Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease:

Prospective analyses from the Predictors Study

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Article abstract—*Objective:* To examine whether either extrapyramidal signs or psychotic features are associated with more rapid progression of Alzheimer's disease. *Background:* It has been unclear whether extrapyramidal signs and psychosis are predictors of faster course or are simply late signs. *Methods:* Two hundred thirty-six patients with mild Alzheimer's disease were recruited in three cities and followed semiannually. *Results:* Using Cox proportional hazards models that adjusted for age, sex, disease severity, and estimated duration of illness at study entry, the presence of extrapyramidal signs at entry was associated with higher relative risk (RR) of reaching moderate cognitive (RR = 2.35, 95% CI = 1.12 to 4.92) or functional (RR = 2.31, 95% CI = 1.37 to 3.90) severity, nursing home entry (RR = 2.51, 95% CI = 1.32 to 4.76), or death (RR = 3.04, 95% CI = 1.31 to 7.05). Psychosis predicted only the functional end point (RR = 1.85, 95% CI = 1.18 to 2.90). Using regression models, modified Mini-Mental State scores declined 1.30 points (95% CI = 0.16 to 2.44) per 6-month interval, more among patients with than those without extrapyramidal signs; patients with psychosis declined 1.15 (95% CI = 0.52 to 1.77) more mMMS points per interval. *Conclusions:* This study confirms extrapyramidal signs and psychosis as robust predictors of disease end points and rapid progression in Alzheimer's disease.

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The aim of the Predictors Study[1] is to develop a model of the progression of AD that can predict disease course in individual patients. We recruited 236 patients with mild probable AD attending three medical centers and are following them at 6-month intervals. A major hypothesis of the study is that the presence of extrapyramidal signs (EPS) or psychotic features at the initial study visit would be predictive of more rapid disease course.

We previously reported[2] a series of analyses examining the effect of the presence of these variables on two measures of disease severity at baseline: the modified Mini-Mental State Examination (mMMS),[3] an index of global intellectual function, and part 1 of the Blessed Dementia Rating Scale (BDRS),[4] a measure of functional capacity. EPS were associated with lower mMMS scores, whereas delusions were associated primarily with impaired functional capacity. These effects were independent of the influence of age and disease duration.

We now report the results of preliminary prospective analyses that directly assess the predictive value of EPS and psychosis for disease course. We approached this issue in two ways. We first evaluated whether the presence of a potential predictive sign was associated with a higher relative risk (RR) of reaching a series of end points representative of different stages of disease severity. We then evaluated the association of these signs with rates of disease progression, expressed as an index of the change over time in the mMMS and BDRS.

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Methods. *Subjects.* Two hundred thirty-six patients with probable Alzheimer's disease were recruited into the study at three sites: Columbia University, Johns Hopkins University School of Medicine, and Massachusetts General Hospital. Details of inclusion and exclusion criteria and recruitment methods have been previously described.[1] Each patient was required to meet NINCDS-ADRDA criteria[5] for probable Alzheimer's disease (pAD) except for the allowances for lesions described below. Intellectual impairment was documented by neuropsychological testing with the standard clinical batteries of each institution. Although actual test batteries differed somewhat at each center, they all included tests of memory, orientation, abstract reasoning, language, attention, and construction. To ensure that severity of dementia was mild at study entry, all patients were required to have an mMMS score of 30 or above (corresponding to approximately 16 on the standard Mini-Mental State Examination[6]). To ensure accurate initial assessment of psychotic symptoms, all patients were required to be maintained off antipsychotic medications for at least 1 month before their initial evaluation.

Exclusion criteria included history or current clinical evidence of substance abuse, schizophrenia, schizoaffective disorder, or major affective disorder prior to the onset of intellectual decline; any ECT treatment within 2 years of recruitment, or 10 or more ECT treatments at any time; history or clinical signs of stroke or a Hachinski Ischemic Score[7] of 5 or more; presence of CNS infection, post-traumatic dementia, toxic-metabolic encephalopathy, cancer, or hematologic, pulmonary, renal, hepatic, or endocrine disorders, Huntington's disease, or multiple sclerosis; or a diagnosis of Parkinson's disease or parkinsonism at any time before the onset of memory loss or intellectual decline. The intent was to exclude active disease that might contribute to cognitive impairment and yield a clinical diagnosis of possible (instead of probable) AD. Patients with small subcortical lesions on CT or MRI that were clinically and historically silent and were judged to be less than 2 cm in diameter were included. Diffuse symmetric periventricular lesions, such as those consistent with small-vessel ischemic change or infarcts or indicative of CSF absorption abnormalities, were not grounds for exclusion. However, patients with cortical lesions of any size or location, or with focal cortical atrophy in a specific vascular distribution, were excluded.

