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Predicting cognitive and behavioral functions in patients with dementia: Practical prognostic models of logarithmic and linear regression

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ABSTRACT

Aims: This study provides data on predicting changes in cognitive functions, behavioral independences and disturbances in dementia patients by differential modeling with logarithmic and linear regression. **Methods:** This longitudinal study included two data analysis groups. Group one: 24 dementia patients for identification of cognitive and behavioral changes over time in group data; group two: 15 dementia patients to ensure correlation of the group data applied to prediction of each individual's degree of cognitive and behavioral changes. Group one mini-mental state examination, functional independence measure and dementia behavior disturbance scale scores were assessed initially and 3 and 6 months thereafter during hospitalization and were regressed on the logarithm and linear of time. In group two, calculations of the scores were made for the first two scorings after admission to tailor logarithmic and linear regression formulae to fit an individual's degree of changes at 9 and 12 months. **Results:** Changes in data over time resembled both logarithmic and linear functions. However, the scores sampled at two baseline points based on logarithmic regression modeling estimated prediction of cognitive and behavioral changes more accurately than did linear regression modeling. **Conclusion:** This simple-to-use logarithmic modeling accurately predicted changes in cognitive functions, behavioral independence and disturbances in patients with dementia.

Keywords: Behavioral independence and disturbance, Cognitive function, Dementia, Logarithmic regression modeling, Prognosis

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INTRODUCTION

Dementia is characterized by a progressive loss of social and cognitive functions such as memory, language, recognition, reasoning and judgment [1]. These cognitive

dysfunctions are associated with limitations in daily living, including decrease in behavioral independence and increase in behavioral disturbances [2–5], two of the most problematic aspects for people with dementia and their caregivers. Therefore, rehabilitation intervention focuses on maintaining and improving cognitive and behavioral functions. Previous studies noted that rehabilitation intervention including cognitive training, physical fitness and behavioral training was associated with positive treatment effects for combined cognitive, physical and behavioral outcomes in patients with dementia [6–8]. However, it is still difficult to predict the change in cognitive impairments, behavioral independences and disturbances. Longitudinal studies to predict cognitive and behavioral functions traditionally used correlational analysis with linear regression modeling [9]. In addition, both the trend line slope and the rate at which an individual's data change were assessed in single-subject research to deduce individual recovery by correlating group data [10–13]. Moreover, previous studies examined whether logarithmic modeling was applicable to the prediction of functional changes in patients after stroke [14–16], traumatic brain injury [17], heart disorder [18] and cancers [19]. Despite previous studies pointing out the importance of rehabilitation intervention for patients with dementia, these patients have been systematically excluded from such research on functional predictions. Questions to be answered include whether the changes over time in cognitive function, behavioral independence and disturbance resemble a linear regression or logarithmic model, and which model is the better predictor of these factors? If, with the previous knowledge of the applicability of logarithmic and linear regression modeling for prediction of functional changes in patients with other diseases, changes over time in cognitive function, behavioral independence and disturbance of patients with dementia can be similarly clarified, this knowledge could improve the quality and efficacy of rehabilitation and facilitate the proper definition of intervention goals for patients with dementia.

We, therefore, undertook a longitudinal study in which differential modeling of logarithmic and linear regression was used to predict the changes in cognitive function, behavioral independence and disturbance occurring in patients with dementia.

MATERIALS AND METHODS

Subjects

The criteria for patient eligibility in this study were a diagnosis of dementia, hospital inpatient, no palsy or delirium and the wish to participate. We used the clinical criteria published by the Stroke-Alzheimer disease and Related Disorders Association (ICD-10) and the National

Institute of Neurological and Communicative Disorders to diagnose dementia [20]. The sample size in the first data analysis group was based on a desired 80% statistical power to detect a 0.6 effect size (r) in the Mini-Mental State Examination (MMSE) [21], Functional Independence Measure (FIM) [22] and Dementia Behavior Disturbance Scale (DBDS) [23, 24] scores with a two-sided α of 5%. Insertion of 1-power (0.80), α (0.05) and effect size (0.60) values in the Hulley matrix derived a sample size of 24 [25]. We adopted stricter sample size estimation in the second data analysis group for accurate prediction: a desired 80% statistical power to detect a 0.7 effect size (r) in the MMSE, FIM and DBDS scores with a two-sided α of 5%. A sample size of 19 was derived by insertion of 1-power (0.80), α (0.05) and effect size (0.70) values in the Hulley matrix [25]. The authors therefore planned to recruit approximately 24 and 19 patients for the first and second data collections, respectively.

