Dependence Clusters in Alzheimer Disease and Medicare Expenditures

A Longitudinal Analysis From the Predictors Study

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Introduction: Dependence in Alzheimer disease has been proposed as a holistic, transparent, and meaningful representation of disease severity. Modeling clusters in dependence trajectories can help understand changes in disease course and care cost over time.

Methods: Sample consisted of 199 initially community-living patients with probable Alzheimer disease recruited from 3 academic medical centers in the United States followed for up to 10 years and had ≥2 Dependence Scale recorded. Nonparametric K-means cluster analysis for longitudinal data (KmL) was used to identify dependence clusters. Medicare expenditures data (1999-2010) were compared between clusters.

Results: KmL identified 2 distinct Dependence Scale clusters: (A) high initial dependence, faster decline, and (B) low initial dependence, slower decline. Adjusting for patient characteristics, 6-month Medicare expenditures increased over time with widening between-cluster differences.

Discussion: Dependence captures dementia care costs over time. Better characterization of dependence clusters has significant implications for understanding disease progression, trial design and care planning.

Key Words: Alzheimer disease, Dependence Scale, Medicare expenditure, cluster analysis

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Alzheimer disease (AD) and its progression over time are often characterized clinically by impairment in cognition, function, and behavior. Early symptoms often include memory loss and impaired cognition, later stages are characterized by functional decline, behavioral disturbances are common but tend to be more difficult to predict. As disease progresses, patients decline in all of these domains but relative contributions from each to patients' decline change over time. Numerous scales have been developed to measure impairment in cognition, function, and behavior. However, these scales are sometimes difficult to understand and are limited in their meaningfulness to patients, caregivers and health care providers.[1,2] Tracking disease progression by focusing on impairment in cognition, function, or behavior separately may not capture the full impact of the disease. Regardless of their individual contribution, limitations in cognition, function, and behavior ultimately lead to patients needing increased assistance from and dependence on others. As a result, a unifying conceptual framework of dependence in AD has been proposed as a more holistic, transparent, and meaningful representation of disease severity.[1,3]

The Dependence Scale (DS), which directly measures the amount of assistance patients require, has been widely adopted as a measure of disease severity.[3–6] A number of studies have examined the relationship between dependence and costs of care for patients with dementia.[7–12] Several showed DS as an independent predictor of cost over and above measures of function, cognition, behavioral problems, and comorbid conditions.[8–11] One study showed that the DS explained as much variation as measures of cognition, function, and behavior combined.[11] Two path analyses reported that the impact of cognition, function, and neuropsychiatric symptoms on costs was largely mediated by dependence.[7,11]

Although these existing studies clearly established the relationship between the DS and cost of care, they have an underlying assumption that the study population can be represented by a single pattern of change, or can be stratified by a few pre-specified risk factors such as age, sex, and disease history. In reality, patients differ from one another in their rate of increasing dependence. Few people may actually follow the pattern of average decline. Rather, there may exist subsets of patients whose trajectories differ from average patterns. Not accounting for this potential heterogeneity may obscure clinical impact of study findings.[13,14] In this paper we use a nonparametric longitudinal clustering method based on k-means clustering[15] to explore the possibility that there are different trajectories of dependence, each with a unique time course and associated costs.

Our primary aims were to (1) identify distinct DS cluster patterns in a cohort of AD patients whom we have followed from early stages of the disease for up to 10 years, and (2) examine the relationship between DS cluster pattern

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and total and component Medicare expenditures over time. We hypothesized that different DS clusters will differentiate Medicare expenditures.

