Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

Explainable boosting machine approach to identifying risk factors for Parkinson's disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Risk factors
Explainable boosting machine

Received: Jul 29, 2024
Accepted: Sep 03, 2024
Available Online: 26.09.2024

DOI:
10.5455/annalsmedres.2024.07.155

Abstract

Aim: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms. The diagnosis and management of PD have been significantly impacted by recent advancements in epidemiology, genetics, biomarkers, and therapeutic approaches. This study aimed to identify potential risk factors for PD and assess their contribution to PD risk using the Explainable Boosting Machines (EBM) model, a machine learning approach.

Materials and Methods: The dataset utilized in this research, accessible to researchers, comprised 2105 individuals and included 32 clinical and laboratory predictors across various categories, along with a response feature indicating PD diagnosis (yes/no). Statistical analyses, such as the Mann-Whitney U and Pearson chi-square tests, were conducted to determine significant differences between PD diagnosis groups.

Results: The study identified several predictors as significantly different between the groups, including age, sleep quality, diabetes, depression, tremor, rigidity, bradykinesia, postural instability, and scores from assessment scales like UPDRS, MoCA, and Functional assessment. The EBM model effectively classified PD cases, demonstrating high accuracy, sensitivity, specificity, AUROC, and positive-negative predictive values. The "UPDRS" score emerged as the most influential predictor in the model, with higher scores indicating an increased risk of PD.

Conclusion: Future research, with more samples and predictors, can delve deeper into the interaction of these predictors and explore the potential for developing targeted interventions for PD prevention and management.

Introduction

Parkinson's disease (PD) is a degenerative ailment of the nervous system that worsens with time. It is marked by a combination of symptoms affecting movement and other bodily functions. The diagnosis and management of PD have been greatly influenced by recent progress in epidemiology, genetics, biomarkers, and therapy techniques. PD has a prevalence rate of 1-2 cases per 1,000 individuals, and this rate tends to rise as people become older [1].

Advancements in the study of PD have had a significant influence on how we diagnose and treat the condition. This emerging area of study explores the fundamental processes (pathophysiology) of the illness, the circumstances that cause it (etiology), and possible treatments. An important objective is to identify dependable biomarkers for PD. These have great potential for aiding in the early detection of diseases, monitoring how they develop over time, and assessing the effectiveness of treatments. Research on biomarkers, especially in biofluids such as cerebrospinal fluid (CSF) and blood, has made substantial progress. These indicators can identify the present stage of a disease, estimate the speed at which it will proceed, and perhaps predict the future clinical course [2, 3].

Significantly, the progress in machine learning and deep learning algorithms is being used to enhance the precision of diagnoses and forecast how patients will respond to certain treatments [4]. These innovative methods provide a look into the future of detecting and diagnosing the early stages of PD. The implications of the epidemiological discoveries go beyond a more profound understanding of PD. They facilitate the advancement of customized medical approaches, customizing treatment tactics based on the specific characteristics of each patient. Moreover, these breakthroughs show great potential for developing disease-modifying treatments that can decelerate or completely stop the evolution of PD, eventually reducing the substantial burden that this neurodegenerative sickness imposes

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on people and healthcare systems [5-7].

Although the exact cause of Parkinson's disease is not known, certain factors are thought to increase the risk of the disease: age, gender, genetic factors, environmental factors, consumption of dairy products, melanoma history and traumatic brain injury [8].

This study aimed to predict possible/candidate risk factors for PD and determine their contribution to PD risk by using the Explainable Boosting Machines (EBM) model, which is one of the machine learning models that has recently been used in the health field.

Materials and Methods

Data set

In this study, the "Parkinson's Disease Dataset Analysis" (https://www.kaggle.com/datasets/rabieelkharoua/parkinsons-disease-dataset-analysis), [9] which is open access to researchers in the Kaggle environment, was used. Since this study was conducted on a publicly available clinical data set, Ethics Committee approval is not required. The data set, which includes candidate risk factors and assessment scale scores for PD prediction, consisted of 2105 individuals, 32 clinical-laboratory predictors (in 6 sub-categories, presented in Table 1), and one response feature (PD Diagnosis; Yes/No). The gender distribution of the participants was 1068 (50.7%) males and 1037 (49.3%) females. The age distribution of all participants was 69.6±11.6 years.

