

The Rate of Cognitive Decline and Risk of Reaching Clinical Milestones in Alzheimer Disease

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Background: Previous studies revealed that cognitive test scores were related to functional outcome in Alzheimer disease (AD). However, the relationship between the rate of cognitive decline at the initial disease phase and the risk of reaching clinical milestones in subsequent years has not yet been examined.

Objective: To examine whether the rate of cognitive decline predicts the risk of reaching functional milestones in patients with probable AD.

Design: A 5-year prospective study was conducted at 3 sites.

Setting: Outpatient research and treatment centers.

Participants: Patients diagnosed with probable AD (N=236; mean age, 73 years; 59% women; mean years of education, 13).

Main Outcome Measures: Modified Mini-Mental State

Examination (mMMSE) scores were used to assess the rate of cognitive decline over time. Total dependence score and 2 clinical milestones: (1) the need to be dressed, groomed, and washed and (2) receiving a level of care equivalent to a placement in a health-related facility, were derived from the Dependence Scale.

Results: General estimating equation analyses revealed that the rate of cognitive decline during the entire follow-up period was positively related to an increase in total dependence scores. Cox analyses showed that a fast rate of decline during the first year was related to an increase in the risk of reaching clinical milestones in subsequent years. Analyses controlled for age, sex, education, and baseline mMMSE scores.

Conclusion: A fast rate of cognitive decline was associated with increasing risk of reaching clinical milestones in AD.

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THE USE of neuropsychological test scores to predict patients' everyday functioning is an important issue that has been studied extensively.¹ The statistical relationship between measures of cognition and those of functional ability or disability has been documented in numerous studies,²⁻⁴ but the utility and extent of this association have been the subject of criticism as well.^{5,6}

Several cross-sectional studies have demonstrated an association between cognitive status and everyday functioning in elderly persons.^{7,8} A review of longitudinal studies⁹ concluded that initial scores on measures of cognition predict future functional disability. Furthermore, a recent longitudinal study¹⁰ provided descriptive data regarding the association between decline in cognition and functional ability in a large sample of elderly persons.

The association between cognitive test scores and everyday functioning is especially relevant in dementia, in which both are affected. Such a relationship has been demonstrated in cross-sectional studies,¹¹⁻¹⁵ where cognitive and functional measures share about 15% to 40% of variance. A prospective study¹⁶ showed that initial Mini-Mental State Examination (MMSE) scores were related to decline on a number of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) at 12 months' follow-up. Loss of ADLs and IADLs during 1 or 2 years of follow-up was related to the rate of cognitive decline during the same period.¹⁷ Further, studies have shown a hierarchical loss of functional independence when IADLs are lost prior to ADLs.¹⁶⁻¹⁹

An important issue that has yet to be addressed in prospective studies is whether

the rate of cognitive decline during the initial phase of AD can provide incremental prediction, beyond that available from baseline cognitive test scores or demographic variables, of the time until reaching specific clinical milestones in the disease course.

The current study examined the relationship between the rate of cognitive decline and the risk of increasing dependence over a 5-year period in patients diagnosed with probable AD. To accomplish this goal, items of the Dependence Scale²⁰ were summed to provide a continuous index of changes in dependence during the follow-up period. Furthermore, we used Cox survival analyses to evaluate whether the rate of cognitive decline during the first year of follow-up predicts the risk of reaching specific clinical milestones in subsequent years of follow-up. The study focused on 2 dichotomized functional milestones: (1) the need to be dressed, groomed, and washed and (2) receiving a level of care equivalent to a placement in a health-related facility. Selection of these 2 outcome measures was based on clinical and statistical considerations. To be suitable for survival analysis, the outcome measures cannot be present in all or most individuals early in the disease process or, conversely, cannot rarely occur at all.²¹ The first milestone, the need to be dressed, groomed, and washed, was selected because it was thought to represent a significant loss of functional independence that, although rarely observed in the early disease process, is a frequent outcome in the later stages of AD. Item analysis of the Dependence Scale, which was conducted at baseline²² and over time,¹⁸ as well as frequency analysis in the current study (see the "Results" section) suggested that this particular behavior would be a good candidate for survival analyses carried out during a 5-year follow-up period. The second milestone represents an overall loss of functional independence, which results in around-the-clock supervision of personal care, safety, or medical care. Thus, these 2 outcome measures were deemed appropriate to examine whether the rate of initial cognitive decline provides incremental prediction regarding the risk of reaching functional milestones in subsequent years of follow-up.

