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Dynamic Prediction of Excessive Daytime Sleepiness Through Random Survival Forest: An Application of the PPMI Data

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Abstract

Parkinson's disease (PD) is the second most widespread neurodegenerative disease worldwide. Excessive daytime sleepiness (EDS) significantly correlates with de novo PD patients. Identifying predictors is critical for the early detection of disease. We investigated clinical and biological markers related to time-dependent variables in sleepiness for early detection of PD. Data were obtained from the Parkinson's Progression Markers Initiative study, which evaluates the progression markers in patients. The dataset also includes various longitudinal endogenous predictors. The measures of EDS were obtained through the Epworth Sleepiness Scale (ESS). The random survival forest method, which can deal with multivariate longitudinal endogenous predictors, was used to predict the probability of having EDS in PD. The rate of having EDS among PD patients was 0.452. The OOB rate was 0.186. The VIMP and minimal depth indicated that the most important variables are stai state, JLO, and the presence of the ApoE4 Allele. In early PD, EDS is a good indicator of the diagnosis of the PD and it increases over time and has associations with several predictors.

1. Introduction

Parkinson's disease (PD) is one of the most widespread age-related neurodegenerative diseases worldwide [1]. Although this complex disease is defined by its motor symptoms, non-motor symptoms are quite common and mostly more visible than motor symptoms. Lack of sleep and wakefulness during the day are among the most widespread non-motor symptoms (NMS). Excessive daytime sleepiness (EDS) impacts 16% to 74% of subjects with PD and increases with the duration of the disease and severity [2]–[4]. This symptom has a negative effect on life quality ([2], [5]), and the clinical symptoms of PD differ by disease duration, cognitive impairment, autonomic dysfunction, gender, age, depression, anxiety, and severe motor symptoms [6]–[8]. EDS is a considerably significant variable, especially in moderate to advanced PD compared to healthy controls (HC) [2], [3].

The existence of EDS has a negative impact on cognitive impairment and the development of a higher risk of dementia [9]. The baseline characteristics regarding EDS in cohort de novo untreated Parkinson patients and HC in the Parkinson Progression Markers Initiative (PPMI) [10] concluded that there was no significant difference between the two groups. EDS was measured with the Epworth Sleepiness Scale (ESS) and defined as true if ESS ≥ 10. There are few studies to assess EDS in de novo PD patients [11]–[13]. Each of them has very

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small data, with less than 25 de novo PD patients and one HC. All of them have the same conclusion: EDS does not have a negative impact on untreated PD patients. However, more up-to-date studies indicated that EDS is a part of NMS [14], [15]. Therefore, the uncertainty remains regarding EDS in de novo patients. Abbott et al. [16] stated that EDS is one of the risk factors for developing PD.

So far, there have been very few empirically published accounts of longitudinal change in EDS in PD patients. Tholfsen et al. [17] investigated it in 153 de novo subjects with PD and concluded that the patients with PD had significantly more EDS over time. Breen et al. [7] found that the prevalence of EDS has risen over time. Amara et al. [18] examined the association between clinical, imaging, and biological variables and longitudinal changes in EDS over time with the comparison of HCs. No previous studies have examined the patient-specific risk of PD related to individual longitudinal changes over time. In light of this gap, we aimed to characterize the biological and clinical factors associated with EDS in PD through the investigation of longitudinal trajectories amongst patients in the cohort study.

When the longitudinal and event time processes are associated in the dynamic prediction context, joint modelling is the most effective way to cope with this relationship [19]. Joint models (JM) model the longitudinal and event-time outcomes simultaneously via shared random effects. The method was first developed by Wulfsohn and Tsiatis [20] and extended by Henderson [21]. The method is investigated in detail with the methodological development and advances in [22]. The methodology for the incorporation of multivariate longitudinal data is extended in [23]–[25]. Due to the complexity of the method and the computational burden, the method has been limited to only 2-3 longitudinal biomarkers. Therefore, this brings us to the dynamic prediction with large-dimensional longitudinal predictors: the competing risk random survival forest [26], [27]. Random forest is a common method applied in many disciplines [28], [29]. Random survival forest (RSF) is accurately predicts the event risk and has become widespread since it has the capability of handling a variety of covariates. Nevertheless, this method has been unable to incorporate time-dependent predictors. Thus, Devaux et al. [30] proposed an alternative way to RSF with multivariate longitudinal time-dependent covariates.

This study set out to develop a model for individual dynamic prediction of EDS, associated with clinical and biological factors in the PPMI cohort.

