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Development of Parkinson's Dementia Prediction Model Using Regression with Optimal Scale †

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Abstract: The objectives of this study were to develop a model for predicting Parkinson's disease Parkinson's disease with dementia (PDD) based on a neuropsychological test using a nationwide survey conducted by Korea Centers for Disease Control and Prevention and present baseline data for detecting Parkinson's dementia earliest. This study targeted 289 patients with Parkinson's disease (110 PDD and 179 MCI) who were 65 years or older. Regression with optimal scale was used to identify the independent relationship between each neuropsychological test and PDD. The analysis results were presented with a regression coefficient, standard error by bootstrap (n=1,000), quantification index (HAYASI I score), odds ratio, and 95% CI. In the regression with optimal scale analysis, K-MMSE(b=-0.52, SE=0.16) and H&Y staging (b=0.44, SE=0.19) were significantly ($p<0.05$) effective models to distinguish PDD from PD-MCI even after adjusting for all tests (Parkinson's motor symptoms and neuropsychological tests). The results of this study showed that the number of optimal categories was 10 for K-MMSE and 7 for H&Y staging. The results of this study suggested that the optimal classification scores of MMSE-K and H&Y staging, among various neuropsychological tests, could be utilized as an effective screening test for the early discrimination of PDD from PD-MCI.

Keywords: quantification index; HAYASI I score; Parkinson's disease dementia; MMSE; MoCA

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1. Introduction

Parkinson's disease was generally reported as a motor disorder showing a combination of weakness, tremor, and rigidity. However, as a number of studies [1,2,3] on Parkinson's disease have been accumulated over the past 20 years, it has been confirmed that it accompanies various symptoms including an autonomic nerve disorder, affective and sensory disorders such as depression, and cognitive disorders, in addition to motor disorders. Particularly, it has been reported that Parkinson's disease with dementia (PDD) occurs frequently in Parkinson's disease. Aarsland et al. (2005)[4] conducted a systematic review and reported that one in three patients with Parkinson's disease had PDD. Pigott et al. (2015) [5] carried out a longitudinal study, which followed PD patients with normal cognition for 6 years, and reported that 47.7% of them progressed to dementia. As shown in previous studies, PDD is more likely to develop in patients with Parkinson's disease. Since patients with PDD are accompanied by non-motor symptoms such as cognitive impairment, as well as a motor disorder, caregivers of them suffer from a heavier burden of care for caregivers is further increased [6,7]. Therefore, efficiently detecting PDD as soon as possible is an important issue in geriatrics.

Nevertheless, South Korea has relatively insufficient epidemiological data on the cognitive function of cognitive impairment in a senile stage than the United States and Europe. Although community-based studies on Parkinson's disease conducted in South

Korea have focused on patients in a small and medium-sized city, no study has developed a prediction model based on a nationwide epidemiological survey [8]. Furthermore, if all the variables used in the analysis are numeric variables, general linear model can be used. However, when the variables are ordinal or nominal, it is difficult to fit the data using the general linear model. An alternative method to overcome this limitation may be to build a regression with optimal scale model using the transformed variables, which are obtained by calculating the optimal scaling using alternating least squares iteratively.

Therefore, it is clinically meaningful to identify neuropsychological tests (e.g., cognitive tests, depression tests, and Parkinson's motor symptoms) that are effective in detecting PDD from Parkinson's Disease–Mild Cognitive Impairment (PD-MCI) by using regression with optimal scale based on a nationwide epidemiological survey and check the optimal classification scores of the tests. The objectives of this study were to develop a model for predicting PDD based on a neuropsychological test using a nationwide survey conducted by Korea Centers for Disease Control and Prevention and present baseline data for detecting Parkinson's dementia earliest.

2. Method

2.1. Data source

It is a secondary data use study that analyzed Parkinson's Disease with Dementia Epidemiologic Data after receiving an approval (No. KBN-2019-1327) from the Distribution Committee and an approval (No. KBN-2019-005) from the Research Ethics Review Committee of the National Biobank of Korea under Korea Centers for Disease Control and Prevention. The epidemiologic data of patients with PDD were collected from 14 tertiary care providers nationwide from January to December 2015 under the supervision of the Korea Centers for Disease Control and Prevention. Health surveys on health behaviors were conducted using computer-assisted personal interviews (CAPI). This study targeted 289 patients with Parkinson's disease (110 PDD and 179 MCI) who were 65 years or older.

