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CLASSIFYING NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH ALZHEIMER'S DISEASE

By

Saw-Myo Tun

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ABSTRACT

CLASSIFYING NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH ALZHEIMER'S DISEASE

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Objective: The aim of the study was to conceptualize neuropsychiatric symptoms in Alzheimer's disease patients, as distinct symptom profiles with differential disease outcomes. Five outcomes of interest in the study were caregiver distress, quality of life, functional impairment, nursing home placement, and survival. **Method:** Cluster analysis was used to categorize 122 patients with Alzheimer's disease, based upon their neuropsychiatric symptoms, as assessed by the Neuropsychiatric Inventory (NPI). The presence, severity, and frequency of symptoms were considered. After identification of the subgroups, the predictive validity of the categorization was tested on the following: 1) group differences in caregiver distress at baseline using ANCOVA; 2) group differences in quality of life and functional impairment over a 2-year period using repeated measures ANOVA; and 3) group differences in time to nursing home placement and time to death over a 3-year period using Cox proportional hazard models. **Results:** Based on the presence of neuropsychiatric symptoms, three subgroups were identified: Minimally Symptomatic, Highly Symptomatic, and Predominantly Apathetic. At baseline, the scores on a caregiver distress measure differed significantly between the clusters ($p = 0.00$). Over a 2-year period, the subgroups were predictive of quality of life ($p = 0.00$). Similarly, over the same 2-year period, functional impairment was differentially predicted by the subgroups ($p = 0.00$). As for time to nursing home placement over a 3-

year period, the results were significant ($p < 0.05$) with the Highly Symptomatic group showing the highest risk. In addition, the rates of survival were significantly predicted by the subgroups ($p < 0.05$), with the Minimally Symptomatic group having the lowest risk. Based on the severity and frequency of neuropsychiatric symptoms, 2-cluster and 4-cluster solutions were produced. The 4-cluster solution provided a better differentiation of the symptom profiles than the 2-cluster solution. The 4 clusters were: Minimally Symptomatic, Affective/Apathetic, Predominantly Apathetic, and Highly Symptomatic with Psychotic Features. Cross-sectionally, these four subgroups differentially predicted caregiver distress ($p = 0.00$). Over a 2-year period, the clustering predicted significant differential outcomes in quality of life ($p = 0.00$), and in functional impairment ($p < 0.01$). Moreover, cluster membership was predictive of nursing home placement ($p < .05$) and survival ($p < 0.01$) over a 3-year period. **Conclusions:** Neuropsychiatric subgroups, using the cluster analysis method, were able to predict differential outcomes, and identify those with an increased risk for a worse prognosis. Specifically, the clustering based on the presence, severity and frequency of symptoms, were able to predict outcome in caregiver distress, quality of life, functional impairment, nursing home placement, and survival. Thus, the results highlighted the importance of detecting and treating neuropsychiatric symptoms in Alzheimer's disease patients.

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Classifying Neuropsychiatric Symptoms in Patients with Alzheimer's Disease

Specific Aims

Neuropsychiatric symptoms, such as apathy, agitation, hallucination, delusion, and depression, have long been acknowledged as the secondary resultants of neuropathological changes associated with dementia. Furthermore, it has been recognized that the presence of such neuropsychiatric disturbances contributes to a worse prognosis, including a more rapid functional and cognitive decline, and an increase in caregiver distress (Ballard et al., 2000; Cummings, 2003a; Norton, Malloy, & Salloway, 2001; Teri, 1997). Nevertheless, as the importance of neuropsychiatric symptoms in dementia becomes more apparent, it seems to highlight the limitations in the present conceptualization of the symptoms. Such limitations in conceptualization can have detrimental effects in that they can potentially hamper our understanding of the pathophysiology of the symptoms as well as their resulting clinical correlates. Thus, in the current study, the primary purpose was to determine whether neuropsychiatric disturbances in dementia patients could be better conceptualized as distinct symptom profiles that predict differential disease courses. In doing so, the study attempted to overcome some of the methodological limitations of previous studies by using statistical methods that allowed for grouping of dementia patients with psychiatric symptoms into meaningful clusters. In addition, we examined the presence, severity, and frequency of symptoms. A critical component of the study was that predictive validity of membership of such groupings was tested on four patient outcomes and one caregiver outcome. Thus, the research has two specific aims. (1) To identify groups of dementia patients with

similar profiles of neuropsychiatric symptoms based upon caregiver's responses on the Neuropsychiatric Inventory (NPI). The group membership was based on the presence, and the severity and frequency of the symptoms. (2) To test the ability of group membership to predict caregiver and patient outcomes. Possible covariates such as severity of functional and cognitive impairments, severity of Parkinsonism, severity of other medical problems, and age were adjusted at baseline.

Background and Significance

As one ages, the risk of dementia grows at an incremental rate in such a way that by the time an individual reaches the age of 80, he or she has a 1 in 6 chance of developing dementia (Jorm, 1991). Of the significant number of older adults who develop dementia, a sizable portion also goes on to develop neuropsychiatric symptoms in addition to the cognitive impairments. According to recent estimates, neuropsychiatric disturbances are believed to be present in 74-75% of the individuals with dementia (Lyketsos et al., 2002; Weiner et al., 2005). Moreover, disturbances of this nature substantially increase the likelihood of a worse outcome in a number of domains, including a decrease in activities of daily living, an increase in cost of care, and more likelihood of nursing home placement (Murman et al., 2002; Gilley et al., 2004; Norton, Malloy, and Salloway, 2001; Kopetz et al., 2000; Lyketsos et al., 1997). Thus, a combination of a high prevalence rate and the debilitating nature of the psychological disturbances have propelled researchers to search for an underlying pathophysiology of the symptoms and their clinical correlates. It has been suggested that such undertakings could pave the way for the development of more effective interventions that could lessen the hardship on the patients and their caregivers (Aalten et al., 2003; Frisoni et al., 1999).

In recent years, however, concerns have been raised regarding the methodologies employed in the study of neuropsychiatric symptoms. Traditionally, the study of neuropsychiatric disturbances entailed focusing exclusively on one symptom, such as depression, and examining its impact on the patient (e.g. Lyketsos et al., 1997; Payne et al., 2002). However, it has been postulated that such an approach disregards the high co-occurrence of neuropsychiatric symptoms in dementia patients (Frisoni et al., 1999; Lyketsos et al., 2001b). For example, a study by Lyketsos and colleagues (2002) found 55% of the dementia patients endorsed 2 or more neuropsychiatric disturbances. Hence, given a particularly high co-morbidity of symptoms, the exclusion approach of previous studies has a limited capacity for finding consistent patterns in outcome research and for offering clinically meaningful causal relationships (Aalten et al., 2003; Frisoni et al., 1999: Lyketsos et al., 2001b; Holthoff et al., 2005).

In order to better reflect the clinical picture of neuropsychiatric disturbances in dementia, two alternative strategies have been employed in recent studies. In one such approach, the method of factor analysis is used to create meaningful groups of symptoms that are most likely to co-occur as assessed by a scale measuring neuropsychiatric symptoms. For example, this approach has been used with the BEHAVE-AD, the Neuropsychiatry Inventory (NPI), and the Present Behavioral Examination. Despite variations in symptoms included in each factor, most studies found 3 factors, with mood, psychosis, and hyperactivity/frontal factors being the most consistent findings (Aalten et al., 2003; Frisoni et al., 1999; Hope et al., 1997; McShane, 2001; Schrenizer et al., 2005). Nevertheless, although this method addresses the problem of focusing too narrowly on a particular symptom, factor analysis does not place patients into subgroups. Instead, it

places patients on a continuum of a continuous factor score. If subgroups are to be derived, then an arbitrary cut off score must be defined on each factor score. Furthermore, since the method of factor analysis allows for individual patients to be included in more than one factor, it does not create well-defined groups of individuals with distinct symptom profiles (Lyketsos et al., 2001b). Thus, it is not an ideal approach for examining the differential outcomes of individuals based upon their neuropsychiatric symptom profiles.

Another strategy that has been employed in recent studies of neuropsychiatric disturbances is to create groups of individuals, with differing symptom profiles, using a latent class analysis method (e.g. Lyketsos et al., 2001b; Moran et al., 2004). Although solutions derived from latent class analysis correspond to that of factor analysis, the purpose of this approach is to identify meaningful groups of individuals rather than groups of variables (von Eye & Bergman, 2003). Hence, the latent class analysis approach avoids the problem of the same individuals being included in multiple subgroups. This particular feature makes latent class analysis more suitable for use in neuropsychiatric outcome studies.

Based on the results of their latent class analysis study (2001b) and that of an epidemiological study (2000), Lyketsos and colleagues (2001a) derived a classification system for categorizing neuropsychiatric symptoms in Alzheimer's disease patients. Although their effort toward the development of an empirically-driven classification system should be applauded, their methodologies did not account for the severity of neuropsychiatric symptoms. As aptly observed by Meyers (2001), the failure to account for severity and frequency of symptoms is a serious flaw in the study of neuropsychiatric

disturbances in that a patient who occasionally experiences a mild symptom of agitation is deemed to have a similar degree of pathology as that of a patient endorsing persistent and severe agitation. Along the same line, such disparate individuals will be expected to have comparable clinical outcomes. However, such a line of reasoning is intrinsically problematic, and outcome research based on such a conceptualization will have limited applicability (Meyers, 2001).

The present study addressed some of the limitations of previous studies in the field in the following ways: 1) Psychiatric symptoms of neurological origin in dementia patients were conceptualized as clusters of symptoms that co-occur together, rather than as disparate symptoms. The presence of symptoms as well as the severity and frequency of disturbances were explored. 2) To maximize the predictive validity of groups of individuals on outcomes, individual patients were placed in non-overlapping categories rather than in multiple categories.

Clustering of Symptoms

To accomplish the above-stated aims, it was proposed that the method of cluster analysis is a suitable approach for such undertaking. First, if one's goal was to have a classification system that could predict outcomes in individual patients, then it would be preferable to use a grouping method that is person-oriented in nature than a variable-centered approach (von Eye & Bergman, 2003). After the decision was made to use a person-oriented method, the investigator was left with an array of choices in grouping methods, including cluster analysis and latent class analysis. Of those possible classification methods, the method of cluster analysis allowed for the most flexibility in

using both continuous and categorical variables, and also in correcting for the high intercorrelations among some of the NPI domains.

By employing this flexible approach, the study was able to consider both the presence of symptoms, which is categorical in nature, and the severity and the frequency of symptoms, which are continuous. Also, cluster analysis has been suggested as a suitable method for looking at differences in profiles between individuals while avoiding the loss of critical information (von Eye, Mun & Indurkhya, 2004). On the other hand, von Eye and co-authors (2004) note that the use of cluster analysis sometimes raises the concern of arbitrariness. To address such a concern, the authors outlined a series of decision making steps to ensure the choice of cluster analysis method is based on a well-justified position rather than a blind application of the method.

Here, a few of the critical steps in the decision making process are reported. First, there is a decision concerning whether there are disjointed or overlapping clusters. Given that one of the main objectives of this research is to identify non-overlapping symptom profiles, a disjoint cluster approach was a natural choice. A second critical decision concerns the hierarchical versus non-hierarchical structures of the clusters. In this regard, an assumption of the study, that the clustering of patients into smaller groups will have an interpretable meaning, led to the choice of a hierarchical method. The third, and a fundamental decision of the study, relates to the choice of base measures. Because the study was interested in examining the presence of neuropsychiatric symptoms, which is categorical, as well as their severity and frequency, which is continuous, the use of Pearson's correlation was the most suitable, as it allowed for an examination of both categorical and continuous data.

A decision was made to analyze the presence of symptoms, and the severity of symptoms in parallel, as it allowed the study to accomplish two aims. First, in previous studies, the classification was based only on the presence of symptoms. Thus, by including the presence of symptoms in the study, it made it feasible to compare the findings of the present research with those of prior studies. Second, as Meyers (2001) noted, the severity and frequency of symptoms are potentially important considerations in neuropsychiatric research. However, to our knowledge, there has not been any study to consider this aspect. Hence, we incorporated the severity and frequency of symptoms into the study on an exploratory basis. Findings from both approaches are presented. A precedent for the use of a similar methodology has been set in previous studies, including a study on substance use and adjustment in adolescents (Tubman et al., 1991).

Predictive Validity of Clusters

In the second segment of the study, the clinical utility of the classification was tested. When classifying individuals into subgroups, the usefulness of the procedure depends not only on the identification of distinct groups, but also on establishing the predictive validity of these groups (von Eye & Bergman, 2003). Therefore, this research examined the differential impacts of neuropsychiatric symptom profiles on various domains of clinical interest.

