Which Alzheimer Patients Are at Risk for Rapid Cognitive Decline?

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ABSTRACT

In the current study of 1062 Alzheimer's disease (AD) patients, we employed receiver operating characteristic curve analysis to identify characteristics of patients at increased risk for rapid cognitive decline. The patients are participants at one of the nine Alzheimer's Disease Research Centers of California. Rapid decline was defined as a 3-point or greater loss on the Mini-Mental State Examination (MMSE) per year, post visit. The independent variables were age at clinic visit, age at symptom onset of AD, MMSE at patient visit, years of education, gender, ethnicity, living arrangement, presence of aphasia, delusions, hallucinations, and extrapyramidal signs. Receiver operating characteristic curve analysis indicated that AD patients presenting with moderate to severe aphasia, age at clinic visit of 75 years or less, and an MMSE greater than 7 were at increased risk for rapid cognitive decline. This information could help clinicians target these patients for pharmacologic interventions, facilitate long-term care planning, and potentially create savings by delaying or stabilizing the course of the disease. (J Geriatr Psychiatry Neurol 2002; 15:000–000).

Clinicians continually face a variety of decisions, ranging from attempts to match individual patients with the treatment most likely to produce benefit and least likely to produce side effects, to identifying which patients are at greatest risk for negative clinical outcomes, and thus are in greatest need of intervention. Alzheimer's disease (AD) is an illness for which the identification of patients at high risk for rapid disease progression is particularly relevant. Many investigators stress the importance of intervening in the early stages of AD to prolong functionality and extend the time to institutionalization.[1–4] Identifying those at high risk for rapid cognitive decline could help target these patients for pharmacologic interventions; benefit clinicians, families, and policy makers by facilitating planning for long-term care; and potentially create savings by delaying or stabilizing the course of the disease. The administration of cholinesterase inhibitors such as tacrine and donepezil has been associated with modest improvements in cognition in AD patients, and such interventions could be particularly important in those AD patients at greatest risk for a rapid rate of cognitive decline.

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In this study of 1062 AD patients, with 1472 associated clinic visits, who were evaluated at nine Alzheimer's Disease Research Centers of California (ARCCs), we employed receiver operating characteristic curve (ROC) analysis for identifying the characteristics of AD patients at risk for rapid cognitive decline. This analysis is a signal detection technique, well established and widely used in medical research for establishing the sensitivity and specificity of medical tests. In 1992, Kraemer expanded and developed the use of ROC specifically for prediction studies.[5]

Traditionally, randomized clinical trials and/or epidemiologic studies provide information on the risk factors for specific illnesses and the prognostic significance of these risk factors. These studies tend to employ linear models that focus on identifying which variables increase risk for a specific outcome rather than identifying which patients are at greatest risk for that outcome. Additionally, linear models yield risk scores that are often difficult to apply to the individual patient who is being evaluated. Receiver operating characteristic curve analysis, on the other hand, provides information regarding the characteristics of patients at greatest risk for the specified clinical outcome. Such information not only adds a level of precision but may also be easier to apply clinically. Using information on variables that would be readily available or could more easily be assessed by clinicians during a patient visit, we employed the ROC method to identify characteristics of AD patients at increased risk for rapid cognitive decline.

METHODS

Design and Subjects

The study design was a naturalistic, longitudinal sample with clinical data. The overall sample was composed of 1062 patients with possible or probable AD from nine ARCCs. Subjects were AD patients, between 40 and 96 years of age at the time of their inclusion in the study (mean = 74.07, SD = 8.20), with 704 females and 358 males participating. The mean Mini-Mental State Examination (MMSE)[6] at entry into the current study was 18.4 (SD = 6.1; range 4–30). Eighty-five patients were black, 92 were Hispanic, 845 were Caucasian, and 40 were of other ethnicities (Table 1). Table 2 presents the number of subjects in each dementia stage at the time of their entry into the study and the associated MMSE range for each stage. Patients presenting with an MMSE < 4 were not included in the study at entry.