2.2. Variable measurement

Lable (outcome variable) was defined as PDD by medical diagnosis. To understand the difference in the general characteristics of subjects according to the type of Parkinson's cognitive disorder, this study compared gender (male or female), age (60-74 years old, or 75 years or older), Parkinson's disease family history (yes or no), Alzheimer's disease family history (yes or no), education period (middle school or lower, or high school or higher), mainly used hand (left hand or right hand), and medical history (traumatic brain injury, hypertension, carbon monoxide poisoning, diabetes, hyperlipidemia, and stroke).

Explanatory variables (neuropsychological tests) included GDS[9], H&Y staging[10], Global Clinical Dementia Rating (CDR) score[11], Schwab & England ADL[12], the Korean Instrumental Activities of Daily Living (K-IADL) [13], Total score of The unified Parkinson's disease rating scale (UPDRS) [14], Motor score of UPDRS, the Korean Mini-Mental State Examination (K-MMSE) [15], the Korean-Montreal Cognitive Assessment (K-MoCA) [16].

2.3. Regression with Optimal Scale

Regression with optimal scale transforms each variable appropriately by considering the scale of each variable in this generalized linear regression model. When the transformation for the dependent variable Y is $\theta(Y)$ and the transformation for the independent variable X is $\sigma(X)$, the parameters, which are the intercept and slope of a linear regression equation, are a form of minimizing the sum of squares of the error, and the formula is presented in Equation 1.

$\min SSQ(\theta(Y) - \beta\sigma(X))$ (Equation1)

SSQ stands for the sum of squares, and the conversion variable has a standardization constraint. It is to find the value making the sum of squares error smallest by performing

the least squares regression of transformed variables (e.g., $\theta(Y)$, $\sigma_1(X_1)$, ..., $\sigma_n(X_n)$). The categorical regression analysis with standardization constraints is presented in Equation 2.

$$\text{minSSQ}(\theta(Y) - \sum_{i=1}^{n} \beta_i \sigma_i(X_i)) \quad \text{(Equation2)}$$

Regression with optimal scale was used to identify the independent relationship between each neuropsychological test and PDD. The analysis results were presented with a regression coefficient, standard error by bootstrap (n=1,000), quantification index (HAYASI I score), odds ratio, and 95% CI.

When independent significance was confirmed in the regression with optimal scale, the Cochran-Armitage trend test was used to determine whether p values had a linear trend based on the reference group. The formula of the Cochran-Armitage trend test is presented in Equation (3).

$$T = \frac{\sum_{i=1}^{R} n_{i1}(R_i - \bar{R})}{\sqrt{p_{.1}(1-p_{.1})s^2}} s^2 = \sum_{i=1}^{R} n_{i.}(R_i - \bar{R})^2 \quad \text{(Equation 3)}$$

3. Results

3.1. General characteristics of subjects by the prevalence of dementia

The results of chi-square test showed that age, gender, the highest level of education, mainly used hand, Parkinson's disease family history, Alzheimer's disease family history, carbon monoxide poisoning history, traumatic brain injury history, stroke history, diabetes, hypertension, and hyperlipidemia were not significantly different between PDD and PD-MCI.

3.2. Results of neuropsychological tests

Figure 1 shows a bagplot that visualizes the location, spread, skewness, and outlier of the test results.