Patients who satisfied the eligibility criteria were classified by simple randomization by using table of random numbers into two groups to analyze data for the prediction of cognitive functions, behavioral independences and disturbances. The data in the first group was analyzed to identify the changes over time in cognitive functions, behavioral independences and disturbances in the group data. The data in the second group was analyzed to ensure that the correlation of the group data was applicable in predicting the degree of cognitive function, behavioral independence and disturbance in each individual and in predicting individual scores by logarithmic and linear regression modeling on the basis of the individual slope of the early phase of change in cognitive function, behavioral independence and disturbance.

This study was approved by the Institutional Review Board at Niigata University of Health and Welfare (17132-090805). All participants and their next of kin were given a brief explanation of the study aims and the testing procedure prior to participation. Written informed consent was obtained from each literate participant and all participants' next of kin. For all participants, the assessments of cognitive functions, cognitive training, physical fitness and behavioral training were immediately stopped if the patient showed a rejective attitude. This study was performed in accordance with the principles of the Declaration of Helsinki.

Assessment of cognitive functions, behavioral independences and disturbances

We used the MMSE to evaluate cognitive functions. The MMSE is commonly used in both research and clinical practice to assess a patient's cognitive mental state [26], including the patient's attention, orientation, language, immediate and short-term recall and ability to follow simple oral and written instructions. MMSE scores range from 0 to 30: lower scores indicate increased

cognitive impairment [21]. The reliability, sensitivity and specificity of the MMSE have been proven [27]. A score of 23/24 is the accepted cutoff point indicating the presence of dementia.

We used the FIM to evaluate behavioral independences in a patient's life because of its widespread use at rehabilitation facilities and ease of scoring [22]. FIM scores range from 0 to 126 for the assessment of 13 motor items and 5 cognitive items. Motor FIM involves the items of self-care, sphincter control and mobility, and cognitive FIM involves the items of comprehension, expression, social interaction, problem solving and memory. Each item is scored across seven levels, ranging from one point (total dependence) to seven points (total independence). The FIM has shown good inter- and intra-rater reliability [28]. A physical and occupational therapist and nurse who regularly worked with the participant assessed the FIM items.

The physical and occupational therapist and nurse having the most regular contact with the participant rated the participant's frequency of behavioral disturbances with the DBDS, which was chosen because of its wide use in the assessment of behavioral disturbances in dementia. Scoring for the DBDS is based on a frequency scale with a 5-point range in which 0 indicates never and 4 indicates all of the time. The test-retest reliability of the measure is moderate to high, and its internal consistency is also high [23].

Procedure

To identify the change over time of cognitive functions, behavioral independences and disturbances, assessments with the MMSE, FIM and DBDS were done on three different occasions in the first data analysis group: initial assessment and at three months (second assessment) and six months (third assessment) thereafter. To ensure that the correlation of the group data applied to the prediction of the degree of change in cognitive function, behavioral independence and disturbance in each individual, each assessment was done four times for the second data analysis group: initial assessment and at 3, 9 (fourth assessment) and 12 months (fifth assessment) thereafter for each participant. All patients received conventional cognitive training and physical fitness and behavioral training for 3–4 days per week by an occupational therapist, physical therapist and speech therapist.

Data analysis

In the first data analysis group, logarithmic [13–15] and linear [10, 25, 29] regression analyses were undertaken to identify the change over time in cognitive functions, behavioral independences and disturbances in the group data using the following formulae:

$$f(t) = a + b \ln(t) \quad (1)$$
$$f(t) = a + b(t) \quad (2)$$

where t is the number of months since initial assessment, a is the score, and b is the slope of the changes in cognitive functions, behavioral independences and disturbances.