Basic statistical analyses

Shapiro-Wilk normality test was first applied for the quantitative predictors in the data set. Mann-Whitney U and Pearson chi-square tests were applied according to predictor types to determine whether there was a statistically significant difference between PD diagnosis groups. $p \leq 0.05$ type I error level was accepted and statistical analyses were performed in R (version 4.1.2) software.

Predictor preprocessing for modeling

Outlier analysis was applied for the numerical estimators in the data set without missing data. Multiple Imputation by Chained Equations (MICE) based LightGBM algorithm was applied for outlier detection. The optimal predictor selection process was applied to determine the ones that contribute the most to the modeling among the 32 estimators in total. For this task, XGBoost-based permutation importance analysis was performed. Python (version 3.10.0) software and the miceforest [10] and PiML [11] libraries were used in this stage.

EBM modelling

The EBM [12] is a sophisticated machine learning model that effectively models patterns in data sets and also in a way that outputs can be easily interpreted. EBM combines decision trees, generalized additive linear models, and boosting techniques to construct explainable predictions which allow researchers to understand the model's decision-making process. It also can improve model prediction and interpretation performance by automatically detecting and incorporating the binary interaction terms of the predictors into the model. The EBM model can explain the contribution to model performance on a sample basis. Explainable sample-based estimates are important in the context of disease prediction because the role of individual effects on model performance can be observed and, more importantly, understanding the model's individual estimates on a person-by-person basis helps detect errors and improve the model. By understanding why some estimates are wrong, the model can be improved. EBM, which has recently been frequently used especially in health applications, is preferred by researchers due to its high prediction performance, explainable outputs, and reasonable modeling time. EBM can be expressed in the following form:

$$g(E[y]) = \beta_0 + \sum \int_j (x_j)$$

Where g is the link function that fits the additive model to regression or classification. $\int_j$ is feature function is learnt by EBM using boosting technique.

To test the learning performance of the EBM model, the dataset was randomly divided into two parts, 80% training and 20% testing. The training data set was used to train the EBM model, while the test data set was used to test model prediction performance. The processes at this stage were realized using the InterpretML [12] library in Python.

Evaluation of model performance

Accuracy, sensitivity, specificity, positive-negative predictive values, and area under the Receiver Operating Characteristics (ROC) curve (AUROC) metrics were used to evaluate the model classification performance. These are metrics that are often used in binary classification tasks and more details can be found in the following study [13].

Results

The descriptive statistics of the predictors according to the distribution of PD and related p-values are presented in Table 1. According to the table, there is a statistically significant difference between the diagnostic groups in terms

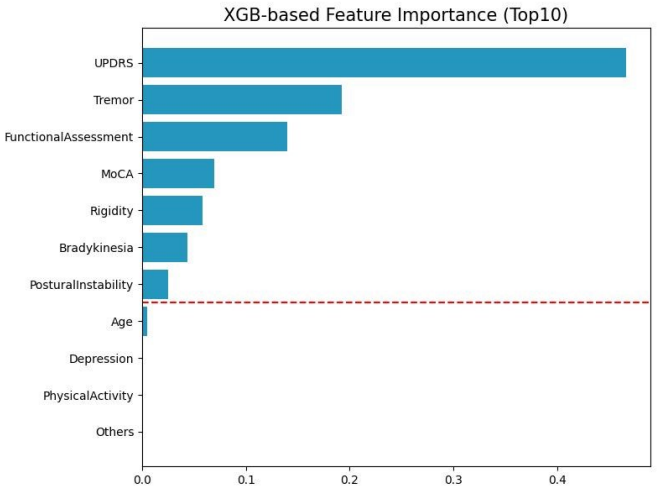

Figure 1. The selected predictors by the XGB-based Feature Importance feature selection algorithm.