Procedures. All patients were seen at 6-month intervals and underwent the following procedures.

Onset dating and features. At the initial visit, the physician estimated disease duration based on interview of the patient and informants. Disease onset was estimated separately by a standardized onset interview technique that systematically queries the earliest date of the earliest manifestation of specific disease symptoms as well as the latest point at which these symptoms were not present.[8]

Extrapyramidal signs. Selected items from the Unified Parkinson's Disease Rating Scale[9] were used to rate EPS. The reliability of the scale for use in pAD has been established.[10] Voice changes, facial immobility, resting tremor, rigidity (neck and each limb), brady- or hypokinesia, and posture and gait abnormalities were rated as either absent (0), slight (1), mild-moderate (2), marked (3), or severe (4) (see reference 10 for complete form). Signs were coded as either idiopathic, probably induced by current neuroleptic medication, or possibly induced by previous neuroleptic medication. If a patient's signs were possibly or probably drug-induced, then that patient was not included in the analyses that used EPS as a predictor. For all analyses, patients who had at least one sign rated as mild-moderate (2) were considered to have EPS. We used this criterion because ratings of EPS of this severity are more reliable and are apt to be noted by the average clinician.[10]

Psychosis and behavioral changes. A semi-structured interview, the Columbia University Scale for Psychopathology in Alzheimer's Disease,[11] was used to elicit information about symptoms of delusions, hallucinations, illusions, depressed mood, and other specific behavioral signs occurring during the month prior to assessment. Specific delusions queried included paranoid delusions, delusions of abandonment, somatic delusions, and misidentifications. The scale assesses delusion severity based on frequency and the readiness of the patient to accept the truth if corrected. For the current analyses, we utilized both a broad definition of delusions, not requiring them to be persistent or resistant to correction, as well as a stricter definition that required these features.

Cognitive assessment. Cognitive function was examined using the mMMS.[3] This instrument includes all items from the standard Mini-Mental Status Examination[6] and also includes the Wechsler Adult Intelligence Scale Digit Span subtest[12] and additional attention/calculation, general knowledge, language,[13] and construction items. The maximum score on this test is fifty-seven. This is a valid and reliable instrument[14] that is brief yet informative. We used an mMMS score of 15 as an end point in our analyses because we consider it representative of moderate pAD.

Functional assessment. Functional capacity was rated with the BDRS.[4] The reliability and validity of this instrument have been established, and it has proved to be useful in evaluating longitudinal changes in function. We developed a structured interview to guide and standardize BDRS administration. We used a BDRS score of 15 as a specific end point for prediction, representing moderate functional impairment.

Equivalent institutional care rating. We rated the "equivalent institutional care" (EIC) that the patient was receiving.[15] This rating is the second section of a dependency scale that rates the patient's need for care; it summarizes the interviewer's impression, based on all available interview data, of the care the patient received and required regardless of location. Categories include limited home care, adult home (a supervised setting with regular assistance in most activities), and health-related facility. We used the EIC rating of health-related facility as an end point for prediction.

Data analyses. Cox analysis. Cox analyses focused on two predictors, EPS of mild to moderate intensity that were not drug-induced and the presence of the psychotic symptoms—ie, delusions or hallucinations. We chose four end points that we thought had clinical significance: reaching an mMMS score of 15 (moderate cognitive disability), a BDRS score of 15 (moderate functional disability), receiving the equivalent (EIC) of health-related facility care, and death. For each combination of predictor and outcome, we calculated a Cox proportional hazards model that used months from the initial visit as the timing variable. Since preliminary analyses revealed that a patient's age influenced survival, all Cox analyses were stratified by the patient's age at first visit (using the median age of 72 years as the cut-point). A standard set of covariates was included in each analysis: baseline

mMMS score, gender, and estimated duration of illness. The Cox analyses were also used to generate survival curves for patients who did and did not have a predictor at the initial visit. To simplify presentation of the survival curves, we did not stratify them by age. Since preliminary analyses revealed no age group by predictor interactions, we are satisfied that these curves are representative of survival across the two age groups.

To investigate the independent predictive value of EPS and psychosis, additional Cox models were constructed for each end point that included both predictors simultaneously.

Since patients who did not have EPS or psychosis at the initial visit could develop them during the follow-up period, the Cox analyses were also recalculated with the predictors treated as time-dependent covariates. The same standard set of covariates was included in these analyses as well.

The four end points included in our analyses were selected because they are relevant to the progression of AD. Since there is the chance that they are intercorrelated, we adjusted the significance level of the separate, parallel Cox analyses for each end point. We report increased RR for reaching an end point only when the alpha level is <0.01, which represents a conservative adjustment from the $p < 0.05$ level. However, we continue to present 95% confidence limits for the RR values because we view these analyses as exploratory and want to identify predictors worthy of future analysis.

