Risk factors analysis of depression in early stage of Parkinson’s disease

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Abstract. Parkinson's disease (PD) is the second-most common neurodegenerative disease and affects about 2-3% of the population of age 65 years or over, worldwide. One of the symptoms that often occurs in patients with PD is depression in about 40-50% of them and is very common in early stages of the development of PD. Numerous studies have been conducted with various results in identifying risk factors for depression in PD patients. While, the mechanism of depression is not yet known in detail in PD patients. In this study, a decision tree method was used to differentiate PD patients who underwent depression from those who did not and identify risk factors associated with the depression. We propose the Synthetic Minority Over-sampling Technique (SMOTE) to handle imbalanced class in the data. Data on 257 patients with early stage of PD in the Parkinson's Progression Markers Initiative (PPMI) database were used. The overall important risk factors associated with depression in patients with early-stage of PD are alpha synuclein (α-syn) levels, gender, SEADL (Schwab & England - Activities on Daily Living) score, STAI (State & Trait Anxiety Inventory) - State score, putamen binding ratio on the left side of the brain, RBDSQ (REM Sleep Behaviour Disorder-Questionnaire) score, and age when diagnosed with PD. The accuracy, precision, and recall of the model are 95.18%, 92.15%, and 94.12%, respectively. Moreover, the AUC and F1 score are 0.949, and 0.9312, respectively, supporting the high accuracy of the resulting model.

1. Introduction
Parkinson's disease (PD) is a neurodegenerative brain function disorder that causes shaking, stiffness, difficulty walking, balance disorders, and impaired coordination [1]. Evidence suggests that the degeneration of striatal dopamine plays important role in motoric symptoms [2]. Although PD is still considered as a motor disorder, it is also known to cause non-motoric symptoms, including anhedonia and depression, cognitive disorder, autonomic dysfunction, hyposmia, and sleeping disorder [3]. In this paper, we will focus on examining factors that might explain depression, a symptom that often occurs in PD.

Depression is a common and serious medical illness and negatively affects how a person feels, thinks, and acts [4]. Depression occurs in about 40-50% of PD patients and is very common in early stages of the development of PD [5]. Previous research has established that the mechanism of depression is not yet known in detail in PD patients [6].

Data mining has been widely used in the medical field in identifying and validating risk factors associated with depression in PD, such as the use of logistic regression to compare the relationship between depression incidence and at age of diagnosis, PD duration, and disease staging [7].
addition, logistic regression also yields a comparable accuracy with other classification methods [8-10]. Other methods that also have been shown to produce high accuracy in classification problem related to medical data are support vector machines (SVM) [11], random forest [12], naïve Bayes classifier [13], and decision tree [14].

Logistic regression method could handle the linear relationship of variables well, but it is not optimal to overcome the effects of the interaction between variables. While, the mechanism of decision tree can automatically detect and incorporate the interaction that might occurs among the measurements, which a common condition in medical health data. While it is criticised for the tendency of overfitting, a cautious pruning technique could overcome the problem [15]. Hence, decision tree method is proposed to better handle the interaction effect between variables. It is also easier in terms of interpretation of results compared to other classification algorithms, flexible enough to handle numeric and categorical variables, and can handle missing values. This method can also model many data partitions that is not easily achieved by other classification methods that depend on one decision [16]. Besides, the results of the model provide clear information about the factors that are significant in prediction or classification [17].

Since depression is very common in early stages of the development of PD, this will cause the problem of imbalanced data. This condition might have caused the model to learn less from the minority class, resulting in the model to failing to predict each class properly (especially the minority class) and might reduce the model’s performance [18]. Some rebalancing strategies could be used to handle this problem, such as over-sampling and under-sampling. However, over-sampling might likely to cause overfitting since it increases the amount of minority class by duplicating samples. On the other hand, under-sampling method might remove valuable information from majority class since it reduces the amount of majority class by removing samples. Hence, we used Synthetic Minority Over-sampling TEschnique (SMOTE) to handle imbalanced data class as it is not just blindly duplicate the data, but by generating “synthetic” data in minority data classes based on the k-nearest neighbour principle [19]. This method outperformed the over- and under-sampling methods in handling imbalanced data, as showcased in [20].