METHODS

PARTICIPANTS

A total of 236 participants who were enrolled in the Predictors Study participated in the present investigation. Patients were recruited and studied at 3 sites: 91 patients at Columbia Medical Center, New York, NY, 84 at Johns Hopkins School of Medicine, Baltimore, Md, and 61 at Massachusetts General Hospital, Boston. At the Columbia site, patients were recruited from the Memory Disorder Center and from physicians' private practices through the Alzheimer's Disease Research Center. Each consecutive patient who met the inclusion but not the exclusion criteria of the study was included, except for those who did not consent to participate or who lived too far and were unable to return to the hospital for regular follow-up. At the Johns Hopkins site, patients were recruited from the Dementia Research Center and from physicians' private practices. At the Massachusetts General Hospital site, patients were recruited from the Geriatric Neurobehavioral Center, an outpatient service. In addition, 14 patients were recruited from a long-

term care facility, and 8 patients also entered a physostigmine study.

All patients were diagnosed with probable AD.^{23,24} The inclusion and exclusion criteria as well as the evaluation procedures of the Predictors Study have been fully described elsewhere.^{25,26} In brief, diagnoses were made in consensus meetings and were based on neuropsychological test scores, findings from neurological examinations and brain imaging studies, and demographic information that was obtained from significant others. Exclusion criteria were clinical or historical evidence of stroke, history of alcohol abuse or dependence, any electroconvulsive treatment within 2 years of recruitment or 10 or more electroconvulsive sessions at any time, and history or current clinical evidence of schizophrenia or schizoaffective disorder that started before the onset of intellectual decline. At entry into the study, patients were required to have mild to moderate dementia, which was operationalized as a modified MMSE (mMMSE) score of 30 or higher (equivalent to 16 or higher on the Folstein et al²⁷ MMSE).

In the Predictors Study, patients are evaluated every 6 months. The mean (SD) number of 6-month visits for the entire sample was 6.7 (5.5), indicating that, on average, patients have been followed up for approximately 3.5 years. All the participants and 6-month study visits were used for the general estimating equation (GEE) analysis examining the risk of reaching each milestone as a function of cognitive status at each available visit.

A subset of 172 patients who had completed 3 consecutive 6-month mMMSE evaluations during the first year of follow-up was selected for the Cox analysis, which examined the relationship between the rate of initial cognitive decline and the risk of reaching clinical milestones in subsequent years.

MEASURES

Cognition

Cognition was assessed using the mMMSE.²⁷ Modifications to the original MMSE include the addition of digit span forward and backward,²⁸ 2 additional calculation items, recall of the current and 4 previous presidents of the United States, confrontation naming of 10 items from the Boston Naming Test,²⁹ 1 additional sentence to repeat, and 1 additional figure to copy. The mMMSE has a maximum score of 57 points, with lower scores indicating poorer cognitive function. Test-retest reliability is high ($r=0.95$), and correlations with the original MMSE ($r=0.89$), the Blessed Memory Information Concentration test ($r=0.93$), and full-scale IQ ($r=0.66$) are indicative of adequate validity.³⁰

