

Neuropsychiatric Symptoms and Mortality Among Patients With Mild Cognitive Impairment and Dementia Due to Alzheimer's Disease

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Abstract

Background

Neuropsychiatric symptoms (NPS) could increase mortality risk in people with dementia due to Alzheimer's disease (AD). However, whether NPS affects mortality risk in people with mild cognitive impairment (MCI) and whether any specific syndrome of NPS influences this risk are still unclear.

Methods

In total, 984 participants with dementia due to AD, 338 with MCI, and 365 controls were enrolled. Over a mean of 5-year follow-up, cause of death data were obtained from the Ministry of Health and Welfare in Taiwan. NPS were assessed using Neuropsychiatric Inventory Questionnaire (NPI-Q), and psychosis, mood, and frontal domain scores were determined. Survival analyses were conducted to determine the hazard ratio (HR) of death.

Results

In controlled analyses, HR of death for AD was 2.19 (95% confidence interval [CI] = 1.29–3.71) compared with the control group, whereas no statistical significance was noted for the MCI group. A high NPI-Q score (above the median score) increased mortality risk for both the MCI and AD groups, with HRs of 2.32 (95% CI = 1.07–5.03) and 2.60 (95% CI = 1.51–4.47), respectively. Among NPI-Q domain scores, only high mood domain, but not psychosis or frontal domain, scores increased death risk for both the MCI (HR = 2.89, 95% CI = 1.00–8.51) and AD (HR = 2.59, 95% CI = 1.47–4.55) groups.

Conclusions

Mortality risk is high for patients with AD. Not only for AD, patients with MCI presenting with NPS, particularly mood symptoms, have high death risk.

Background

Dementia due to Alzheimer's disease (AD) is the major leading cause of death worldwide [1], with an estimated survival period of 3–8 years from diagnosis to death depending on age at onset [2]. Many people in the early stages of AD are unaware of their condition and are not identified to have AD by health care authorities. Mild cognitive impairment (MCI) is identified as a clinical entity that represents a prodromal stage of dementia. Patients with MCI present cognitive impairment that is less severe and does not affect independency in activities of daily living. Some patients with MCI may develop dementia in the following years [3]; however, others may remain in the MCI stage or even return to cognitive normalcy [4]. Studies investigating clinical outcomes have suggested that patients with MCI have a decreased life span [5-9].

Several factors affect mortality in patients with dementia, including behavioral disturbance, namely neuropsychiatric symptoms (NPS) [10]. NPS, including psychosis and mood and behavior symptoms, are core features of AD [11]. Usually, they emerge primarily in people with late-stage disease, but these symptoms manifest commonly in early stages and prodromal phases, such as MCI [12]. However, thus far, no study had investigated the effect of NPS on mortality in patients with MCI.

NPS are heterogeneous and are not a unitary condition and hence should be regarded as groups of symptoms; three to five groups of NPS have been identified [13-18]. Regrouping NPS into syndromes has been supported by several underpinning neurobiology findings and outcomes across each group of NPS [14, 19, 20]. However, the prognosis of each syndrome of NPS has not been clearly studied. Each group of NPS could lead to various outcomes of cognitive disorder, including mortality.

We adapted a prospective design to study mortality in patients with AD or MCI. The aims of this study were to investigate the hazard risk of mortality in patients with AD or MCI in comparison with cognitively normal subjects. Next, we investigated the mortality risk associated with NPS in patients with AD or MCI. Furthermore, we examined the associations between the domains of NPS and mortality risk in AD and MCI. We hypothesized that NPS confer a mortality risk to patients with AD or MCI. Certain domains of NPS have a higher mortality risk than others.

Methods

Participants

Patients with newly diagnosed AD or MCI were recruited from three teaching hospitals. The inclusion criteria of AD or MCI were (1) age of 60–90 years, (2) diagnosis of probable AD as described by the National Institute on Aging–Alzheimer’s Association [21] or MCI according to the revised consensus criteria from 2004 [22], and (3) at least one knowledgeable caregiver who could report observations of the patient’s behaviors. The exclusion criteria were (1) other major neurological illnesses (e.g., stroke, Parkinson disease, epilepsy, and traumatic head injury) or (2) comorbid with other types of dementia. A control group was enrolled from outpatient clinics. Participants were enrolled from July 2012 to January 2019. Completed written consent forms were obtained from all study patients and their caregivers before study initiation. The protocol of the study was approved by the institutional review boards of three hospitals.

Mortality data

All-cause mortality was defined as the date of disenrollment due to death, as per the records of the Taiwan Ministry of Health and Welfare, which maintains a national database of all citizens’ coded death certificates. The years of follow-up for each individual were calculated from the baseline to the date of death or the end of the follow-up period on May 31, 2019, whichever occurred earlier. The causes of death were coded according to the 10th Revision of [International Classification of Diseases \(ICD-10\)](#). Deaths were classified as all-cause, dementia and senile syndrome (ICD-10 codes F00–G30), cancer (ICD-10

codes C00–D49), cardiovascular disease (ICD-10 codes I00–I99), and respiratory disease (ICD-10 codes J00–J99).

Assessments

All participants underwent a standardized assessment, including a clinical interview, cognitive and behavioral assessment, laboratory tests, and brain imaging study. Cognitive function was assessed using Mini-Mental State Examination (MMSE) [23], and dementia staging was determined according to Clinical Dementia Rating scores [24]. Physical Self-Maintenance Scale (PSMS) was used to assess disability severity of activities of daily living (ADL). PSMS is a six-item questionnaire that assesses the following tasks: toilet, feeding, dressing, grooming, physical ambulation, and bathing. A 5-point scale for responses ranges from total independence to total dependence [25]. The possible score ranges from 0 to 24, and a high score is indicative of poor functioning.