Patients were classified into three groups: those whose score improved, maintained or worsened in reference to b. To assess the fit of the predictive model, we tested the fit of the change over time in cognitive functions, behavioral independences and disturbances and used conventional models of logarithmic and linear regression on the basis of the intraclass correlation coefficient (ICC) and coefficient of determination (R^2).

In the second data analysis group, to ensure that the correlation of the group data applied to the prediction of the degree of cognitive function, behavioral independence and disturbance in each individual, we assessed the MMSE, FIM and DBDS scores at the initial and second assessments. The change in each patient's score between the two assessments (difference between initial and second assessments) was the basis for the scaling coefficient in the equation, using the following formulae:

$$a_{log} = a_1 + (a_2 - a_1) [\ln(t_2/t_1)]^{-1} \ln(t_{4\,or\,5}/t_1) \quad (3)$$
$$a_{lin} = a_1 + (a_2 - a_1)(t_2 - t_1)^{-1}(t_{4\,or\,5} - t_1) \quad (4)$$

Where a_{log} is the predicted score by the logarithmic model, a_{lin} is the predicted score by the linear model, a_i is the score at the ith assessment, and t_i is the ith assessment.

Thus, by using the scores from the first two assessments, these equations can be tailored to forecast the cognitive function, behavioral independence and disturbance of each patient. To assess the individual applicability of this predictive model, R^2 and ICC were determined for comparison of the actual MMSE, FIM and DBDS scores obtained from the fourth and fifth assessments with the predicted values derived from the model formula. the P values < 0.05 were considered to indicate statistical significance. PASW Statistics 19 software (IBM, New York, USA) was used for all statistical analyses.

RESULTS

Identification of changes over time in cognitive functions, behavioral independences and disturbances

In the initial data analysis group, we enrolled 24 patients (5 men, 19 women, mean±standard deviation of age 85.4 ± 7.5 years) who met the eligibility criteria from the participating hospitals between February 2013 and November 2014. Patient characteristics are listed in Table 1.

The average time since the initial assessment from admission was 532.5 days (77-3406 days). Time-series plots of MMSE, FIM and DBDS scores for all 24 participants are shown in Figure 1, and the data is given in Table 2.

The time series change of the MMSE score was improved in 45.8% (n = 11), maintained in 16.7% (n = 4) and worsened in 37.5% (n = 9). Although the R^2 values from both logarithmic and linear regression modeling were high, that obtained with logarithmic regression ($R^2 = 0.843$, $p < 0.001$) was marginally higher than that obtained with linear regression ($R^2 = 0.812$, $p < 0.001$). The time series change of the FIM score was improved in 41.7% (n = 10), maintained in 25.0% (n = 6) and worsened in 33.3% (n =8). Both the logarithmic and linear regression models had high R^2 values (logarithmic modeling: $R^2 = 0.996$, $p < 0.001$; linear modeling: $R^2 = 0.995$, $p < 0.001$). The time series change of the DBDS score was improved in 41.7% (n = 10), maintained in 20.8% (n = 5) and worsened in 37.5% (n = 9). Although both the logarithmic and linear regression models had high R^2 values, the R^2 value obtained with the linear regression model ($R^2 = 0.909$, $p < 0.001$) was slightly higher than that obtained with the logarithmic regression model ($R^2 = 0.817$, p < 0.001).

Assessment of model fit

In the second data analysis group, we enrolled 15 patients (8 men, 7 women, age 82.9±7.3 years) who met the eligibility criteria from the participating hospitals. Characteristics of these patients are listed in Table 1. To deduce each individual's change from the correlation of the group data, we assessed the rate of change (b) within the early-phase (initial and second assessment) data of each individual in this group. Using sampled early-phase scores from the MMSE, FIM and DBDS, we could tailor the logarithmic and linear model formulae to forecast each patient's change. We performed linear regression

Table 1: Characteristics of the study groups at the initial assessment

Characteristic	First data collection	Second data collection	
Participants (n)	24	15	
Age (y)	85.4±7.5	82.9±7.3	
Sex (n)			
Male	5	8	
Female	19	7	
MMSE	14 (10−18)	18	(11−20)
FIM	79.5 (44.8−93)	79	(60−95)
DBDS	13.5 (7.5−19.5)	13	(9−24)

Values are mean ± SD, n, or median (interquartile range).
MMSE   Mini-Mental State Examination,
FIM   Functional Independence Measure,
DBDS   Dementia Behavior Disturbance Scale

analysis and determined the ICC both to compare actual and predicted values and to determine if the modeling formulae could accurately predict the MMSE, FIM and DBDS scores that were obtained. The results of the linear regression analysis and ICC for the agreement of the logarithmic and linear models of all 15 participants are shown in Figure 2 and Table 3.