METHODS

Participants and Setting

The sample was drawn from the Predictors 2 cohort, and consisted of 199 community-living patients with probable AD recruited from 3 sites in the United States: Columbia University Medical Center, Johns Hopkins School of Medicine, and Massachusetts General Hospital.[16] Inclusion and exclusion criteria are fully described elsewhere.[16] Briefly, subjects met Diagnostic and Statistical Manual of Mental Disorders-3rd revision criteria for primary degenerative dementia of the Alzheimer type and NINDS-ADRDA criteria for probable AD.[17,18] Enrollment required a modified Mini-Mental State Examination (mMMS) score ≥ 30.[19] The mMMS (range: 0 to 57) is an expanded measure of global cognitive status based on the original Folstein Mini-Mental State Examination (MMSE),[20] and includes the Wechsler Adult Intelligence Scale,[21] Digit Span subtest, as well as additional attention/calculation, general knowledge, language, and construction items. A conversion equation, mMMS = 1.73 MMSE+2.81, can be used to relate mMMS to the original MMSE. An mMMS score ≥ 30 is therefore equivalent to $\sim \geq 16$ on the original MMSE.[19,20] Recruitment of patients began in 1998 with ongoing follow-up until 2016. After the baseline visit, all patients were re-evaluated semiannually. Patients who did not respond at a particular visit could respond at a subsequent visit. Patients were followed for varying number of years, reflecting both ongoing accrual of patients and patient deaths. Median years of follow-up was 5 years from baseline. The cluster analysis included 182 participants who were followed at least 5 years (10 visits) with at least 2 DS assessments.

The study was approved by the appropriate local Institutional Review Boards. Written informed consent was obtained from all participants. Because patients were followed at academic AD centers and participated in the same multisite study and diagnosed with the same case conferencing protocol, they were well-characterized, with high degrees of certainty and consistency across sites in AD diagnosis. Eighty-one patients have had brain autopsies. Postmortem diagnoses have been completed for 79 patients, 69 of whom (87.6%) had AD-type pathologic changes based on CERAD and NIA-Reagan Criteria.[22,23]

Individuals were matched to Medicare Beneficiary Summary File using social security number and Medicare beneficiary ID. The study period for the current analysis was defined to begin with individuals' first clinical visit or beginning of Medicare data availability (January 1, 1999), whichever is later, and to end with the last clinical visit, end of Medicare data availability (December 31, 2010 at the time of data acquisition), or death. Eight subjects who could not be identified in Medicare data were dropped. Because Medicare claims from individuals who were covered under managed care plans are incomplete, we followed CMS Chronic Condition Warehouse guidelines and excluded observations from subjects who were not covered by Medicare fee-for-service providers for 10 or more months during a calendar year (or had no >1 month which is not covered by fee-for-service during the year of death if the participant died).[24] Medicare claims analysis included 174 remaining subjects.

DS

The DS consists of 13 items, representing a wide range of level of care required by a patient, from relatively subtle items such as needing reminders or advice to more gross forms such as needing to be fed.[4] All items deal with patients' needs. In some cases, the need is only for supervision, without any specific tasks linked to the need. The instrument is designed to be administered to a reliable informant who lives with the patient or one who is well-informed about the patient's daily activities and needs. With the exception of the first 2 items (needs reminders to manage chores, needs help to remember important things such as appointments) which are coded as 0 (no), 1 (occasionally, at least once a month), and 2 (frequently, at least once a week), responses to the rest of the items are coded dichotomously and indicate whether the patient requires assistance in a particular item (0 = no, 1 = yes). The total DS score is the sum of scores on all 13 items (range: 0 to 15), and provides a continuous index of progressively greater dependence on others. The full DS Questionnaire is included in the Supplemental Materials (Supplemental Digital Content 1, http://links.lww.com/WAD/A289).

Clinical and Demographic Characteristics

Patient cognitive status was measured by mMMS.[19,20] Lower mMMS scores indicate worse cognitive status. Functional capacity was measured by the Blessed Dementia Rating Scale (BDRS) Parts I (Instrumental Activities of Daily living) and II (Basic Activities of Daily living).[25] Total BDRS score is the sum of scores on all items (range = 0 to 17), with higher scores indicating worse functional status. The Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), a semistructured interview administered by a physician or a trained research technician, was used to measure patients' psychotic, behavioral, and depressive symptoms.[26,27] The Unified Parkinson's Disease Rating Scale was used to measure extrapyramidal signs.[27] Patients' medical histories were used to construct a modified version of the Charlson index of comorbidity.[28] Comorbid conditions included myocardial infarct, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, cerebrovascular disease, gastrointestinal diseases, mild liver disease, diabetes, chronic renal disease, and systemic malignancy. No patients reported clinical strokes, metastatic tumors, or acquired immunodeficiency syndrome at baseline. Patients' age, sex, and highest level of education were also recorded.