Rate of disease progression. To examine predictors of the rate of AD progression, we used a regression approach. For each patient, linear regression was used to estimate the slope of mMMS and BDRS scores over time, expressed in terms of the 6-month study intervals. Multivariate linear regression analyses were then used to examine predictors of these slopes. Each patient's slope was weighted by the inverse of the standard error of the slope so that data from the more reliable slopes would be more heavily weighted in the analyses. Age, gender, and age at onset were forced into the analyses as covariates. Although the slopes describe disease progression, they do not reflect initial level of performance. To address this issue, follow-up analyses also forced in the baseline mMMS or BDRS score.

Results. Mean patient age at intake into the study was 73.1 ± 8.9 (mean ± SD) years. Mean estimated duration of illness was 6.9 ± 9.2 years. There were 96 men and 140 women; 84% of the group were non-Hispanic whites. Mean mMMS at intake was 37.9 ± 5.6 (by design, no patient's mMMS score was below 30); mean BDRS was 8.0 ± 3.5.

At baseline, 26 patients had at least one EPS that was rated in the mild to moderate range and was not drug-induced. Fifteen patients had EPS that were definitely or possibly drug-induced. One hundred three patients had at least one psychotic feature; 95 had delusions and 22 had hallucinations. There was no systematic relationship between the presence at baseline of EPS and psychotic symptoms (χ^2=1 .59, $p < 0.21$).

Mean age at the first visit was 72.4 ± 8.5 in subjects without and 77.7 ± 9.9 in subjects with EPS ($p < 0.01$ for comparison of the two groups). It was 71.7 ± 9.3 in patients without and 74.9 ± 8.1 in patients with psychosis ($p < 0.01$). At the first visit, mean estimated duration of illness was 3.8 ± 2.5 in subjects without and 4.6 ± 2.7 in those with EPS (NS), and was 3.8 ± 2.5 in patients without and 4.2 ± 2.7 in those with psychosis (NS). Of those with EPS, 40.5% of the patients without and 34.6% of those with EPS were men (NS); 43.2% of patients without and 37.9% of patients with psychosis were men (NS).

Table. Summary of Cox analyses*

Outcome	Predictor	Standard RR, 95% confidence limits	Time-dependent RR, 95% confidence limits
mMMS ≤15	EPS	2.35, 1.12-4.92	1.99, 1.18-3.67
	Psychosis	1.20, 0.69-2.11	0.94, 0.55-1.60
	EPS and psychosis		
	EPS	2.48, 1.19-5.19	Not calculated
	Psychosis	1.28, 0.74-2.23	Not calculated
BDRS ≥15	EPS	2.31, 1.37-3.90	1.92, 1.25-2.94
	Psychosis	1.85, 1.18-2.90	2.07, 1.32-3.26
	EPS and psychosis		
	EPS	2.82, 1.66-4.79	Not calculated
	Psychosis	2.14, 1.35-3.39	Not calculated
Nursing home equivalent care	EPS	2.51, 1.32-4.76	216, 1.42-3.29
	Psychosis	1.53, 0.96-2.43	1.50, 0.99-2.27
	EPS and psychosis		
	EPS	2.57, 2.35-4.88	Not calculated
	Psychosis	1.66, 1.03-2.67	Not calculated
Death	EPS	3.04, 1.31-7.05	Not calculated
	Psychosis	0.87, 0.42-1.81	Not calculated
	EPS and psychosis		
	EPS	3.18, 1.35-7.48	Not calculated
	Psychosis	0.78, 0.35-1.70	Not calculated

* All analyses control for baseline mMMS score, gender, and estimated duration of illness and are stratified by patient's age at first visit. For each outcome, the two predictors were first included in separate Cox analyses, and then were included simultaneously in a single Cox analysis. Cox analyses were also calculated with each predictor treated as a time-dependent covariate.
mMMS Modified Mini-Mental State Examination.
BDRS Blessed Dementia Rating Scale.
EPS Extrapyramidal signs.
RR Relative risk.

All patients were followed for at least 6 months. Two hundred one were followed for ≥1 year, 136 for ≥2 years, 79 for ≥3 years, and 32 for ≥3.5 years.

Cox analyses. The presentation of findings is organized around the four major end points: mMMS of 15, BDRS of 15, EIC comparable with health-related-facility care, and death. The table summarizes the results of the Cox analyses.

mMMS of 15. Fifty-nine patients reached this end point, which is suggestive of moderate disease severity. The RR for reaching this end point was significantly increased in patients with EPS (RR = 2.35, CI = 1.12 to 4.92). Figure 1 presents the survival curves for reaching an mMMS of 15 in patients with and without EPS at the initial visit.

