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Understanding the Progression of Lewy Body Dementia with Longitudinal Data Modeling

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Abstract
Lewy Body Dementia is the second most common dementia type after Alzheimer's disease. The cognitive decline caused by Lewy Body Dementia affects the patients' performance in daily living and the ability to make decisions. It is critical to understand the course of the disease progression and estimate the cognitive decline trajectory for disease management and care planning. This study analyzed the factors that can be used for the Clinical Dementia Rating score estimation and developed a highly customized model using the data obtained from an existing Lewy Body Dementia database. The model will help the understanding of the course of the disease development and is proved to be robust and reliable in making estimation in cognitive decline for patients with Lewy Body Dementia.

Keywords: Lewy Body Dementia, cognitive decline, trajectory modeling

1 Introduction

Lewy body dementia is the third most common dementia in elderly people after Alzheimer's disease and vascular dementia [1], accounting for 30% of the dementia cases among the elderly over the age of 65 [2]. It is a neurodegenerative mental disease that cannot be treated and reversed in the course. This progression course of Lewy body dementia is characterized by changes in thinking and reasoning, gait imbalance, well-formed hallucination [1], delusions, and sleep disturbances besides memory loss. These Lewy body dementia significantly affects individuals' ability to perform social or occupational functions, and brings devastating consequences to the patients and their families. People need the information on how the disease would progress with time to make disease management plans and other care arrangements. It is important to understand the progression trajectory of the disease, so that physicians can give prognosis and other parties such as medical insurance or government agencies have tools to make decisions on reimbursement policies. A model that can simulate the course of cognitive decline would help people to understand the Lewy body dementia progression.

The progression course of Lewy body dementia and the neuropsychiatric symptoms as key indicators of disease progression were investigated to find the natural course of the disease. It was reported that aberrant motor behavior, aggression/agitation, delusions and irritability are less in Patients with Lewy body dementia than patients with Alzheimer's disease and a majority of patients with Lewy body dementia had reoccurring psychotic symptoms [3]. It is also argued that the presence of visual hallucinations in particular, predicted decline v. a stable cognitive trajectory [4]. These findings are very informative for predicting the cognitive decline in Lewy body dementia, however, there is no quantitative model that can describe the process of cognitive decline in Lewy body dementia, and accurately predict the disease progression.

The Clinical Dementia Rating (CDR) score is a dementia staging instrument that is an important predictor for cognitive and functional performance for patients with dementia [5]. Although past studies indicated that Mini Mental State Exam can be used to surrogate of CDR in staging of dementia, CDR compasses a more comprehensive evaluation of six domains that can be scored independently. The six domains include memory, orientation, home and hobbies, judgment and problem solving, personal care, and community affairs. CDR is a four-point Likert scale, with score range from 0 to 3. Each domain is assigned a score, and the score 0 connotes normal- no cognitive impairment and CDR-3 refers to the severe stage of dementia. The intermediate stages are: 0.5 represents 'Very Mild Dementia', 1 is 'Mild Dementia', and 2 indicates 'Moderate Dementia'. In assigning a Global CDR, six domains are scored independently and added together to construct the overall CDR table. Therefore, Global CDR scores range from 0 to 18. Table 1 is the summary of the CDR SUM score stating category table indicating the score range and the corresponding cognitive impairment level.

Table 1. CDR SUM score staging category

CDR SUM score Range	Staging Category
0	Normal
0.5–4.0	Questionable cognitive impairment
0.5–2.5	Questionable impairment
3.0–4.0	Very mild dementia(very early stage)
4.5–9.0	Mild dementia (early stage)
9.5–15.5	Moderate dementia (middle stage)
16.0–18.0	Severe dementia (late stage)

Note: The table is adapted from the study by O'Bryant et al. (2008).