Functional Dependence

The Dependence Scale is a 13-item measure, adapted from an instrument designed by Gurland²⁰ for use with community elderly persons. The reliability and validity of the Dependence Scale have been established.²² It is administered to a person who resides with the patient or is well informed about the patient's daily activities and needs. With the exception of the first 2 items, responses are dichotomous (yes/no) and indicate whether the patient requires assistance in a particular domain. Items assess a number of reported patient needs and are cumulative and hierarchical, indicating progressively greater dependency. The interviewer also completes a 3-level item that rates the "equivalent institutional care" that the patient is receiving. The first level—limited home care—indicates independent living with some help in the case of shopping, cooking, or housekeeping but not with all the tasks. The second level—adult home—includes living in a supervised environment (family members

can serve as supervisors) involving regular help with various chores and constant companionship, security, and legal or financial help. The third level—health-related facility—includes around-the-clock supervision of personal care, safety, or medical care. In addition to the total score, 2 clinical milestones were selected from the Dependence Scale: (1) basic ADL, or the need to be dressed, groomed and washed, and (2) receiving a level of care equivalent to a placement in a health-related facility.

STATISTICAL ANALYSES

General Estimating Equations

General estimating equations were used to calculate the risk of increasing dependence over time as a function of cognitive decline during the entire follow-up period. This analysis used the entire sample (N = 236) across all available patient visits (excluding the baseline visit, which was used as a covariate). This statistical method takes into account the multiple visits per patient as well as the likelihood that an individual's characteristics correlate with one another over time. The repeated measures per patients are treated as a cluster. Also, GEE analysis takes into account the status or changing value of covariates at each visit; mMMSE slope per patient, using all available visit scores, served as an index of the rate of cognitive decline. The median split for the mMMSE slope was used to create 2 dichotomous groups representing slow and fast cognitive decline. Dependence Scale total score was the continuous dependent measure. Analyses controlled for age, education, sex, and baseline mMMSE scores.

Table 1. Participants' Characteristics at Baseline

Characteristic	Entire Sample (N = 236)	Subset Used for Cox Analyses (n = 172)
Age, mean (SD), y	72.7 (9.2)	73.24 (9.3)
Education, mean (SD), y	13.0 (3.6)	13.36 (3.6)
mMMSE score, mean (SD)	37.2 (6.1)	37.8 (5.8)
Sex, %		
Female	59.1	57.9
Male	40.9	42.1
Race/ethnicity, %		
White	93.3	93.3
Black	6.3	6.1
Other	4.0	0.6
Dependence Scale		
Dependence level, mode	2	2
Total score, mean (SD)	5.3 (2.1)	5.2 (2.2)

Abbreviation: mMMSE, modified Mini-Mental State Examination.

Cox Survival Analysis

Cox regression analysis was used to evaluate the relationship between the rate of cognitive decline during the first year of follow-up and the risk of reaching clinical milestones in subsequent years. Rate of cognitive decline was operationalized as the first-year slope of mMMSE performance, per participant, using the baseline, 6-month, and 12-month evaluation test scores. Baseline and 12-month visit scores also were entered as predictors to determine whether the slope provided incremental prediction beyond that available from mMMSE scores alone. Age, sex, and education served as additional covariates. Cox analyses were executed on a subset of the sample (n = 172) who had completed the first three 6-month evaluations and had mMMSE test scores available.

RESULTS

Sociodemographic information as well as baseline scores on measures of cognition and functional dependence for the entire sample and the subset used for the Cox analyses are presented in **Table 1**.

Most patients were white, and 59% were female. Mean age and duration of education were 72.7 years and 13.0 years, respectively. The mean baseline mMMSE score was 37.2, indicating an overall mild level of cognitive impairment. The modal dependence level at baseline was 2 (54% of patients), which suggests that, initially, most patients required limited home care or supervision.²² The subset of patients used for the Cox analyses (n = 172) was comparable to the entire sample on all demographic and functional measures.

The mean Dependence Scale total score and the percentage of patients who reached functional milestones at baseline and at each year of the follow-up period are presented in **Table 2**. As expected, the mean Dependence Scale total score was increased during each year of the follow-up period, as was the percentage of patients who reached the functional milestones.