Setting

The ARCCs are state-funded, university-based, multidisciplinary clinics that specialize in the evaluation of patients with possible progressive cognitive impairment. Patients are typically referred to the ARCCs from a variety of sources, including self-referrals and referrals from senior centers, medical centers, primary care physicians, and other health professionals. As such, patients participating at ARCCs are considered to be representative of AD patients seen in clinical practice in the community.

Data on each patient-caregiver dyad evaluated at each ARCC have been compiled into the Minimum Uniform Dataset (MUDS). Data are collected by a multidisciplinary team that includes neurologists, psychiatrists, neuropsychologists, nurses, social workers, and research assistants during the patient visits. Clinicians at the ARCCs evaluate each patient using a comprehensive medical work-up that includes a physical examination, laboratory tests, neuroimaging, and a comprehensive neuropsychological assessment. Patients are diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[7] This database provides an ethnically diverse community-dwelling patient population. In general, patients were seen annually at their local center, and the data included in this study cover the period from June 1985 through September 1993. Given that a primary objective is to identify AD patients who are declining more rapidly since they may require early intervention, we did not include any patient visits beyond September 1993, at which point cholinesterase inhibitors became available.

Patient Visits

As mentioned, 1062 AD patients participated in the current investigation. The 1062 patients participating had a combined total of 2566 patient visits, with an average of 2.42 visits per patient and an average follow-up period of 14.76 months (SD = 3.01 months). However, we stress that in the current study, the unit of analysis was patient visit. Only those visits that had a follow-up could be included so that the rate of decline on the MMSE could be ascertained. A total of 1472 patient visits had a follow-up visit between 11 and 24 months later. The information available at these 1472 patient visits was analyzed using the ROC method. In other words, we analyzed the data from each patient visit using the information available in the clinical record at that time of the patient visit to predict which individuals would decline most on the MMSE between that visit and their next visit. Rather than including information on the predictor variables for each patient only once and then calculating the rate of change on their MMSE across the entire course of their visits, we treated each visit as a separate data point. Thus, we included information on the variables of interest for each patient at each visit and calculated the rate of change on the MMSE from one visit to the next. Analyzing the data according to visit provides information on the characteristics of patients at risk for more rapid cognitive decline at any given visit and would be independent of the clinician's prior exposure to the patient. We felt that this approach best mimics clinical practice since many clinicians in primary care and other settings may see a patient

Table 1. Demographics and MMSE Scores

	Composition (%)	Mean	SD	Range
Age (yr)		74.1	8.2	40–96
Education (yr)		12.3	3.9	0–26
MMSE score		18.4	6.1	4–30
Gender				
Male	33.7			
Female	66.3			
Ethnicity				
White	79.6			
Black	8.0			
Hispanic	8.6			
Other	3.8			

MMSE = Mini-Mental State Examination.

Table 2. Number of Subjects in Each Dementia Stage at Entry into the Study

	Number of Subjects	MMSE Range of Scores
Stage of dementia		
1	254	24–30
2	528	15–23
3	213	8–14
4	67	4–7

MMSE = Mini-Mental State Examination.

only once. In the current study, the 1062 AD patients participating had a total of 1472 patient visits, with one follow-up visit 11 to 24 months later.

Measures

The clinical outcome of interest in the current study is change on the MMSE. The MMSE is a brief mental status examination designed to quantify cognition by assessing performance on orientation, language, calculation, memory, and visuospatial reproduction. It is widely used as a measure of general cognitive status in AD patients. Several studies have found the mean annual rate of decline on the MMSE to be between 2.5 and 3.5 points a year.[8–12] In the present investigation, over 53% of the patients declined by less than 3 points per year on the MMSE, in the postvisit follow-up period. Additionally, it has been estimated that moderately to severely demented AD patients whose treatment prevented even a 2-point decline could have clinical and cost benefits.[1,13] Thus, in this study, rapid decline was defined as a loss of 3 or more MMSE points per year in the postvisit follow-up period. There are many additional measures of decline, such as time to skilled nursing placement or to death, but in the current study, the MMSE was assessed on all patients, whereas other measures of functional or cognitive decline were not available. The MMSE was administered during each patient visit.

