J Surg Res 2022; 5 (2): 238-251 *DOI: 10.26502/jsr.10020217*

Research Article

Supervised Machine Learning Techniques For the Prediction of Hepatocellular Carcinoma Recurrence

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Received: 22 March 2022; **Accepted:** 29 March 2022; **Published:** 27 April 2022

Citation: Andrea Mega, Luca Marzi, Alessandra Andreotti, Fabio Vittadello, Filippo Pelizzaro, Stefano Gitto, Gilbert Spizzo, Federica Ferro, Antonio Frena, Andreas Seeber. Supervised Machine Learning Techniques For the Prediction of Hepatocellular Carcinoma Recurrence. Journal of Surgery and Research 5 (2022): 238-251.

Abstract

Background & Aims

Hepatocellular carcinoma (HCC) is the most frequent malignant tumor of the liver and its incidence is increasing worldwide. Several treatments are currently available, but predictors of cancer recurrence are poorly characterized. The development of artificial intelligence has recently made available a new tool called Machine Learning (ML). ML allows running strong prediction of several variables, after inputting several data into a dedicated software. This study aimed to create a MLmodel for predicting HCC recurrence.

Patients and methods

In this study, we analyzed retrospectively data of 166 patients who were managed at the Bolzano Regional Hospital between 1998 and 2019. In order to find the best predictive model, either both non-parametric and parametric models were evaluated. Non-parametric models trained in this study were the following: Random Forest (RF), Support Vector

Machine (SVM) and K-Nearest Neighbours (KNN). Parametric model adopted was the logistic regression model with the elastic net algorithm (ENET).

Results

In our dataset, the Random Forest model is the most performant (AUC 0.712). Independently from the treatment performed, age at diagnosis, MELD, the absence of previous obesity, type of diagnosis, BMI, and BCLC emerged as significant HCC recurrence predictors.

Conclusion

ML may be a valuable tool in the prediction of HCC recurrence. Larger sample sizes are needed to create useful tool for the clinical management of patients with HCC.

Keywords: Hepatocellular carcinoma; Supervised Machine Learning; Artificial Intelligence; Prediction of recurrence

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide [1]. Despite the eradication of Hepatitis C Virus (HCV) and the available vaccination for Hepatitis B Virus (HBV), the incidence of HCC is predicted to increase in the coming years, due to population growth, aging and the expansion of Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis (NAFLD/NASH) in Western countries [2]. In HCC, the prediction of prognosis is complex since not only tumor burden, but also residual liver function and general clinical conditions (e.g., performance status) must be take into account. Furthermore, ongoing treatment represents one of the most important prognostic parameters [3]. Despite noteworthy improvements in screening and treatment, the recurrence and/or progression rate and the cancer-related mortality rate remains high [42]. HCC has a high recurrence rate after both surgical resection and orthotopic liver transplantation. In particular, after a liver transplantation patient show a five-year survival rate of 65-81% despite using specific criteria (Milan, USFC, Kyoto) aimed at selecting patients thought to have better long-term outcomes [4,5]. Conventional predictive models to assess the prognosis of HCC include survival analysis, logistic regression, and Cox models [6,7]. These statistical models are usually based on multivariate predictors, such as demographic, clinical, radiological, pathological, and genetic parameters. However, considered the extremely complex prognostic prediction of HCC patients, linear systems might be too simplistic [8]. Artificial intelligence (AI) is a very promising tool that may be useful in overcoming the limitations of traditional statistic and that can improve the prediction of survival and recurrence after treatment [43]. AI refers to the use of computers and related technologies to simulate the intelligent behavior and critical thinking of humans [9]. Although AI has been applied in medicine for the past 30 years, only recent studies demonstrated the ability of this tool to achieve accurate diagnosis and tumor classification, as well as the evaluation of survival and recurrence [44]. Among AI technologies, machine learning (ML) relies on the computer's ability