The purpose of the research is to construct a descriptive and predictive model that is data driven and can help understand the progression of Lewy body dementia and predict the global CDR score for patients with Lewy body dementia. We aimed to explore patterns of Lewy body dementia progression. It is our hope to discover patterns that can provide information to families and patients how Lewy body dementia progression would impact a patient's daily life. This research was done with a purpose to define patterns of cognitive decline and propose a model of effective diagnosis for medical trials and treatments. The hypothesis of the study is that patients with certain features share similar cognitive decline process and the global CDR score can be predicted by these key features, which will be the input of the predictive model.

2 Data

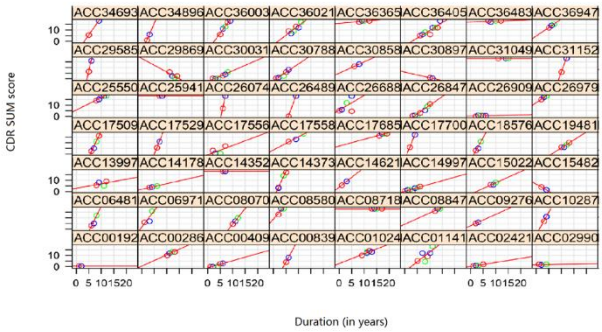
The longitudinal data used to construct the model were extracted from the National Alzheimer's Coordination Center (NACC) UDS database. The database provided comprehensive records of demographic and clinical information on recruited patients since September 2005. These patients made follow-up visits to the center through September 2015 or made contact with the center annually until they were deceased or dropped out. In NACC data, three sections are evaluated for reach diagnosis conclusion: cognitive and behavioral status, Cerebrospinal fluid biomarkers, imaging evidence, and genetic.

The training data was requested in October 2015, and the testing data was requested in June 2016. Due to the time difference of acquiring the data, we have different diagnosis codes in training data and testing data because of version update from V2 to V3. The version change of NACC data include the change of diagnosis codes as well. The previously named "NACCPRET" which is a derived variable for primary etiological diagnosis was recoded as "NACCETPR". The allowable codes were changed accordingly.

For example, in NACC UDS V.2, the diagnosis codes included "1 = Probable Alzheimer's disease", "2 = Possible Alzheimer's disease", and "3 = Dementia with Lewy bodies". In latest version V.3, there is no more "Probable" or "Possible" description. The latest diagnosis codes are "1 = Alzheimer's disease (AD) 2 = Lewy body disease (LBD) 3 = Multiple system atrophy (MSA)". The four most common types of dementia are AD, Lewy bodies, Frontomental dementia and vascular dementia. However, in V2 there are separate categories for "Probable" and "Possible" Alzheimer's disease, but in V3 there were only one code for Alzheimer's disease. So is the case with vascular dementia. In V3, frontomental dementia is divided into "FTLD with motor neuron disease (e.g., Amyotrophic lateral sclerosis (ALS))" and "FTLD, other".

Based on the diagnosis record of the very last visit, we classify the patients as different diagnosis groups. Those who had Lewy bodies were screened from all the subjects to be a best group to test the model for a specific type. There were 730 patients who had the last diagnosis as "Lewy bodies" in our requested data. Of them, 311 were deceased that can be used as training data in model building, 419 were alive, with 1559 observations, that are separated as testing data to verify the model robustness. Figure 1 is the illustration of the relationship between CDR SUM score and the duration of time since onset for 56 randomly selected patients. The duration of time since onset is calculated based on the patient visit time and recorded cognitive decline onset time. Figure 2 is the frequency chart of the CDR SUM scores of the 311patients in the training dataset. It shows all the CDR SUM scores collected during each of their visit to the center.

Figure 1. Panel Plot of 56 patients' trajectory of CDR SUM score. Each



panel is the illustration of duration and CDR SUM score. Horizontal axis is the duration since onset, and vertical axis is the CDR SUM score.