GEE ANALYSES

Results of the GEE analysis revealed that, as expected, the mean Dependence Scale total score increased significantly over time ($\beta = .384, P < .001$; 95% confidence interval, 0.341-0.427). Differences in dependence between the slow and fast rate of cognitive decline groups were not significant at baseline ($\beta = .384, P = .52$). However, the rate of cognitive decline \times time interaction was significant ($\beta = .174, P < .001$; 95% confidence interval, 0.097-0.251), indicating that a fast rate of cognitive de-

Table 2. Dependence Scale Total Score and Clinical Milestones at Baseline and at Each Year During the Follow-up Period

	Baseline	Year of Follow-up				
		1	2	3	4	5
Dependence Scale total score, mean (SD)	5.3 (2.1)	6.9 (2.2)	7.9 (2.5)	9.1 (2.8)	10.0 (2.9)	10.2 (3.3)
Clinical milestone, %						
Need to be dressed, groomed, and washed	3.8	11.6	28.8	45.6	59.1	69.1
Receiving care equivalent to placement in a health-related facility	8.5	21.1	39.4	51.0	60.9	68.1

Table 3. Cox Analyses: Risk of Reaching Clinical Milestones as a Function of mMMSE Scores at Baseline and 12 Months' Follow-up and Rate of Decline (Slope) During the First Year*

Variable	Need to Be Dressed, Washed, and Groomed		Care Equivalent to Placement in a Health-Related Facility	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Baseline mMMSE score	0.957 (0.923-0.993)	.02	0.948 (0.914-0.985)	.006
Baseline and first-year mMMSE slope				
Baseline mMMSE score	0.975 (0.939-1.012)	.19	0.963 (0.927-1.00)	.05
First-year mMMSE slope	0.910 (0.878-0.944)	<.001	0.929 (0.894-0.964)	<.001
End of first-year mMMSE score	0.940 (0.919-0.962)	<.001	0.946 (0.925-0.967)	<.001
End of first-year mMMSE score and slope				
End of first-year mMMSE score	0.972 (0.936-1.00)	.13	0.961 (0.926-0.997)	.04
First-year mMMSE slope	0.938 (0.885-0.993)	.03	0.968 (0.912-1.028)	.28

Abbreviations: CI, confidence interval; mMMSE, modified Mini-Mental State Examination.
*Analyses controlled for age, sex, and education.

Table 4. Cox Analyses: Risk of Reaching Clinical Milestones as a Function of Rate of Decline (Slope) and mMMSE Score

Group*	Need to Be Dressed, Washed, and Groomed		Care Equivalent to Placement in a Health-Related Facility	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
High mMMSE score + large slope	1.666 (0.929-2.987)	.09	1.481 (0.825-2.661)	.19
Low mMMSE score + small slope	1.827 (0.940-3.551)	.08	2.020 (0.976-4.180)	.06
Low mMMSE score + large slope	2.116 (1.383-3.238)	.001	2.650 (1.664-4.222)	<.001

Abbreviations: CI, confidence interval; mMMSE, modified Mini-Mental State Examination.
*Small slope indicates slow rate of decline; large slope, fast rate of decline. The reference group is high mMMSE score and small slope.

cline was associated with an increase in the risk of reaching a greater level of dependence. The regression coefficients and significant values provided above were obtained while controlling for mMMSE baseline scores, age, education, and sex.

COX ANALYSES

Cox regression analyses were used to evaluate the relationship between the rate of cognitive decline during the first year of follow-up and the risk of reaching clinical milestones in subsequent years. The first-year mMMSE slope and baseline and 12-month visit mMMSE scores were entered as predictors. Analyses controlled for age, education, and sex. **Table 3** presents the risk ratios, 95% confidence intervals, and significant levels for the Cox analyses.