The rest of the paper is organized as follows: Section 2 introduces the material and method, listed under two subheadings: the PPMI data and random forest for time-dependent predictors. Section 3 presents results and discussion, and the final section concludes the study.

2. Material and Method

2.1. The PPMI Data

The PPMI is a comprehensive observational, international, multicenter study that is designed for the identification of PD progression biomarkers for the improvement of understanding the disease etiology and to provide key tools to improve the likelihood of success of PD-modifying therapeutic trials. The PPMI aims to provide a wide research community with a standardized, longitudinal dataset and biosample library. The PPMI cohort includes 168 de novo PD patients, and they were followed up for 2 years [10]. Detailed information regarding the study's procedures and inclusion and exclusion criteria is available at the PPMI website, https://www.ppmi-info.org. The dataset is available upon registering and requesting to access data on the aforementioned website, and downloaded on April 1, 2023.

The data are collected at baseline and annually thereafter. Patients were evaluated with the ESS [31], a measure of EDS, where a maximum score of 24 indicates the worst degree of sleepiness. This test has a significant test-retest correlation [32]. The ESS also has a strong correlation with the sleepiness measures in PD [33], [34] and is sensible to switch due to an intervention [35]. The patients were categorized as having EDS when ESS is greater than or equal to 10 and having severe EDS when ESS is greater than or equal to 17 [31]. In addition to ESS, the patients were assessed with the motor symptoms, Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [36]. Non-motor symptoms comprise the Montreal Cognitive Assessment (MoCA) [37], the Hopkins verbal learning test (HVLT) [38], the Benton judgment of line orientation test (JLO) [39], the symbol digit modalities test (SDMT) [40], the University of Pennsylvania smell ID test (UPSIT) [41], the REM Sleep Behaviour Disorder Screening Questionnaire

(RBDSQ) [42], and the State-Trait-Anxiety Inventory (STAI) state and trait sub-scores [43].

2.2. Method: Random Forest for Time-Dependent Predictors

We first consider a dataset of N subjects consisting of Y the outcome, $\mathcal{M}_x$ an ensemble of P time-independent covariates, and $\mathcal{M}_y$ an ensemble of Q time-dependent covariates. In principal, random forest includes an ensemble of B trees and aggregated to obtain predictions.

2.2.1. The Tree Building

The tree building aims at the recursive partition of the individuals into the most homogeneous nodes/groups. For each tree, b $(b = 1, 2, \dots, B)$ h a bootstrap sample from N subject is drawn with a replacement. The individuals that are excluded by the bootstrap comprise the out-of-bag (OOB) sample, OOB^b. At each node $d \epsilon \mathcal{D}^b$, the following steps utilizing $N^{(d)}$ are repeated recursively:

1. A random subset of covariates $\mathcal{M}^{(d)} = \left\{\mathcal{M}_x^{(d)}, \mathcal{M}_y^{(d)}\right\} \subset \{\mathcal{M}_x, \mathcal{M}_y\}$ is selected to improve accuracy and minimize the correlation between trees. The size of $\mathcal{M}^{(d)}$ is called tuning parameter, mtry.
2. For each time-dependent variable in $\mathcal{M}_y^{(d)}$:
   a. The linear mixed effect model proposed by Laird and Ware [44] is employed at each node d.
   b. An ensemble of $\mathcal{M}_{y\star}^{(d)}$ of subject time-fixed variables is derived.
3. New ensemble of candidate variables $\mathcal{M}_\star^{(d)} = \left\{\mathcal{M}_x^{(d)}, \mathcal{M}_{y\star}^{(d)}\right\}$ is defined.
4. For each candidate variable $W \in \mathcal{M}_\star^{(d)}$:
   a. A series of splits $c_W^{(d)}$ is built according to the values of the variable that leads each time into two groups.
   b. The distance between two groups is calculated.
5. The subjects are split into two groups: those that maximize the test statistic for survival outcomes or those that minimize the test statistic for categorical and continuous outcomes. The optimal couple is denoted as $\{W_0^d, c_0^d\}$ and this represents the left and right daughter nodes, $2d$ and $2d + 1$, respectively.
6. Step 1 to 5 are repeated on the daughter nodes till the stopping criteria are met.

Two stopping criteria to pursue with the stopping of a node are defined: nodesize, a minimal number of individuals in each of the daughter nodes and minsplit, a minimal number of events. Once the stopping criteria is met, the node is counted as a terminal node or leaf $h \in \mathcal{H}$.

In each leaf, a summary $\left(\pi^{h^b}\right)$ is presented utilizing the subjects of the leaf of the tree b.