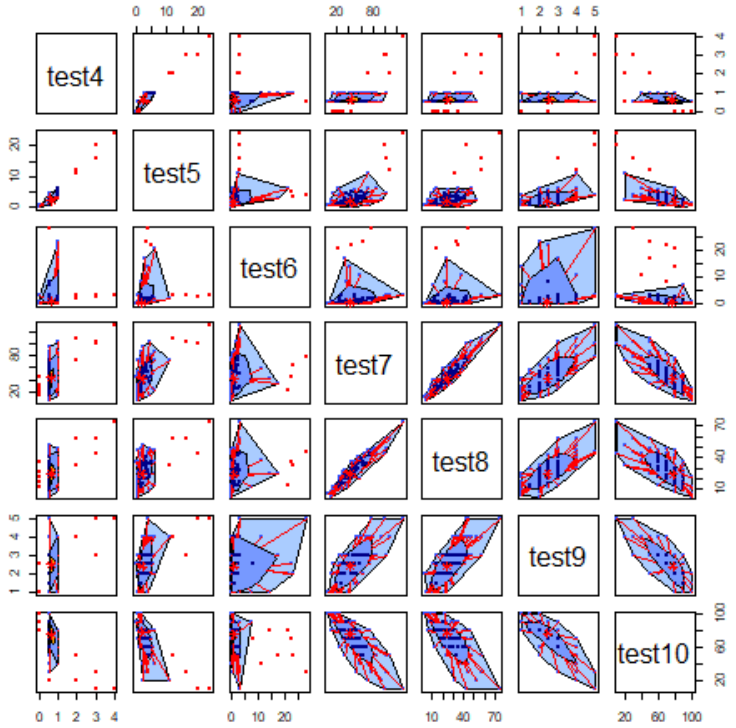


Figure 1. A bagplot that visualizes the location, spread, skewness, and outlier of the test results.

3.3. Results of regression with optimal scale

The analysis results of regression with optimal scale are presented in Table 1. K-MMSE(b=-0.52, SE=0.16) and H&Y staging (b=0.44, SE=0.19) were significantly (p<0.05) effective models to distinguish PDD from PD-MCI even after adjusting for all tests (Parkinson's motor symptoms and neuropsychological tests).

Table 1. Results of regression with optimal scale.

	b	SE by boost [1]	df	F	p
K-MMSE	-.522	.168	2	9.684	<0.001
KMoCA	-.206	.238	3	.750	.527
CDR (Global CDR score)	.127	.269	1	.222	.639
CDR (sum of boxes)	-.271	.412	3	.431	.732
K-IADL	.237	.224	2	1.119	.334
UPDRS (Total UPDRS score)	.433	.444	3	.949	.423
UPDRS (Motor UPDRS score)	-.338	.330	3	1.045	.380
H&Y staging	.440	.197	3	5.008	.004
Schwab & England ADL	.353	.333	2	1.123	.333

[1] SE by boost=Standard error by bootstrap (with n=1,000).
KMMSE=Korean version of mini mental state examination; K-MoCA=Korean version of montreal cognitive assessment; CDR=Clinical dementia rating; K-IADL=Korean version of instrumental activities of daily living; UPDRS=Untitled parkinson disease rating; H&Y staging=Hoehn and Yahr staging); Schwab & England ADL(Schwab & England avtivities of daily living scale).

The quantification index (HAYASI I score) of K-MMSE and H&Y staging is presented in Table 2 and Figure 3, respectively. The results of this study showed that the number of optimal categories was 10 for K-MMSE and 7 for H&Y staging. The OR and 95% CI by the optimal categories of K-MMSE and H&Y staging are presented in Table 3. When discriminating PDD from PD-MCI, PD-MCI patients who had 23 or 24 points in K-MMSE had a 4.5-fold higher risk of PDD than those who had 25 or higher in the test. Moreover, those who scored 21 or 22 points in the test, those who scored 19 or 20 points in the test, those who scored between 15 and 18 points in the test, and those who scored between 3 and 14 had a 2.7-fold, 13.3-fold, 22.4-fold, and 55-fold higher risk, respectively, than those who had 25 or higher in the test. The results of Cochran-Armitage Trend test showed a significant relationship (P for trend <0.001) between the increase in OR and the K-MMSE score (optimal categories score).

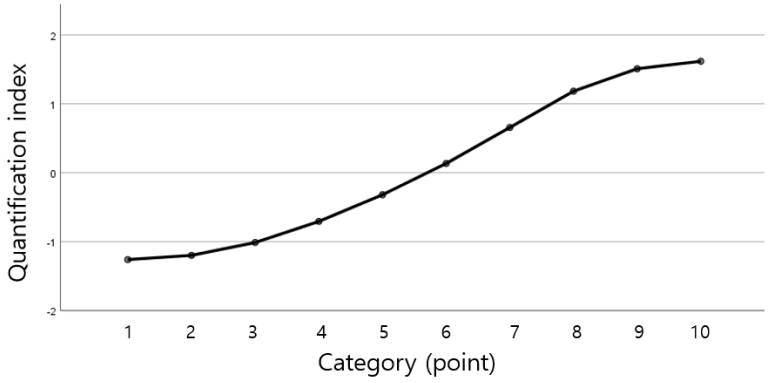
Table 2. Quantification index.