Caregiver burden. The first domain was caregiver burden. Greater numbers of older adults continue to live in the community as they age, and when they stay in their own homes, they often rely on their family members to be the primary caregivers (Gonzalez-Salvador et al., 1999). As such, understanding the role of the caregivers and the challenges they face becomes essential block in order to have a complete clinical

picture of the dementia patient. In the case of neuropsychiatric disturbances, evidence is accumulating that caregivers do indeed experience a greater degree of burden and a decreased quality of life in the presence of these symptoms (Ballard et al., 2000; Gonzalez-Salvador et al., 1999; Lyketsos et al., 1997; Shin et al., 2005; Teri, 1997). In fact, the distress associated with caring for AD patients has been linked specifically to neuropsychiatric disturbances, but not to cognitive or functional impairments (Craig et al., 2005). However, the results of the previous studies were based on a traditional approach of looking at a single symptom and examining its impact. Given the highly co-morbid nature of neuropsychiatric symptoms, there is a potential that the findings are still an underestimation of the actual extent of caregiver burden. Therefore, this research investigated how co-occurring neuropsychiatric disturbances contributed to caregiver distress.

Functional impairment. The second domain we considered is functional impairment of the dementia patient. Although the role of cognitive deterioration on functional impairment has been well-established, our knowledge of the contribution of neuropsychiatric disturbances to functional impairment is limited. Here again, this limitation can partly be attributed to research that examines the effects of symptoms in isolation. Based on the available data, however, it is known that neuropsychiatric disturbances have a negative impact on activities of daily living (Hargave, Reed, & Mungas, 2000; Norton, Malloy, & Salloway, 2001; Tekin et al., 2001; Weiner et al., 2005). Therefore, in the present study, we sought to gain a fuller understanding of the impact of neuropsychiatric symptoms on functional impairment by examining it longitudinally over a 2-year period of time. It is recognized that the longitudinal design of

the study may raise the question of the stability of neuropsychiatric disturbances over time. Nevertheless, several findings are in agreement that neuropsychiatric symptoms, once present, are highly likely to persist over the course of the dementia (Devanand et al., 1997; Levy et al., 1996; Steinberg et al., 2003, 2004).

Quality of life. The third domain we examined was the quality of life in dementia patients. As intuition might lead one to expect, neuropsychiatric symptoms adversely impact quality of life in dementia patients. For instance, in a study by Gonzalez-Salavador and colleagues (2000) that looked at quality of life in dementia patients residing in a long-term care setting, depression was associated with a lower quality of life. An interesting finding, however, is that a follow-up study of the same population by Lyketsos and associates (2003) found that depression did not further contribute to a decline in quality of life during the 2-year follow-up period. The findings suggested that when depression is detected, it was possible to provide necessary interventions to prevent further deterioration in quality of life. Similar to findings by Lyketsos and co-workers (2005), a recent study also reported quality of life to be stable over a 1-year period in AD patients (Selwood, Thorgrimsen, & Orrell, 2005). However, this study reported anxiety, in addition to depression, to be factors in predicting lower quality of life. Since these two studies were the first of their kind to consider the effects of depression and anxiety on change in quality of life over time, further research is needed to test these findings, and to incorporate the possible impact of co-morbid neuropsychiatric symptoms on quality of life. In the current study, the effects of neuropsychiatric symptoms on quality of life in dementia patients were considered over a 2-year period.

Nursing home placement and survival rate. As a purely longitudinal component of the study, we also examined the rate of nursing home placement and survival rate. It is recognized in the field that these two aspects are important considerations in the lives of patients with dementia for a number of reasons. First, the decision to place a family member into a nursing home setting can have a tremendous psychological impact on both the caregiver and the patient (Thomas et al., 2004). Second, the decision to institutionalize a dementia patient is also a matter of financial consideration. As estimated by Butler (1995), a delay in institutionalization by one month for every person over the age of 65 in the US could save $60 billion a year in the cost of care. Third, availability of information on approximate survival rates could aid end of life decisions for the family and the patient. Therefore, the study considered the differential impact of neuropsychiatric symptoms on the rates of nursing home placement and survival.

It should be noted that in considering the rate of nursing home placement, it is recognized that differences in caregiver characteristics, such as martial status, could potentially influence the outcome. For instance, it is conceivable that an AD patient with a spouse as a primary caregiver would have a decreased likelihood of being placed in a nursing home compared to a patient with an adult child as a caregiver. Thus, the present study controlled for marital status in examining the rate of nursing home placement.

Rationale

The primary aim of the current study was to refine the conceptualization of neuropsychiatric disturbances in dementia; however, the results of the study may be applicable to both scientific research and clinical applications. First and foremost, it is hoped that by conducting this project, we would be able to arrive at a more satisfactory

conceptualization and categorization of neuropsychiatric disturbances that can predict patient and caregiver outcomes. Such a conceptualization would also aid in conducting further research at the neurobiologic level. For example, a natural step that could potentially follow the present study is to apply the classification in examining whether genetic polymorphism associated with neuropsychiatric symptoms in patients with dementia are associated with the categorization of patients based upon neuropsychiatric disturbances. Moreover, identification of subgroups of dementia patients with distinct neuropsychiatric symptom profiles may contribute to detection of subtypes of dementia with possibly different neurobiologic underpinnings (Aalten et al., 2003; Lyketsos et al., 2001b). Overall, if the categorization of symptoms shows predictive validity, it may provide evidence for applying the subgroups to neurobiologic research.

Potentially, the study also has more immediate clinical implications. As noted by previous studies, the current *Diagnostic and Statistical Manual of Mental Disorders – IV* (DSM-IV) does not contain specific criteria for denoting neuropsychiatric symptoms associated with dementia (Aalten et al., 2003; Lyketsos et al., 2001b). However, a new edition of the DSM is expected to redress the situation and an empirically-driven classification system can help contribute to that effort.

Another potential clinical application is that if the results of the study show detrimental impact of neuropsychiatric disturbances in a number of domains, it may highlight the importance of detection and intervention to healthcare professionals. Furthermore, if NPI proves to be useful in classification of the symptoms as well as providing external validity, it would lend further support for its use in the clinical setting. By completion of the 15-minute NPI battery, the healthcare provider would be able to

identify patients at risk for poor outcomes based upon their neuropsychiatric profile. This would allow healthcare providers to target these patients for psychological and pharmacological interventions that may improve their neuropsychiatric symptoms. It is anticipated that better management of neuropsychiatric symptoms would result in an improvement in the patient's functional abilities and quality of life and a decrease in caregiver's burden. Further studies could examine the impact of neuropsychiatric symptom profiles on costs of care in our current healthcare system and measure the economic impact of focused interventions to improve neuropsychiatric disturbances in this population of patients.

The present study was a secondary data analysis study with cross-sectional and longitudinal components. Specifically, data from the initial time point were used to classify AD patients into groups based upon the presence, severity, and frequency of neuropsychiatric symptoms. After the classification, the groupings were used to predict the level of caregiver distress cross-sectionally. Also, the groups were used to predict the functional impairment and quality of life longitudinally. In addition, the longitudinal design of the study enabled the investigator to examine the between-group differences in time to nursing home placement and in survival over the 3- year period.

Since the present study was the first study to categorize neuropsychiatric symptoms using cluster analysis, and to incorporate severity and frequency of symptoms, there were no a priori hypotheses regarding the outcome of the categorization. Similarly, the current study was the first to consider the impact of neuropsychiatric symptoms based on clusters of symptoms. In addition, given that the second segment of predicting

caregiver and patient outcomes rested on the results of categorization, there were no specific a priori hypotheses regarding subgroup differences.

However, more general hypotheses can be made. (1) It is predicted that there will be well-defined patterns of neuropsychiatric symptom profiles among dementia patients, as tested by cluster analysis. Previously, grouping based on latent class analysis, which is the closest approximation to cluster analysis, had identified three groups: absent/mono-neuropsychiatric symptom group, predominantly affective, and psychotic syndrome. Similar groupings are expected. (2) Based on the class membership as identified in part 1, groups will differ in terms of the level of caregiver distress croo-sectionally as tested by analysis of covariance. Previous reports of specific symptoms associated with caregiver distress have varied. However, it is expected that more symptomatic groups, such as predominantly affective or psychotic syndrome group, will lead to greater caregiver distress than non- or mono-symptomatic group. (3) Class membership will predict the rate of decline on the quality of life scale over a 2-year period as tested by repeated measures analysis of variance. Based on available literature, subgroups with affective symptoms will be expected to have lower quality of life than the non- or low symptomatic groups. (4) Class membership will predict the rate of functional decline over a 2-year period as tested by repeated measures analysis of variance. Previous studies indicated that apathy and psychotic symptoms predict functional impairments. Therefore, we identify subgroups with similar characteristics, those subgroups will be expected to have greater functional decline. (5) Class membership will predict the differential time to nursing home placement in dementia patients over a 3-year period as tested by survival analysis. Based on previous literature, groups with high symptoms are expected to be at

greater risk for nursing home placement. (6) Class membership will predict the differential time to death in dementia patients over a 3-year as tested by survival analysis. Limited information is available on the relationship between neuropsychiatric symptoms and survival. However, one study has shown depression to be associated with greater risk of death. Therefore, subgroups with affective symptoms are expected to have lower chances of survival.

Methods

Participants

The participants were drawn from an ongoing study, the Cost of Health in Alzheimer's disease Relative to Gained Effectiveness (CHARGE), at Michigan State University (Murman et al., 2002; Murman et al., 2003). Participants who met the study criteria were recruited by mail from six neurology practices and three geriatric medicine practices in Michigan. The inclusion criteria for the study were a clinical diagnosis of probable Alzheimer's disease using the Alzheimer's Disease and Related Disorders Association-National Institute of Neurological Communicative Disorder and Stroke (NINCDS-ADRDA) criteria, and the availability of an informant who was in direct contact with the patient at least once a week. Given that different types of dementia may have distinctive neuropsychiatric profiles, only patients with the AD diagnosis were included to maintain the homogeneity of the sample.

Of the 692 eligible participants, 128 patients (18%) responded and were subsequently included in the study. However, at the stage of data analysis, 6 participants with MMSE score of 0 were excluded from the study, as this score indicated very severe dementia, and the patient may have became mute by this stage of dementia. Therefore, the informant may not be able to detect symptoms such as hallucination and delusions, and may subsequently underreport these symptoms. Thus, the final sample used for the study was 122.

Ninety-seven percent of the participants in the study were Caucasian. The mean age of the participants was 76.2 years (SD = 9.0), and the mean level of education was

12.9 years (SD = 3.1). Fifty-five percent of the participants were female. In many cases, spouses served as the informants for the study (60%). In the remainder of the cases, daughters (30%), other relatives (7%), and friends of the patient (3%) were the informants. Twenty-two percent of the sample resided in a long-term care setting at baseline. Of these, 41% lived in an assisted living setting, 30% in a foster care home, and 18% in a nursing home. The type of long-term care for 3 (11%) of the participants was not known. Also of note, 2 participants (2%) dropped out from the study after the first wave of data collection, and their data were not used for the longitudinal portion of the study.

Measures

The study used 5 questionnaires, 3 yearly interviews, a cognitive measure and a neurological rating scale. Of those, the Neuropsychiatric Inventory, the Cumulative Illness Rating Scale, the Mini-Mental Status Exam, and the Modified Colombia University Parkinson's Disease Rating Scale were given at the initial time point. The Dependence Scale and the Health Utilities Index were given at the initial time point, and at each of the yearly follow-up. The interviews were given at each yearly follow-up.

Neuropsychiatric Inventory (NPI). NPI was used to assess the AD related behavior symptoms that were present in the past month. This structured interview was developed by Cummings and colleagues (1994) to examine the presence, severity, and frequency of ten commonly observed neuropsychiatric symptoms in dementia patients. The ten domains included in the interview are delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. The NPI uses an informant to report on symptoms that they have observed in

the patient in a specific time period. Furthermore, the design of the measure focuses only on those symptoms that are present, thus allowing for an efficient use of the examiner's time without sacrificing information. For example, one of the questions used to assess hallucinations asked, "Does the patient talk to people who are not there?" If a behavior is present, further inquires are made as to the behavior severity and frequency.

In a report by Cummings (1997), the NPI was noted to have a strong inter-rater reliability with r ranging from 0.94 to 1.0, and a test-retest reliability ranging from 0.79 to 0.86. Moreover, it was reported that NPI has a good construct and content validity, and therefore is commonly used in dementia research (Lyketsos et al., 2001b; Schneider, 2001; Holthoff et al., 2005). In the current study, the score indicating the presence of a neuropsychiatric symptom as well as the domain score that incorporates the severity and frequency of the symptom were used. In the presence of a neuropsychiatric disturbance, the domain score can range from 1 to 12. For example, if the informant endorses a symptom, such as depression, he/she will rate the severity of that symptom, which ranges from 1 to 4, and rate the frequency of the symptoms, which can range from 1 to 3. The domain score is the severity of symptom x the frequency of symptom.