to “learn” and improve from past examples without being programmed [45]. Deep learning (DL) is a subset of ML and a computer software that mimics the network of neurons in a brain, where the learning phase occurs through a neural network. Since ML models can include a lot of variables, it is advantageous and can become a promising tool compared to the traditional statistical models [45]. Consequently, with the introduction of AI several computer models have been developed for the prediction of tumor characteristics or of recurrence risk, using ultrasound-based radiomic signatures [10], contrast-enhanced computed tomography (CT) [11-13] or magnetic resonance imaging (MRI) [14]. Other authors have also developed predictive models in patients undergoing radiofrequency ablation (RFA) based on Support Vector Machine (SVM) [15]. Algorithms have been created using the combination of CT images and clinical data to predict response to transarterial chemoembolization (TACE) [16], DL models using CT or ultrasound images [17,18], ML techniques by combining MRI with clinical data [19], or SVM techniques to genetic analysis [20]. To date, algorithms have been developed to predict the response and survival after TACE, stereotaxic body radiotherapy (SBRT), RFA and liver resection. In addition, AI techniques were evaluated to providing information on the predictive power of biomarkers [21-34]. The aim of this study was to create a predictive model for elaboration the recurrence of HCC after treatment, and to identify the most important clinical features associated with disease recurrence, regardless of the type of treatment, using Supervised Machine Learning techniques.

2. Materials and Methods

2.1 Cohort description

Data were retrieved from the Italian Liver Cancer (ITA.LI.CA.) database, a national registry that prospectively collect the data of patients with HCC managed in 20 Italian centers. Currently, the database includes 171 patients diagnosed with HCC between January 1998 and December 2018. Informed consent was obtained as usual for medical, surgical, and radiological treatments, but not specifically for patient data to be used in this retrospective study. Details about patient data collected for this study are described in S1.

2.2 Machine Learning Models

For the training of ML models and subsequent accuracy evaluation, the dataset was randomly divided in a training/validation set (70% of cases) and a test set (30% of cases). 5-fold cross-validation with 20 repetitions was applied. Considered that the Receiver Operating Characteristic (ROC) curve is more robust than classical accuracy, especially in the case of unbalanced outcomes [35], it was used as metric in the training process. In this study, both non-parametric models and parametric models have been evaluated. The nonparametric models trained were the following: Random Forest, Support Vector Machine and K-Nearest Neighbours. As parametric model, we used the logistic regression model with the elastic net algorithm [36]. A disparity in the frequencies of the observed classes can have a significant negative impact on the fit of the model. To solve this problem, we used the "up-sampling" method [37], which randomly samples (with replacement) the minority class (absence of relapse) to be of the same size as the majority class (presence of relapse) (Figure 1).

Therefore, the metrics used in this study are the following:

- Balanced precision: the quality of a positive prediction made by the model. Precision refers to the

number of true positives divided by the total number of positive predictions (i.e., the number of true positives plus the number of false positives).

- Balanced recall: the ability of a model to find all the relevant cases within a data set. Recall refers to the number of true positives divided by the number of true positives plus the number of false negatives. In binary classification, recall is called sensitivity or true positive rate.
- Balanced accuracy: the percentage of correct predictions for the test data.
- F1 balanced metric: The F1 score is the 2*((precision*recall)/(precision+recall)). It is also called the F Score or the F Measure. The F1 score conveys the balance between precision and recall.

Having used the ROC metric in training the model, the optimal cut-off was appropriately investigated, and the performance metrics have been calculated using this cut-off (and not the default one equal to 0.5) [38].

The statistical analyses have been performed using the caret package in R, version 4.1.0 [39].

3. Results

3.1 Characteristics of the population used for Model Building

For the present study, the 171 patients managed at the Bolzano Regional Hospital from 1998 and 2019 were analyzed. After the exclusion of 5 patients without complete data, the final dataset was composed of 166 patients. Medical examinations were conducted between 1998 and 2020. The number of medical examinations for each patient varies from a minimum of 1 to a maximum of 10. The median follow-up was 520.5 (range, 23 days – 11.8 years). About 2/3 of the patients (65.7%) showed at least one recurrence during the study observation and therefore the outcome variable is unbalanced. Demographic and clinical characteristics of patients included in this study are described in table 1.