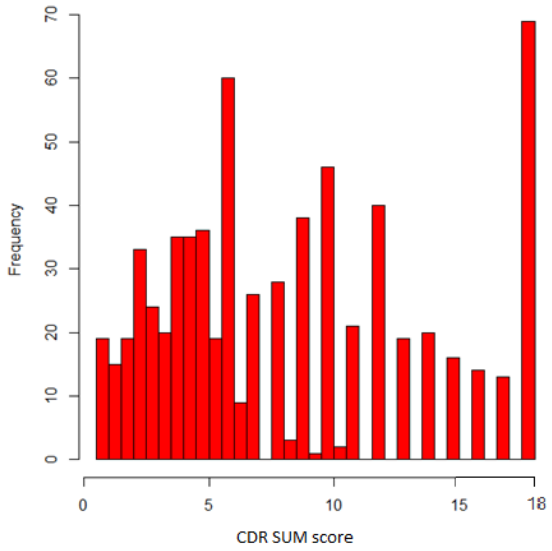


Figure 2. Histogram for observed CDRSUM values in Lewy bodies dementia. The x-axis represents actual CDRSUM value in training data, and y-axis is the frequency appeared.

3 Modeling method

Longitudinal studies have long played a critically important role in biological and social science, such as developmental psychology, behavioral science, and empirical clinical studies. Modelling for the trajectory of a longitudinal data can be referred to as growth curve model or trajectory model. These models include repetitive measurements for the same subject along with time.

The hidden mechanism of dementia pathology is very complex and the manifestation of individual performance in daily life is highly variable. Therefore, choosing the correct modelling tool can be difficult. Although several modeling methods are available to construct a model for longitudinal data, such as regression model, multilevel model [6] [7], hierarchical linear model, these modeling methods require normality assumptions. Semiparametric modeling method does not need normality assumptions and is increasingly used to capture subtle changes in longitudinal data. In semiparametric mixed effect model, ordinal variables that even in a small sample size can be fitted in nonparametric models.

This study select global CDR score as the interested indicator of cognitive decline in Lewy body dementia, which will be the dependent variable in the model. The variable is denoted as CDR SUM in the dataset and in the model. Based on the research results of past studies, we select the two types of variables that includes demographic and medical features of the patients to construct the model [7]. The time-constant variables that would be in the model are duration since the onset, sex, years of education, and onset age. The rest of factors are time-varying variables: vascular health conditions and neuropsychiatric symptoms. These factors are also available in the NACC UDS database. Duration, education level, and onset age are derived variables that were created from the dataset. Vascular health conditions included heart attack/cardiac arrest (CVHATT), transient ischemic attack (CBTIA), atrial fibrillation (CVAFIB), stroke (CBSTROKE), and diabetes (DIABETES). The 12 neuropsychiatric symptoms including delusions (DEL), hallucinations (HALL), agitation (AGIT), depression (DEPD), anxiety (ANX), elation/euphoria (ELAT), apathy/indifference (APA), disinhibition (DISN), irritability (IRR), aberrant motor behavior (MOT), nighttime behavior (NITE), and changes in appetite or the consumption of certain foods (APP). Except duration is a continuous variable, other variables are categorical variables that 0 means absent of the symptom and 1 means symptom presence during the recent visit. Three second level interaction terms were included (duration × onset age, duration × gender, and duration × education level) in the model as well based on the previous research findings in modeling the trajectory of cognitive decline in dementia [7].

Table 2. Time constant variables in the model

Time constant variable	Variable Name	Codes
Gender	SEX	1 (Male); 2 (Female)
Years of education	EduLevel	">=12 years" (above high school education) "< 12 years" (below high school education
Age at onset	Ageonset	"Young" (<=66 years old) "Middle" (>66 and <=86 years old) "Old" (>86 years old)

The proposed semiparametric model of this study has three components, the average effect of time is represented by a penalized smoothing spline. The response variable y_{ij} is assumed to depend on the combination of an average effect of time and other covariates, as shown in Equation (1).
The effect of time and other covariates on CDR SUM score (the response) is complicated. Nonlinearity itself cannot fully explain the heterogeneous shape of trajectories. Therefore, penalized spline and its mixed model representation is a good solution to feature individual profiles.

$$y_{ij} = f(t) + \sum_{q=1}^{c} \theta_k x_{iq} + \sum_{l=1}^{d} \mu_k z_{ijl} + \epsilon_i(t_{ijr}) \quad (1)$$

$f(t)$ is a panelized spline smooth function which reflects the overall trend

$$f(t) = \beta_0 + \beta_{1jr} t_{ijr} + \beta_{2jr} t_{ijr}^2 + \sum_{k=1}^{K} u_k (t_{ijr} - \mathrm{K}_k)_+^2 \quad (2)$$
$$0 < \mathrm{K}_1 < \mathrm{K}_2 < \cdots < \mathrm{K}_K < \max(\boldsymbol{t_{ijr}})$$

of CDR SUM score along with time.