Screen for Caregiver Burden. This is a 25-item measure constructed to assess the objective prevalence of the patient's distressing behaviors and the level of subjective distress the caregiver experiences in response to the behaviors (Vitaliano et al., 1991). For example, it includes items, such as, "My spouse doesn't cooperate with the rest of the family", and "I feel so alone as if I have the world on my shoulder." The informant reports as to whether the statements are true, and rates the distress associated with each statement.

For this measure, Vitaliano and colleagues (1991) reported an alpha coefficient of 0.89 and a test-retest reliability of 0.70 for a 15-month interval. In the study, the total score on the measure was used to evaluate the distress experienced by the caregiver.

Dependence Scale. This scale is designed to measure the functional decline associated with progression of dementia, as reported by an informant who is familiar with the patient's daily activities (Stern et al., 1994). The measure contains 13 items, and the items are converted to determine the level of dependency ranging from 0 to 5, with 0 being the lowest level of dependency. Examples of items include, "Does the patient have to be fed?" and "Does the patient need to be escorted when outside?" Stern and colleagues (1994) reported the scale to have an intraclass correlation of 0.90, indicating strong interrrater reliability, and a good validity with other functional impairment scales. This measure was included to examine the patient's functional impairment.

Health Utilities Index (HUI). The HUI is a reliable, general health-related quality of life measure that can be administered in a survey format to informants. It consists of six domains applicable to patients with AD that are combined in a multiplicative function to derive a single, preference-weighted quality of life score on a zero to one continuous scale (Feeny et al., 1995). For example, the informant is asked to rate on patient's mobility, attribute sensation, emotion, fertility, cognition, self-care, and pain. The HUI correlates significantly with important signs and symptoms of AD, including severity of the patient's cognitive impairment, neuropsychiatric symptoms, functional impairment, and Parkinsonism (Murman et al., 2002). The scale provides an assessment of health status, and, in addition, it provides a utility-based estimate of the value of health state based upon population-based studies using the standard gamble technique.

Follow-up Interviews. At each yearly follow-up interview, the informant was asked whether the patient had been placed in a nursing home facility, which included traditional nursing home setting, an assisted living facility, and an adult foster care home, or had died. The interviewer recorded the date of such event, which was used to calculate the time to events over the follow-up period.

Measures of confounding variables:

Mini-Mental Status Exam (MMSE). The MMSE is a commonly used measure for determining the level of cognitive functioning in an individual. It has been reported that MMSE is appropriate for use in examining the progression of cognitive decline and is able to capture a wide range of cognitive impairment in patients with AD (Folstein, Folstein, & McHugh, 1975). The score ranges from 0 to 30, with scores below 24 indicating some cognitive deficits. In the present study, score on the MMSE was used to adjust for cognitive impairments at baseline.

Cumulative Illness Rating Scale (CIRS). In order to control for the potentially confounding impacts of co-morbid medical conditions on outcome measures, the CIRS was used to evaluate the presence and the severity of co-morbid medical conditions in the patient. This measure calculates the severity and the presence of co-morbid medical conditions based upon the functioning of the 13 organ systems (Linn, Linn, & Gurel, 1968), and has been used successfully to predict hospitalization and death (Miller et al., 1992). Examples of the organ systems assess include cardiac and respiratory functioning. The score ranges from 14 to 70. The higher score on the scale indicates a more severe co-morbid medical condition.

Modified Colombia University Parkinson's Disease Rating Scale. This scale is used to quantify the presence of signs of Parkinsonism that are commonly observed in patients with Parkinson's disease and AD. Examples of symptoms assessed include resting tremor, rigidity, bradykinesia, and posture abnormalities. Each symptom is rated on a four-point scale of absent, slight, mild-moderate, and severe. The score ranges from 0 to 28. The reliability of this scale is respectable, as has been previously reported (Richards et al., 1991). Severity of Parkinsonism predicts rate of functional decline and is correlated with some neuropsychiatric symptoms (e.g. psychosis). Thus, we used the total score on this scale to adjust for group differences in Parkinsonism at baseline that may influence outcomes.

Procedure

After obtaining informed consent, trained examiners interviewed the patient and his or her informant separately for approximately 45 minutes. During the interview with the patient, he or she was asked to undergo a neurological exam and an assessment of neuropsychological functioning. The informant, meanwhile, provided the examiner with information on patient's symptoms, co-morbid medical conditions, level of functional impairment, quality of life, cost of care for the patient, and the level of distress experienced as the caregiver. A year after the initial interview, the informant was contacted yearly for 3 years by mail to complete surveys and by phone for an interview. In these follow-up contacts with the informant, he or she reported on the patient's level of functioning, quality of life, changes in symptoms, and significant events in the past year such as hospitalization, institution or death. The participants were compensated with a

$25.00 check after the initial interview, and with a $15.00 check after each of the yearly follow-up interviews.

Results

Cluster Analysis

To account for both the presence and the severity of neuropsychiatric symptoms, 2 sets of cluster analyses were conducted. For both of the analyses, weighted scores were used to correct for high intercorrelations observed between some of the NPI domains. In the first set of analyses, we considered the presence of symptoms on the NPI. Given that the presence of symptoms is a categorical variable, we used the Ward's minimum sum of squares method with Pearson's correlation as a base measure. In the second set of analyses, the severity x frequency of symptom score on the NPI was considered. Here again, Ward's method with Pearson's correlation as a base measure was used. The use of Pearson's correlation as a base measure in both sets of analyses allowed for examination of overall pattern of clustering, such as curvature similarities (von Eye, Mun, & Indurkhya, 2004). Since Ward's method, like other types of hierarchical agglomerative methods, is sensitive to outliers, a non-exhaustive approach was used (Everitt et al., 2001).

At the conclusion of the two analyses, it is possible that groupings based upon presence of symptoms and groupings based upon severity x frequency of symptoms would yield different symptom profiles that have unique outcome predictabilities worth examining. Therefore, the study conducted two parallel analyses on outcome measures. A precedent for such a methodological approach has been set in previous studies (Tubman et al., 1991). The SPSS 13.0 (2005) and the SYSTAT 10.0 (2002) statistical software packages were used to conduct the descriptive analyses, correlations, and cluster analyses.

Presence of Neuropsychiatric Symptoms

Based on the presence of neuropsychiatric symptoms, cluster analysis suggested a 3-cluster solution. Cluster mean profiles are presented in Table 1. Cluster 1 (N = 38) had the lowest mean score on the NPI, and thus was deemed to be Minimally Symptomatic. Cluster 2 (N = 53) had the highest mean score on the NPI, and the group as a whole appeared to be Highly Symptomatic. Cluster 3 (N = 31) had a moderate degree of symptoms, and an examination of the distribution of scores indicated that the group was Predominantly Apathetic. (See Table 1, Figure 1).

Hence, for the second segment of the study, the predictive validity of these three subgroups was examined. *Severity of functional* and *cognitive impairments*, *severity of Parkinsonism*, *co-morbid medical conditions*, *martial status* and/or *age* were adjusted at base line. The decision to adjust for a covariate was based on previous reports in the literature of a relationship with the outcome, and on examination of cluster differences for a particular variable. For instance, if a particular variable was previously found to be a significant predictor of the outcome variable of interest, we examined whether there were significant differences between the clusters, and if so, the variable was included in the model.

Caregiver Distress. At baseline, caregiver distress was assessed using the Screen for Caregiver Burden as reported by the informants. On this scale, the Minimally Symptomatic group had a total mean score of 12.79 (SD = 11.02), the Highly Symptomatic group had a total mean score of 23.51 (SD = 11.55), and the Predominantly Apathetic group had a total mean score of 17.10 (SD = 10.27).

Using ANCOVA, the significance of group differences in distress scores was tested. Initially, in the overall models, the covariates of *co-morbid medical conditions, the presence of Parkinsonism, age, and the severity of cognitive and functional impairments* were included. However, only *functional impairment* as a covariate was a significant predictor. Thus, in the final model, only *functional impairment* was included as a covariate. After controlling for the covariate, *functional impairment,* the three subgroups differed significantly on the total mean score for caregiver distress ($F = 5.93$, $p = 0.00$; 9% explained variance).

Post-hoc analyses indicated that the Minimally Symptomatic group and the Highly Symptomatic group differed ($p = 0.00$), in such a way that the caregivers of the Minimally Symptomatic group had lower distress than the Highly Symptomatic group. Furthermore, the Highly Symptomatic group and the Predominantly Apathetic group differed significantly ($p < .05$) in such a way that the caregivers of the Predominantly Apathetic group had a lower score on the caregiver distress scale.

Quality of Life. Over a 2-year period, the participants' quality of life was assessed using the HUI. Means and standard deviations of the HUI scores for each of the subgroups are presented in Table 2.

To test for group differences in quality of life over the 3 time points (Baseline, Year 1, Year 2), repeated measures ANOVA was performed. Possible covariates (*the presence of Parkinsonism, cognitive impairments,* and *functional impairments)* were entered as well. The results indicated that the main effect of neuropsychiatric subgroups was significant (F (2, 94) = 17.05, $p = 0.00$, 26.6% of the variance explained). Additionally, the linear Time effect was significant (F (2, 94) = 6.66, $p < .05$, 6.6%

variance explained). However, the interaction term between Time and neuropsychiatric subgroups was not significant (see Figure 2).

Post hoc Tukey tests indicated that mean scores on HUI differed significantly between the Minimally Symptomatic group and the Highly Symptomatic group (p = 0.00), with the Highly Symptomatic group having a lower quality of life. Additionally, the Highly Symptomatic group and the Predominantly Apathetic group showed significant differences in mean scores (p <.05), with the Predominantly Apathetic group having a higher quality of life.

Functional Impairment. The degree of functional impairment was assessed in the sample over a 2-year period, using the Dependence Scale. Means and standard deviations of the scores on this scale are presented in Table 3.

Repeated measures ANOVAs were performed to test the cluster differences in functional impairment at three time points (Baseline, Year 1, Year 2). The covariates, *the presence of Parkinsonism,* and *cognitive impairments,* were included. The results indicated that the main effect of neuropsychiatric subgroups, was significant (F (2, 93) = 9.22, p = 0.00, 16.4% explained variance). However, linear and quadratic Time effects and Group x Time were not significant (see Figure 3).

To further differentiate the findings, post hoc Tukey tests were performed. The findings showed significant mean differences between the Minimally Symptomatic group and the Highly Symptomatic group (p < .05), with the Minimally Symptomatic group having a lesser degree of functional impairment.

Nursing home placement. During the follow-up interviews, information was collected on whether the patient moved into long-term care or died during follow-up. The

date of such events was recorded and used to calculate time to events during the 3 years of follow-up. Cox proportional hazard models were used to perform survival analysis of nursing home placement and mortality outcomes. The use of survival analysis allowed for inclusion of continuous and/or dichotomous variables in the models, thus allowing for baseline adjustment of covariates. For these analyses, differences in the time to nursing home placement or death were compared in neuropsychiatric subgroups, after adjusting for important baseline differences in the subgroups, such as *presence of Parkinsonism, cognitive impairment, marital status, age*, and *comorbid medical conditions*. The choice of covariates to be included in the model was based on previous reports, observed correlations, and significant group differences in scores in the sample, and our aim of finding the most parsimonious model.

At the 3-year time point, 11 of the 32 (34%) in the Minimally Symptomatic subgroup, 27 of the 49 (55%) in the Highly Symptomatic subgroup, and 11 out of 27 (41%) in the Predominantly Apathetic subgroup had been placed into nursing homes. On average, the number of days to nursing home placement was 918.28 days for the Minimally Symptomatic group, 694.79 days for the Highly Symptomatic group, and 802.57 days for the Predominantly Apathetic group. Figure 4 illustrates the observed survival curves in days to nursing home placement in the three subgroups.

The Cox proportional hazard model showed that the overall model, which included the 3 cluster solutions based on the presence of neuropsychiatric symptoms, and the covariate of *presence of Parkinsonism*, predicted time to nursing home placement ($p = 0.00$). Of the covariates that were considered, only *presence of Parkinsonism* ($p < .05$) was significant. It should be noted that adding other covariates of *functional*

impairment, age, martial status and *severity of co-morbid conditions*, did not produce an appreciable difference in the overall fit of the model. Thus, after adjusting for the covariate *presence of Parkinsonism*, the subgroups, based on the presence of neuropsychiatric disturbances, significantly predicted nursing home placement over a 3-year period ($p < .05$). However, post-hoc pair-wise comparisons did not yield significant results (See Table 4).

Survival. At the 3-year time point, 5 of 37 (14%) in the Minimally Symptomatic group, 20 of 53 (38%) in the Highly Symptomatic group, and 12 of 31 (39%) in the Predominantly Apathetic group had died. The mean numbers of days alive for each group were as followed: 1051.40 days for the Minimally Symptomatic group, 905.70 days for the Highly Symptomatic group, and 966.01 days for the Predominantly Apathetic group. Figure 5 illustrates the observed survival curves for time to death in the 3 subgroups.