Medicare Expenditures

Medicare expenditures were obtained from Medicare Standard Analytic Files and included all covered services (inpatient, outpatient, physician, durable medical equipment, skilled nursing, home health, and hospice care). We computed total expenditures in 6-month intervals since baseline, reflecting actual payments to each beneficiary every 6 months. Expenditures were adjusted to $2018 using the medical care component of the Consumer Price Index.

Statistical Analysis

Nonparametric K-means cluster analysis for longitudinal data (KmL)[15] was used to identify distinct clusters of participants with similar DS trajectories. To find latent trajectory classes, parametric approaches such as latent mixed growth model analysis require assumptions of trajectories (eg, linear, quadratic, cubic) and distributions of observations (eg, Gaussian).[29,30] In the current analysis, since the DS ranges between 0 and 15, with varying distribution over time, making distributional assumptions is likely to be too rigid. Because of ceiling and floor effect of

the scale, modeling trajectories using parametric approaches can require too many parameters. We therefore chose to relax the parametric assumptions and explore the possibility that there are different trajectories of dependence using a nonparametric approach. As a nonparametric approach, KmL has the advantage of not requiring specific forms of longitudinal trajectories or distributions of the observations. Optimal number of clusters was determined using the maximum votes between Calinksi and Harabatz criterion,[31] Ray and Turi criterion,[32] and Davies and Bouldin criterion.[33] To describe participants in each identified cluster, baseline participant characteristics were compared by cluster using 2-sample t tests for continuous variables and χ^2 tests for categorical variables. We further evaluated the predictive ability of each baseline characteristic separately and when combined using repeated cross-validation. For each run, data were split into 80% training and 20% test set. Logistic regression was estimated with cluster membership as the dependent variable and baseline characteristics as predictors in the training set. Area under the receiver operating characteristic curve (AUC) was computed to evaluate prediction performance of the estimated regression model using the test set. This process was repeated 100 times, and the mean and 2.5% and 97.5% quantiles were computed. For the identified clusters, baseline DS scores and rate of change were compared between clusters using linear regression and linear mixed effect regression with time as a continuous variable. Cluster analyses were performed in R version 3.5.1[34] and KmL (version 2.4.1).[15]

After DS trajectories were identified, we computed Medicare expenditures over time by DS cluster. Generalized linear mixed models was used to estimate the relationship between DS trajectory group and Medicare expenditures.[35] Appropriateness of distributional family and link functions were examined using modified Park tests. Final estimation model additionally controlled for patient's baseline age, sex, education, baseline function, cognition, psychiatric symptoms, extrapyramidal signs, APOE-4 allele, and indicators for comorbidities in the Charlson index. Because the sample was overwhelmingly non-Hispanic White, race and ethnicity were not included as control variables. Time, measured in 6-month intervals as a continuous variable, and interaction between cluster and time were included to estimate time trends. Average marginal effects of each variable on predicted mean expenditures (marginal effects of the x's on $E[y|x]$) were reported. For categorical variables such as DS cluster, marginal effects estimates the between-group difference in the adjusted predicted expenditures. Estimation was performed using Stata 13.0.[36]