The number of knots K is fixed and large enough to ensure the flexibility of the curve. $\mathrm{K}_1 \ldots, \mathrm{K}_k$ are a set of distinct fixed knots ranging from 0 to $\max(\boldsymbol{t_{ijr}})$. The knots are chosen as quantiles of t_{ijr} with probabilities

$$(t_{ijr} - \mathrm{K}_k)_+ = \begin{cases} t_{ijr} - \mathrm{K}_k & : \ if \ t_{ijr} - \mathrm{K}_k > 0 \\ 0 & : \ if \ t_{ijr} - \mathrm{K}_k \geq 0 \end{cases} \quad (3)$$

1/(K+1), … ,K/(K+1). We use truncated lines as the basis for regression. In Equation (2), u_k refers to the weight of each linear function and $(t_{ijr} - \mathrm{K}_k)_+$ refers to the the *k*th linear function with a knot at K_k.

Referring back to the regression model, the basis of the spline model for $\boldsymbol{f(t)}$ is

$$[1 \quad t_{ijr} \quad t_{ijr}^2 \quad (t_{ijr} - \mathrm{K}_1)_+ \quad \ldots \quad (t_{ijr} - \mathrm{K}_k)_+ \quad (t_{ijr} - \mathrm{K}_1)_+^2 \ldots (t_{ijr} - \mathrm{K}_k)_+^2] \quad (4)$$

In semiparametric mixed effect model, there is possibility that systematic within-subject correlation exists. In other words, we assume the outcome variable has more correlation if the observations are closer in time collected. The way to express the correlation can be through the random effect for the intercept and the random effect for the slope. We allow this correlation effect by defining an exponential correlation function in the term $\epsilon_i(t_{ij})$ in Equation (1).
In this model, the term $\epsilon_i(t_{ij})$ represents the within-patient variation, comprising of an exponential correlation function $\delta_i(t_{ij})$ and measurement error ω_{ij}:

$$\epsilon_i(t_{ij}) = \delta_i(t_{ij}) + \omega_{ij} \quad (5)$$

Where ω_{ij} is the residual component, where $\omega_{ij} \sim \mathrm{N}(0, \sigma_\omega^2)$. The distribution of $\delta_i(t_{ij})$ follows a multivariate normal density with mean 0 and variance-covariance matrix $\sum$:

$$\delta_i(t_{ij}) \sim MVN(0, \sum) \quad (6)$$

Also $\delta_i(t_{ij})$ follows exponential correlation function $\rho(t)$:

$$\rho(t) = Corr(\delta_i(t_0), \delta_i(t + t_0)) = e^{(-\frac{|t|}{\tau})} \quad (7)$$

Where τ is the rate of decay for the correlation function for time between observations of $|t|$. $\rho(t)$ allows observations farther apart in time are less correlated.

4 Apply data into the model

The semiparametric model proposed above considers the relationship between time and CDR SUM score is following a curve instead of simply a quadratic relationship. The curve is a typical trajectory that the factor "DURATION" does to "CDRSUM", and other individual characteristics would add more additional influence on "CDRSUM". The model is featured as "semiparametric" because the curve is smoothed to be proxy for the mean population curve, and other effects are modeled by parametric function. It is assumed that there is serial correlation among the CDR SUM score recorded of the same patient in disparate time points. We allow patients with higher CDR SUM score more strongly affected by time. The simplest and most commonly observed is the first-order autocorrelation. A current observation of the error term is a linear function of the previous (lagged) observation of the error term. In this study, we assume the serial correlation relationship decay as time increase. The longer time intervals are, the weaker the correlation between two observed CDR SUM scores will be.