Using the Cox proportional hazard model, the overall model, which includes the 3 clusters and *the presence of Parkinsonism* as a covariate, significantly predicted death ($p = 0.00$) over a 3-year period. In addition, *the presence of Parkinsonism* ($p = 0.00$) was a significant predictor of death. Inclusion of additional covariates did not contribute to a significant change in the model. Thus, with *the presence of Parkinsonism* included, the clusters based on the presence of neuropsychiatric symptoms remained a significant predictor of death over the 3-year period ($p <.05$). Additionally, post-hoc pair-wise comparisons between the subgroups indicated that the Highly Symptomatic group was 3.6 times more likely to die than the Minimally Symptomatic group. Moreover, the Predominantly Apathetic group was 3.2 times more likely to die than the Minimally Symptomatic group. See Table 4.

Severity and frequency of neuropsychiatric symptoms

Based on the severity and frequency of neuropsychiatric symptoms, cluster analysis suggested 2-cluster and 4-cluster solutions. In the 2-cluster solution, individuals in Cluster 1 (N = 69) endorsed minimal symptoms, whereas individuals in Cluster 2 (N = 53) endorsed a high level of symptoms. In the 4-cluster solution, Cluster 1 (N = 42) was composed of individuals who were Minimally Symptomatic. In Cluster 2 (N = 39), individuals with Affective/Apathetic symptoms, such as depression, anxiety, and apathy, were present. Cluster 3 (N = 27) included individuals who were Predominantly Apathetic. Individuals in Cluster 4 (N = 14) were Highly Symptomatic with Psychotic Features. Characteristics of the subgroups for 4-cluster solution are presented in Table 5. Graphical presentation of mean profiles for the clusters is shown in Figure 6.

One major advantage of the 4-cluster solution over the 2-cluster model in this portion of the analyses is that the 4-cluster solution provides a finer differentiation of the symptom profiles. In other words, the 4-cluster solution provides information on the roles of the Affective/Apathetic group (Cluster 2) and the Predominantly Apathetic group (Cluster 3), in addition to the low and high symptom groups seen with the 2-cluster solutions. Thus, a decision was made to omit the 2-cluster solution from further discussion.

Also, it is noted that the emergence of cluster solutions with the use of Pearson's correlation as a base measure to examine severity and frequency of symptoms provides support for the validity of the clusters. Specifically, given that the severity and frequency of symptoms is a continuous variable, elevation in profiles, rather than the overall pattern, in theory would be the natural basis for clustering. However, the use of Euclidean

distance to account for elevations in profiles produced clusters that were less robust than the use of Pearson's correlation. This suggests that the clusters were robust across different base measure, and hence, indicates a strong case for validity of the clusters.

Caregiver Distress. At baseline, the Minimally Symptomatic group had a total mean score of 11.90 (SD = 9.32) on the Caregiver Burden Scale. The Affective/Apathetic group had a total mean score of 23.59 (SD = 10.65). The Predominantly Apathetic group had a total mean score of 16.41 (SD = 8.65). The Highly Symptomatic group had a total mean score of 28.50 (SD = 15.31).

ANCOVA was used to examine the group differences in Caregiver Burden scores. As with the presence of symptoms, the covariates of *co-morbid medical conditions, the presence of Parkinsonism, age,* and *the severity of cognitive and functional impairments* were initially included. Again, only *functional impairment* as a covariate was a significant predictor. Thus, in the final model, only *functional impairment* was included as a covariate. After controlling for the covariate, *functional impairment,* the four subgroups differed significantly on the total score of caregiver distress (F = 9.332; p = 0.00; 19% explained variance).

Post hoc comparisons indicated that the Minimally Symptomatic group differed significantly from the Affective/Apathetic group (p = 0.00), in that their caregivers experience less distress. Similarly, the caregivers of the Minimally Symptomatic group experience less distress than the caregivers of the Highly Symptomatic group (p = 0.00). In addition, the caregivers of the Affective/Apathetic subgroup endorsed higher distress than the Predominantly Apathetic subgroup ($p < .05$). Lastly, the Predominantly

Apathetic subgroup showed lower level of caregiver distress than the Highly Symptomatic subgroup ($p = 0.00$).

Quality of Life. Mean and standard deviations of HUI scores for the four subgroups are presented in Table 6.

Using repeated measures ANOVA, the cluster differences in mean scores was tested at three time points (Baseline, Year 1, Year 2). Potentially confounding variables, *the presence of Parkinsonism, cognitive impairments,* and *functional impairments,* were adjusted. The results indicated a significant main effect of neuropsychiatric subgroups ($F (3, 93) = 13.51$, $p = 0.00$, 30.4% explained variance). Also, the linear Time effect was significant ($F (2, 93) = 6.66$, $p < .05$, 6.6% explained variance). The interaction between Time and the subgroups was not significant (See Figure 7).

Post hoc Tukey tests indicated 3 significant group mean differences. The mean scores between the Minimally Symptomatic group and the Affective/Apathetic groups differed significantly ($p = 0.00$), with the Minimally Symptomatic group having a higher score on the HUI. The mean scores between the Minimally Symptomatic group and the Highly Symptomatic with Psychotic Features group differed significantly ($p = 0.00$), with the Highly Symptomatic with Psychotic Features group having a lower score on the HUI. Lastly, the Affective/Apathetic group and the Predominantly Apathetic group showed significant differences in mean scores ($p < .05$), with the Predominantly Apathetic group having a higher quality of life than the Affective/Apathetic group.

Functional Impairment. The four subgroups' means and standard deviations on the Dependence Scale are presented in Table 7.

Repeated measures ANOVA was performed to test the group differences on the Dependence Scale over a 2-year period. The covariates, *the severity of cognitive impairments, the presence of Parkinsonism,* and *the severity of co-morbid medical conditions,* were adjusted. The results showed the main effect neuropsychiatric subgroups to be significant (F (3, 93) = 5.19 p =.00, 14.3% explained variance). In addition, linear Time effect (F (2, 93) = 5.00, $p < .05$, 5.1% explained variances), and linear Group x Time effect (F (3, 93) = 2.93, $p < .05$, 5.2% explained variances) were significant (see Figure 8).

Post hoc Tukey tests indicated a significant group mean differences between the Minimally Symptomatic group and the Affective/Apathetic subgroup ($p = 0.00$), with the Affective/Apathetic group having a greater degree of functional impairment.

Nursing Home Placement. In Table 8, the number of individuals placed in nursing homes after a 3-year period and the average time to nursing home placement are presented for each cluster. Survival curves for the 4-cluster solution are presented in Figure 9.

In the model, the covariate, *the presence of Parkinsonism*, was included. An inclusion of *severity of co-morbid medical conditions*, *marital status*, and *severity of cognitive* and *functional impairments* did not make an appreciable difference to the overall model. Findings from the Cox proportional hazard model showed that the overall model, which included the 4 clusters, along with *the presence of Parkinsonism*, was a significant predictor of nursing home placement ($p = 0.00$). In addition, *the presence of Parkinsonism* ($p = 0.00$) was a significant covariate. Similarly, the differential outcome of nursing home placement as predicted by the 4-clusters solution was significant (p

<.05). Post-hoc pair-wise comparisons between the clusters did not yield significant results. See Table 4.

Survival. Table 8 shows the number of individuals in each subgroup that died and the mean times to death. The survival curves are presented in Figure 10. The overall Cox proportional hazard model, which included the 4-cluster solution and the covariate *presence of Parkinsonism,* was significant ($p = 0.00$) in predicting mortality over a 3-year period. Inclusion of other covariates, *age, cognitive* and *functional impairments,* did not change the model. *The presence of Parkinsonism* was a significant covariate ($p = 0.00$). Moreover, cluster membership was a significant predictor of death ($p < .01$). Specifically, a post-hoc pair-wise comparison indicated that the Highly Symptomatic group was 9.4 times more likely to die over a 3-year period than the Minimally Symptomatic group ($p = 0.00$). See Table 4.

Discussion

Overall, the current findings appear to provide evidence that AD patients with neuropsychiatric symptoms can be meaningfully grouped based on the presence of symptoms, as well as the severity and frequency of symptoms. A decision was made to present the findings on the presence and the severity of symptoms in a parallel fashion, rather than attempt to aggregate the findings, as aggregation could potentially lead to a loss of critical information. In addition, this approach allowed the investigator to use the established method of classifying based on the presence of symptoms, and concurrently explore the potential benefits of incorporating severity and frequency of symptoms. As mentioned previously, a precedent for such an approach has been set (e.g. Tubman et al., 1991).

The first major finding of the study was that based on the presence of neuropsychiatric symptoms, patients with AD can be categorized into three distinct neuropsychiatric profiles: Minimally Symptomatic, Highly Symptomatic, and Predominantly Apathetic. Using the same methodology, a categorization of AD patients based on the severity and frequency of symptoms yielded two possible ways of grouping. With the first possibility, patients can be parsimoniously identified as minimally or highly symptomatic. However, with this strategy, limited information can be gained beyond the general impact of neuropsychiatric symptoms on the individual. With the second possible way of grouping, on the other hand, a finer differentiation can be achieved as 4 distinct symptom profiles were identified: Minimally Symptomatic, Affective/Apathetic, Predominantly Apathetic, and Highly Symptomatic with Psychotic

Features. Here, in addition to the impact of high and low symptoms, we have information on the Affective/Apathetic and the Predominantly Apathetic subgroups.

In reviewing the various profiles that emerged based on the presence and the severity of symptoms, it was of note that the Minimally Symptomatic subgroup was found consistently across the different methods of clustering. This finding was reflective of the clinical picture in that a segment of the AD population has been noted to be relatively unaffected by neuropsychiatric disturbances (Cummings, 2003; Lyketsos et al., 2001b; Moran et al., 2004).

In the current sample, this finding was of particular interest in that being minimally symptomatic did not appear to be a function of severity of cognitive impairments, as cognitive functioning was comparable across subgroups. Recently, similar findings have been reported by Weiner and colleagues (2005). Thus, the severity of AD pathology alone, as measured by cognitive decline and global degeneration of the brain structures, does not necessarily account for the presence of neuropsychiatric symptoms. Rather, it hints at a differential regional involvement in the process of neuronal degeneration as a potential contributor to differential symptom development in AD patients. Therefore, there is support for the view that the brain regions affected by AD pathology can differ between individuals in such a way that some individuals have a greater vulnerability to be affected disproportionately in one region rather than another (Cummings, 2003a; Cummings, 2003b; Weiner et al. 2005). Thus, it would be of interest to further explore the biological and the environmental characteristics that are particular to the minimally symptomatic segment of the AD population.

In addition to the Minimally Symptomatic subgroup, a second notable subgroup we identified was the Predominantly Apathetic group. The emergence of apathy as a distinct neuropsychiatric profile is supported by previous reports (Boyle & Malloy, 2003; Landes, Sperry, & Strauss, 2005; Lyketsos et al., 2002). Similarly, the present finding that the Affective/Apathetic group is a distinct group is also consistent with the literature. Specifically, previous attempts to classify neuropsychiatric symptoms had found the "affective factor" to be one of the most consistent findings across different classification methods (Aalten et al., 2003; Craig et al., 2004; Frisoni et al., 1999; Hope et al., 1997; McShane, 2000; Schreinzer et al. 2005). Additionally, this differentiation of apathy from a combined affective and apathy symptoms has been reported previously. Specifically, Lyketsos and co-workers (2001a) found that a subgroup of AD patients endorsed apathy without depression, whereas another subgroup endorsed both depression and apathy. Similar findings have been reported in other studies (Holthoff et al., 2005; Landes et al., 2001; Starkstein et al., 2001).

Of note, the current findings showed that the use of frequency and severity of symptoms to classify resulted in an identification of a combined Affective/Apathy subgroup. Therefore, using severity and frequency of symptoms as the criteria for classification may prove to be advantageous in that it identifies the affective/apathy profile, which has unique potentials for predicting disease outcomes.

A third subgroup identified by the clustering methods is the high symptomatology group. Specifically, the clustering based on the presence of symptoms yielded a Highly Symptomatic group, whereas the clustering based on the severity and frequency produced a Highly Symptomatic with Psychotic Features group. There has been a precedent for

isolation of psychotic symptoms as a distinct symptom profile (Mirakur et al., 2004; Firsoni et al., 1999; Lyketsos et al., 2001b; Schneider & Dagerman, 2004). Furthermore, there have been previous reports of an association between psychotic symptoms and an overall high symptomatology (Bassiony et al., 2000). Moreover, in previous studies, there had been reports of psychotic symptoms and high levels of neuropsychiatric symptoms associated with more severe dementia (Craig et al., 2005). However, current findings were not in supportive of these prior studies, as the cognitive impairments did not differ significantly between groups.