Category (point)	quantification index
3-14	-1.260
15-18	-1.198
19-20	-1.013
21-22	-.706
23-24	-.320
25	.135
26	.656
27	1.183
28	1.508
29-30	1.616

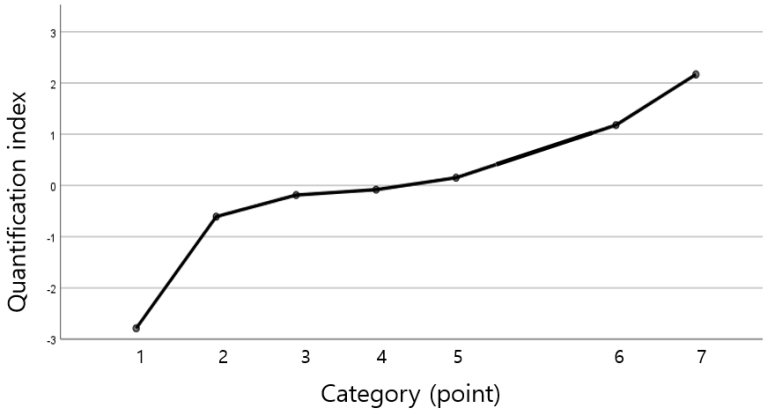
(A) K-MMSE

Category (point)	quantification index
1.0	-2.787
1.5	-.609
2.0	-.187
2.5	-.081
3.0	.151
4.0	1.179
5.0	2.167

(B) H&Y staging



(A) K-MMSE



(B) H&Y staging

Figure 3. Quantification score graph among K-MMSE and H&Y staging.

Table 3. Optimal classification scores: OR and 95% CI.

Optimal classification scores	B	S.E.	Wald	P	OR (95% CI)
K-MMSE 25+ (Ref)			69.856	<0.01	
23-24	1.499	.473	10.035	.002	4.478 (1.77, 11.32)
21-22	2.731	.494	30.522	<0.01	15.345 (5.82, 40.43)
19-20	2.587	.549	22.195	<0.01	13.294 (4.53, 39.00)
15-18	3.111	.505	37.937	<0.01	22.441 (8.33, 60.39)
3-14	4.008	.799	25.185	<0.01	55.020 (11.50, 263.19)
H&Y staging 1.0-2.5 (Ref)					
3.0-5.0	1.110	.350	10.079	.001	3.035 (1.52, 6.02)

4. Discussion

In this study, MMSE-K and H&Y staging were independently related in differentiating PDD from PD-MCI even after adjusting for other tests such as Parkinson's disease motor symptoms and neuropsychological tests. Moreover, when the optimal classification scores were calculated, the increase in OR according to categories showed a significant proportional trend.

It is not easy to accurately detect and diagnose Alzheimer's disease (AD) or dementia with Lewy bodies (DLB) by identifying the pattern of cognitive impairment in PDD by using neuropsychological tests [17]. This is because, first, it is difficult to determine whether dementia is the cause of a patient's cognitive impairment symptoms [18]. Patients with Parkinson's disease often take a variety of medications. They may experience temporary cognitive decline or confusion, which is easily mistaken for dementia, as side effects of medications (e.g., anticholinergics, amantadine, anxiolytics, and sedatives) that they take [19]. Second, there is a possibility that cognitive impairment may occur temporarily due to endocrine statuses such as depression, electrolyte imbalance, and dehydration or systemic diseases such as other infections [20]. Third, even if dementia is diagnosed, it is necessary to effectively differentiate it from other types of degenerative dementia, such as AD or, especially, DLB [20]. The results of this study suggested that the optimal classification scores of MMSE-K and H&Y staging, among various neuropsychological tests, could be utilized as an effective screening test for the early discrimination of PDD from PD-MCI to overcome these obstacles. They can be used effectively for clinically determining whether PD-MCI patients develop into PDD or whether existing PDD is getting worse by conducting these tests when a PD-MCI patient visits the hospital for the first time as baseline information and carrying them out sequentially at regular visits to measure clinically meaningful changes. Further longitudinal studies are required to confirm the performance of MMSE-K and H&Y staging in predicting the progression of PD-MCI to PDD.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, Byeon. H.; methodology, Byeon. H.; software, Byeon. H.; validation, Byeon. H, Y.; formal analysis, Byeon. H.; writing—original draft preparation, Byeon. H.; writing—review and editing, Byeon. H; visualization, Byeon. H. All authors have read and agreed to the published version of the manuscript."

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Informed Consent Statement: Please add "Informed consent was obtained from all subjects involved in the study."

Conflicts of Interest: Declare conflicts of interest or state "The authors declare no conflict of interest."

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