Table 2. Parameters of semiparametric model for Lewy bodies

	Value	Std. Error	t-value	p-value
(Intercept)	3.09	1.80	1.72	0.09
DURATION	0.04	0.44	0.09	0.93
I(DURATION^2)	0.08	0.02	3.37	0.00
AgeonsetOld	0.24	2.25	0.11	0.91
AgeonsetYoung	-0.21	0.99	-0.21	0.83
EduLevel>=12 years	-1.40	1.00	-1.40	0.16
SEX	-0.29	1.02	-0.28	0.78
CVHATT	0.37	0.21	1.77	0.08
CVAFIB	-0.02	0.25	-0.08	0.93
CBSTROKE	0.15	0.16	0.92	0.36
CBTIA	-0.26	0.17	-1.51	0.13
DIABETES	0.58	0.49	1.18	0.24
DEL	1.10	0.33	3.35	0.00
HALL	0.81	0.30	2.70	0.01
AGIT	0.76	0.32	2.34	0.02
DEPD	-0.46	0.29	-1.62	0.11
ANX	0.30	0.30	1.01	0.31
ELAT	-0.77	0.62	-1.25	0.21
APA	0.51	0.29	1.77	0.08
DISN	0.57	0.38	1.51	0.13
IRR	-0.01	0.32	-0.04	0.97
MOT	1.08	0.33	3.22	0.00
NITE	0.01	0.29	0.03	0.97
APP	0.23	0.28	0.81	0.42
DURATION:AgeonsetOld	-0.87	0.98	-0.89	0.38
DURATION:AgeonsetYoung	-0.15	0.24	-0.61	0.54
DURATION:SEX	0.49	0.27	1.80	0.07

The residual plot for predicted value in Figure 3 shows uniformity except for several outliers. The residual value is the observed value minus predicted value. Therefore, we can see that the predicted value has high chances to be overestimated than actual value. For example, when CDR SUM score is 18, most of the predicted values are actually not as large as 18, the positive residual error is smaller than 5. However, because of the ceiling effect of CDR SUM score scale (maximum 18 points), the rest of the predictions are larger than 18, and we can avoid the prediction error by forcing the maximum prediction value as 18. Figure 4 is the histogram plot of the residues after maximum prediction value of 18 is applied to the model. The distribution of residual frequency resembles normal distribution, and this indicates that the prediction model for Lewy body dementia explains the data well.

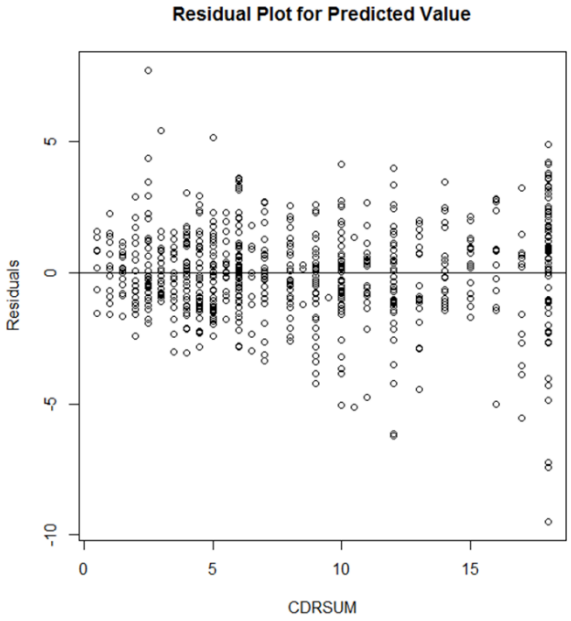


Figure 3. Residual plot for semiparametric model for Lewy body dementia. The x-axis represents actual CDRSUM value in training data, and y-axis is the value of residuals.