Motivated by the above-mentioned outcomes, in this paper, we propose to implement decision tree method to differentiate PD patients who experienced depression from those who did not, and further identify risk factors related to the depression in PD patients, as well as a Synthetic Minority Over-sampling TEschnique (SMOTE) to handle imbalanced class in the data. The remainder of the paper is organized in the following parts. Section 2 briefly describes the material (data set) and methods used in our work. Section 3 details experimental results and discussion and finally this paper is summarized in Section 4.

2. Method
2.1. Data
Data of 257 PD patients, consisting of 11 not depressed and 246 depressed at stage 1 – 2 (measured by Hoehn & Yahr Staging) were obtained from the Parkinson's Progression Markers Initiative (PPMI) database as of per-8 January 2020. PPMI is a prospective, longitudinal study designed to identify PD progression biomarkers as mentioned on the website https://www.ppmi-info.org. In total, we use 22 features, regarding demography, motor, non-motor, Dopamine Transporter scanning (DAT Scanning), and levels of Cerebrospinal Fluid (CSF). Depression was assessed using the 15-item Geriatric Depression Scale (GDS), with a recommended cut-off score of ≥ 5 to indicate the presence of clinically significant depressive symptoms [21]. The demography of the patients included gender, age at diagnosis of PD, and family history with PD. Motoric performances were assessed using Schwab & England – Activities on Daily Living (SEADL), Tremor Dominant (TD) subtype, and Prominent Bradykinesia and Gait Instability (PIGD) subtype.

Non-motoric performances were using Scales for Outcomes in Parkinson’s Disease – Autonomic Dysfunction (SCOPA-AUT) for autonomic dysfunction, Montreal Cognitive Assessment (MoCA) for global cognitive abilities, and State-Trait Anxiety Inventory (STAI) for State and Trait
anxiety. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP) was used to screen for ICD and compulsive behaviour. Sleeping disorders included Rapid Eye Movement (REM) Sleep Behaviour Disorder and Excessive Daytime Sleepiness (EDS) were assessed using REM Sleep Behaviour Disorder-Questionnaire (RBDQS) and Excessive Sleepiness Scale (ESS), respectively. Dopamine Transporter scanning (DAT Scanning) measures the level of Dopamine Transporter (DAT) availability in right and left of putamen and caudate. While Cerebrospinal Fluid (CSF) included the levels of amyloid-beta 142 (αβ-142), alpha-synuclein (α-syn), tTau, and pTau.

2.2. Decision tree

Decision tree is a supervised learning method that splits data into several subgroups such as branches. This method produces a model in the form of a hierarchical tree structure and graph that is easy to interpret. Since the objective of this study is to predict whether a PD patient is having a depression or not, then we use classification tree. Figure 1 shows an example of decision tree and its structure.

![Decision Tree Diagram](image-url)

**Figure 1.** Segments in the dataset created by decision tree (left) and structure of a decision tree (right)

Classification tree is built by partitioning the dataset according to a series of rules, or questions. These splits are chosen by choosing a point in the features to be the splitting point that would result in a more homogenous class. In this study, the feature as the splitting rule are chosen based on Gini index criterion. Suppose there is a data set $D$, namely training data at node $D$. The Gini index which measures the impurity of $D$ as follows,

$$Gini(D) = 1 - \sum_{i=1}^{m} p_i^2.$$  \hspace{1cm} (1)

A split on a feature that produces the highest Gini index difference between the parent and child nodes is sought. To stop the tree from growing too complex, we used several stopping criteria, that is achieving class homogeneity, the minimum number of observations for the terminal node is less than 20/3, or the threshold for Gini index difference for a split is 0.01 \cite{22}. The terminal node will stop splitting if either one of those criteria is fulfilled. After the tree was built, we determine the class for each terminal node where the majority class will be set as the label for terminal node.