2.2.2. Out-of-Bag Individual Prediction of the Outcome

The overall OOB prediction $\hat{\pi}_\star$ for an individual $\star$ is found through the tree-based predictions of $\star$ as below:

$$\hat{\pi}_\star = \frac{1}{|\mathcal{O}_\star|} \sum_{b \in \mathcal{O}_\star} \hat{\pi}^{h_\star^b} \quad (1)$$

where $|\mathcal{O}_\star|$ represents the length of $\mathcal{O}_\star$ and $\hat{\pi}^{h_\star^b}$ denotes the Aalen-Johansen estimator in leaf $h_\star^b$ of the b. Tree.

2.3. Out-of-Bag Error

The OOB error measures the difference between the observed and predicted values. The Integrated Brier score (IBS) between τ_1 and τ_2 is defined as follows:

$$errOOB = \int_{\tau_1}^{\tau_2} \frac{1}{N} \sum_{i=1}^{N} \widehat{\omega}_i(t)\left\{\mathbb{1}_{(T_i \le t, \delta_i = k)} - \hat{\pi}_{ik}(t)\right\}^2 \mathrm{dt} \quad (2)$$

where T is the event time, k is the cause of interest, and $\widehat{\omega}$ (t) is the estimated weights, that considers censoring [45].

2.4. Variable Importance

The variable importance (VIMP) quantifies the loss of predictive performance in case of removal of the link between predictor and the response variable [27]. Such a link is broken with the permutation of the predictors at the individual level for time-independent variables and at the observation level for time-dependent variables. Large VIMP value represents good prediction ability for the predictor.

3. Results and Discussion

We aimed to predict the subject probability of having EDS in patients with Parkinson's disease using social, demographic, and clinical variables (sex, presence of the ApoE4 Allele, and baseline count of lymphocytes).

The dataset is split into two: training (2/3 of subjects) and testing (1/3 of subjects) datasets. The random forest is built by specifying the linear mixed models for each longitudinal predictor using the `DynForest` function. The outcome objects were the event indicator and event time data. For the hyperparameters, we chose `mtry=7`, `nodesize=5`, and `minsplit=2`. When the type of outcome is survival, the Fine&Gray statistic test is used as the splitting rule and the cumulative incidence function (CIF) as the leaf statistic. The assessment of the predictive ability of the model is made with the out-of-bag error (OOB). When the outcome of interest is survival, the OOB error is computed using the integrated Brier Score (IBS) [45]. The OOB error for the model is obtained from the mean of the subject-specific OOB error. The computed OOB error from the starting time to the maximum of the time-to-event is 0.186. The rate of having EDS in 168 Parkinson's patients is 0.452. It means that 76 patients have EDS and the rest do not have EDS.

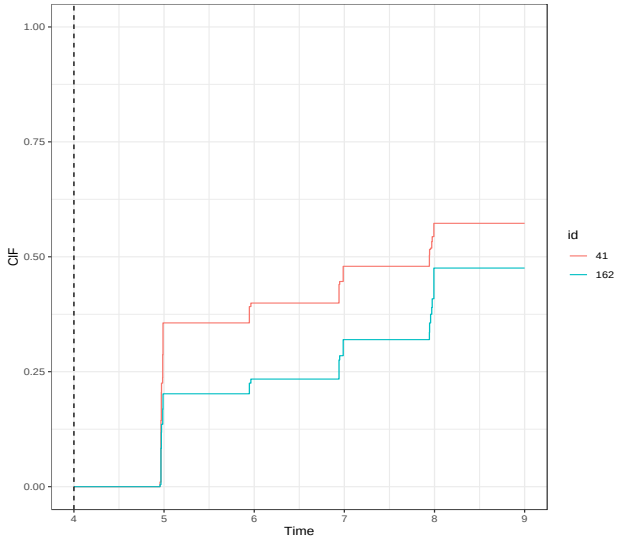

Figure 1. Predicted CIF for individual 41 and 162.

We also predict the outcome for new individuals using the trained random forest. Dynamic prediction can be made by specifying a prediction time, and landmark from which the prediction is made. Only the individuals still at risk at the landmark time (dashed vertical line, at 4 years) are selected for illustration purposes, and subject-specific CIF is predicted using dataframe for those who are at risk at 4 years. Figure 1 displays the CIF of the outcomes of individuals 41 and 162. The risk of having the event for individual 41 had a rapid rise in year 5. After 8 years from landmark time, individual 41 has a higher probability of having EDS than the other.