When EPS were treated as a time-dependent covariate, they were associated with increased risk of reaching this end point (RR = 1.99, CI = 1.18 to 3.67). In the time-dependent models, the RR of reaching the end point increases when the patient has EPS at more than one study visit. For example, the RR of reaching the end point for a patient who had EPS at baseline and for five follow-up visits was 62.58 (CI = 2.67 to 105.83).

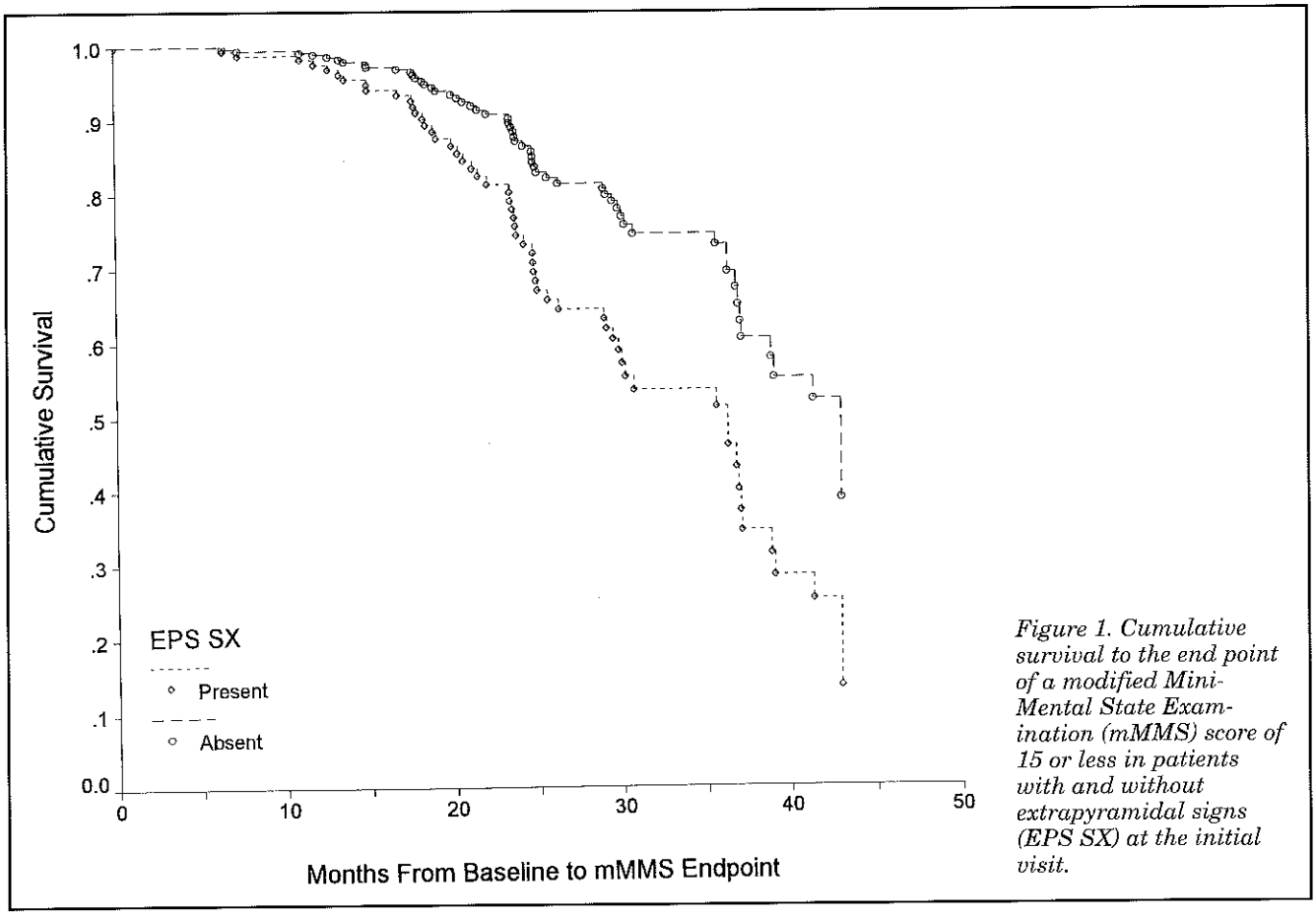

Figure 1. Cumulative survival to the end point of a modified Mini-Mental State Examination (mMMS) score of 15 or less in patients with and without extrapyramidal signs (EPS SX) at the initial visit.

The presence of psychotic symptoms at baseline was not associated with increased risk of reaching this end point (RR = 1.20, CI = 0.69 to 2.11). When psychosis was treated as a time-dependent covariate, it was not associated with increased risk of reaching this end point.