As for potential causal explanations for an emergence of this subgroup, recent studies pointed to neurobiologic explanations. First, one study found that a decrease in serotonin level in the temporal cortex was associated with an increase in psychotic symptoms in AD, especially among women (Garcia-Alloza et al., 2005). Additionally, there had been suggestions of underlying genetic predisposition for the development of psychotic symptoms with AD, and its associated neurological changes (Sweet et al., 2005; Holmes et al., 2001). Further research is needed to replicate these findings and to validate the region- and gene-specific neurobiologic basis for the development of certain neuropsychiatric symptoms.

Impact of neuropsychiatric symptoms on outcome measures

In addition to the primary objective of identifying neuropsychiatric symptoms as distinct symptom profiles, the aim of this research also was to test the predictive validity of subgroups on outcome measures. The present findings indicated that the subgroups, regardless of whether the groups were based on the presence of symptoms, or on the

severity and frequency of symptoms, were able to predict caregiver distress, quality of life, functional impairment, nursing home placement, and mortality.

Caregiver Distress. The extent of caregiver distress was differentially predicted by the subgroups. More specifically, based on the presence of symptoms, the caregivers of the Highly Symptomatic subgroup endorsed a greater degree of burden than the Minimally Symptomatic and the Predominantly Apathetic group. Based on the severity and frequency of symptoms, however, the caregivers of the Minimally Symptomatic and the Predominantly Apathetic groups showed less distress than the Affective/Apathetic and the Highly Symptomatic with Psychotic Features groups. These findings suggested that caregivers are less burdened when the AD patients have a low level of neuropsychiatric symptoms, or when their primary symptom is apathy. In addition, this finding illustrated how the use of severity and frequency of symptoms to classify could provide greater differential pathways to disease outcomes, as burden experienced by caregivers of the Affective/Apathy group resembled that of the Highly Symptomatic group, rather than that of the Predominantly Apathetic group.

These findings were in agreement with previous reports of high level of neuropsychiatric symptoms associated with greater caregiver distress and lower quality of life for the caregiver (Craig et al., 2005; Shin et al., 2005). However, it appears that the burden is partly determined by the type of symptom, rather than by the general presence of symptoms, as had been suggested previously (Teri, 1997; Rinaldi et al., 2005). As reviewed by Ballard and colleagues (2000), severe mood disturbances, aggression, restlessness, and apathy had been suggested in previous studies to be the symptoms most associated with distress. In the current study, mood disturbances were consistent with the

Affective/Apathy, and aggression and restlessness were consistent with the Highly Symptomatic group. Therefore, our findings appeared consistent with symptom-specific findings from the literature. However, the current findings were not in support of apathy causing greater distress in caregivers. One hypothesis is that the discrepancy in findings is due to the incorporation of *functional impairment* as a covariate in our model. In particular, it has been suggested that a more comprehensive examination of caregiver burden, in addition to the NPI score, would produce a more accurate assessment of the relationship between caregiver distress and neuropsychiatric symptoms (Rinaldi et al., 2005). However, when this hypothesis was tested by removing the covariate *functional impairment* from the model, our findings remained the same. Further studies are needed to test the validity of ours and previous findings.

As for why affective and high level of symptoms, in particular, cause greater burden in caregivers, one potential explanation is that certain types of symptoms, such as hallucination, depression, and agitation, adversely impact the quality of the relationship between the patient and his or her caregiver. Therefore, when the quality of the relationship is poor, the emotional reserve the caregiver has for handling behavioral disturbances may be diminished. In fact, there has been a report of a decrease in quality of the relationship between AD patient and the caregiver as predictive of caregiver's depression and anxiety (Mahoney et al., 2005). Another potential explanation for the findings is that affective and high symptoms may entail greater functional impairment, placing greater practical burden on the caregiver. In addition, the caregiver may feel anger and resentment toward the patient's dependency (DeKosky & Orgogozo, 2001). In the present study, consistent with previous reports, only functional impairment, as a

covariate, was a significant predictor of caregiver distress. Overall, the results suggested that caregivers of AD patients with affective and high neuropsychiatric symptoms experience greater burden. Hence, future studies involving interventions strategies targeted toward these particular populations of caregivers may lessen the burden.

Quality of Life. The differences in quality of life between AD patients were predicted by the neuropsychiatric subgroups over a 2-year period. Post hoc analyses indicated that based on the presence of symptoms, the Minimally Symptomatic and the Predominantly Apathetic subgroups showed higher quality of life than the Highly Symptomatic group. Based on the severity and frequency of symptoms, the Minimally Symptomatic group showed higher quality of life than the Affective/Apathetic group and the Highly Symptomatic with Psychotic Features group. Additionally, the Affective/Apathetic group had a lower quality of life than the Predominantly Apathetic group.

Although previous studies have not considered the impact of co-morbid neuropsychiatric symptoms on quality of life, the current findings are consistent with previous findings that affective symptoms, particularly depression, have a negative impact on quality of life (Fassino et al., 2002; Logsdon et al., 1999; Gonzalez-Salavador et al., 2000; Selwood et al., 2005). However, the results were not in support of previous indications that quality of life is stable over time, as findings did show a significant time effect (Lyketsos et al., 2003; Selwood et al., 2005).

Potentially, this discrepancy in findings could be attributed to differences in measures used to study quality of life. In the present study, the HUI, which is a specific measure of quality of life based on general health status, was used. In the field of

pharmacoeconomics, the HUI is commonly used to calculate quality adjusted life years. Although this provides one objective means of examining quality of life, the use of the HUI discounts other factors contributing to quality of life, such as having strong social support. Such differences in the focus of the quality of life measures likely contributed to the differences in findings between this research and prior research regarding time effects.

One proposed explanation for the finding of neuropsychiatric symptoms' adverse impact on quality of life is that the presence of symptoms causes greater distress in the AD patient (Cummings, 2003a). Cummings (2003a) suggested that this distress, in turn, decreases the quality of life. Therefore, the development of interventions aimed at the symptoms, and their associated distress, may potentially increase quality of life for the AD patient.

Functional Impairment. The neuropsychiatric subgroups differentially predicted functional impairments over a 2-year period. Post hoc analyses indicated that based on the presence of symptoms, the Minimally Symptomatic group showed a slower rate of decline in functional impairment than did the Highly Symptomatic group. Based on the severity and frequency of symptoms, the Affective/Apathetic group showed a higher rate of functional decline than the Minimally Symptomatic group.

Previously, the impact of neuropsychiatric symptoms on functional impairment had been examined using the total NPI score or the individual symptom approach. Based on these reports, the present findings are consistent with the general consensus of behavioral symptoms having an adverse impact on functional impairment (Weiner et al., 2005; Norton, Malloy, & Salloway, 2001; Tekin et al., 2001). However, our findings

differed from previous findings of apathy (Boyle et al., 2003) and hallucination (Mok et al., 2004) predicting significant decline in functioning. Potentially, these discrepancies in findings might have been due to differences in the approach used; that is, whether individual symptoms examined alone versus incorporation of co-occurring symptoms.

In addition to the main effects of neuropsychiatric subgroups, the study found *cognitive deficits* and *presence of Parkinsonism* to be significant covariates. These findings were also consistent with previous reports (Mok et al., 2004; Boyle et al., 2003; Lyketsos et al. 2005). Therefore, interventions aimed at reducing functional impairment should consider neuropsychiatric symptoms, cognitive impairments, and presence of Parkinsonism.

Lastly, based on the severity and frequency of symptoms, post-hoc analyses indicated a significant time by group interaction between functional impairment and neuropsychiatric subgroups. Specifically, in the first year of the study, the Highly Symptomatic with psychotic feature group showed a slight decrease in functional impairment in relation to the Affective/Apathetic subgroup. However, in the second year of the study, the Highly Symptomatic group showed a significant increase in functional impairment in relation to the Affective/Apathetic subgroup. Potentially, this finding can be explained by the fact that the majority of the patients in the Highly Symptomatic group were likely on antipsychotic medications and that by the second year of the study significant side effects associated with the longer-term use of the medications contributed to the decline in functioning.

Nursing Home Placement. Both clustering approaches showed neuropsychiatric subgroups to be predictive of differential times to nursing home placement over a 3-year

period. However, post-hoc pair-wise comparisons were not significant. The null findings of the pair-wise comparison tests can likely be explained by two factors. First, although our full model indicated overall significant results for the subgroups, the findings were less robust in that only 2 out of the 3 significance tests typically used in survival analysis showed significant findings. Thus, findings from this portion of the analyses should be interpreted with caution. Second, due to the nature of the study, the pair-wise comparisons entailed lower power, as samples were smaller in post hoc analyses than in the original model. Therefore, the likelihood of the tests detecting group differences was smaller.

Thus, although post hoc tests did not indicate specific group differences, observations of the means and the graphs suggested that individuals with high symptom profiles were at a higher risk for nursing home placement. In contrast, individuals with minimal symptoms consistently were at a lower risk for nursing home placement. Hence, the high symptom profile might be a risk factor for nursing home placement. These findings are consistent with previous reports (Balestreri et al., 2001; Colerick & George, 1986; Gilley et al., 2004; Kopetz et al., 2000; Yaffe et al., 2002).

One explanation for the finding of individuals with high symptom profiles having a higher risk for nursing home placement potentially is that their caregivers have difficulty coping with the unsettling nature of neuropsychiatric symptoms. In particular, it has been reported that caregivers find certain symptoms, such as psychotic symptoms, especially difficulty to handle (Moh et al., 2005). Behavioral modification programs to manage the high level of symptoms may result in reduced caregiver distress and delay the time to nursing home placement (Gilley et al., 2004 Lichtenberg et al., 2005). Also,

psychoeducational programs and support for caregivers may reduce the need for nursing home placement. Such implementation of intervention strategies early in the symptom development could lead to a reduction in the overall cost of care (Butler, 1995).

Survival. Both clustering methods predicted differential rates of death over a 3-year period. Post hoc pair-wise comparisons indicated that based on the presence of symptoms, the Highly Symptomatic group was 3.6 times more likely to die than the Minimally Symptomatic group over a 3-year period. Similarly, the Predominantly Apathetic group was 3.2 time more likely to die than the Minimally Symptomatic group over a 3-year period. Based on the severity and frequency of symptoms, the Highly Symptomatic group was 9.6 times more likely to die than the Minimally Symptomatic group over a 3-year period. Thus, it suggested that an overall high neuropsychiatric symptom profile increases the risk of death over a 3-year period.

To our knowledge, there has been one other study to consider the effects of high neuropsychiatric symptom profile on mortality in AD, and the findings are consistent with present findings (Weiner et al., 2005). Also, there are two additional studies that examined the impact of individual neuropsychiatric symptoms on mortality. In one study, an increase risk of mortality was found when depression was present (Ganguli, Dodge, & Mulsant, 2002). In the second study, tactile hallucination was associated with greater risk of mortality (Suh et al., 2005). Given the limited research in this domain, further studies are needed to replicate the findings.

A potential explanation for the increased risk of mortality associated with high symptom profile is that in recent studies, there were indications that certain atypical antipsychotic medications used for the treatment of psychotic symptoms in dementia may

increase the risk of mortality (Schneider, Dagerman, & Insel, 2005). In addition, there have been previous reports of an increased risk of cerebrovascular incident with Risperidone (Bordaty et al., 2003). Therefore, it is conceivable that an increase risk of mortality observed in the study for individuals with high symptom profile could partially be attributed to the use of antipsychotic drugs in these patients. In future studies, it would be of importance to consider drug use when examining the relationships between neuropsychiatric symptoms and mortality in AD.

Study's Implications:

Findings from the study have both research and clinical implications. First, in terms of research, the results of the current study provide empirical support for the categorization of neuropsychiatric disturbances using cluster analysis. Hence, if the method is validated in replication studies, its use in future studies might potentially aid with finding greater consistency in outcomes. Also, it offers a tool for which neurobiologic origins of neuropsychiatric symptoms can be explored. For instance, rather than looking specifically at the neurological basis for depression in AD, it allows the researcher to examine a profile of co-occurring symptoms associated with depression. By taking such an approach, consistency in findings with regard to neurological changes in AD can potentially be achieved. By the same token, the method can be applied to exploration of possible subtypes in AD. There have been suggestions of subtypes of AD that show unique neuropathology, disease characteristics, including neuropsychiatric profiles, and disease outcomes (Aalten et al., 2003; Lyketsos et al., 2001b; Cook et al., 2003). An empirically-validated approach to classifying neuropsychiatric disturbances may aid in an effort to address this possibility. From our findings, the clustering based on

the severity and frequency of symptoms appears suitable for research purposes, as it identified an additional meaningful subtype to that of clustering based on the presence of symptoms.