We chose the following characteristics of AD patients as the independent variables since they represent measures routinely acquired at regular patient visits at each of the ARCCs and are routinely assessed by clinicians evaluating AD patients: age at clinic visit, age at symptom onset of AD, MMSE at time of patient visit, years of education, gender, ethnicity, living arrangement, presence of aphasia, delusions, hallucinations, and extrapyramidal signs (EPS). The presence of aphasia, delusions, hallucinations, and EPS was assessed by an ARCC clinician during each patient visit. Aphasia was classified into one of three categories: no aphasia present, mild or questionable aphasia present, and presence of moderate or severe aphasia. Delusions, hallucinations, and EPS were indicated as being absent, questionable, or present.

Statistical Analysis

The first step in conducting ROC analysis is to define the clinically relevant outcome and to choose success/failure criteria. As described above, the criterion for failure is defined as a loss of 3 or more points on the MMSE per year in the subsequent postvisit follow-up time period, whereas success is defined as not exhibiting such a decline.

The ROC is a nonparametric technique that does not, as linear models do, make restrictive linearity and additivity assumptions. It is capable of isolating characteristics and combinations of characteristics without making assumptions of uniformity. Multiple potential predictors can be evaluated simultaneously. The ROC indicates interactions among predictors and can isolate subgroups that demonstrate different patterns of performance. In essence, the ROC searches all of the independent variables and their associated cutpoints (in this study, patient variables) and identifies those with the optimal balance between sensitivity and specificity for identifying those particular patients with the specific outcome of interest (in this study, more rapid decline on the MMSE). Once the optimal variable and associated cutpoint are identified, the association with the success criterion is tested against a stopping rule (in the current study, the stopping rule is a 2 x 2 chi-square test significant at less than the 1% level). If the association passes the rule, the sample is divided into two groups according

to performance on the optimal variable. The ROC analysis is then restarted, independently, for each of these two subgroups. The ROC procedure examines every variable and associated cutpoint to see if either group can be further differentiated. The result is a decision tree (Figure 1). The subgroups in the various branches become smaller and smaller as the ROC analysis proceeds. The ROC procedure will stop when it hits the stopping rule, and/or when a subgroup has too small a sample size for further analysis, and/or when there are no further variables selected (for further details regarding ROC analysis, see Kraemer[5]).

RESULTS

As illustrated in Figure 1, at the beginning of the current ROC analysis, 46.1% of the 1472 patient visits were associated with rapid decline in the postvisit follow-up period. The first variable and cutpoint isolated by the ROC analysis was the presence of moderate or severe aphasia (chi-square = 35.9, $P < .001$). Of 529 patient visits at which there was a diagnosis of moderate or severe aphasia, 299 (56.5%) of these visits were actually associated with rapid decline. Of the remaining 943 patient visits at which there was a diagnosis of mild or no aphasia, 380 (40.3%) were associated with rapid decline. As can be seen in Figure 1, this group of 943 patient visits was not further differentiated by the ROC procedure because the stopping rule went into effect.