In order to understand the importance of the predictors, VIMP statistics are presented in Figure 2. Stai state was the most important variable, which has the association with having EDS, with an average gain in IBS of 5.2%, followed by JLO and ApoE4 Allele (gains of 3.8% and 2.5%, respectively). In the case of correlated variables, the variables may be re-grouped into dimensions, and the VIMP can be calculated at the dimension group level. Figure 3 shows that 2 non-motor predictors (stai state and stai trait) in group 2 attained a mean gain of 8.7%.

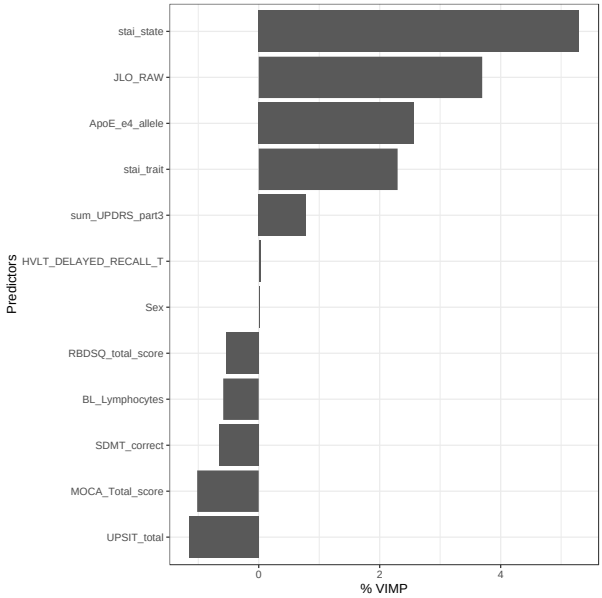

Figure 2. Importance variable.

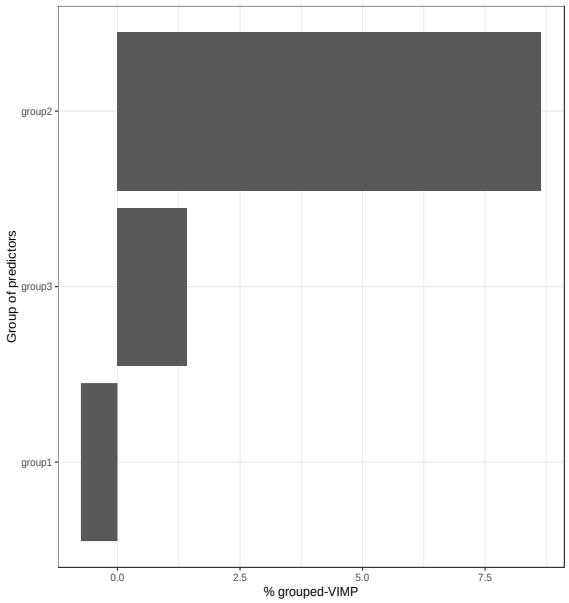

Figure 3. Grouped importance variable (gVIMP), Group1: MOCA, HVLT, JLO, SDMT, UPSIT and RBDSQ; Group2: Stai trait and stai state; Group3: ApoE4 and lymphocyte.

In order to better understand the tree-building process, the minimal depth utilizing large mtry hyper parameter is computed and shown by the predictor and feature in Figure 4. Stai trait has the lowest average minimal depth. The same inference can also be seen for the minimal depth plot regarding features. The lowest average minimal depth belongs to stai trait features. These indicate that the stai predictors are the most efficient predictors for splitting the subjects into homogenous subgroups. These outcomes can also be seen in variable importance plots.