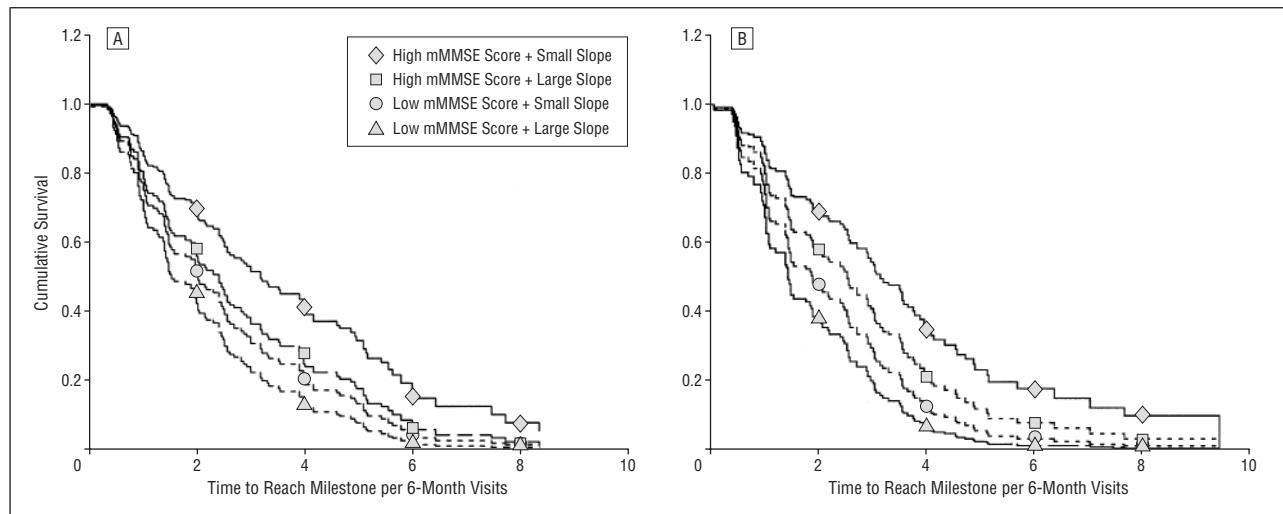
Baseline mMMSE scores were related to the risk of reaching both clinical milestones in subsequent years (Table 3). However, when baseline mMMSE scores and the first-year slope were included in the same model, the latter provided incremental prediction not available from baseline mMMSE scores alone. As expected, 12-month-visit mMMSE scores were significantly related to the risk of reaching clinical milestones in subsequent years. Cox analyses that included the first-year slope and 12-month mMMSE scores revealed that only the former remained significant in predicting the need to be dressed, groomed, and washed, whereas the opposite was observed for receiving a level of care equivalent to placement in a health-related facility.

To further explore how the association between the first-year slope and 12-month mMMSE scores was related to functional outcome, median splits for both predictors were calculated (median slope, -4.3; median 12-month mMMSE score, 33) to delineate 4 groups: (1) high 12-month mMMSE score and small slope (ie, slow rate of decline); (2) high 12-month mMMSE score and large slope (ie, fast rate of decline); (3) low 12-month mMMSE score and small slope; and (4) low 12-month mMMSE score and large slope. These 4 groups were entered as categorical predictors in Cox analysis predicting the risk of reaching the 2 clinical milestones. The group with the high mMMSE score and small (protective) slope served as the reference group against which the other 3 groups were compared. A summary of these analyses is presented in **Table 4**. Survival curves of these 4 groups are illustrated in the **Figure**.

There were statistically significant differences in the risk of reaching both clinical milestones between the reference and the low mMMSE score and large slope groups. The other 2 groups were at intermediate levels that statistically did not differ from the reference group.

COMMENT

Most studies (cross-sectional and longitudinal) examining the relationship between cognitive status and daily functions in AD correlated baseline cognitive test scores with IADL and ADL measures. Typically, results showed a positive relationship between cognitive performance and functional competence. Relatively few longitudinal stud-



Survival curves for the need to be dressed, groomed, and washed (A) and for receiving a level of care that is equivalent to a placement in a health-related facility (B) by modified Mini-Mental State Examination (mMMSE) score and the first-year slope of mMMSE performance. Small slope indicates a slow rate of decline; large slope, a fast rate of decline.

ies have investigated clinical milestones in AD.^{19,31} Galasko et al¹⁷ found that the rate of cognitive change during a 2-year follow-up period differed between AD patients who reached or did not reach clinical milestones during the same period. These analyses did not control for demographic variables or initial cognitive scores.