Classification problems are evaluated using confusion matrix, where the result of the class predictions is compared with the actual class \cite{23}. From this confusion matrix, evaluation metrics can be derived to assess the performance of the classification model, in this study, we used Accuracy, Precision, Recall, and F1-score. Accuracy evaluates the overall efficiency of the model. However, accuracy can be a misleading evaluation measure when the data class is imbalanced because more weights are placed on the majority class than on the minority class making it more difficult for a classifier to perform well on the minority class \cite{24}. Hence, we used recall to measure the proportion of correctly identified positive classifications is classified as positive. Precision, on the other hand, measure the model’s exactness. While, F1-score conveys the balance between the precision and recall. Table 1 shows confusion matrix.
Table 1. Confusion matrix

|                  | Predicted Negative | Predicted Positive | Total       |
|------------------|--------------------|--------------------|-------------|
| Actual Negative  | True Negative (TN) | False Positive (FP)| TN + FP     |
| Actual Positive  | False Negative (FN)| True Positive (TP) | TP + FN     |
| Total            | TN + FN            | TP + FP            | TP + FP + TN + FN |

The calculation below shows how the score of accuracy, precision, recall, specificity, and F1-score were obtained.

\[
\text{Accuracy} = \frac{TP + TN}{TP + FP + TN + FN} \quad (2)
\]

\[
\text{Precision} = \frac{TP}{TP + FP} \quad (3)
\]

\[
\text{Recall} = \frac{TP}{TP + FN} \quad (4)
\]

\[
\text{Specificity} = \frac{TN}{TN + FP} \quad (5)
\]

\[
F1 - \text{score} = 2 \times \frac{\text{precision} \times \text{recall}}{\text{precision} + \text{recall}} \quad (6)
\]

Other evaluations are the ROC graph, that is a two-dimensional graph with a true positive rate (recall) on the Y axis and a false positive rate (1 - specificity) on the X axis. To compare between the models, it is possible to evaluate the ROC performance by converting it to a single scalar value, namely the Area Under ROC Curve (AUC). The higher AUC, the better the performance of the model at distinguishing between the positive and negative classes.

2.3. Synthetic Minority Over-sampling Technique (SMOTE)

In this section, we briefly discuss the use of SMOTE to handle imbalanced class data. This method deals with the problem of imbalanced data classes by generating “synthetic” data in minority data classes based on the k-nearest neighbor principle. To find its nearest neighbor, Euclidean distance is used for numerical features, while Value Difference Metrics (VDM) is used for categorical features [11].

Synthetic samples for numeric data are generated in the following way: Take the difference between the feature vector (sample) under consideration and its nearest neighbor. Multiply this difference by a random number between 0 and 1 and add it to the feature vector under consideration. This step is taken to generate a particular value between two given observations within the given range. While, for categorical data, we can create new synthetic samples by taking the majority vote of the feature vector under consideration and its nearest neighbors. Figure 2 shows the illustration of SMOTE.
In this study, we use five nearest neighbors ($k = 5$) [11]. For instance, if the amount of over-sampling ($\alpha$) needed is 300%, the amount of generated synthetic minority class observation is three times as before. If we under-sample the majority class ($\gamma$) at 200%, it would mean that the modified dataset will contain twice as many elements from the minority class as from the majority class. For example, if we have 10 samples from minority class and 200 samples from majority class, we generate 30 synthetic samples or three times (300%) as before in minority class and we under-sample majority at 200%, the minority class would end up having 40 samples and majority class having 60 samples.

2.4. Study design
To summarize what will be done in the next data analysis, we will use R software using `rpart` package for decision tree method [22] and `DMwR` package for SMOTE method [25]. Data of 257 PD patients, consisting of 11 not depressed and 246 depressed with 22 features, consisting of 16 numerical features and 6 categorical features will be analyzed. For SMOTE rebalancing strategy, we will use 3 schemas to generate synthetic sample on minority class using different parameters of $\alpha$ and $\gamma$, where schema 1 use over-sampling only, while both of schema 2 and 3 also use under-sampling with different $\gamma$ parameters. Furthermore, the decision tree model will be applied directly to the entire schemes of the SMOTE parameters and validated using the Leave-One-Out Cross Validation (LOOCV). The most optimum model will be evaluated based on model performance measures, such as precision, recall, AUC, and F1-score.