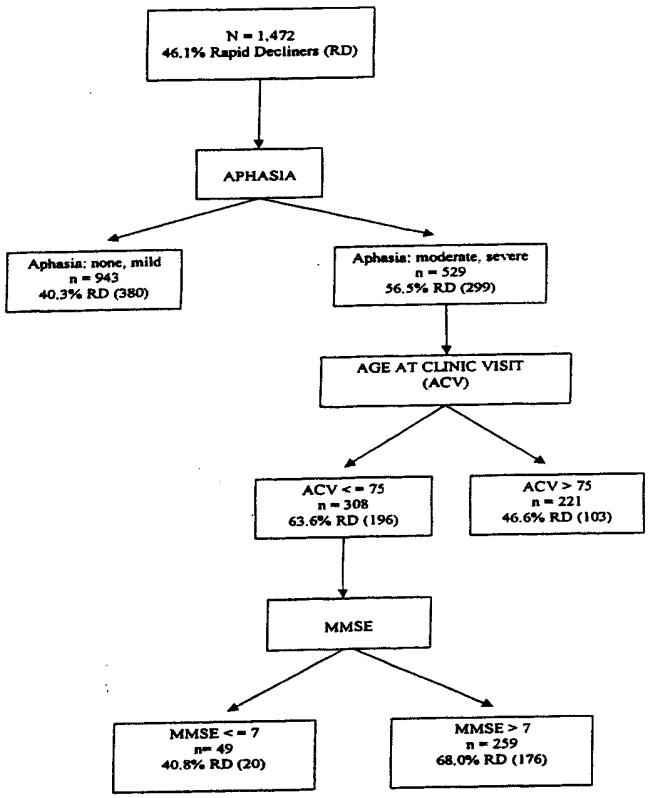

Figure 1. Receiver operating characteristic curve derivation of subgroups at differential risk for rapid decline. MMSE = Mini-Mental State Examination.

However, the 529 patient visits, at which there was a diagnosis of moderate to severe aphasia, were further differentiated by age at clinic visit, with a cutpoint of ≤ 75 years of age (chi-square = 15.19, $P < .001$). Of 308 patient visits at which the patient carried a diagnosis of severe or moderate aphasia and age at clinic visit was ≤ 75 years of age, 196 (63.6%) were associated with rapid decline. These 308 patient visits were further differentiated according to their MMSE. Of 259 patient visits with an MMSE > 7, 176 (68.0%) were rapid decliners, compared with 20 (40.8%) of 49 patient visits with an MMSE ≤ 7 (chi-square = 13.11, $P < .001$). At this point, the stopping rule went into effect for all branches, and the ROC procedure ceased. No further variables and cutpoints were identified.

As Figure 1 shows, ROC analysis indicated that AD patients presenting with moderate to severe aphasia, age at clinic visit ≤ 75 years of age, and an MMSE > 7, were at increased risk for rapid decline.

DISCUSSION

Our results indicate that AD patients presenting with moderate to severe aphasia, age at clinic visit ≤ 75 years of age, and an MMSE > 7 were at greatest risk for rapid decline. The importance of identifying which AD patients are at risk for accelerated decline is attested to by the substantial literature that aims to identify predictors of such decline. Many characteristics of AD patients have been associated with a more rapid rate of disease decline. These include family history of dementia,[14] age of symptom onset and severity of illness at initial examination,[15–19] EPS,[4,20–22] gender,[23] ethnicity,[24] years of education,[23,25] psychoses,[4,18,23] agitation,[19] sleep disturbance,[4] aggressive behavior,[4] and apolipoprotein E genotype status.[26] In accordance with the findings of the current study, prior investigations have also suggested the existence of a relationship between the presence of aphasia and the rate of decline.[20,27,28] Traditionally, such studies of rate of decline in AD patients employ linear models. However, these studies have sometimes yielded mixed findings. The results of our ROC analysis suggest that certain variables may be associated with decline only in certain subgroups of AD patients. In the current study, age at clinic visit and MMSE score were associated with increased risk for rapid decline in patients with moderate to severe aphasia. Sixty-eight percent of patients with these characteristics were rapid decliners. Yet neither age at clinic visit nor MMSE score was associated with rapid decline in AD patients with mild or no aphasia present. Only 40% of patients with the same characteristics but with no or mild aphasia were rapid decliners.