Socio-demographic variables	
Female gender, No (%)	15 (9.0)
Age at diagnosis (years)	67.9 (9.27)
HCC diagnosis	
Type of HCC diagnosis, No (%)	
Unknown	1 (0.6)
Surveillance	62 (37.0)
Causal	73 (44.0)
Symptomatic	30 (18.1)
Patient's medical history	
Alcohol, No (%)	
No	53 (31.9)
Yes	109 (65.7)
not evaluated	4 (2.4)
HBsAg, No (%)	
Negative	152 (91.6)
Positive	14 (8.4)

anti-HCV, No (%)	
Negative	123 (74.1)
Positive	43 (25.9)
Comorbidities	
BMI, No (%)	
not known	25 (15.1)
Underweight	1 (0.6)
normal weight	52 (31.3)
Overweight	69 (41.6)
Obesity	19 (11.4)
Previous obesity (BMI> 30), No (%)	
No	107 (64.5)
Yes	21 (12.7)
not evaluated	38 (22.9)
HCC staging at time T0, No (%)	
Child-Pugh Score	
A	138 (83.1)
B	25 (15.1)
C	3 (1.8)
MELD	9.7 (3.47)
BCLC, No (%)	
A	65 (39.2)
B	30 (18.1)
C	64 (38.6)
D	7 (4.2)
HCC treatments	
HCC main treatment/therapy, No (%)	
Curative	94 (56.6)
Palliative	58 (34.9)
Other/unknown	14 (8.4)
Outcome variable	
Recurrence, No (%)	
Absent	57 (34.3)
Present	109 (65.7)

Quantitative variables were expressed as mean (SD), qualitative variables as number (%) unless otherwise specified.

Table 1: Demographic and clinical characteristics of the patients.

3.2 Selection of the Most Suitable Model Building

In general, in the ML models, it is possible to define a specific function to choose the optimal tuning parameters. By default, the algorithm chooses the tuning parameter associated with the "best" performance (in our case the largest). Moreover, it is possible to use the "one standard error" rule of Breiman et al. [4], who suggest that the tuning parameter associated with the best performance may overfit. They advise that the simplest model within one standard error of the empirically optimal model is the better choice. All the models adopted in this study have been trained both with the "best" rule and with the "one standard error" rule explained above.

The k-NN is an algorithm used in pattern recognition for the classification of objects based on the characteristics of the objects close to the one considered. It is the simplest algorithm among those used in machine learning [36]. In our study, the model selected with the "best" rule and with the "one'" rule coincide and the tuning parameter selected is equal to 1. If the tuning parameter k is equal to 1 then the object is assigned to the class of its neighbour. In this specific case, it is called "the nearest neighbour algorithm". Table 2 shows that the k-NN is inaccurate for our data ($0.5 < AUC \leq 0.7$). It was expectable as it is known from the literature that this model produces not accurate results. This model was considered as a benchmark for this study.

	K-NN (oneSE = best)	RF (best)	RF (oneSE)	SVM (best)	SVM (oneSE)	ENET (best)	ENET (oneSE)
Computational time (seconds)	13.51	509.45	338.39	254.06	248.52	1,042.82	911.28
Tuning parameters	k = 1	mtry = 11	mtry = 5	C = 3.8	C = 2.84	alpha = 0.942 lambda = 0.013	alpha = 0.706 lambda = 0.044
Balanced precision	0.586	0.685	0.65	0.587	0.587	0.666	0.73
Balanced recall	0.581	0.685	0.665	0.593	0.593	0.6	0.716
Balanced accuracy	0.581	0.685	0.665	0.593	0.593	0.6	0.716
F1 balanced	0.584	0.685	0.658	0.59	0.59	0.631	0.723
AUC value	0.587	0.712	0.641	0.564	0.564	0.551	0.614

Table 2: Machine Learning models results

According to the Random Forest (RF) model trained with the "best" rule, there seems to be overfitting. The mtry equal to 11 seems too high, loosing quite a bit in terms of model accuracy. According to this, the model trained with the "one standard error" rule seems to be faster even if something is lost in terms of test set accuracy (Table 2). In general, the model trained with the "best" rule seems a moderately accurate model in the test set ($0.7 < AUC \leq 0.9$). The Support Vector Machine (SVM) is a useful classification technique in machine learning. SVM identifies the optimal decision boundary that separates data points from different groups and then predicts the class of new observations based on this separation boundary (hyperplane) [36]. The two SVM models ("best" and "oneSE") yield the same results in terms of performance (precision, recall, F1, and accuracy). Compared to the Random Forest, the SVM model seems inaccurate in the test set ($0.5 <$