3. Result and Discussion
3.1. Descriptive statistics
Demographic and clinical features of the study sample are presented in Table 2. Numerical features are summarized using the mean and standard deviation (SD), and categorical features are summarized by the percentage of the existing category.

Based on the above table, in average, depressed PD patients has slightly higher RBDQs score for Rapid Eye Movement (REM) Sleep Behavior Disorder. This leads to the hypothesis that depression PD patients might have higher RBDQs score. On the other hand, notice that male PD patients with depression, in average, has higher $\alpha$-syn levels compared to male PD patients with no depression. This also leads to the hypothesis that the interaction among gender and $\alpha$-syn levels might occur, which a common condition in medical health data. Hence, we will use decision tree method for further analysis.
Table 2. Demographic and clinical features of the study sample.

|                      | %     | Mean (SD) |
|----------------------|-------|-----------|
| **Demography**       |       |           |
| Female               | 31.5  |           |
| Age at diagnosis with PD (yrs) | 64.0 (9.5) |   |
| Family history with PD | 22.1  |           |
| **Motoric assessment** |      |           |
| Tremor Dominant (TD) | 48.2  |           |
| PIGD                 | 23.7  |           |
| SEADL Score          | 88.5 (7.2) | |
| **Non-motoric assessment** |     |           |
| Depression (target)  | 95.7  |           |
| SCOPA-AUT score      | 12.2 (6.5) | |
| STAI-State score     | 31.6 (9.8) | |
| STAI-Trait score     | 32.0 (9.2) | |
| MoCA score           | 26.2 (3.0) | |
| ICD                  | 24.1  |           |
| Compulsive behaviour | 0.8   |           |
| RBDQ5 score          | 6.7 (3.5) | |
| (Depressed)          | 6.8 (3.5) | |
| (Non-depressed)      | 6.1 (3.4) | |
| ESS score            | 6.5 (4.1) | |
| **DAT Scanning**     |       |           |
| Left putamen         | 0.6 (0.2) | |
| Right putamen        | 0.6 (0.3) | |
| Left caudate         | 1.6 (0.4) | |
| Right caudate        | 1.6 (0.5) | |
| **Cerebrospinal Fluid (CSF)** | | |
| αβ-142               | 890.0 (433.1) | |
| α-syn                | 1424.9 | |
| (Male, depressed)    | 1390.7 (578.0) | |
| (Male, non-depressed)| 1200.8 (319.8) | |
| tTau                 | 169.1 (61.8) | |
| pTau                 | 14.2 (5.6)  | |

3.2. Decision tree model without SMOTE rebalancing strategy

In this section, data analysis using decision tree method before rebalancing strategy using SMOTE method. Table 3 shows the confusion matrix while Table 4 shows the performance evaluation of the model.

Table 3. Confusion matrix before rebalancing strategy using SMOTE method

| Status     | Actual          |         |
|------------|-----------------|---------|
|            | Non-depressed   | Depressed |
| Predicted  | Non-depressed   | 0       | 0       |
|            | Depressed       | 11      | 246     |

Table 4. Evaluation of decision tree model performance before rebalancing strategy using SMOTE method

| Accuracy  | Precision | Recall | AUC | F1-Score |
|-----------|-----------|--------|-----|----------|
| 0.957     | N/A       | 0      | 0.500 | N/A      |
Based on Table 4, it shows that even though the model has high accuracy, the model cannot predict the minority class, that is, the non-depressed patients in PD. It may have caused the classification model to be not able to predict the non-depressed class properly because there is not much data to learn to. This may have caused the model to miss-predicted all the non-depressed class as seen on Table 3. This result suggests the need for a balanced data for the model to be able to learn. Thus, we proceed with the SMOTE procedure to generate synthetic data for the minority class prior to conducting the classification process. The result is presented in the subsequent section.

3.3. Decision tree model with SMOTE rebalancing strategy

Table 5 shows the performance evaluation of the models with different parameters of SMOTE.