Table 1. Descriptive and inferential statistical outputs for the predictors.

Predictor	Predictor*		PD diagnosis No (*n* = 801)	PD diagnosis Yes (*n* = 1304)	*p***
Demographics	Age		68 (21)	71 (19)	0.003
	Gender				
		Male	415 (51.80%)	653 (50.10%)	0.44
		Female	386 (48.20%)	651 (49.90%)	
	Ethnicity				
		Caucasian	490 (61.20%)	780 (59.80%)	
		African American	150 (18.70%)	275 (21.10%)	0.46
		Asian	73 (9.10%)	124 (9.50%)	
		Other	88 (11.00%)	125 (9.60%)	
	Education level				
		None	154 (19.20%)	234 (17.90%)	
		High school	312 (39.00%)	528 (40.50%)	0.861
		Bachelor's	250 (31.20%)	406 (31.10%)	
		Higher	85 (10.60%)	136 (10.40%)	
Lifestyle indicators	BMI		26.75 (12.52)	27.48 (12.68)	0.17
	Smoking				
		No	566 (70.70%)	915 (70.20%)	0.81
		Yes	235 (29.30%)	389 (29.80%)	
	Alcohol consumption score		9.73 (9.73)	10.51 (9.59)	0.098
	Physical activity score		4.9 (5.04)	5.14 (5.06)	0.564
	Diet quality score		4.86 (5.12)	4.77 (4.77)	0.297
	Sleep quality score		7.05 (2.97)	6.88 (3.05)	**0.047**
Patient history	Family history of Parkinson's disease				
		No	689 (86.00%)	1109 (85.00%)	0.54
		Yes	112 (14.00%)	195 (15.00%)	
	Traumatic brain injury				
		No	723 (90.30%)	1158 (88.80%)	0.29
		Yes	78 (9.70%)	146 (11.20%)	
	Hypertension				
		No	680 (84.90%)	1118 (85.70%)	0.6
		Yes	121 (15.10%)	186 (14.30%)	
	Diabetes				
		No	703 (87.80%)	1090 (83.60%)	**0.009**
		Yes	98 (12.20%)	214 (16.40%)	
	Depression				
		No	661 (82.50%)	1012 (77.60%)	**0.007**
		Yes	140 (17.50%)	292 (22.40%)	
	Stroke				
		No	768 (95.90%)	1234 (94.60%)	0.19
		Yes	33 (4.10%)	70 (5.40%)	
Laboratory measurements	Systolic blood pressure		133 (46)	134 (46.5)	0.846
	Diastolic blood pressure		91 (30)	90 (29.5)	0.187
	Total cholesterol		228.01 (75.05)	228.76 (75.13)	0.379
	Low-density lipoprotein		125.85 (79.24)	127.54 (72.18)	0.507
	High-density lipoprotein		60.62 (38.59)	58.78 (40.62)	0.372
	Triglycerides		220.36 (176.92)	224.65 (180.59)	0.469
Symptoms	Tremor				
		No	594 (74.20%)	602 (46.20%)	**<0.001**
		Yes	207 (25.80%)	702 (53.80%)	
	Rigidity				
		No	681 (85.00%)	892 (68.40%)	**<0.001**
		Yes	120 (15.00%)	412 (31.60%)	
	Bradykinesia				
		No	711 (88.80%)	957 (73.40%)	**<0.001**
		Yes	90 (11.20%)	347 (26.60%)	
	Postural instability				
		No	742 (92.60%)	1071 (82.10%)	**<0.001**
		Yes	59 (7.40%)	233 (17.90%)	
	Speech problems				
		No	559 (69.80%)	925 (70.90%)	0.58
		Yes	242 (30.20%)	379 (29.10%)	
	Sleep disorders				
		No	600 (74.90%)	989 (75.80%)	0.627
		Yes	201 (25.10%)	315 (24.20%)	
	Constipation				
		No	575 (71.80%)	905 (69.40%)	0.245
		Yes	226 (28.20%)	399 (30.60%)	
PD assessment measures	UPDRS+		48.58 (93.55)	120.2 (78.26)	**<0.001**
	MoCA++		18.19 (16.23)	13.41 (14.26)	**<0.001**
	Functional assessment - PSFS+++		6.22 (4.34)	4.15 (4.87)	**<0.001**

*: Predictors were summarized as median (Interquartile range).
**: *p* values which are ≤0.05 expressed as bold. Mann-Whitney U and Pearson chi-square tests were used for numerical and categorical predicto
to calculate *p* values, respectively.
+: Unified Parkinson's Disease Rating Scale.
++: Montreal Cognitive Assessment.
+++: Patient-Specific Functional Scale.