When both EPS and psychosis were included in the Cox model, only EPS were associated with an increased RR of reaching the end point (RR = 2.48, CI = 1.19 to 5.19). This increased RR was significant only at the $p < 0.02$ level, however.

BDRS of 15. Four patients had reached this end point by their initial visit and were excluded from the analyses. Ninety patients reached this end point during follow-up. The presence of EPS at baseline was associated with increased risk of reaching this end point (RR = 2.31, CI = 1.37 to 3.90). Figure 2 presents the survival curves for this analysis. Results were similar if the BDRS score at baseline was substituted for the mMMS score in the Cox analysis (RR = 2.43, CI = 1.43 to 4.13).

When EPS were treated as a time-dependent covariate, they were associated with an increased risk of reaching this end point (RR = 1.92, CI = 1.25 to 2.94).

The presence of psychotic features was also associated with increased RR of reaching this end point (RR = 1.85, CI = 1.18 to 2.90). However, when baseline BDRS scores were substituted for mMMS scores as a covariate in the analyses, the increase in RR for psychotic features was not significant (RR = 1.57, CI = 0.99 to 2.49). When the presence of psychotic features was treated as a time-dependent covariate, it was associated with increased risk of reaching this end point (RR = 2.07, CI = 1.32 to 3.26).

Nursing home care. Over the follow-up period, 20 patients were judged to have reached the point at which they received the equivalent of nursing home care. The presence of EPS at baseline was associated with elevated risk of reaching this end point (RR = 2.51, CI = 1.32 to 4.76). Figure 3 presents the survival curves for this analysis.

When EPS were treated as a time-dependent covariate, it was associated with increased risk of reaching this end point (RR = 2.16, CI = 1.42 to 3.29).

The presence of psychotic symptoms was not associated with an elevated RR of reaching this end point (RR = 1.53, CI = 0.96 to 2.43). When the presence of psychotic features was treated as a time-dependent covariate, it reached only borderline significance (RR = 1.50, CI = 0.99 to 2.27).

When both EPS and psychosis were included in the Cox model, only EPS were associated with an increased RR of reaching the end point (for EPS, RR = 2.57, CI = 2.35 to 4.88, $p < 0.01$; for psychosis, RR = 1.66, 1.03 to 2.67, $p < 0.05$).

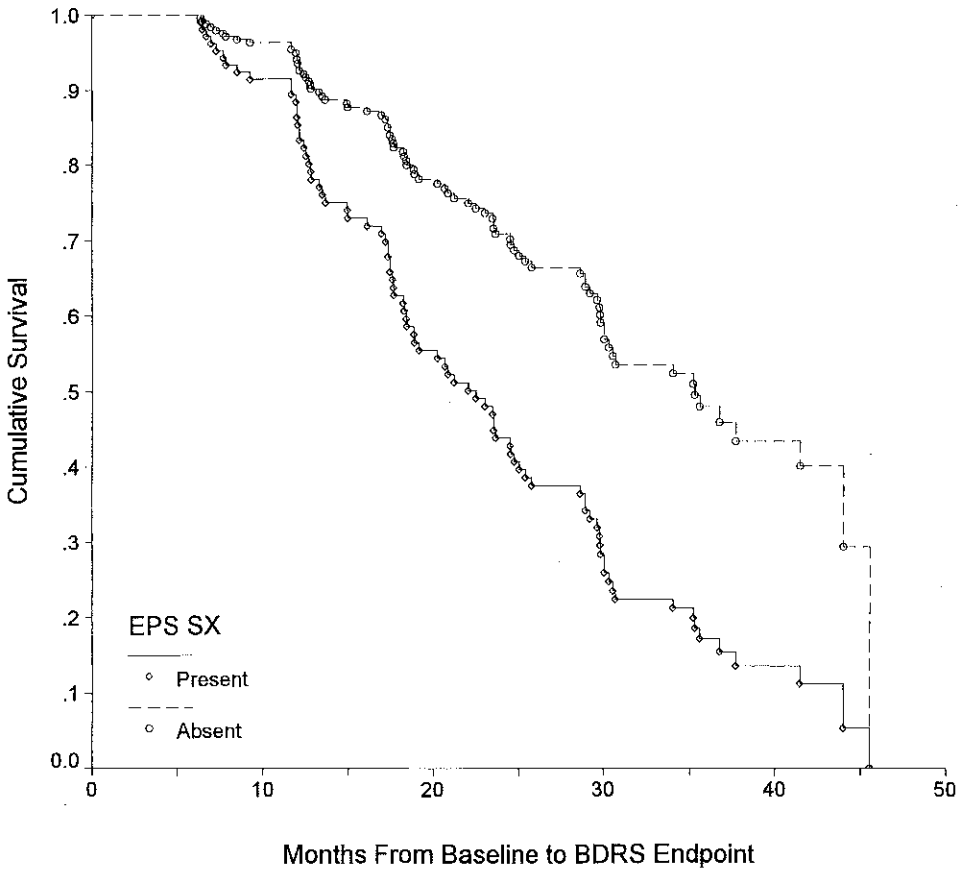

Figure 2. Cumulative survival to the end point of a Blessed Dementia Rating Scale (BDRS) score of 15 or more in patients with and without extrapyramidal signs (EPS SX) at the initial visit.