Table 5. Evaluation of decision tree model performances after rebalancing strategy using SMOTE method

| Schema | α   | γ   | Accuracy | Precision | Recall | AUC   | F1-score |
|--------|-----|-----|----------|-----------|--------|-------|----------|
| 1      | 400 | -   | 0.8173   | N/A       | 0      | 0.5000| N/A      |
| 1      | 800 | -   | 0.9188   | 0.8515    | 0.8687 | 0.9040| 0.8600   |
| 1      | 1200| -   | 0.9126   | 0.8428    | 0.9371 | 0.9180| 0.8874   |
| 1      | 1600| -   | 0.8845   | 0.8374    | 0.9091 | 0.8870| 0.8718   |
| 1      | 2000| -   | 0.8302   | 0.7435    | 0.9913 | 0.8350| 0.8497   |
| 2      | 400 | 100 | 0.9198   | 0.8889    | 0.9697 | 0.9170| 0.9275   |
| 2      | 800 | 100 | 0.9055   | 0.8874    | 0.9371 | 0.9040| 0.9116   |
| 2      | 1200| 100 | 0.9201   | 0.8762    | 0.9840 | 0.9180| 0.9270   |
| 2      | 1600| 100 | 0.9047   | 0.8643    | 0.9654 | 0.9030| 0.9121   |
| 3      | 400 | 200 | 0.9231   | **0.9583**| 0.8364 | 0.9070| 0.8932   |
| 3      | 800 | 200 | 0.9382   | 0.9362    | 0.8889 | 0.8927| 0.9119   |
| 3      | 1200| 200 | 0.9312   | 0.8808    | 0.9301 | 0.9310| 0.9048   |
| 3      | 1600| 200 | 0.9518   | 0.9215    | 0.9412 | **0.9490**| **0.9312**|
| 3      | 2000| 200 | 0.9329   | 0.8875    | 0.9221 | 0.9300| 0.9045   |

According to Table 5, we can see that decision tree model with SMOTE (α = 1600, γ = 200) has the most optimum model performance among 3 schemas and produced the accuracy, precision, recall, AUC and F1-score of 95.18%, 92.15%, 94.12%, 0.949, and 0.9312, respectively. High accuracy shown that the model is quite good to do classification. As well as precision, out of all predicted non-depressed PD, 92.15% were non-depressed PD patients. While, recall shown that out of all actual non-depressed PD patients, the model correctly predicted as much as 94.12%. F1-score also shown that the model has relatively balanced precision and recall values. Furthermore, AUC of 0.9312 shown that the model has quite high of recall value and quite low of FPR value. Figure 3 shows the output decision tree model. Based on the Figure 3, seven out of 22 features were selected as the most important ones to explain the incidence of depression in PD patients. Alpha synuclein (α-syn) levels was selected as the most important feature since α-syn levels have a positive correlation with the development of depression in PD, where α-syn may affect the transporter activity of dopamine, serotonin and norepinephrine and is associated with neurogenetic disorders in the hippocampus [26]. PD patients who are likely to be depressed are the ones who have α-syn levels ≥ 1601 (terminal node 1), or female patients who have α-syn levels ≥ 1601 (terminal node 2), or female patients who have α-syn levels ≥ 1601 and SEADL score < 80 (terminal node 3), etc. Note that the terminal node 2 produced the purest result, as 100% of the node is depressed patients, as well as for terminal node 5. These might be the most important ones and need to be recommended to check.
4. Conclusion

In this paper, we used a decision tree method combined with SMOTE for imbalanced data. We identified risk factors that associated with depression in patients with early-stage of PD: alpha synuclein (α-syn) levels, gender, SEADL (Schwab & England - Activities on Daily Living) score, STAI-State score, putamen binding ratio on the left side of the brain, RBDSQ (REM Sleep Behaviour Disorder-Questionnaire) score, and age at diagnosis of Parkinson's. We also generated profiles for those who are likely to develop depression. The model’s result is satisfactory, as we reached high accuracy, recall, precision, F1-score, and AUC.

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