Table 2. Classification matrix for the prediction results of the EBM model.

Model prediction (PD)	Actual diagnosis (PD)		Total
	No	Yes	
No	**134**	*16*	150
Yes	*16*	**255**	271
Total	150	271	421

Note: Cells with bold numbers true classification, cells with italic numbers represent misclassification.

Table 3. Classification performance metrics of the EBM model.

Metric	Value (95% CI*)
Accuracy	0.92 (0.89 – 0.95)
Sensitivity	0.94 (0.90 – 0.97)
Specificity	0.89 (0.83 – 0.94)
Positive Predictive Value	0.94 (0.91 – 0.96)
Negative Predictive Value	0.89 (0.84 – 0.93)
AUROC	0.95 (0.92 – 0.97)

*: Confidence interval.

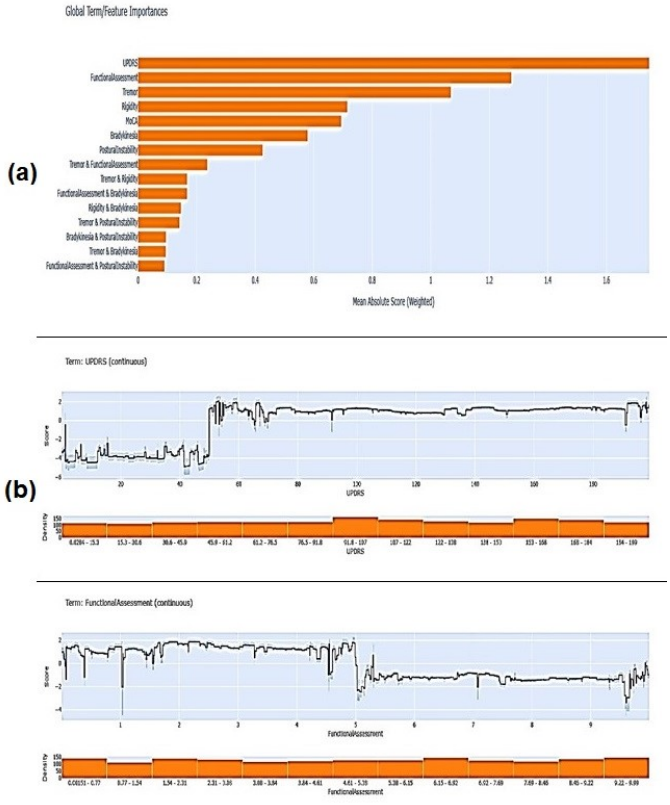

Figure 2. Predictor importances (a), line and density plots of how the PD prediction was affected by changes in the values of the "UPDRS" (b) and "Functional assessment" predictors.

of "Age" in the "Demographic" category. In the "Lifestyle indicators" category, there is a significant difference in terms of "Sleep quality" predictor. In the "Patient history"

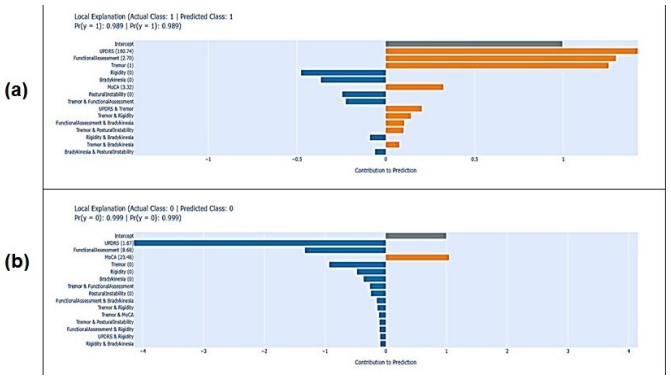

Figure 3. Predictors contributing to the classification of two PD-positive (a) and PD-negative (b) samples by the EBM model.