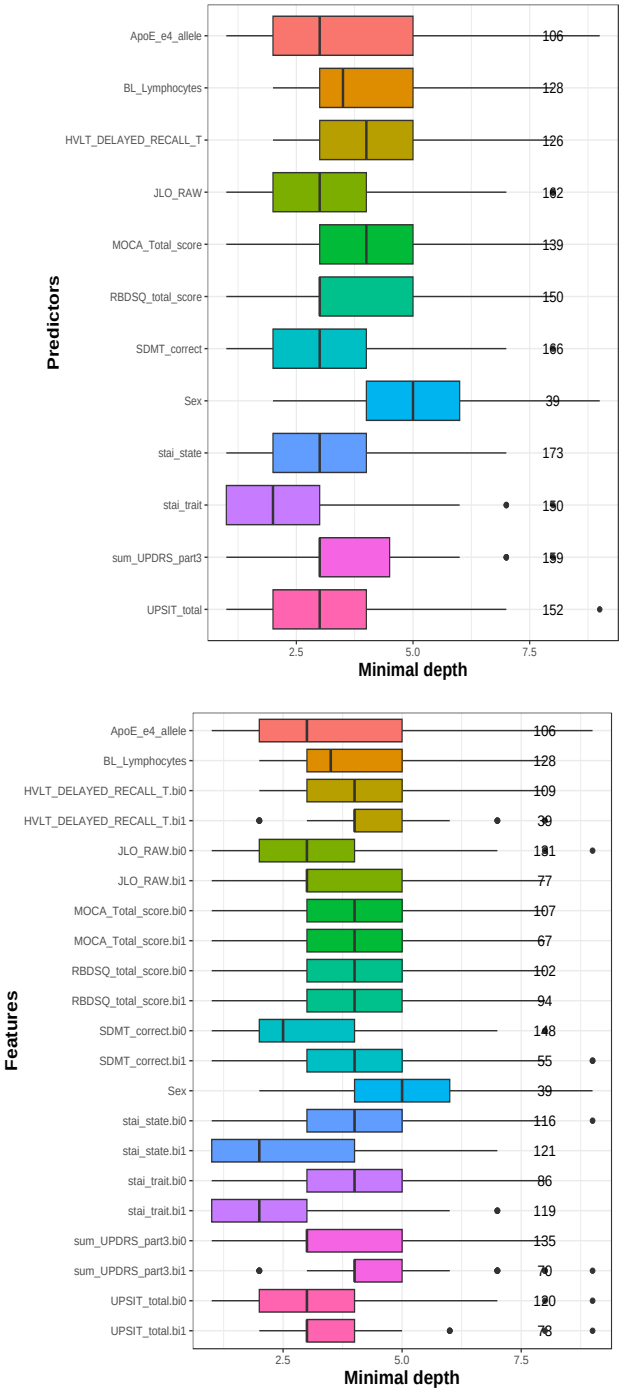

Figure 4. Average minimal depth level by predictor (upper) and feature (lower).

We computed the individual dynamic predictions accounting for multiple longitudinal predictors through the extended random survival forest method in order to deal with time-dependent predictors. The DynForest R package, which is a user-friendly R package and easy-to-use random forest methodology, is utilized to achieve this [46]. Moreover, the importance of the variables using

VIMP, grouped-VIMP and minimal depth are provided.

Some studies have investigated the EDS effect in PD. Feng et al. [47] provided a systematic review and meta-analysis related to EDS in PD. They found that approximately 35.1% of subjects with PD had EDS, and EDS in PD can have association with severe PD. To the best of our knowledge, so far, limited studies have given sufficient consideration to the impact of imaging and biological markers on EDS change over time in PD in Amara et al. [18], Höglund et al. [48], Liu et al. [49], and Pino et al. [50]. They considered the longitudinal change of EDS in patients with PD. Höglund et al. [48] investigated EDS over time associated with PD symptoms. The authors used linear mixed effect models and concluded that EDS did not worsen over the follow-up period and that EDS is a complex nonmotor symptom. This result contradicts ours. On the other hand, Liu et al. [49] and Pino et al. [50] aimed to investigate the effect of sleep problems on longitudinal changes in motor and non-motor symptoms among patients with PD. They both used linear mixed effect, and Liu et al. [49] additionally employed Cox PH models and concluded that patients with PD and have sleep problems progress faster symptoms of more aggressive types of PD. In addition to this, using more advanced methods, Amara et al. [18] implemented the random survival forest method and concluded that EDS had a significant rise over time and had associations with various clinical predictors in early PD. This result is supported by our study. Nonetheless, our study has some advantages (i) it used all available information; (ii) it has a simultaneous analysis of the longitudinal and event time processes; (iii) it allows for complication associations between repeated measurements and event time; (iv) it allows for high-dimensional data.

4. Conclusion and Suggestions

The aim of this study was to investigate individual dynamic prediction of EDS (predict the event - having EDS) with multiple longitudinal time-dependent variables in PD. We identified the most significant clinical markers of rate of progression so that this will benefit clinical care and the testing of new treatments. We also concluded that EDS has a significant effect on patients with PD. Overall, EDS is a clinical manifestation in de novo PD patients. Moreover, this study indicates that many factors, such as stai state, JLO and ApoE4 Allele are the most important variables in EDS in de novo PD patients. Understanding the clinical features of EDS is important to identify early PD and improve life quality.

The prediction model could be improved by considering discrete longitudinal markers (i.e., binary or categorical). Generalized estimated equations can be used instead of generalized mixed models.

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Statement of Research and Publication Ethics

The study is complied with research and publication ethics

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