There are also a number of clinical implications from the study. First, the results contribute to recent efforts in the field to establish an empirically validated classification system for neuropsychiatric symptoms associated with dementia. Prior to this effort, an initial attempt at classification was carried out by a panel of experts at a consensus conference (Finkel, 1996). However, recent developments in the field had called for establishing a system with empirical validation (Aalten et al., 2003; Lyketsos et al., 2001b). Thus, based on findings from a latent class analysis study (Lyketsos et al., 2001b), Lyketsos and colleagues (2001a) proposed criteria for two syndromes: Alzheimer-associated affective disorder and Alzheimer-associated psychotic disorder. It is noted that the criteria set forth for Alzheimer-associated psychotic disorder is consistent with our findings regarding the Highly Symptomatic group.

On the other hand, although the criteria proposed for Alzheimer-associated affective disorder have features resembling our Predominantly Affective group and the Affective/Apathy group, there is a significant divergence. Specifically, the criteria for affective disorder do not include apathy, although the group identified in the original latent class analysis study showed apathy to be highly prevalent. Thus, based on current findings, a proposed revision to the criteria put forth by Lyketsos and colleagues (2001a) would be to differentiate two Alzheimer-associated disorders with affective symptoms. In one, an emphasis would be given to the present of both affective symptoms, such as depression, and apathy, in addition to other 'less prominent' symptoms such as those

proposed by Lyketsos et al. (2001a). In the second, the presence of significant apathy would be the main criterion. However, it is noted that having apathy as the main diagnostic criteria does not exclude the possibility of other symptoms being present to a lesser degree.

Second, the findings identified at-risk profiles for poor patient and caregiver outcomes. Interventions targeted at symptoms associated with these profiles may prove critical in altering the negative outcomes. Such interventions at the level of multiple-symptom that co-occur have been suggested as an effective approach in treating neuropsychiatric symptoms (Tractenberg et al., 2003), as more options for interventions are becoming available in recent years. For instance, there are now a number of behavioral management strategies for use with neuropsychiatric disturbances (Lichtenberg et al., 2005; Politis et al., 2004). In addition, although opinions on the use of pharmacological treatment vary, especially after recent findings on its potential risks, an individualized consideration of risk and benefits has been encouraged (Sink, Holden, & Yaffe, 2005a; Sink, Holden, & Yaffe, 2005b; Rabin & Lyketsos, 2005). In assessing the need for interventions, our study showed NPI to be a useful measure in effectively identifying patients at-risk. Therefore, its use in clinical and research settings was supported.

Also in terms of clinical implications, the findings on the role of apathy were of particular interest. In terms of its impact on nursing home placement, the predominantly apathetic group fell between the low and the high symptom profiles. This made intuitive sense in that the caregivers of the AD patients endorsing apathy would find their apathetic behavior more tolerable and easy to care for than the individuals with high

symptom profile. This was supported by findings on caregiver distress. Therefore, with a lower caregiver distress, there would be less of a need for placing the patient in a long-term care setting. An intriguing result, however, was that even though caregivers may find apathy more tolerable, the presence of apathy appeared just as detrimental as the high symptom profile when it came to predicting mortality. In the 3-cluster solution, the Predominantly Apathetic and the Highly Symptomatic group had similarly low rates of survival. In the 4-cluster solution, the Predominantly Apathetic group had a similar rate of survival as the Affective/Apathetic group. Hence, it suggested that although the presence of apathy in AD patients appears less destructive outwardly, it still has a detrimental impact on the patient's survival, and should not be overlooked as a target for treatment.

Study Limitations

There were a number of limitations in the study. First, it was possible that the presence and the severity of neuropsychiatric symptoms changed as the dementia progressed. Given that the symptoms were assessed at the onset of the study, the potential confounding influence of changes in neuropsychiatric symptoms over the 3-year period could not be evaluated. However, of the available literature on the topic, one study indicated that neuropsychiatric symptoms remained comparable across the study period of a year and a half (Steinberg et al., 2004). Second, the NPI, used to assess neuropsychiatric symptoms in the study, was based on informant reports. Hence, it was conceivable that an informant bias in the reporting of the symptoms might have existed. However, when assessing the presence of symptoms in AD patients with significant cognitive deficits, the use of an informant may be unavoidable. Lastly, although the

initial sample size of 122 AD patients was respectable, the sample size became smaller as subgroups were identified. This was especially true for the 4-cluster solution, which in one of its groups, contained a sub-sample of only 14 patients. The small sample size is a strength of the study in that the cluster profiles were predictive of outcomes. This suggests a robust relationship between the clusters and the outcome variables.

Directions for future studies:

Given the promising indications of neuropsychiatric symptom profiles having differential disease outcomes, replication studies are needed to determine whether similar subgroups emerge in different samples. In addition, further explorations are needed to test the extent of this predictive validity. For instance, it would be useful to test the predictive validity in other outcome measures such as rate of cognitive decline, or differences in medication response as suggested by Lyketsos and colleagues (2001a). Along the same line, future studies could potentially test the usefulness of the methodology employed for classifying neuropsychiatric disturbances in AD to other dementias, such as dementia with Lewy bodies. Such application of the method to other dementias may provide an empirical validation for the clinical use of neuropsychiatric symptoms in differential diagnosis of dementias. Lastly, and perhaps most importantly, if the findings of neuropsychiatric symptom profiles having differential disease outcomes prove to be consistent across other outcome measures and dementias, an exploration into the potential neurobiological underpinnings of the profiles appears warranted. For example, it is possible that the presence of certain underlying genetic characteristics or an involvement of particular brain structures in the disease process predispose an individual to have a certain neuropsychiatric profile (Cummings, 2003; Lam et al., 2004).

Summary

Overall, the findings from the study suggested that cluster analysis was a suitable approach for examining neuropsychiatric symptoms in AD as profiles of symptoms that co-occur. Specifically, in the current study, cluster analysis identified meaningful, well-defined subgroups of AD patients that can predict caregiver and patient outcomes. Additionally, findings from the study showed that such subgroups can be identified based on the presence of symptoms, and on the severity and frequency of symptoms. However, when the two clustering approaches were compared, it appeared that clustering based on the severity and frequency of symptoms provided more information in that it identified a combined Affective/Apathetic group. In certain outcomes, this identification was advantageous in that there were distinct outcomes for this subgroup.

In addition to the subgrouping of neuropsychiatric symptoms in AD patients, the study identified at-risk profiles for clinical outcomes. Therefore, if future replication studies find the groups to be stable across samples, it warrants an investigation into targeted intervention strategies and the neurobiologic origins of the subgroups. By exploring such potentials, the field could move a step closer toward the development of more effective and targeted treatment options for neuropsychiatic symptoms, and thereby may be able to alter the outcomes of patients with AD.

APPENDIX

TABLES AND FIGURES

Table 1

Cluster Mean Profiles for the Presence of Symptoms

	Cluster 1	Cluster2	Cluster3
N	38	53	31
Age	75.79	76.81	76.71
MMSEscore	16.58	15.19	16.71
CIRS score	19.45	21.70	20.48
EPS score	2.84	3.17	3.65
Dependence score	2.76	3.60	3.03
Total NPI score	5.58	28.60	13.74
Delusions	0.08	0.40	0.29
Hallucinations	0.03	0.32	0.16
Agitation	0.11	0.81	0.13
Depression	0.18	0.64	0.42
Anxiety	0.08	0.66	0.42
Elation	0.11	0.21	0.00
Apathy	0.08	0.77	0.94
Disinhibition	0.18	0.57	0.00
Irritability	0.06	0.73	0.11
Aberrant Motor Behavior	0.32	0.51	0.29

Note: Total NPI score = Total score on the Neuropsychiatric Inventory; MMSE score = score on the Mini-Mental Status Exam; CIRS score = score on the Cumulative Illness Rating Scale; EPS score = score on the Modified Colombia University Parkinson's Disease Rating Scale; Dependence score = score on the Dependence Scale.

Table 2

Health Utilities Index Mean Scores for the Presence of Symptoms

	Cluster	N	Mean	S.D.
Baseline	Minimal Symptom	38	0.717	0.20
	High Symptom	53	0.508	0.18
	Apathetic	31	0.644	0.19
Year 1	Minimal Symptom	36	0.707	0.20
	High Symptom	48	0.523	0.20
	Apathetic	30	0.591	0.22
Year 2	Minimal Symptom	37	0.618	0.20
	High Symptom	39	0.431	0.19
	Apathetic	25	0.549	0.22

Table 3

Dependence Scale Mean Scores for the Presence of Symptoms

	Cluster	N	Mean	S.D.
Baseline	Minimal Symptom	38	2.763	1.03
	High Symptom	53	3.604	1.10
	Apathetic	31	3.032	1.05
Year 1	Minimal Symptom	36	3.000	1.12
	High Symptom	48	3.771	1.23
	Apathetic	29	3.276	1.13
Year 2	Minimal Symptom	37	3.351	1.25
	High Symptom	39	3.923	1.22
	Apathetic	25	3.440	1.04

Table 4

Pairwise Compairsons between Clusters

Predictor	β	RR	p-value
Nursing home placement			
Presence of symptoms:			
Cluster 1 vs. Cluster 2	0.525	1.691	0.09
Cluster 1 vs. Cluster 3	0.137	1.147	0.71
Frequency and severity of symptoms:			
Cluster 1 vs. Cluster 2	0.589	1.803	0.08
Cluster 1 vs. Cluster 3	0.388	1.474	0.29
Cluster 1 vs. Cluster 4	0.606	1.834	0.21
Probability of death			
Presence of symptoms:			
Cluster 1 vs. Cluster 2	1.285	3.614	0.01
Cluster 1 vs. Cluster 3	1.171	3.226	0.03
Frequency and severity of symptoms:			
Cluster 1 vs. Cluster 2	0.988	2.685	0.07
Cluster 1 vs. Cluster 3	0.925	2.521	0.11
Cluster 1 vs. Cluster 4	2.240	9.396	0.00

Table 5

Cluster Mean Profiles for the 4-cluster Solution based on the Severity and Frequency of Symptoms

	Cluster 1	Cluster2	Cluster3	Cluster 4
N	42	39	27	14
Age	75.60	75.69	78.22	77.86
MMSEscore	17.67	14.90	16.59	13.00
CIRS score	19.50	22.18	20.74	20.00
EPS score	2.50	3.41	3.78	3.50
Dependence score	2.76	3.51	3.20	3.64
Total NPI score	4.50	25.74	11.78	45.93
Delusions	0.07	0.31	0.26	0.79
Hallucinations	0.05	0.21	0.19	0.57
Agitation	0.19	0.67	0.19	0.86
Depression	0.26	0.72	0.22	0.64
Anxiety	0.17	0.64	0.33	0.71
Elation	0.07	0.21	0.00	0.29
Apathy	0.14	0.80	0.93	0.79
Disinhibition	0.14	0.59	0.11	0.36
Irritability	0.13	0.49	0.25	0.92
Aberrant Motor Behavior	0.21	0.54	0.15	1.00

Table 6

Health Utilities Index Mean Scores for the Severity and Frequency of Symptoms

	Cluster	N	Mean	S.D.
Baseline	Minimal Symptom	42	0.737	0.17
	Affective/Apathetic	39	0.485	0.17
	Apathetic	27	0.668	0.17
	High Symptom	14	0.444	0.16
Year 1	Minimal Symptom	40	0.705	0.19
	Affective/Apathetic	36	0.514	0.18
	Apathetic	26	0.609	0.24
	High Symptom	12	0.481	0.20
Year 2	Minimal Symptom	41	0.644	0.20
	Affective/Apathetic	31	0.423	0.17
	Apathetic	21	0.510	0.24
	High Symptom	8	0.395	0.07

Table 7

Dependence Scale Mean Scores for the Severity and Frequency of Symptoms

	Cluster	N	Mean	S.D.
Baseline	Minimal Symptom	42	2.762	0.98
	Affective/Apathetic	39	3.513	1.12
	Apathetic	27	3.185	1.18
	High Symptom	14	3.643	1.01
Year 1	Minimal Symptom	40	2.850	1.00
	Affective/Apathetic	36	3.778	1.22
	Apathetic	26	3.560	1.26
	High Symptom	12	3.750	1.14
Year 2	Minimal Symptom	41	3.220	1.19
	Affective/Apathetic	31	3.903	1.19
	Apathetic	21	3.476	1.17
	High Symptom	8	4.625	0.52

Table 8

Clusters based on the Severity and Frequency of Neuropsychiatric Symptoms as Predictors of Nursing Home Placement over a 3-year Period

	N	In nursing home	%	Mean # of days nursing home	SD
4-Cluster					
Cluster 1	36	11	31	932.72	324.14
Cluster 2	35	19	54	754.71	416.91
Cluster 3	23	12	52	711.13	421.98
Cluster 4	14	7	50	690.57	475.49