RESULTS

Identifying Dependence Trajectory Groups

Maximum votes between Calinksi and Harabatz criterion,[31] Ray and Turi criterion,[32] and Davies and Bouldin criterion[33] to determine optimal number of clusters showed that 2 clusters were the optimal. Figure 1 shows the longitudinal trajectories of these 2 clusters with average trajectories smoothed by locally estimated scatterplot smoothing (loess) regression, a nonparametric technique that uses local weighted regression to fit a smooth curve through points in a scatter plot.[37] At baseline, DS score in cluster A (mean = 6.10, SD = 2.08) was on average 2.25 points higher ($t_{180} = 7.48$, $P < 0.0001$) than in cluster B (mean = 3.85, SD = 1.94). DS scores worsened in both clusters over time. On average, DS score in cluster A worsened by 0.74 points every 6-month (SE = 0.038, $t_{161.89} = 19.19$, $P < 0.0001$), while DS score in cluster B worsened by 0.42 points (SE = 0.038, $t_{132.11} = 10.95$, $P < 0.0001$). Estimation using a mixed effects model with linear time trend showed that the rate of change over time significantly differed by cluster ($\beta = -0.32$, SE = 0.054, $t_{146.28} = -5.97$, $P < 0.0001$). As such, we identify cluster A as high initial dependence, faster decline, and cluster B as low initial dependence, slower decline.

Characteristics of Dependence Trajectory Groups

Table 1 compares baseline characteristics by DS cluster. Compared with patients in cluster B, patients in cluster A were older, more likely to be female, had worse function and cognition, and more likely to have psychiatric symptoms and extrapyramidal signs. There were no differences between cluster in education, APOE status, and years of follow-up. Although Charlson index did not differ by cluster, rates of liver disease and peripheral vascular disease were higher in cluster B. Repeated cross-validation showed that BDRS [AUC = 0.73, 95% confidence interval (CI) = 0.56, 0.86) and mMMS (AUC = 0.73, 95% CI = 0.56, 0.88) were the best predictors among other baseline characteristics of DS trajectory cluster. When all baseline measures were combined, AUC improved to 0.80 (95% CI = 0.67, 0.93). (Detailed results on cross-validation available upon request.)

Medicare Expenditures Trajectories

Figure 2A and B show observed 6-month and 5-year cumulative Medicare expenditures per patient by DS cluster. For each 6-month interval, Medicare expenditures was higher in cluster A than cluster B (mean expenditures $5456 vs. $2715, range: $2078 to $7649 vs. $1569 to $4933). Over time in 5 years, differences in expenditures between clusters

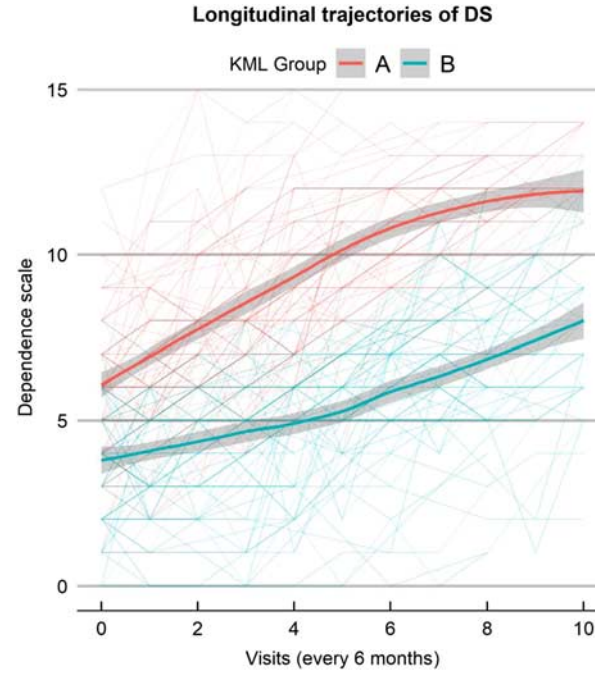

FIGURE 1. Dependence Scale (DS) Cluster Identification. Cluster A: high initial dependence, faster decline. Cluster B: low initial dependence, slower decline. full color online