AUC ≤ 0.7). Finally, Elastic Net (ENET) is a regularized regression method that linearly combines the penalties of the LASSO and RIDGE methods (lambda value). In addition to setting and choosing a lambda value, the elastic net also allows to optimize the alpha parameter, where α = 0 corresponds to the ridge regression and α = 1 to the lasso regression [36]. Compared to the others, ENET seems to be the model that takes the longest to converge to a solution (Table 2). Moreover, it seems inaccurate in the test set (0.5 < AUC ≤ 0.7).

3.3 Performance of the Recurrence P of the Most Suitable Model Building

According to the obtained results, the Random Forest model seems to be the most suitable for our data (AUC value: 0.712). The variable importance analysis was assessed using the average decrease in the nodes' impurity measured by the Gini index during the construction of the random forest model [36]. Age at diagnosis, (Model for End-Stage Liver Disease) (MELD), anamnestic obesity, type of diagnosis, BMI, and BCLC were the six most important variables for recurrence prediction found in this analysis since they are associated with the highest Gini importance. To better understand the effects of the most important variables over classification results, the partial dependence plots [36] for the top 5-predictors have been explored (Figure 2). These plots give a graphical depiction of the marginal effect of a variable on the class probability. Greater y-values indicate that observation for a specific variable is associated with a higher probability for classifying new instances as recurrence. For age at diagnosis the Partial Dependence Plot (PDP) shows an increasing probability from about 50 to 70 years and then a decreasing probability. Conversely, lower MELD score is associated with a higher probability for a relapse (Figure 2). Moreover, surveillance or a casual diagnosis of the HCC is associated with a higher relapse probability compared to symptomatic diagnosis, as well as the absence of previous obesity (Figure 2). A low BMI is associated with a higher recurrence probability. Finally, a higher recurrence probability was also demonstrated for BCLC stage B patients. The learning curve is a plot that relates the accuracy of the learning system (ROC in our case) and the number of training examples used for learning [5]. The learning curve is useful for many purposes including comparing different algorithms, choosing model parameters during design, adjusting optimization to improve convergence, and determining the amount of data used for training. The learning curve (Figure 3) shows that as the training set increases, the quality of the prediction improves (ROC). Therefore, it may make sense to increase the number of cases to improve the performance of the model and make it more generalizable on new data.

4. Discussion

Artificial intelligence and machine learning have the potential to revolutionize the management of cancer patients by predicting their clinical course and outcome. In the past two years, AI methods have been published for the prediction of overall survival and treatment outcomes in HCC. To date, however, there are few clinical prognostic factors capable of predicting HCC recurrence. For this reason, we have performed this study with the aim to establish a new ML model for predicting outcome of HCC patients. ML models are capable to include a large amount of clinical, histological, radiological as well as molecular variables compared to traditional statistical models. The most important challenge in using ML is the careful selection and validation of algorithms to create