Mortality. There were 37 deaths. Cox analyses showed that the presence of EPS at baseline was associated with a greater likelihood of dying sooner (RR = 3.04, CI = 1.31 to 7.05). Figure 4 presents the survival curves for this analysis. EPS could not be used as a time-dependent covariate for mortality because almost all patients who died had EPS prior to death.

The presence of psychotic features was not predictive of mortality.

When both EPS and psychosis were included in the Cox model, only EPS were associated with an increased RR of reaching the end point (RR = 3.18, CI = 1.35 to 7.48).

Alternate definitions of psychotic symptoms. The working definition for delusions used in the analyses above did not require that the delusions be persistent or that the patient be unwilling to be convinced that a delusion was untrue. We recalculated all Cox analyses using stricter definitions of delusions that required these features; results were unchanged.

Rate of progression. The slope of mMMS scores was calculated only for the 190 patients who had test scores available from at least three separate occasions. The mean change in mMMS scores over time was a decline of 3.36 ± 2.98 points per 6-month interval. The inverse of the standard error was used to weight the contribution of each slope to the regression analysis. Weights ranged from 0.13 to 15. After age, gender, and age at onset were forced into the regression analyses, the presence of EPS or psychotic symptoms at baseline was strongly and independently predictive of more rapid decline in mMMS scores ($p < 0.03$). In each 6-month interval, mMMS scores declined an additional 1.30 points (CI = 0.16 to 2.44) in patients with compared to those without EPS. None of the other variables in the regression model was independently associated with significant declines in mMMS scores. Patients with psychosis declined an additional 1.15 (CI = 0.52 to 1.77) mMMS points per interval ($p < 0.01$). Again, none of the other variables in the regression models were independently associated with significant mMMS decline. The contributions of EPS and psychosis to mMMS slope were independent; both remained significant when included simultaneously in the regression analysis. Further, their contribution remained significant when the analysis controlled for patients' baseline mMMS scores.

The slope of BDRS scores was calculated only for the 198 patients who had test scores available from at least three separate occasions. Mean change in BDRS scores over time was an increase of 1.20 ± 1.29) points per 6-month interval; higher scores indicate increased functional difficulty. The inverse of the standard error was used to weight the contri-