group, "Diabetes" and "Depression" predictors are statistically significant. In the "Symptoms" category, significant differences were found for the predictors "Tremor", "Rigidity", "Bradykinesia" and "Postural instability". Significant differences were found between the diagnostic groups for all predictors ("UPDRS", "MoCA" and "Functional assessment") in the "PD Assessment measures" category.

There were no missing values in the data set. In addition, the LightGBM-based MICE algorithm was applied for outlier detection in the quantitative predictors, but no outlier was detected. After applying the predictor selection method, 7 out of 32 predictors ("UPDRS", "Tremor", "Functional assessment", "MoCA", "Rigidity", "Bradykinesia" and "Postural instability") were selected by the XGB-based Feature Importance feature selection algorithm (Figure 1).

Table 2 shows the classification matrix of the trained EBM model on the test dataset. The EBM model correctly classified 389 and misclassified 32 out of the test dataset of 421 participants.

Table 3 presents the evaluation of the PD classification performance of the EBM model with various metrics. The values were obtained using the classification matrix presented in Table 2. The 95% confidence intervals of the metrics were also reported.

In Figure 2 (a), the importance levels (weighted mean absolute score) of the predictors used in training the EBM model were presented. According to the related plot, the "UPDRS" was found to be the predictor with the highest feature importance score. In Figure (a), the predictors reported in binary with "&" symbol are the interaction terms of the related predictors. Figures 2 (b) and (c) show line and density plots of how the PD prediction is affected by changes in the values of the two predictors with the highest feature importance scores. Increases in the "UPDRS" score beyond a value of around 50 appear to increase the risk of PD. Also, it is noticed that the risk of PD decreases at values after about 5 of the "Functional assessment" score.

Figure 3 shows the sample-wise predictions of the EBM model and the relative contribution of the predictors to predictions. Figure 3 (a) shows the sample with positive PD in the actual data (Actual class: 1) and predicted by the EBM model as positive PD (Predicted class: 1). The

probability of PD positive for the relevant sample was estimated at 0.98. It is noticed that "UPDRS" and "Functional assessment"are the first two predictors that play an important role in the positive prediction of the EBM model. For this sample, the "UPDRS" value is calculated as 180.74 and the "Functional assessment" value is calculated as 2.7. Figure 3 (b) shows the sample with negative PD in the actual data (Actual class: 0) and predicted by the EBM model as positive PD (Predicted class: 0). The probability of PD negative for the relevant sample was estimated at 0.99. For this sample, the "UPDRS" value was calculated as 1.87 and the "Functional assessment" value was calculated as 8.68.

Discussion

In this study, statistical inference methods and EBM, an explainable machine learning model, were used together to investigate the predictive ability of various categories of predictors in predicting PD. In this context, firstly, it was investigated whether there was a statistically significant difference between PD diagnosis groups in terms of 32 predictors in total. At the end of this process in which Mann-Whitney U and Pearson chi-square tests were used, significant differences were found between PD diagnosis groups in terms of "Age", "Sleep quality", "Diabetes", "Depression" "Tremor", "Rigidity", "Bradykinesia", "Postural instability", "UPDRS", "MoCA", and "Functional assessment" predictors.

The fact that the median age in the PD positive group was significantly higher than the median age in the PD negative group reveals that age is a natural risk factor for PD, which is also known as an aging-associated disease. Sleep quality score was significantly lower in the PD-positive group. A meta-analysis study [14] conducted in 2020 revealed that individuals with PD have poor sleep quality. However, the calculated p-value close to the type-I error level and the median score difference of 0.77 between the two groups may suggest that sleep quality is a low effect size predictor of PD.