Despite a mixture of time series changes in the improved, maintained and worsened MMSE scores, the R^2 values between the actual and predicted MMSE scores at 9 and 12 months (third and fourth assessments) were moderate for both the logarithmic (9 month: $R^2 = 0.440$, $p = 0.004$; 12 month: $R^2 = 0.540$, $p = 0.001$) and linear (9 months: $R^2 = 0.295$, $p = 0.021$; 12 month: $R^2 = 0.342$, $p = 0.013$) regression models (Figure 2 and Table 3). In addition, ICC values between the actual and predicted MMSE scores at 9 and 12 months were high for both the logarithmic (9 month: ICC = 0.817, $p = 0.002$; 12 month: ICC = 0.860, $p < 0.001$) and linear (9 month: ICC = 0.717, $p = 0.012$; 12 month: ICC = 0.740, $p = 0.008$) regression models. On the basis of the MMSE scores, the R^2 and ICC values of logarithmic modeling were higher than those of linear regression modeling for predicting the MMSE scores at 9 and 12 months.

Although there was also a mixture of time series changes in the improved, maintained and worsened FIM scores, the R^2 and ICC values between the actual and predicted FIM scores at 9 and 12 months (third and fourth assessments) were high for both the logarithmic (9 month: $R^2 = 0.810$, $p < 0.001$, ICC = 0.946, $p < 0.001$; 12 month: $R^2 = 0.799$, $p < 0.001$, ICC = 0.943, p < 0.001) and linear (9 month: $R^2 = 0.754$, $p < 0.001$, ICC = 0.931, $p < 0.001$; 12 month: $R^2 = 0.942$, $p < 0.001$, ICC = 0.985, $p < 0.001$) regression models.

As well, despite a mixture of time series changes in the improved, maintained and worsened DBDS scores, the R^2 values between the actual and predicted DBDS scores at 9 month (third assessment) were moderate for both the logarithmic ($R^2 = 0.488$, $p = 0.002$) and linear ($R^2 = 0.340$, $p = 0.013$) regression models. In addition, ICC values between the actual and predicted DBDS scores at 9 month were high for both the logarithmic (ICC = 0.834, $p = 0.001$) and linear (ICC = 0.722, $p = 0.011$) regression models. On the basis of the DBDS scores, the R^2 and ICC values of logarithmic modeling were higher than those of linear regression modeling for predicting the DBDS score at 9 month. Moreover, this fitted all patients whose time series change was improved, maintained or worsened. However, R^2 and ICC values between the actual and predicted DBDS scores at 12 month (fourth assessment) were not significant for either the logarithmic ($R^2 = 0.158$, $p = 0.079$; ICC = 0.584, $p = 0.056$) or linear ($R^2 = 0.099$, $p = 0.135$; ICC = 0.391, $p = 0.182$) regression models.

Table 2: Time course of MMSE, FIM, and DBDS scores

		Initial assessment	3 months	6 months	Logarithmic model		Linear regression model	
					R²	p	R²	p
MMSE	Improving (n=11)	10 (4–12)	13 (10–18)	13 (11–16)				
	Maintaining (n=4)	20 (16–20)	19 (17–21)	20 (16–20)				
	Worsening (n=9)	15 (14–18)	14 (13–16)	12 (9–16)				
	Total (n=24)	14 (10–18)	14 (11–18)	13 (11–18)	0.843	<0.0001	0.812	<0.0001
FIM	Improving (n=10)	85 (47–100)	90 (58–102)	90 (55–102)				
	Maintaining (n=6)	77 (43–89)	77 (43–89)	77 (43–89)				
	Worsening (n=8)	62 (42–98)	63 (37–87)	55 (36–81)				
	Total (n=24)	80 (45–93)	78 (49–91)	77 (46–91)	0.996	<0.00001	0.995	<0.0001
DBDS	Improving (n=10)	14 (10–22)	9 (7–17)	8 (5–14)				
	Maintaining (n=5)	9 (7–17)	9 (7–17)	9 (7–17)				
	Worsening (n=9)	13 (3–22)	15 (3–23)	15 (6–25)				
	Total (n=24)	14 (8–20)	9 (6–18)	11 (6–16)	0.817	<0.0001	0.909	<0.0001