The current study evaluated the relationship between cognitive decline and the risk of increasing dependence level during a 5-year follow-up period. The GEE analyses reaffirm and bolster previous findings demonstrating that fast rate of cognitive decline was related to more severe dependence, while controlling for demographic variables and baseline mMMSE scores. Furthermore, the rate of cognitive decline during the first year of follow-up was related to an increase in the risk of reaching 2 selected clinical milestones in subsequent years of follow-up. There was a significant inverse relationship between the rate of cognitive decline and the risk of reaching these clinical milestones. Fast rate of decline was related to a shorter time until patients reached clinical end points, whereas a slow rate was associated with a delay of such outcome. Further, the rate of cognitive decline provided an incremental prediction not available from baseline cognitive test scores alone while controlling for age, sex, and education.

Inclusion of 12-month mMMSE scores and the first-year slope as continuous covariates in the same Cox model produced mixed results. Although the slope's statistical contribution to the prediction of the risk associated with one clinical milestone exceeded that of 12-month mMMSE scores, the opposite was found for the second clinical milestone. To further explore the competing and likely partially overlapping contribution of these 2 variables, 4 categorical groups representing a combination of high and low mMMSE scores and slopes were generated. Cox survival curves revealed that high mMMSE scores and small slope (ie, slow rate of decline) were related to what appears to be a "protection" against reaching clinical milestones, whereas low scores and large slope (ie, fast rate of decline) were associated with an increase in the risk

of reaching such outcomes. Of interest were the 2 intermediate groups (high mMMSE score and large slope; low mMMSE score and small slope) that did not differ statistically from the reference group. Although the statistically insignificant difference between the 2 high mMMSE score groups may be used to argue against the contribution of the slope, the lack of statistical difference between the low and high mMMSE score groups with small slopes may be interpreted as supportive of the notion that slow rate of cognitive decline is associated with a delay of functional outcome regardless of initial cognitive scores.

Although patients were required to have a total mMMSE score of 30 or above at entry to the current study, their follow-up began at somewhat different phases of the disease course. Consequently, the first year of follow-up may not be viewed as equivalent to the first year of onset of AD for each of the patients. Nonetheless, this study addresses the issue of whether cognitive decline during the first year of clinical follow-up provides incremental information regarding the risk of reaching clinical or functional milestones in subsequent years of follow-up. In this context, the findings suggest that the rate of cognitive decline during this initial phase of follow-up provides information that is not available from cognitive test scores alone or demographic variables regarding the risk of reaching clinical end points in future years of follow-up.

The focus of this study was on 2 functional milestones, the need to be dressed, groomed, and washed and care equivalent to placement in a health-related facility, that typically do not occur until the late stages of AD. However, based on previous research^{18,22} it was reasonable to expect that these 2 selected outcome measures would be reached by a sufficient number of patients within the 5-year follow-up period to deem them appropriate for use in survival analysis. Milestones that occur during the early phases of AD (IADLs) or conversely were not expected to occur within the 5-year duration of the study were not included. However, the relationship we found between the rate of cognitive decline and risk of reaching the 2 mile-

stones selected for the current study is likely to be generalizable to other functional milestones as well.

Although the slope has been used as an indicator of the rate of cognitive decline in AD in other studies as well^{17,32} it is important to emphasize that we do not assume a linear decline over the entire disease course.³³ Instead, linear regression, although imperfect, is a conservative approach that constitutes an adequate estimate of the rate of cognitive decline.

In summary, the rate of cognitive decline is related to functional outcome. Specifically, fast rate of decline during the first year of follow-up is related to greater risk of reaching clinical milestones in subsequent years.

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