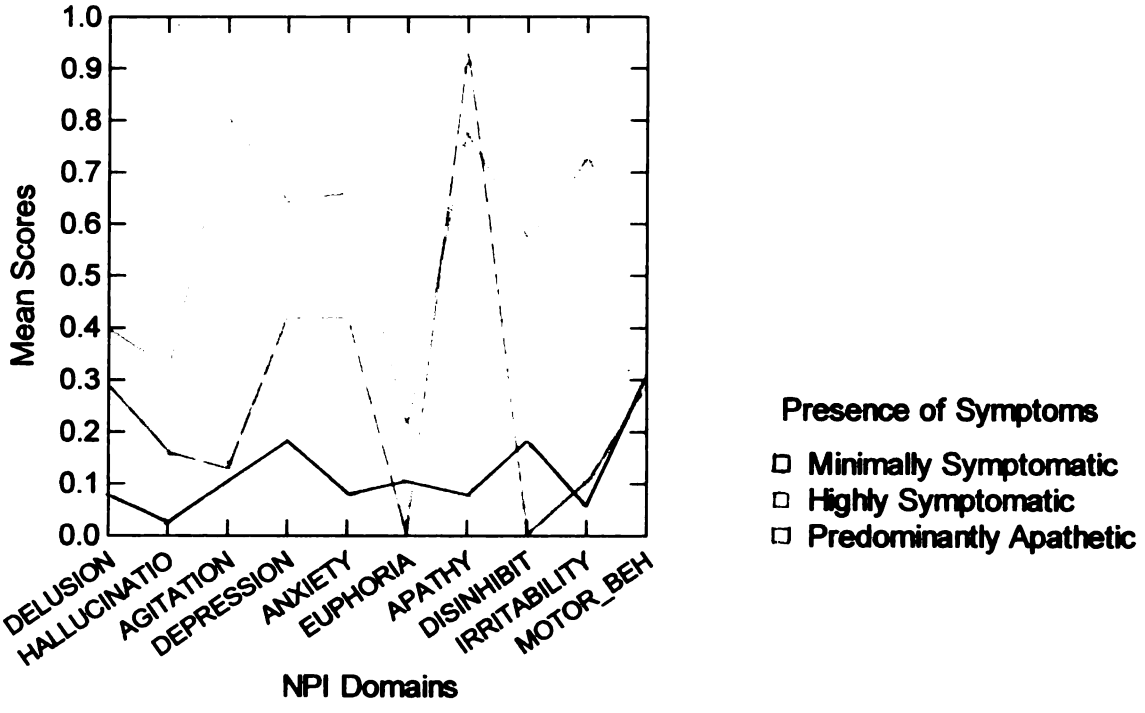
Table 9

Clusters based on the Severity and Frequency of Neuropsychiatric Symptoms as Predictors of Mortality over a 3-year Period

	N	Died	%	Mean # of days death	SD
4-Cluster					
Cluster 1	41	5	12	1054.73	150.11
Cluster 2	39	13	33	968.69	234.43
Cluster 3	27	10	37	957.63	246.27
Cluster 4	14	9	64	820.50	307.63

Figure 1

Cluster Means of Neuropsychiatric Symptoms based on the Presence of Symptoms



Images in this dissertation are presented in color.

Figure 2

Quality of Life over a 2-Year Period based on the Presence of Symptoms

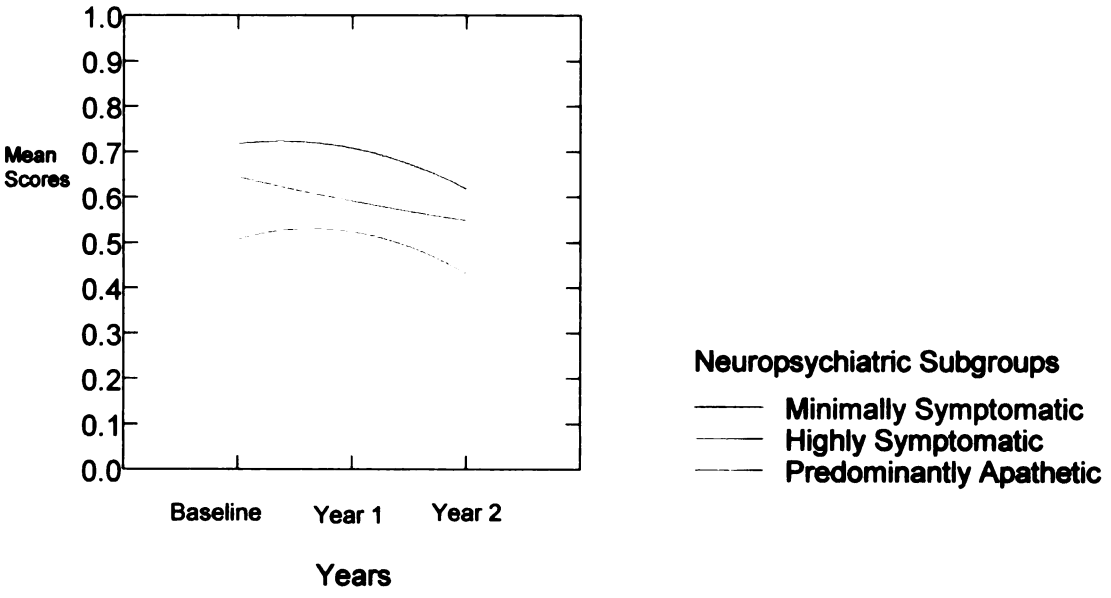


Figure 3

Functional Impairment over a 2-Year Period based on the Presence of Symptoms

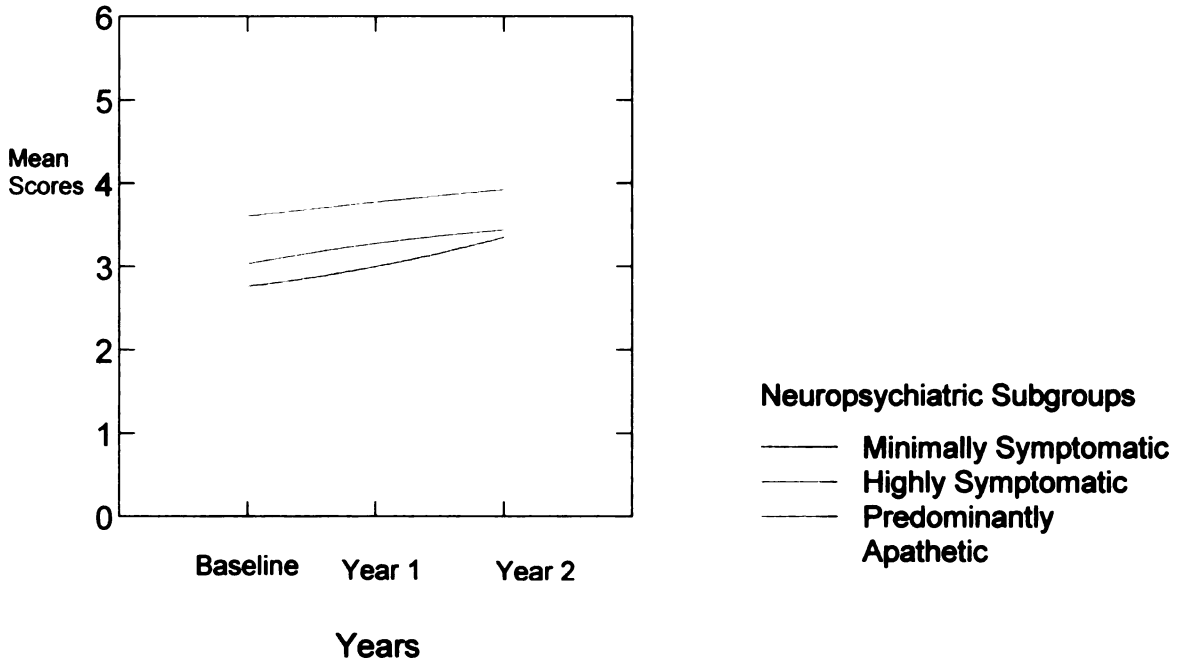


Figure 4

Estimated Probability of Nursing Home Placement based on the Presence of Symptoms

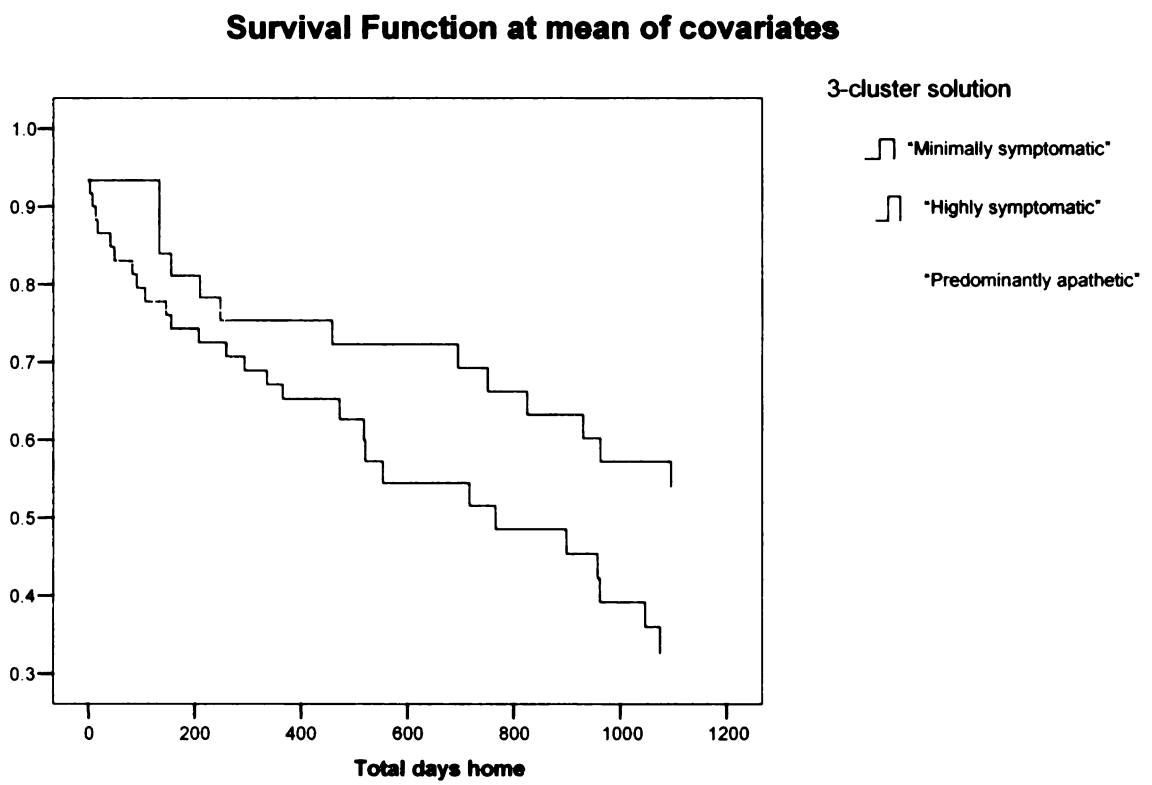


Figure 5

Estimated Probability of Death Based on the Presence of Symptoms

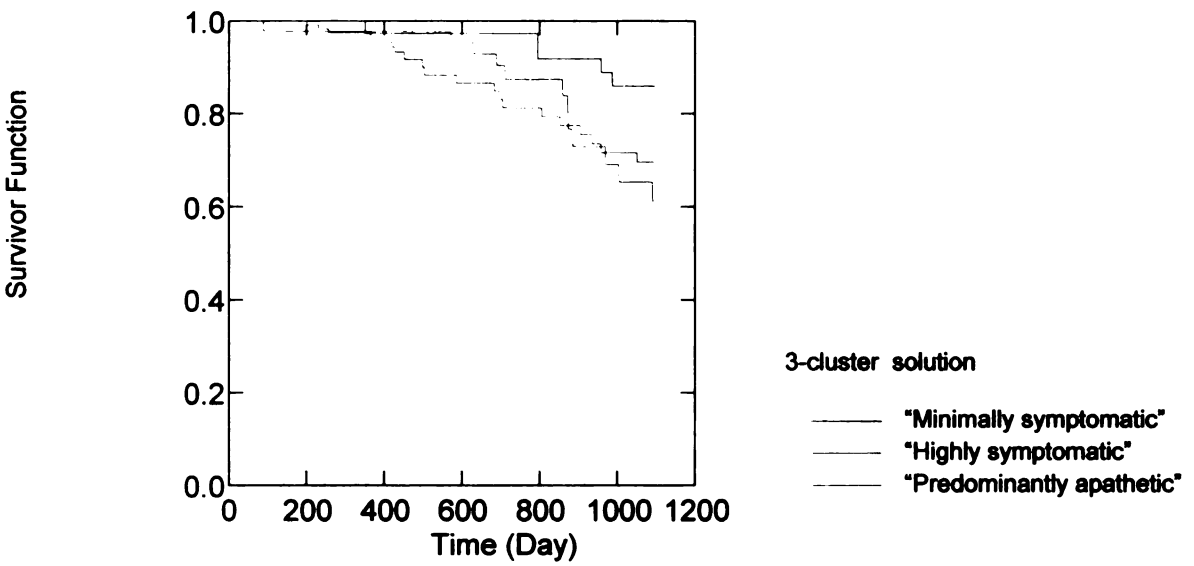


Figure 6

4-Cluster Means of Neuropsychiatric Symptoms based on the Severity and Frequency of Symptoms