The ROC analysis thus provides information regarding how interactions among variables identify different subgroups of AD patients at increased risk for rapid

decline. Variability among prior studies regarding predictors of rate of decline in AD may reflect differences in the characteristics of the AD population under investigation. The linear models traditionally employed in these studies are limited in their ability to identify subgroups of at-risk patients and to identify predictor variables and interactions among them within those subgroups. In linear models, the interactions must be specified ahead of time. In general, regression models include, at most, first-order interactions. If an interaction is not specified, the regression model cannot identify the interaction and, in effect, remaps the missing interaction effect into the main effects and into error. In ROC analysis, interactions do not have to be prespecified.

In a review article, Cummings stressed the heterogeneous nature of AD, emphasizing the potential existence of subgroups of AD patients with different pathophysiologic and clinical profiles.[29] In particular, he identified disproportionate presence of aphasia relative to other cognitive impairments as representing a potential subgroup of AD. The findings of the current investigation suggest that AD patients with moderate to severe aphasia may indeed represent a distinct subgroup and that ROC analysis may be ideally suited to the identification of such subgroups.

However, ROC analysis is not without its limitations. It is important to stress that ROC analysis is not testing hypotheses and no causal relationships can be concluded from the data. However, relationships can be inferred, thus yielding hypotheses that can be independently tested in further studies. Since ROC analysis subdivides the population, if the initial sample is too small, the number of cases in each subgroup may be too few for any further subdivisions to occur and the ROC analysis will stop simply because of limited sample size. Thus, ROC analysis is best conducted on large sample sizes. Additionally, ROC analysis will capitalize on chance unless a stringent significance level is enforced in the stopping rule. When the linear model assumptions of logistic regression analyses (LRA) are satisfied, and when all strong interactions are included in the linear model, the results of ROC and LRA are likely to be very similar. But regression models can assign the same risk score to patients who have, in fact, very different combinations of characteristics. The type of classification algorithm yielded by ROC analysis may be more directly relevant to clinical decision making than simply having regression coefficients or knowing that a clinical feature correlates with certain outcomes. Receiver operating characteristic curve analysis can also take the differential clinical costs of false positives and false negatives into account, which linear models cannot. Thus, it may be useful in seeking the most cost-effective way of recognizing those at risk of a clinically significant outcome.

There are some limitations of the current study, which should be considered in interpreting the results. The finding regarding performance on the MMSE likely reflects the fact that patients presenting with an MMSE ≤ 7 have less opportunity for decline. Additionally, in the current study, we considered decline only on the MMSE as our outcome measure, and, as mentioned, other clinically relevant outcome measures, such as functional abilities, may be important to consider in future investigations. With respect to the identification of characteristics of AD patients at increased risk for rapid cognitive decline, the current study included a limited number of predictor variables. However, those variables included in our analyses are relatively easy to assess on AD patients. Given that the analysis was based on patient visits, the results could be particularly useful for informing clinicians in the field who may not have immediate access to other information and who may see the patient only over a limited number of visits. However, future studies might employ ROC analysis for the investigation of a broader range of variables. Overall, the presence of moderate to severe aphasia, age 75 years or younger, and MMSE scores > 7 characterized 18% of presenting AD patients. Additionally, these characteristics identified 26% of all rapid decliners. Although these represent moderate proportions, the ability to characterize one in four patients who will exhibit rapid decline is certainly of clinical value.

Knowing that patients presenting with moderate to severe aphasia, age ≤ 75 years of age, and an MMSE > 7 are at greatest risk for rapid decline could help the clinician target these patients for pharmacologic interventions, facilitate planning for long-term care, and potentially create savings by delaying or stabilizing the course of the disease. It has been estimated that moderately to severely demented AD patients whose treatment prevented even a 2-point decline in the MMSE could potentially save about $3700 annually per patient.[13] The information yielded from ROC analysis also might serve to inform subject recruitment for clinical trials. Moreover, future use of ROC analysis could include the identification of predictors of response to medications, such as donepezil, for the treatment of AD.

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