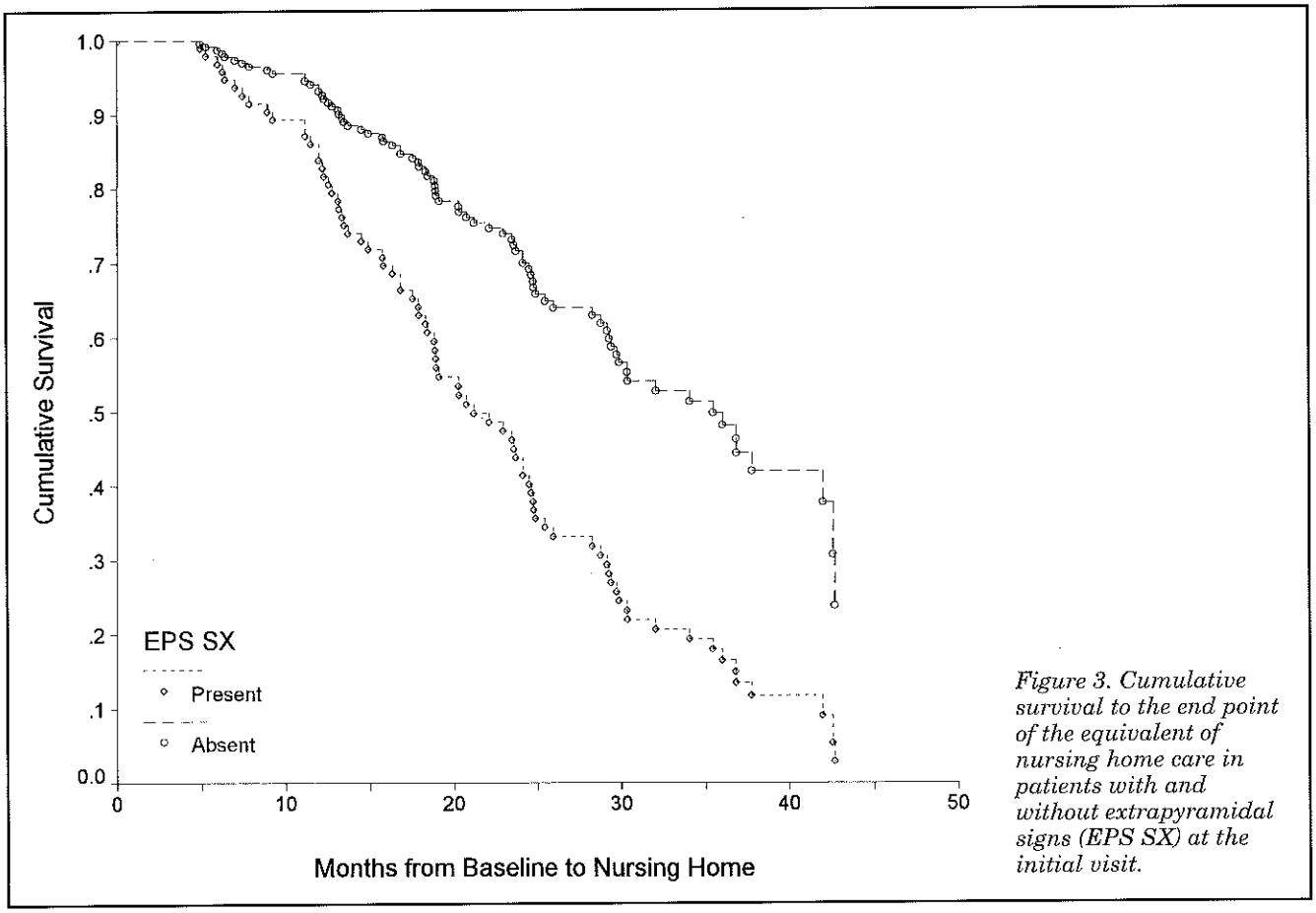

Figure 3. Cumulative survival to the end point of the equivalent of nursing home care in patients with and without extrapyramidal signs (EPS SX) at the initial visit.

bution of each slope to the regression analysis. Weights ranged from 0.36 to 15. After age, gender, and age at onset were forced into the regression analyses, the presence of EPS was associated with more rapid increase in BDRS scores ($p = 0.03$). In each 6-month interval, BDRS scores increased an additional 0.59 points (CI = 0.59 to 1.12) in patients with compared to those without EPS. None of the other variables in the regression equation contributed significantly to the change in BDRS scores. The relationship between EPS and change in BDRS scores remained after controlling for baseline BDRS scores. Psychotic features were not associated with a more rapid change in BDRS scores.

Discussion. These analyses suggest that the presence of EPS or psychotic features at a patient's initial visit are robust markers of more rapid disease course.

While our previous reports suggested an association of these clinical signs with more rapid disease progression,[16-18] several features of the current study design add weight to the current observations. This cohort is larger than that of most previous studies and has been followed at regular intervals for a longer time, which provided additional statistical power to the analyses. Also, we recruited patients from three different medical centers, ensuring that the diagnosis of AD and the identification of predictive signs were not idiosyncratic to a single institution.

An important issue when evaluating predictors of course in AD is whether the predictive signs actually indicate a faster course or simply that the patient's disease is more advanced. We specifically selected patients with relatively mild disease severity at entry so that the predictive signs could not be considered simply a feature associated with late disease. In addition, the Cox and linear regression model analyses controlled for disease severity and duration at baseline. We therefore believe that EPS and psychosis are truly predictive of a more rapid disease course.

In the Cox models, EPS were more useful than psychosis for predicting the different end point outcomes considered. There are several reasons why this might be the case. First, EPS were associated with an array of specific pathologic changes in a clinicopathologic study.[19] These pathologic changes might be more consistently related to disease progression. Second, EPS may be more consistently observed than psychosis. Aside from measurement error, it is reasonable to assume that EPS, once manifested, will remain. Alternatively, the prevalence of psychosis may vary as a function of AD severity (eg, reference 20). Despite these considerations, psychosis had a unique predictive effect in the random effects models and clear utility as a predictor.