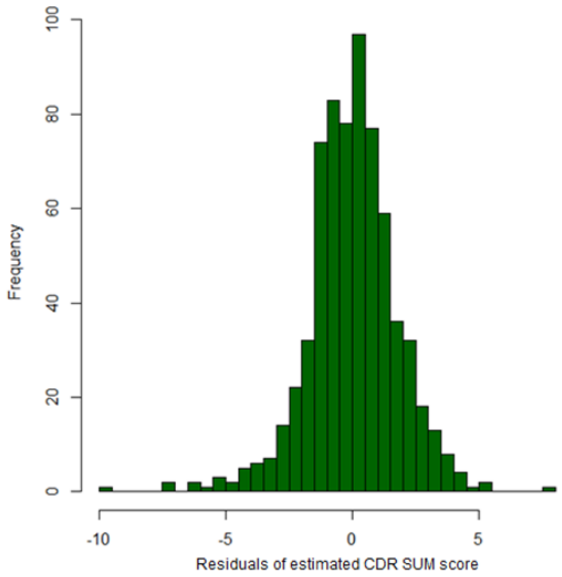


Figure 4. Histogram of residuals.

From the perspective of training data fit, the model did well in fitting and explaining the training data. However, in order to generalize the model, validating the model by test data is essential. Again, bootstrap technique is used to generate random testing data among the alive patient records. In order to examine the goodness-of-fit for the mixed models, R-squared (R^2, also known as coefficient of determination) was used as the first measurement of model goodness-of-fit statistic. R-squared is widely used for linear regression model for examining how well the model fits the data. However, R-squared is only appropriate in linear regression model. Therefore, the linear model of fitted and observed values as shown in Equation (8) was made and then the R-squared in Equation (9) was evaluated for this linear model. R-squared measures the proportion of the observed value variation that is explained by the linear model. The second measurement is the correlation in Equation (10) between the fitted and the observed values. The higher the correlation, the better the fitted values from a certain model simulate the observed value.

$$\hat{y}_k = a^*(y_k) + b \tag{8}$$

$$R^2 = 1 - \frac{\sum(y_k - \hat{y}_k)^2}{\sum(y_k - \bar{y})^2} \tag{9}$$

$$r = \frac{n(\sum y_k \hat{y}_k) - (\sum y_k)(\sum \hat{y}_k)}{\sqrt{[n\sum {y_k}^2 - (\sum y_k)^2][n\sum {\hat{y}_k}^2 - (\sum \hat{y}_k)^2]}} \tag{10}$$

R-squared measures the proportion of the observed value variation that explained by the linear model. The correlation coefficient between the fitted and the observed indicates how well the predicted values fit for the observed values. The higher the correlation, the better the fitted values from a certain model simulate the observed value. The correlation between predicted value and observed value is 0.9037924, which shows high prediction accuracy. Accordingly, the R-squared of semiparametric model for Lewy bodies group is 0.8168407, indicating that nearly 82% of the variations can be explained by the proposed semiparametric model.

5 Discussion

Neuropsychiatric symptoms including delusion, hallucination, agitation, and motor disturbance, are all indicators of higher CDR SUM score. History of stroke presence and history of heart attack/cardiac arrest have smaller impact on increasing CDR SUM score. The symptoms of anxiety and appetite change also indicate higher CDR SUM scores. Night time behavior (awakening during the night, rising too early or taking excessive naps during daytime) and presence of irritation have minimal effect on CDR SUM score. Furthermore, along with time, female gender showed higher CDR SUM score than their male counterpart. This could be the result of longer survival time for females.

It can be identified that older age at onset (>86 years old), more than high school education (>=12 education years), presence of elation and depression were indicators that bring down the CDR SUM score. Education level was the most influential factor among these four indicators. Transient ischemic attack had minimal negative effect on CDRSUM score. Among the factors in the model, there is little evidence that onset age, Sex, heart attach/cardiac arrest, atrial fibrillation, transient ischemic attack, diabetes, presence of elation, depression (DEPD), anxiety (ANX), elation/euphoria (ELAT), apathy/indifference (APA), disinhibition (DISN), irritability (IRR), aberrant motor behavior (MOT), nighttime behavior (NITE), the interaction between duration and age at onset, and the interaction between duration and education level are significant (p>0.05).