a predictive model In this study, considering a large number of variables (socio-demographic, diagnosis of HCC, patient's medical history, comorbidities, residual liver function, HCC staging at diagnosis, treatments), including patients` outcome, we developed a supervised ML model to predict HCC recurrence. Moreover, six variables that can predict the recurrence of HCC, regardless of the type of treatment, have been identified. Among the three non-parametric models (Random Forest (RF), Support Vector Machine (SVM) and K-Nearest Neighbors (KNN)) and the parametric one (ENET) adopted, the Random Forest algorithm appears to be the most suitable for predicting the risk of HCC in our data. The six most important variables predicting HCC recurrence according to this model are age at diagnosis, MELD, the absence of previous obesity, type of diagnosis, BMI, and BCLC stage. According to our model instead, the type of treatment does not appear among the most predictive parameters. In our study, the likelihood of HCC recurrence increases from age 50 to 70 and then decreases. Cho E. et al. [40] described distinct clinical features among elderly HCC patients that could explain this finding. Elderly patients with HCC had fewer HCC nodules than younger patients and less liver fibrosis [40]. Furthermore, cancers in elderly patients tend to be more encapsulated, well-differentiated, and associated with less vascular invasion [40]. However, the size of HCC nodules in elderly patients was larger than that found in younger patients most likely due to the absence of regular HCC surveillance [40]. According to the model used, patients who did not have previous obesity and were underweight have a higher probability of HCC recurrence. Although this finding may be unexpected, 88% of the population in our study developed HCC on cirrhosis, and sarcopenia is a well-known characteristic of cirrhotic patients. Chang KV et al. [41] demonstrated that muscle loss is associated with increased all-cause mortality and tumor recurrence in HCC patients. Furthermore, we found that lower MELD values are associated with a higher likelihood of recurrence while both surveillance and random diagnosis of HCC are associated with a higher likelihood of recurrence. These results could be determined by the small sample size and the characteristics of our population. Survival in patients with chronic liver disease and successfully treated HCC is mainly affected by early hepatic decompensation (cit.). Longterm preservation of liver function may allow for the emergence of HCC and therefore of initiating a specific treatment (cit.). Finally, the learning curve shows that as the training set increases, accuracy improves. This could be promising for increasing sample size and obtaining more generalizable models in an independent data set. The present study had several limitations. The analysis of the results may have been limited by the sample size. Second, the few histological data may not emerge as a prognostic factor. In conclusion, AI and the models obtained with ML, analyzing a large number of variables, could provide predictive models that help predict the risk of recurrence. This study represents a "proof of concept" (also given the large number) and it opens the way to other studies with a larger number of patients, which also allows for differentiation by type of treatment.