Values are median (interquartile range).
MMSE   Mini-Mental State Examination, FIM   Functional Independence Measure, DBDS   Dementia Behavior Disturbance Scale.

Table 3: Assessment of model fit

		Logarithmic model				Linear regression model			
		R²	p	ICC	p	R²	p	ICC	p
MMSE	9 months	0.440	0.004	0.817	0.002	0.295	0.021	0.717	0.012
	12 months	0.540	0.001	0.860	<0.0001	0.342	0.013	0.740	0.008
FIM	9 months	0.810	<0.0001	0.946	<0.0001	0.754	<0.0001	0.931	<0.0001
	12 months	0.779	<0.0001	0.943	<0.0001	0.942	<0.0001	0.985	<0.0001
DBDS	9 months	0.488	0.002	0.834	0.001	0.340	0.013	0.722	0.011
	12 months	0.158	0.079	0.584	0.056	0.099	0.135	0.391	0.182

MMSE   Mini-Mental State Examination, FIM   Functional Independence Measure, DBDS   Dementia Behavior Disturbance Scale,
ICC   Intraclass Correlation Coefficient

DISCUSSION

Changes in cognitive function, behavioral independences and disturbances of the patients with dementia could be predicted. Our results showed that (a) the change over time in MMSE, FIM and DBDS scores resembled both logarithmic and linear regressions for group data, (b) MMSE, FIM and DBDS scores over the one-year longitudinal assessment improved, maintained or worsened, and (c) MMSE, FIM and DBDS scores sampled at two different time on the basis of logarithmic regression modeling could accurately predict each individual's cognitive function, behavioral independence and disturbance with the improved, maintained or worsened score. Particularly, MMSE, FIM and DBDS scores sampled at two baseline points on the basis of logarithmic regression modeling could estimate the prediction of changes in cognitive function, behavioral independence and disturbances more accurately than could linear regression modeling. We believe that the model formula based on logarithmic regression modeling could be useful to predict changes in cognitive function and behavioral independences and disturbances in patients with dementia.