TABLE 1. Baseline Characteristics of Dependence Trajectory Groups

	Cluster A High Initial Dependence, Faster Decline	Cluster B Low Initial Dependence, Slower Decline	
N	**99**	**83**	
Variables	**Mean (SD)**	**Mean (SD)**	***P***
Age	76.8 (7.7)	73.8 (7.1)	0.001
Female (%)	66.7	43.4	0.002
Years of education	14.3 (3.0)	14.9 (3.3)	0.229
Charlson comorbidity score	1.5 (2.0)	1.9 (2.8)	0.971
Individual comorbidity (%)			
Hypertension	45.9	42.2	0.613
Diabetes	13.3	10.8	0.619
Myocardial infarction	7.1	8.4	0.746
Congestive heart failure	12.2	16.9	0.377
Cerebrovascular disease	11.2	19.3	0.130
Chronic obstructive pulmonary disease	12.2	16.9	0.377
Liver disease	4.1	12	0.046
Chronic renal disease	7.1	12	0.260
Systemic malignancy	12.2	12	0.968
Peripheral vascular disease	5.1	13.3	0.054
APOE-4 allele (%)			
No 4s	35.4	37.3	0.639
One 4	32.3	36.1	
Two 4s	9.1	10.8	
Dependence Scale	6.1 (2.1)	3.9 (1.9)	0.0001
Modified Mini-Mental State Examination	35.6 (6.3)	40.9 (5.8)	0.0001
Folstein Mini-Mental State Examination	21.1 (3.2)	23.7 (3.1)	0.0001
Blessed Dementia Rating Scale	9.0 (3.8)	5.7 (3.6)	0.0001
Presence of psychiatric symptoms (%)	40.4	21.7	0.007
Extrapyramidal signs (%)	22.1	4.9	0.0001
Years of follow-up	7.8 (3.8)	6.6 (3.1)	0.251

accumulated to $54,557 for cluster A, twice as high as $27,153 for cluster B.

Generalized linear mixed models estimation results showed that after controlling for patient's demographic and clinical characteristics, the DS trajectory cluster was significantly associated with Medicare expenditures (Table 2). Although the magnitudes of the effects were small, time, and interaction between time and cluster were both statistically significant, suggesting an overall increase in expenditures over time, and a slightly faster rate of increase in expenditures in cluster A than cluster B. Taking the interactions into account, results showed an average increase of $255 in Medicare expenditures per person every 6 months, and being in cluster A was associated with an average of $1604 higher Medicare expenditures than cluster B. Patient's function, but not cognition or psychiatric symptoms, still had a small but significant effect on Medicare expenditures in the full model. A 1-point increase in the BDRS was associated with $253 higher expenditures. Extrapyramidal signs were associated with $4864 higher Medicare expenditures. Myocardial infarction and liver disease also were associated with higher Medicare expenditures.