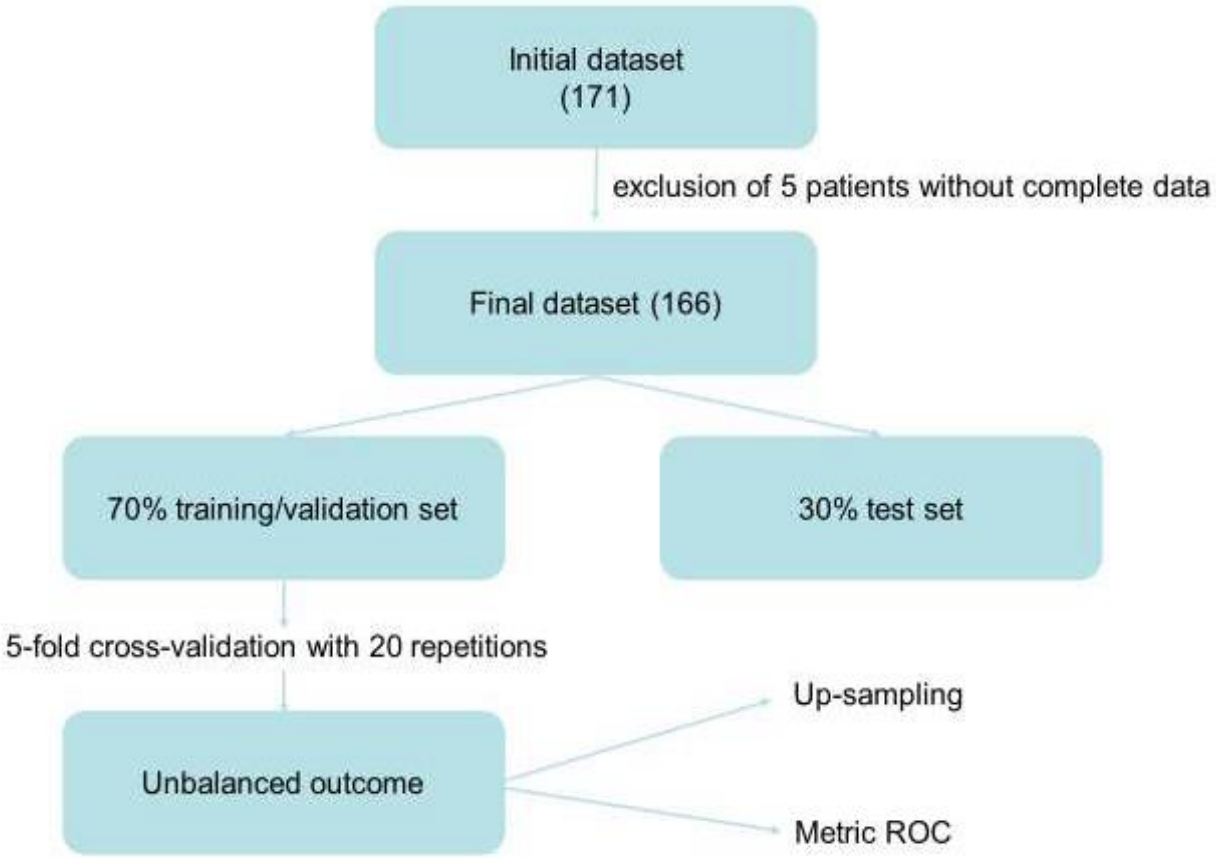

Figure 1: Model Building of Machine Learning

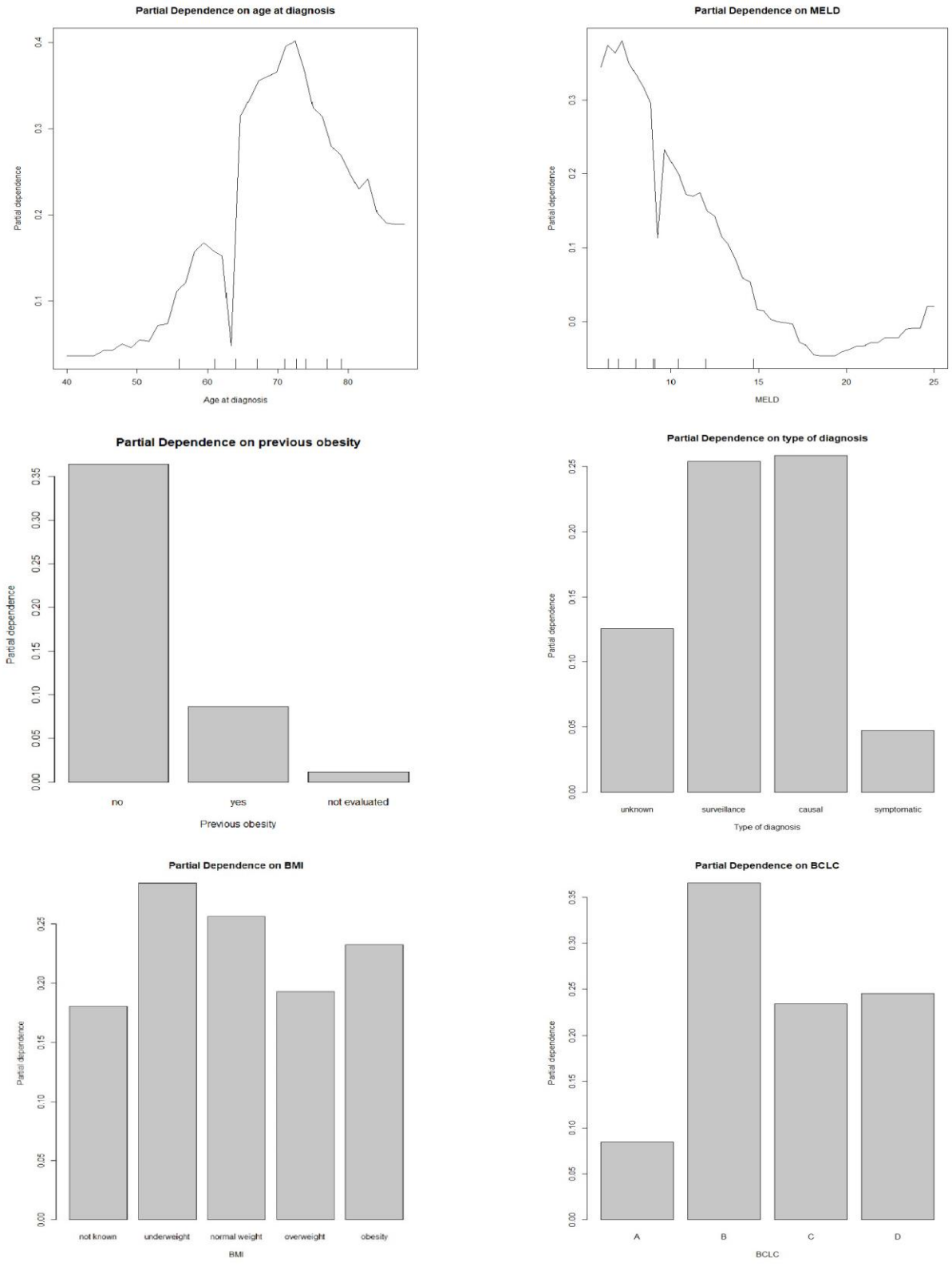

Figure 2: Partial dependence plots