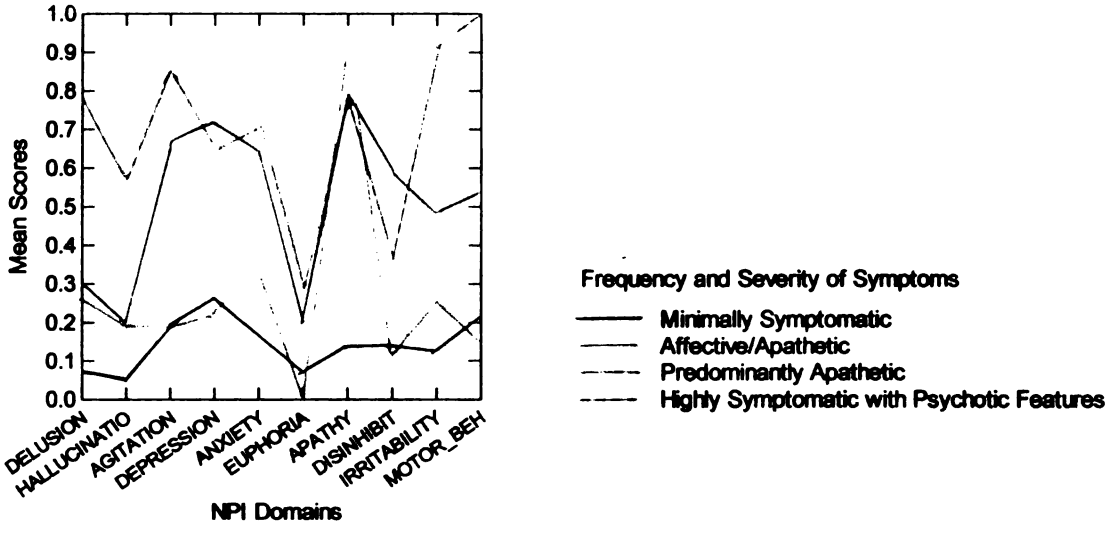


Figure 7

Quality of Life over a 2-Year Period based on the Severity and Frequency of Symptoms

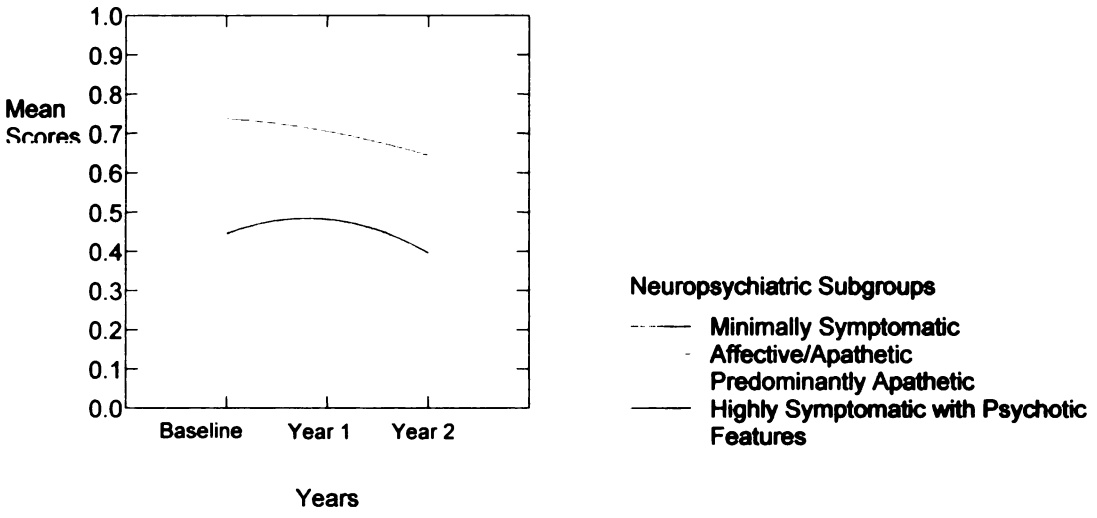


Figure 8

Functional Impairment over a 2-Year Period based on the severity and Frequency of Symptoms

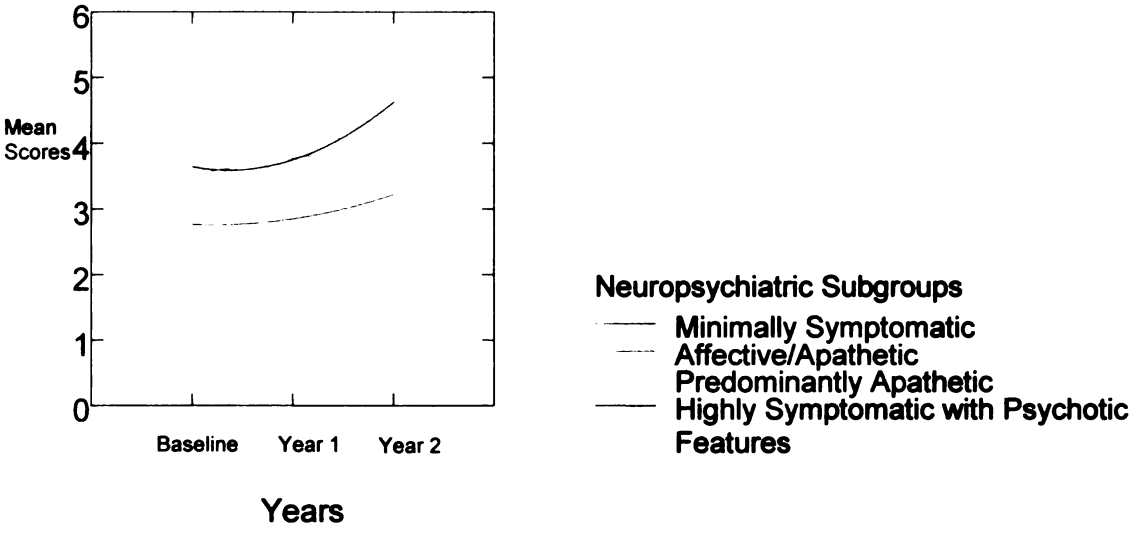


Figure 9

Estimated Probability of Nursing Home Placement based on the Severity and Frequency of Symptoms

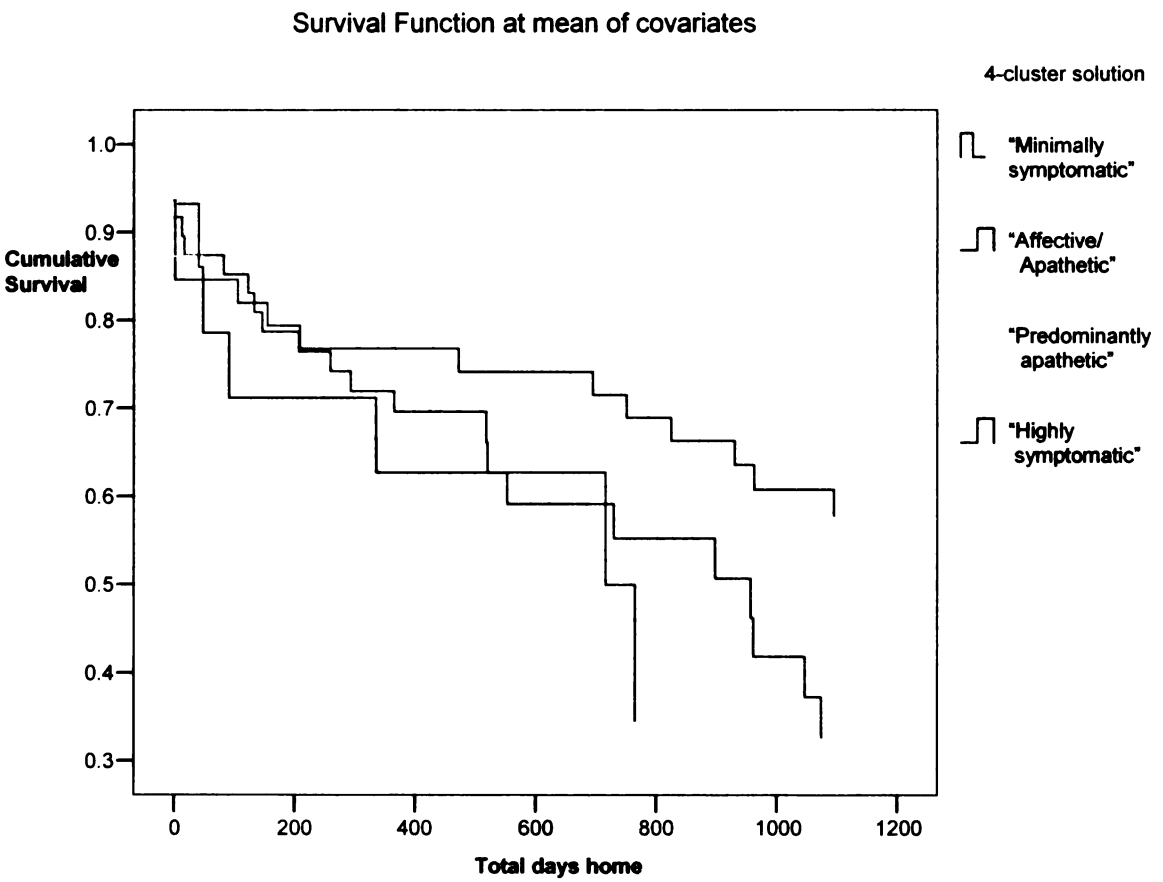
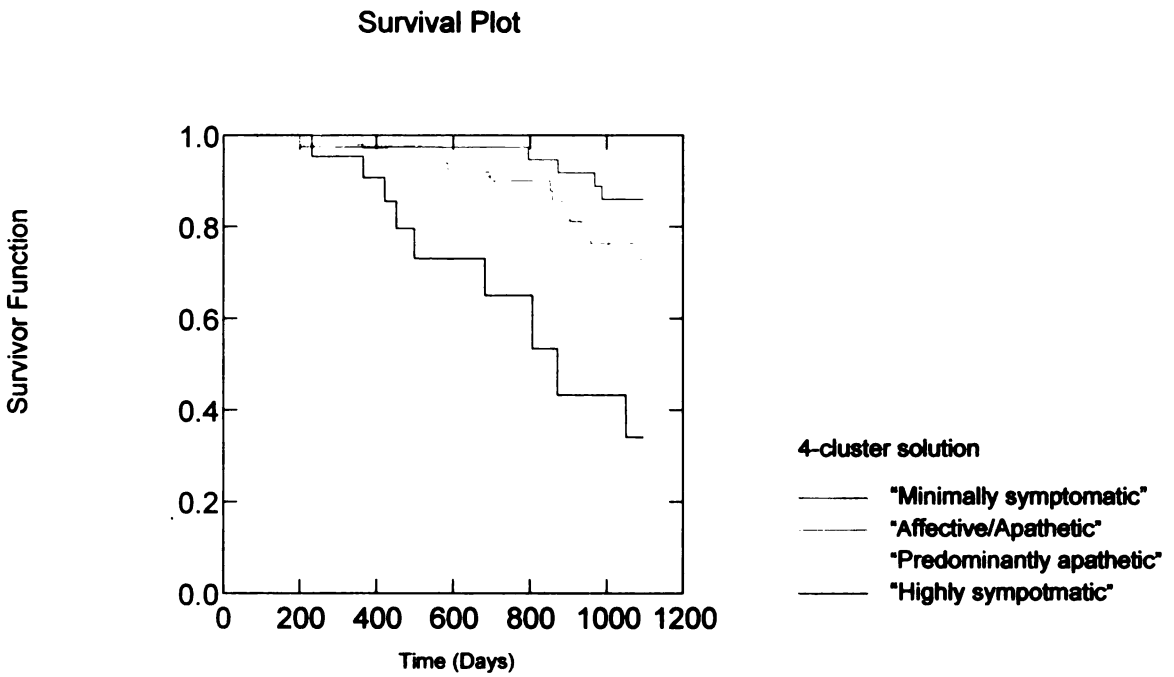


Figure 10

Estimated Probability of Death based on the Severity and Frequency of Symptoms



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