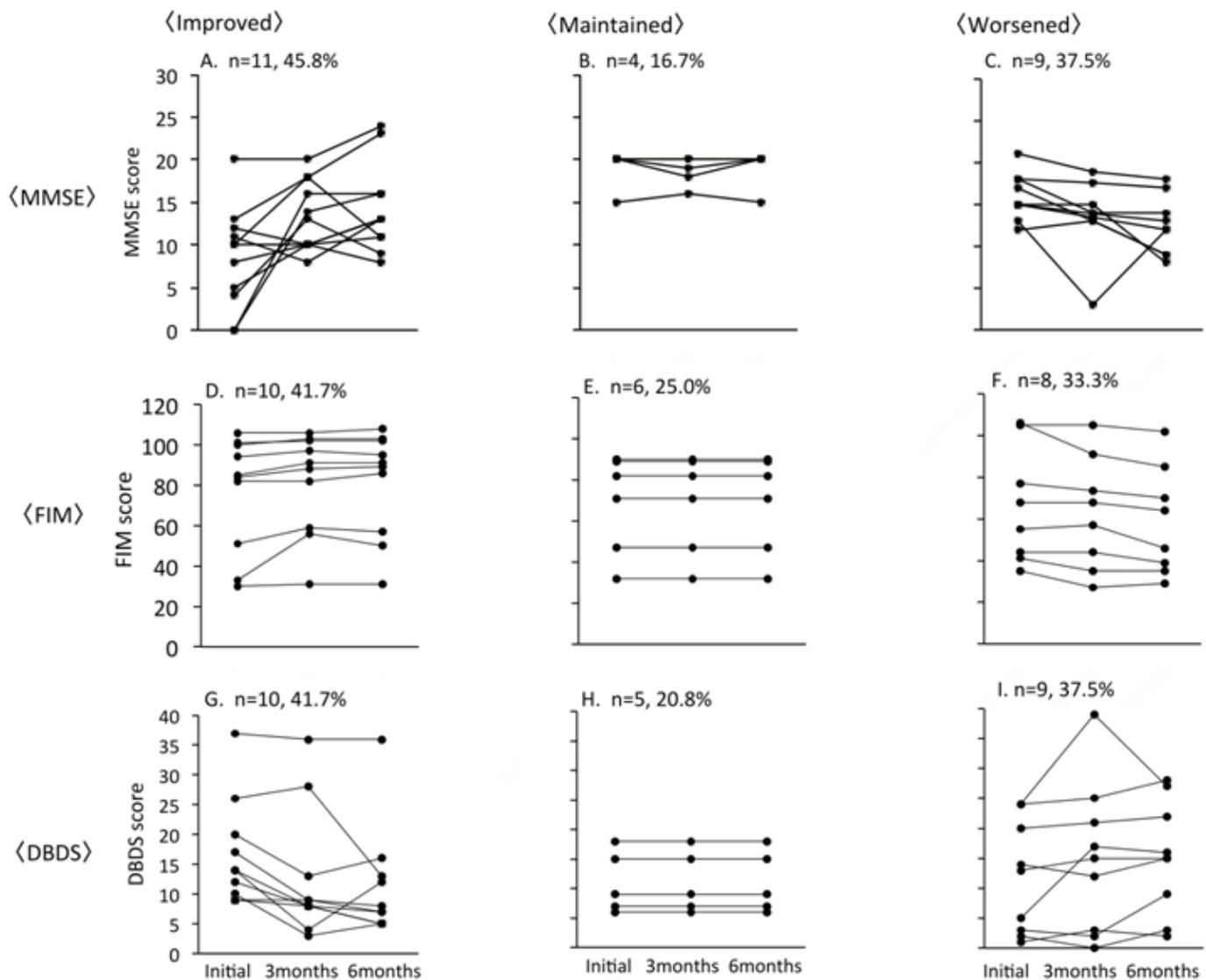
Figure 1: Time course of MMSE, FIM and DBDS scores.
Plots of improved (A), maintained (B) and worsened (C) MMSE scores; improved (D), maintained (E) and worsened (F) FIM scores; and improved (G), maintained (H) and worsened (I) DBDS scores are shown.
MMSE   Mini-Mental State Examination, FIM   Functional Independence Measure, DBDS   Dementia Behavior Disturbance Scale

Some studies exist that address the trajectories of cognitive function, behavioral independences and disturbances in dementia. Only a few longitudinal studies investigated the decline in cognitive function in dementia [30, 31]. In addition, previous studies showed that both the severity of cognitive impairment and the decline in the levels of behavioral independence influenced behavioral change in nursing home residents [32, 33]. Banerjee et al. [34] reported large changes in functional ability to be more strongly associated with changes in self- and caregiver-reported quality of life at 12 months. Moreover, Oshima et al. [35] suggested that recovery speed over the time course following the onset of apoplexy decreased the behavioral independence score logarithmically. Both Suzuki et al. [14,16] and Koyama et al. [15] reported that

the use of logarithmic modeling to calculate predicted values allowed functional recovery following a stroke to be accurately and powerfully forecast. However, such research on functional prediction has systematically excluded people with dementia. An additional new observation in the present study was that in patients with dementia, logarithmic modeling could accurately predict each individual's changes in cognitive function, behavioral independence and disturbance.