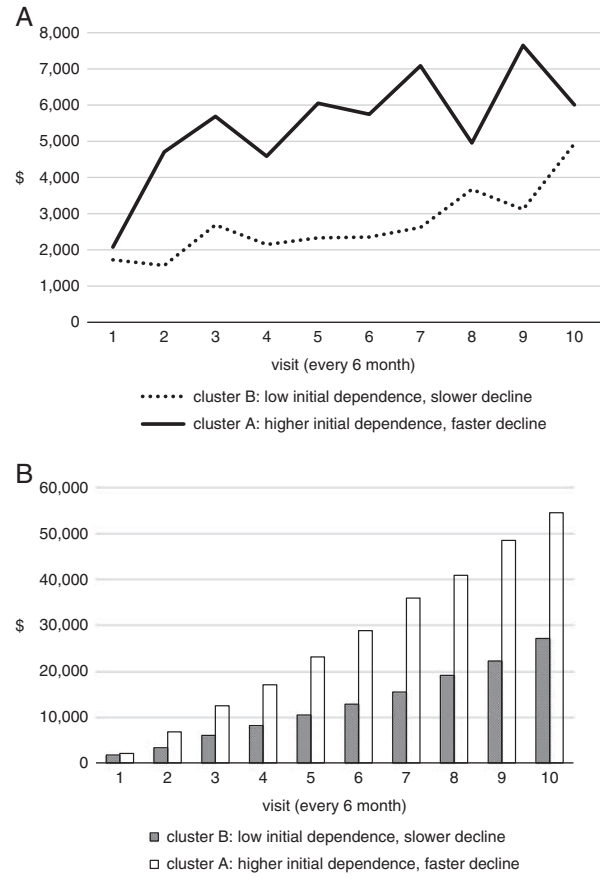

FIGURE 2. Six months and cumulative Medicare expenditures by Dependence Scale (DS) clusters. A, Six-month Medicare Expenditures over time. B, Cumulative Medicare Expenditures. Cluster A: high initial dependence, faster decline. Cluster B: low initial dependence, slower decline.

Sensitivity Analysis

To examine stability of the identified clusters, we repeated the KmL analyses using subjects with up to 3 years of follow-ups (6 visits). Applying the same inclusion criteria, 180 subjects were included (2 subjects were excluded due to lack of number of follow-ups within 3 y). KmL identified 2 clusters with similar trajectories as found when 5-year follow-up data were used. Concordance between cluster identifications was 94%; only 10 subjects were clustered differently. Baseline characteristic comparison remained similar. Results from comparison of Medicare expenditures between clusters also remained similar.

DISCUSSION

In this cohort of patients with initially mild AD followed for up to 10 years, we identified 2 distinct clusters of patients with subtle differences at baseline and rate of decline in dependence over time. Patients in one cluster had higher initial dependence and faster rate of decline, those in the other had lower initial dependence and slower decline. At baseline, patients in the lower dependence cluster, with an average of DS score of 3.8, needed household chores done for them.[38] Those in the higher dependence cluster, with an average of 2.25 points higher dependence score,

TABLE 2. Estimated Relationship Between Dependence Scale Cluster and Medicare Expenditures

	Coefficient Estimates		Average Marginal Effect	
Variables	**Coefficient (SE)**	**95% Confidence Interval**	***dyldx* (SE)**	**95% Confidence Interval**
Dependence Scale cluster faster vs. slower decline	0.807 (0.229)*	0.358, 1.256	1604 (646)**	338, 2870
Interval	0.080 (0.014)*	0.053, 0.107	255 (62)*	133, 376
Dependence Scale cluster×interval	0.048 (0.022)**	0.004, 0.092		
Age	−0.011 (0.009)	−0.028, 0.006	−52 (42)	−134, 29
Female	−0.079 (0.126)	−0.326, 0.167	−374 (598)	−1546, 798
Education	0.017 (0.020)	−0.021, 0.056	81 (93)	−102, 264
APOE-4 missing	0.026 (0.167)	−0.301, 0.353	157 (1000)	−1803, 2116
Any APOE-4 allele	−0.380 (0.205)	−0.782, 0.022	−1875 (1013)	−3861, 110
Blessed Dementia Rating Scale	0.054 (0.017)***	0.020, 0.087	253 (88)***	80, 425
Mini-Mental State Examination	0.019 (0.018)	−0.017, 0.055	91 (87)	−80, 263
Psychiatric symptoms	−0.205 (0.165)	−0.528, 0.119	−967 (793)	−2521, 586
Extrapyramidal signs	1.029 (0.227)*	0.585, 1.473	4864 (1265)*	2385, 7343
Hypertension	0.227 (0.124)	−0.017, 0.470	1072 (605)	−114, 2259
Diabetes	0.133 (0.186)	−0.232, 0.498	629 (886)	−1107, 2365
Myocardial infarct	0.691 (0.245)***	0.212, 1.170	3267 (1239)***	838, 5696
Congestive heart failure	−0.359 (0.214)	−0.779, 0.061	−1695 (1051)	−3755, 364
Cerebrovascular disease	−0.029 (0.204)	−0.428, 0.371	−136 (964)	−2025, 1753
Chronic obstructive pulmonary disease	0.297 (0.212)	−0.118, 0.711	1403 (1017)	−590, 3395
Liver disease	0.943 (0.367)**	0.225, 1.662	4458 (1848)**	836, 8080
Renal disease	0.250 (0.289)	−0.315, 0.816	1182 (1365)	−1493, 3857
Cancer	0.004 (0.253)	−0.492, 0.500	19 (1197)	−2326, 2365
Peripheral vascular disease	0.140 (0.140)	−0.134, 0.414	609 (614)	−594, 1812