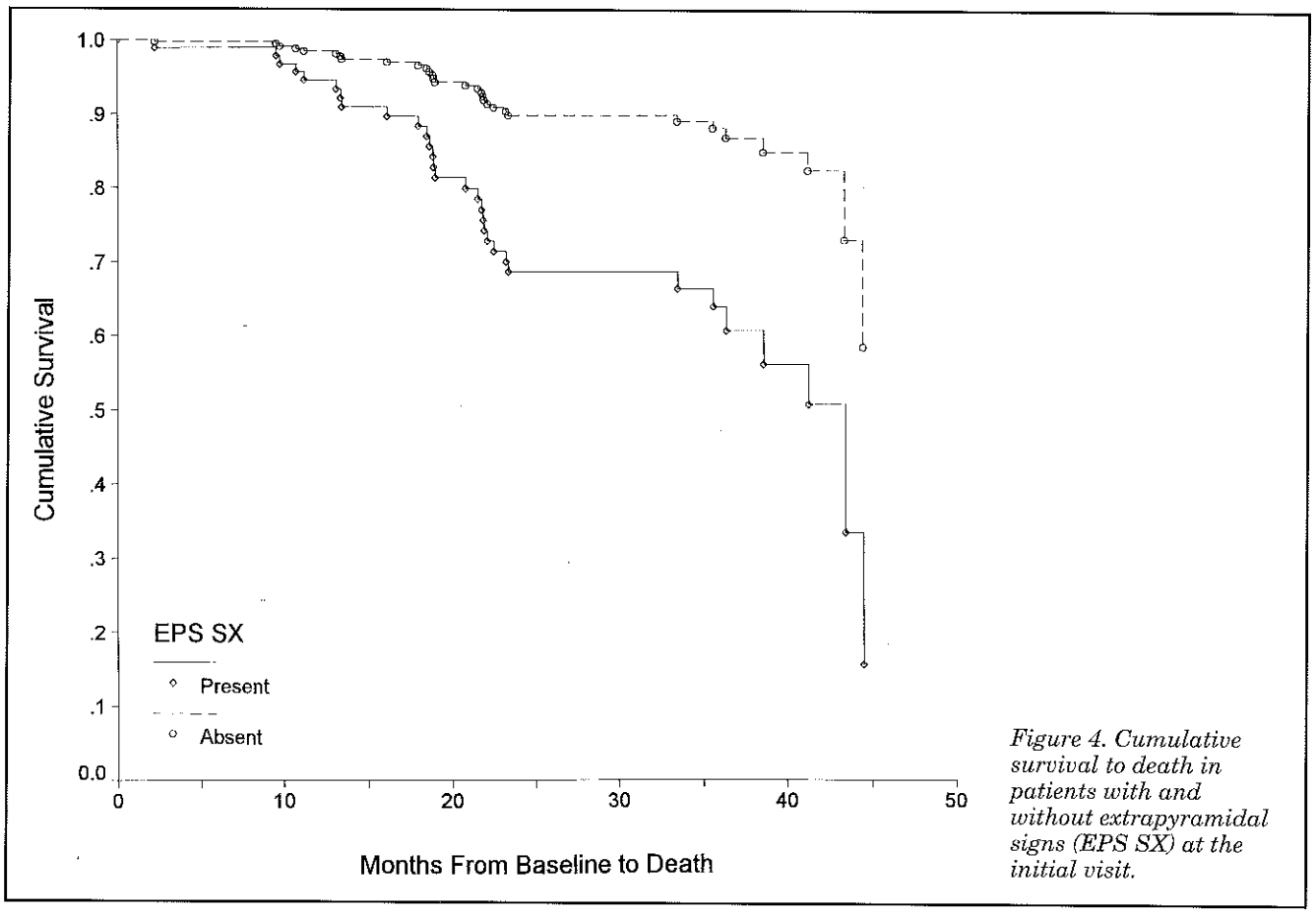

Figure 4. Cumulative survival to death in patients with and without extrapyramidal signs (EPS SX) at the initial visit.

The use of the predictors as time-dependent covariates reflects the observation that they may emerge at any point in the disease. We previously reported actuarial analysis of similar data acquired from a smaller cohort, demonstrating that almost all patients will develop EPS and psychotic symptoms at some point in the disease.[21] These clinical signs may themselves represent points in disease progression. In this approach, earlier emergence of these clinical signs may indicate more rapid progression overall. The disadvantage of the time-dependent covariate approach for developing models to predict disease course is that future changes in predictor status are unknown at the time the prediction is made.

EPS were associated with differential rates of disease progression, but this does not establish EPS as a marker of disease subtypes. This determination awaits fuller understanding of the neuropathologic correlates of these clinical signs. The presence of EPS may relate to specific pathologic changes.[19] Recently, descriptions of a "Lewy body variant" of Alzheimer's disease suggest it might be characterized by a specific neuropsychological profile, an abnormal EEG, and parkinsonism.[22] Because our follow-up of the present cohort includes information about the inception of EPS and behavioral manifestations, we may eventually be in a position to investigate the clinical and pathologic correlates of the Lewy body variant and contrast it with EPS or psychotic features seen in isolation. This determination must await more postmortem data.

In summary, the current data suggest that EPS and psychosis are predictors of a more rapid disease course. We anticipate that these clinical signs will be useful in fulfilling the eventual goal of the Predictors Study, which is to develop a specific algorithm for predicting the disease course of individual patients.

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