When analyzed in terms of the presence of diabetes, there was a higher proportion of samples with diabetes in the PD-positive group compared to the PD-negative group. Studies found that people with type 2 diabetes have a higher risk of developing Parkinson's disease [15, 16]. Although statistically significant, it was observed that the "Diabetes" predictor was not selected by the predictor selection phase. This may be attributed to the low effect size (Phi coefficient = 0.057) of the "Diabetes" predictor. The presence of depression is one of the risk factors for PD, with one study showing that the risk of developing PD was 3.24 times higher in patients with depression [17]. However, similar to the "Diabetes" predictor, it was not entered into the model in the predictor selection analyses, possibly because it is a low effect size (Phi coefficient = 0.059) predictor.

When Tables 2-3 are considered together, it is seen that the EBM model shows an acceptable classification performance. In the model where 32 out of 421 individuals were classified incorrectly, it is seen that all performance metrics had values of 0.89 and above.

In terms of the "Tremor" predictor, a significant difference was found between the groups and it was the 3rd most important predictor contributing to the PD diagnosis classification of the EBM model. Tremors in various parts of the body are one of the most prominent visual symptoms of PD and that severely reduce the quality of life in patients [18]. In addition to tremor being an important marker of PD, it is also important to identify the source of tremor. For this, machine learning-driven approaches have been used in the classification of essential/parkinsonian tremor [19, 20].

Along with "Tremor", previous studies revealed that "Rigidity", "Bradykinesia" and "Postural instability" are classical and important markers of PD that are considered in clinical assessment [21-23]. The outputs from the EBM model showed that after "Tremor", these 3 predictors were the symptoms that contributed most to the classification performance of the model and the increased risk of PD. In addition, as can be observed in Figure 2 (a), the binary interactions of these symptoms were also included in the training process by the EBM model, but it was observed that the single effects of these symptoms contributed more to the model prediction performance.

UPDRS [24] is a comprehensive scale used commonly to assess the severity and progression of Parkinson's disease. This scale assesses the different dimensions of the PD (motor, behavioral, sensory, etc.), providing physicians and researchers with a clearer point of view. In this study, PD diagnostic groups were found to be statistically different in terms of UPDRS. In addition, UPDRS was the predictor that contributed the most to the classification performance of the EBM model. Although there is no universal cut-off point for total UPDRS score in predicting PD, when considered together with other risk factors examined in this study, it can be stated that the risk of PD increases in samples with a total score of 50 and above (Figure 2 (b)).

PSFS [25] is a subjective measurement tool used to assess a patient's functionality in activities of daily living. It is especially preferred in individuals with musculoskeletal problems [26]. Furthermore, studies have revealed that the PSFS is an informative and useful tool for PD assessment [27, 28]. As can be noticed from the EBM results, individuals with a PSFS total score of 5 and above were found to have an increased risk of PD (Figure 3 (c)).

The MoCA [29] scale is a test that can be used for early diagnosis of PD dementia by detecting cognitive impairments (such as mild memory loss, and attention deficit) [30]. A statistically significant difference was observed between PD diagnosis groups in terms of total MoCA score. When evaluated in terms of the EBM model, the model was the 5th predictor to add to the prediction performance.

Conclusion

In this study, the EBM model was employed to identify potential risk factors for PD and assess their contribution to PD risk. The EBM model effectively classified PD cases, demonstrating high accuracy, sensitivity, specificity, and positive-negative predictive values. The "UPDRS" score emerged as the most influential predictor in the model,

with higher scores indicating an increased risk of PD. Additionally, the study highlighted the importance of other predictors like tremor, functional assessment, MoCA, rigidity, bradykinesia, and postural instability in PD prediction.

Our study has some limitations, including the relatively low sample size and the lack of an external validation cohort.

Future research, with more samples and predictors, can delve deeper into the interaction of these predictors and explore the potential for developing targeted interventions for PD prevention and management. In addition, the generalizability and reliability of the EBM model's outputs may increase with multicenter studies.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

Since this study was conducted on a publicly available clinical data set, Ethics Committee approval is not required.

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