In our study, although logarithmic modeling based on MMSE scores could accurately predict the patterns of individual changes in cognitive function one year after the initial assessment, that based on DBDS scores could not predict behavior disturbance at the same time point. Several studies reported the association of dementia
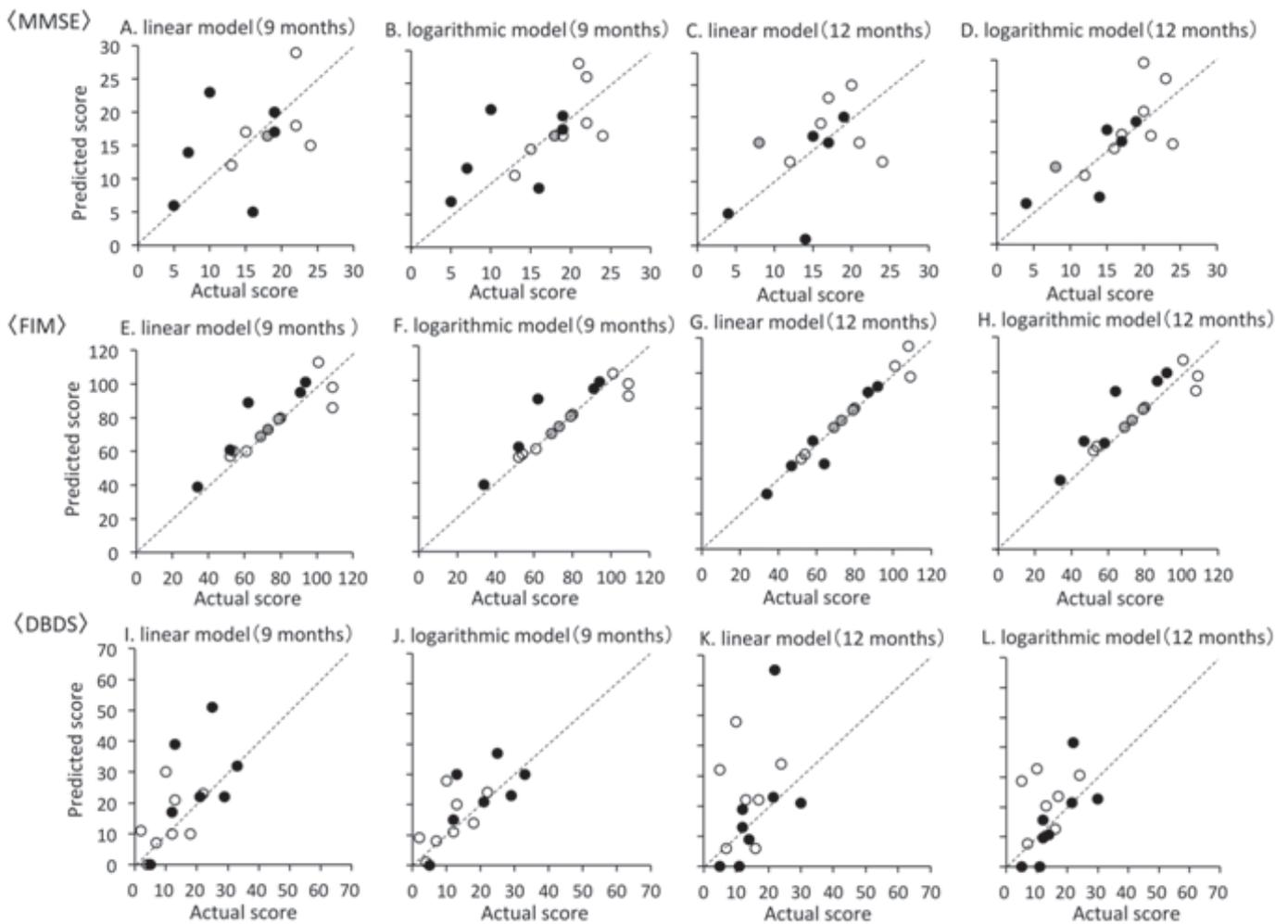
Figure 2: Scatterplots showing the relations between actual and predicted MMSE, FIM and DBDS scores.
Actual and predicted MMSE scores at 9 (A) and 12 (C) months by linear regression modeling and at 9 (B) and 12 (D) months by logarithmic modeling. Actual and predicted FIM scores at 9 (E) and 12 (G) months by linear regression modeling and at 9 (F) and 12 (H) months by logarithmic modeling. Actual and predicted DBDS scores at 9 (I) and 12 (K) months by linear regression modeling and at 9 (J) and 12 (L) months by logarithmic modeling. Improved (white circles), maintained (gray circles) and worsened (black circles) MMSE, FIM and DBDS scores are shown.
MMSE Mini   Mental State Examination, FIM   Functional Independence Measure, DBDS   Dementia Behavior Disturbance Scale