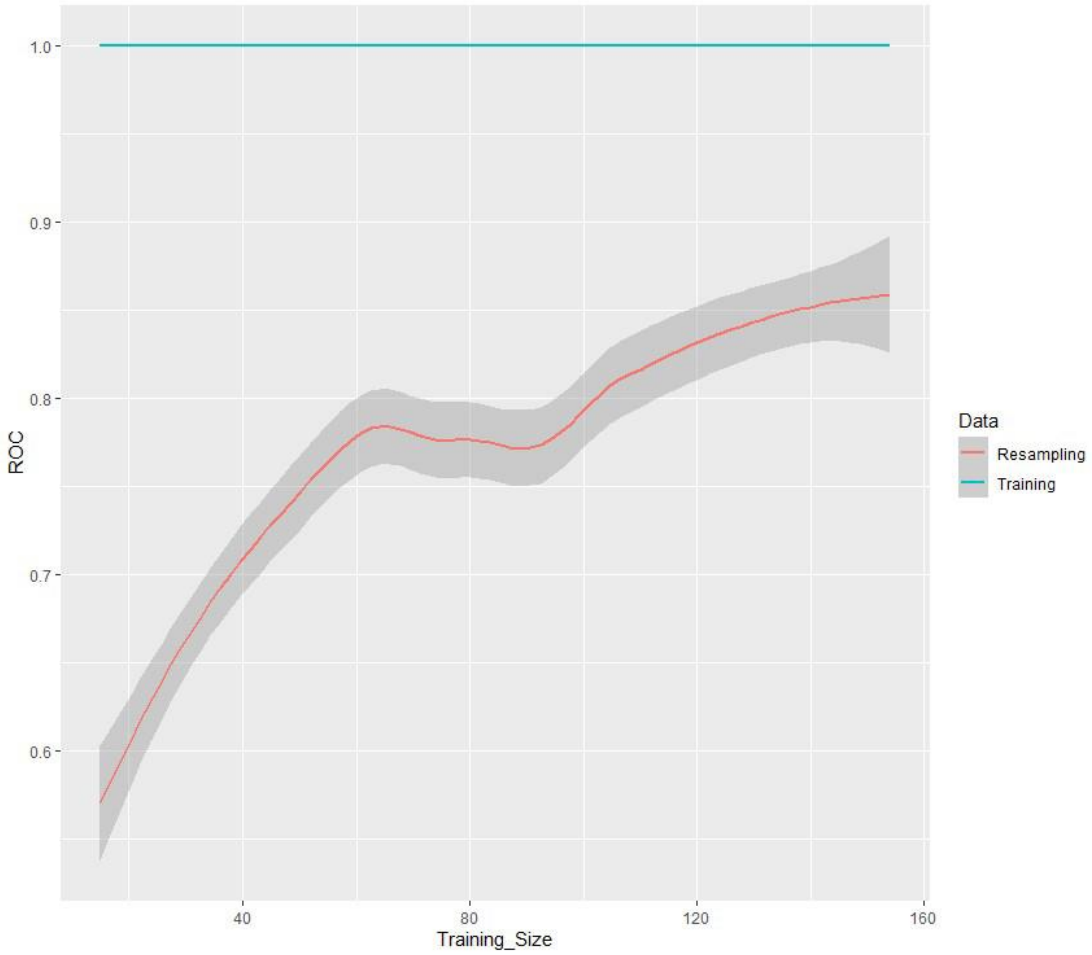

Figure 3: The learning curve of the Random Forest model

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