*$P < 0.001$.
**$P < 0.05$.
***$P < 0.01$.

needed to be escorted when going outside or accompanied when bathing or eating. DS score for patients in the higher initial dependence cluster worsened by 1.5 points every year, while DS score in the lower initial dependence cluster worsened by 0.8 points every year. These rates of decline are in line with earlier reports showing that in patients with mild AD, those who remained stable in their level of care need worsened ∼1 point in the DS in 18 months while those experiencing a decline in their level of care need worsened ∼2 points during the same period.[6] The distinct clusters of dependence are consistent with previous reports of heterogeneity in the disease course. For example, Holtzer et al[39] reported that lower baseline cognitive scores and faster rate of decline was associated with increased risk of reaching worse clinical milestones at follow-up. Results in this study shows that differential rate of decline in the DS trajectory provides information above and beyond those from baseline data alone on the trajectories of disease progression.

There were statistically significant differences in age, cognition, function, and psychiatric symptoms at baseline between patients by dependence cluster. However, most of these differences are minor and all subjects met entry criteria requiring mild disease severity at baseline. The largest between cluster differences are in psychiatric symptoms and extrapyramidal signs, both of which have been related to more severe disease course.[4,8] Here we observed them as associated with different trajectories of change in dependence.

Several studies have shown that increased cost of dementia care with increased dependence.[7–12] Except for 1 study,[11] cost outcomes in these studies have been computed using self-reported utlization measures. Our study extends this line of inquiry by highlighting substantial differences in Medicare expenditures between distinct dependence clusters. The magnitude of our estimates are comparable to those from existing studies using self-reported costs. A small but significantly different rate of increase in expenditures between clusters highlights the cumulative effects on cost of care over time from faster rate of decline.

There are several limitations to this study. Patients were selected from tertiary care university hospitals and specialized diagnostic and treatment centers and thus represent a nonrandom sample of those affected by AD in the population. Our sample also was predominantly White, non-Hispanic, and highly educated. Caution is needed in generalizing the results of this study to patients of other ethnicities, lower levels of education and income and to community AD patients. Relative homogeneity of our sample may mask differences in clinical measures and patterns of dependence trajectory and health care utilization. For example, Black and Hispanic patients with moderate to severe dementia have been shown to have higher prevalence of dementia-related behavioral problem than Whites.[40] Sociodemographic differences among different racial/ethnic groups also may influence patterns of health care utilization and modify the effects of the clinical variables. Future research will need to examine dependence trajectories and associated cost trajectories in samples that are more representative of the general population.

Dependence as an overall measure of dementia progression should be considered as a complementary measure that allow an intuitive and readily understandable common language for multiple stakeholders in assessing the impact of dementia, translating clinical changes into costs, or assessing potential benefits of interventions. It should not be considered as a replacement for other measures.

A major contribution of this study lies in the rigorous clinical evaluation, diagnosis and long-term follow-up that patients received. Clinical diagnosis took place in university hospitals with specific expertise in dementia and was based on uniform application of widely accepted research-based

criteria via consensus diagnostic procedures. Our cohort had high rates of follow-up with little missing data. Clinical signs were ascertained and coded in standardized fashion at each visit. Patients were recruited at early stages of the disease and followed semiannually for up to 10 years. Linkage to Medicare expenditures avoids recall biases associated with self-rated health care utilization and difficulties in assigning cost estimates from utilization. The cohort therefore describes the full range of disease progression and Medicare expenditures over time, permitting more accurate estimates of trajectories and associated costs.

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