with behavioral disturbances [22]. Neville and Byrne [3] found behavioral disturbance to be more frequent when cognitive impairment was greater. However, Baumgarten et al. [23] suggested that there was no relative correlation between the severity of dementia and behavioral disturbance. Thus, further elucidation of the relation between the severity of dementia and levels of behavioral independence and behavioral disturbance is needed. It might be difficult to clearly define the predictors of behavioral disturbance because of the multidimensional conditions caused by factors such as severity of dementia, age, medication and socio-demographic characteristics. Thus, the relation between behavioral disturbance and multiple important covariates will require further study. Moreover, previous studies suggested that patients with cognitive impairments as reflected by baseline MMSE scores, were affected by types of dementia and

the multiple covariates of age and years of education [9, 36]. In the future, a greater number of patients with dementia will need to be studied to better investigate the relation between changes in cognitive function, behavioral independence and disturbance and multiple other important covariates. The results of the present study might be more generally applicable if a greater number of patients can be included and a more detailed examination that classifies participants according to their covariates is undertaken.

Nevertheless, our results are relevant for clinical practice because they may enhance therapy. Teri et al. [37] showed that a 3-month period of home-based exercise training performed combined with caregiver training in behavioral management techniques improved depression and physical health in dementia patients. Rolland et al. [38] found that a one-year training program comprising

simple exercises slowed the decline in the performance of the activities of daily living in dementia patients. Santana-Sosa et al. [39] found that a 12-week training program comprising joint mobility and coordination exercises and resistance training performed in a nursing home with low-cost equipment improved the overall functional capacity of the dementia patients significantly. Recently, the prevention of cognitive decline through physical activity as a main behavioral strategy has garnered much interest. One meta-analysis showed the greater positive effect on cognition of combining resistance training with aerobic-based exercise training rather than with aerobic-based exercise training alone [40]. Liu-Ambrose et al. [41] showed significant improvement of executive functioning after six months with a patient-customized home-based program that combined strength retraining with balance exercises. Recently, Brown et al. [42] showed that a 6-month group-based exercise program including resistance training significantly improved cognitive performance of fluid intelligence. In addition, various other approaches are available for the rehabilitation of patients with cognitive dysfunction, including compensation or strategy training, restorative therapies, and several behavioral approaches [43]. By improving behavioral independences and disturbances, the time spent assisting patients can be shortened, thus reducing caregiver burden and improving patient mood and their sense of control over their environment, which might delay their permanent institutionalization [2, 3, 44]. In other studies [10, 45–48], graduated prompting and reinforcement training for errorless learning were reported to increase behavioral independence in people with dementia. Rogers et al. [49] noted that although residents with dementia can benefit from behavioral rehabilitation by being more appropriately involved in their own care and less disruptive, behavioral rehabilitative care still requires much more time than usual care. Many problems must be considered when addressing the challenges of slowing the decline in cognitive function and of behavioral independences and disturbances in patients with dementia. Our results suggest that accurate prediction of cognitive function, behavioral independences and disturbances can define proper intervention goals, length of hospitalization and effective use of resources for individual patients with dementia. These findings will contribute to an increasingly evidence-based approach to rehabilitation intervention for these patients. As the knowledge relating to predictive modeling grows, more appropriate treatment regimens will be available for selection in the future.

CONCLUSION

The quality and efficiency of rehabilitation intervention are improved by accurate predictions based on a proper definition of intervention goals for individual patients with dementia. Logarithmic modeling based on Mini-Mental State Examination (MMSE), Functional Independence Measure (FIM), and Dementia Behavior Disturbance Scale (DBDS) scores could accurately predict the recovery of cognitive function, behavioral independence and disturbance in patients with dementia. With its use of simple mathematical procedures, we believe this logarithmic modeling will be easy to use in daily clinical practice.

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Author Contributions
Aki Watanabe – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Makoto Suzuki – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
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Michinari Fukuda – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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