It is worthy to be noted that although the p-value for the interaction item between Duration and Sex (male=1, female=2) is only 0.07, the coefficient of 0.49 implies that the CDR SUM score increases faster as the duration become longer for female patients than the male counterparts. Similarly, the interaction between Duration and Ageonset are not significant in the terms of reported p-values, however, it should be noted that the coefficient for DURATION: AgeonsetOld is -0.87 while the coefficient for DURATION: AgeonsetYoung is -0.15. Patients with onset age older than 86 years (Ageonset: "Old" is defined as >86 years old) in the dataset generally has slower progress rate than patients whose age onset are younger than 66 years (Ageonset:"Young" is defined as <=66 years old).

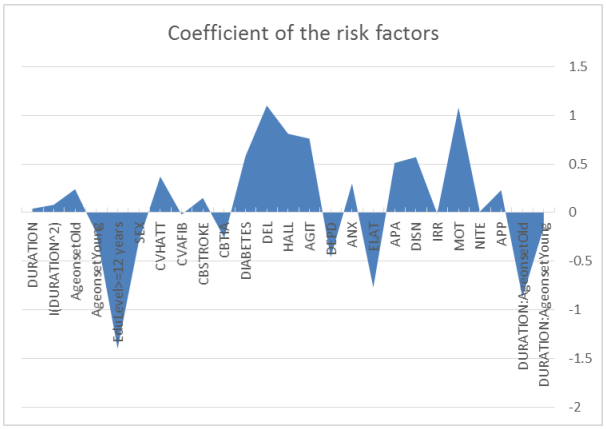


Figure 5. The estimated coefficient of the risk factors for the prediction model

The modeling results agree with the previous studies on the effects of the psychiatric symptoms, especially for delusion, hallucination, motor disturbance. However, the model does not support the sleep disturbance or appetite change are strong predictors of fast cognitive decline.

It should be noted that although the semiparametric model effectively give prediction results of the CDR SUM scores, it does not consider the cognitive reverse and cognitive compensation mechanism that may exist and triggered by factors such as educational or occupational attainment. Furthermore, leisure activities, social and financial status, and care levels are not available in the research dataset, which may also are important predictors of the cognitive decline levels.

6 Conclusion

Lewy body dementia is a cognitive disorder that is associated with cognitive decline. Cognitive decline is the impairment of the capacity to perform higher mental processes of reasoning, remembering, paying attention, understanding, and problem solving compared to one's normal performance. The progress of cognitive decline is heterogeneous. Some patients experience fast cognitive deterioration and have short survival time after cognitive decline onset; some patients maintained constant cognitive level until death; some patients had cognitive reversion back to normal and then impaired cognition again. Patients and their families need to know what to expect with regards to cognition decline behavior, what level of severity would cognition and functional ability reach along with time, and how long they would survive. Therefore, it is a critical problem to simulate the trajectory of cognitive decline in spite of the heterogeneity of its nature.

We assume certain factors are associated with the decline course and patients with Lewy body dementia who share similar profiles would have similar decline trajectories. The CDR SUM score reflects the level of the cognition decline affecting patient's standard of living. Therefore, it is a good indicator to study and make prediction. The study developed a robust trajectory model for predicting cognitive decline based on existing patient profiles. Time is a primary factor to be studied in dementia progression. Although age is the strongest risk factor for dementia, we use duration and age at onset together to represent the effect of time. Based on the conclusion of past studies, we examined gender, years of education, and vascular health conditions, and existence of neuropsychiatric symptoms. Two metrics were used to validate the prediction accuracy, and it shows that the psychiatric symptoms of delusion, hallucination, agitation, and motor disturbance are strong indicators of higher CDR SUM score, while effect of high education level (more than 12 years) could possibly bring down the CDR SUM score and the patients manifest a slower decline rate.

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