subjects.

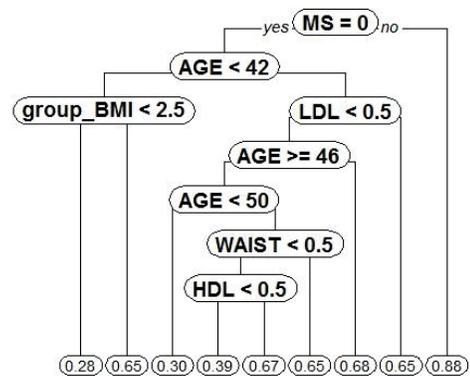


Fig. 3. A decision tree for female.

We had 6 input variables in DT to build the classification model. Similar to the model for the males, we intended to compare the performance of different methods. The training set consisted of 447 random observations, which was 90% of 497 samples. The remaining 10% was utilized as the testing set (50 observations). The tuning process of classifiers gave

the following parameter values: $k=20$ in KNN, $n_{tree}=2000$ in Bagging, $n_{tree}=2000$ and the number of variables tried at each split=2 in RF, $c=0.5$ in linear SVM, $c=0.125$ and $\gamma=0.125$ in RBF SVM. Table 3 summarizes the results.

In general, the performance of RF was better than those of the other methods for the female model. In RF model, the accuracy and sensitivity reached 80% and 82.8% respectively while the specificity behaved less convincingly if we input merely the preselected 6 variables. This implied that whether a female had NAFLD or not might highly depend on the 6 selected factors.

Table 3. Female classifier performances on different models.

	Accuracy (%)	Sensitivity (%)	Specificity (%)
KNN	74.0	75.9	71.4
Bagging	72.0	75.9	66.7
RF	80.0	82.8	76.2
SVM (Linear)	66.0	55.2	81.0
SVM (RBF)	74.0	72.4	76.2

5 Discussion

Compared to the literature reviews whose accuracy falls in the interval of 60% and 75%, our models obviously perform better. It is worth noting that the difference of CT between M. Birjandi *et al.* [11] and ours is the type of input variables. The clinical test items the author input were regarded as quantitative variables, so the algorithm would pick the best threshold as the split point. On the other hand, we took a physician's advice and converted the predictors into binary variables based on medical normal range to make results more meaningful.

As for the great variation in risk factors identified by different groups, it may attribute to the inherent difference of the datasets from each ad hoc group. A cross-sectional study pointed out that the racial difference existed in the prevalence of NAFLD for U.S. population [24]. In spite of small racial diversity in Taiwan, the main difference between several studies can be explained by the inconsistent lifestyle in each community.

Although the best performance (RBF SVM) for the male model seems acceptable, some limitations exist in our studies. Firstly, our framework still involves human efforts in labeling and choosing variables. Second, the sample size needs to be increased for the sake of better outcome.

Besides, it is obviously to see that the male classifiers outperform the female classifiers. We summarize the reasons in the following aspects: first of all, the sample size of female population is not as big as the male population. Since the more the training data is, the better the classifier can be. In our case, 497 female samples are smaller than 605 male samples indeed. Second, the proportion of variables in the female dataset differs from that in the male dataset. Generally speaking, the

physiological state of the female population is not the same as that of the male population. That is also why the variables selected for male and female are distinctively different. Third, female gender is not one of risk factors of NAFLD in Taiwan according to the studies mentioned previously [7, 9, 10]. Hence, it may be hard to find out a significant association between female gender and NAFLD.

6 Conclusion

In this work, we observed that metabolic syndrome, body mass index, triglyceride, total cholesterol, age, waist to hip ratio, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol might be the risk factors of NAFLD for males while metabolic syndrome, body mass index, age, waistline, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol might be those for females. The results suggest that RBF SVM produced a better classification for males while RF performed better in female model. However, no evidence suggests that female gender has high risk at NAFLD from predecessors' work. Additionally, the performance of the female classifiers is apparently outperformed by the male classifiers. From Taiwanese clinical point of view, the variables selected by decision tree seems to be suitable. Hence, we infer from the study that a combination of variable selection model, i.e., DT, and the classification model, RBF SVM, have the potential to classify NAFLD in males properly.

7 References

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