The presence and severity of NPS were assessed using Neuropsychiatric Inventory Questionnaire (NPI-Q) [26]. The 12 NPI-Q items were delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, euphoria/elation, irritability/lability, disinhibition and aberrant motor activity, eating habit change, and sleep problems. A score of 0 indicates no symptom, whereas scores of 1–3 (with higher scores indicating more severity) indicate the presence of symptoms. Three symptom groups of NPI-Q were derived as follows: mood (indicated by anxiety, apathy, and dysphoria items), psychosis (irritability/lability, delusions, hallucinations, and agitation/aggression), and frontal symptoms (euphoria and disinhibition) [27]. Item scores of each symptom domain were computed to generate mood, psychosis, and frontal subscores.

Controlled variables

Self-administered questionnaires for study participants or the family of patients with AD were used to collect data on age, sex, education year, and medical history, including hypertension, diabetes mellitus, stroke, hyperlipidemia, and cardiovascular disorders. Medical diseases were considered present based on a self-report of physician-diagnosed diseases or medication use. At least one of APOE e4 alleles was also treated as covariate.

Statistics analysis

Continuous variables are expressed as mean \pm standard deviation (SD) and categorical variables as percentages. The significance of differences in continuous variables across diagnoses was examined using an independent *t* test or one-way analysis of variance, as appropriate. The difference in the distribution of categorical variables was examined using a chi-square test. We first derived the survival curve of the three diagnostic groups by using the Kaplan–Meier survival analysis with log-rank tests. Then, Cox proportional hazard regression analysis was performed to examine mortality risk. Covariates included age, sex, education, medical diseases (cardiovascular diseases, hypertension, diabetes, stroke, and dyslipidemia), and MMSE and ADL total scores at baseline. Three Cox proportional hazard

regression models were used. Model I was used to investigate the cognitive diagnosis (controls, MCI, and AD). Model II was to study diagnosis/NPS variables, which included control, MCI with low score of NPI-Q (MCI/NPS-), MCI with high score of NPI-Q (MCI/NPS+), AD with low score of NPI-Q (AD/NPS-), and AD with high score of NPI-Q (AD/NPS+). Finally, Model III was used to investigate the mortality risk of diagnosis/NPI domains (mood, psychosis, and frontal). High and low total scores of NPI-Q or subscores of NPI-Q domains were defined based on the cutoff of median scores among all patients with AD or MCI. Multicollinearity among variables was detected by examining the correlation matrix of correlation coefficients, assuming that no values were >0.7 [28]. The level of significance was set at $p < 0.05$ (two-tailed).

Results

At baseline, 984 patients with AD, 338 patients with MCI, and 365 controls were identified and included in this study. Demographic and clinical data are shown in Table 1. Among patients with AD, 50% were women, and the mean (SD) age was 78.2 (7.9) years; among patients with MCI, 49.7% were women, and the mean (SD) age was 72.4 (78.8) years. Mean (SD) follow-up time was 5.1 (2.6) years for people with AD, 4.0 (2.0) for people with MCI, and 4.4 (2.2) for controls.

In total, 291 participants (17.2%) died during the follow-up period, and 248 patients had AD (248/983 = 25.2%), 22 had MCI (22/340 = 6.5%), and 21 were controls (21/364 = 5.8%). The incidence rates of death per 1000 person-years were 50.5 for AD, 12.9 for MCI, and 11.5 for control. The mean survival period was 5.5 years for AD and 6.4 years for MCI using Kaplan–Meier survival analysis with log-rank tests. Significant differences were observed between AD and MCI groups ($p < 0.001$) and between AD and control groups ($p < 0.001$), whereas no differences were observed between MCI and control groups ($p = 0.336$). Causes of death across the three groups are listed in Table 1. The most common cause of death in the AD group was cardiovascular disease, followed by respiratory diseases and cancer. The order of causes of death in the AD group differed from that in the MCI and control groups.

In the Cox proportional hazard regression models controlled for age, sex, education, medical diseases (hypertension, diabetes, cardiovascular disease, hyperlipidemia, and stroke), and total scores of MMSE and ADL (model I), the hazard ratio (HR) of mortality was 2.14 (95% confidence interval [CI] = 1.26–3.64, $p = 0.005$) for the AD group and 1.16 (95% CI = 0.60–2.24, $p = 0.66$) for the MCI group compared with the control group (Fig. 1).

Cutoff of the median score of NPI-Q was 3/4, and accordingly, the total score of NPI-Q was divided into high (total score ≥ 4) and low (total score ≤ 3) scores. In the Cox proportional hazard regression model (model II) with the same covariates as that in model I, compared with controls, the HRs were 0.75 (95% CI = 0.33–1.73, $p < 0.50$) for MCI/NPS-, 2.30 (95% CI = 1.06–5.01, $p = 0.035$) for MCI/NPS+, 1.74 (95% CI = 1.00–3.04, $p = 0.05$) for AD/NPS-, and 2.58 (95% CI = 1.49–4.46, $p = 0.001$) for AD/NPS+ (Fig. 2). The mean survival duration was 5.3 years for AD/NPS+, 5.9 years for MCI/NPS+, and 5.9 years for AD/NPS-, as revealed by Kaplan–Meier survival analysis with log-rank tests. On adding a variable of defined daily

dose (DDD) of antipsychotics [29] to model II, the results revealed that the mortality risk of each group did not alter significantly, and DDD of antipsychotics did not increase mortality risk (HR = 2.78, 95% CI = 0.66–11.69, $p = 0.16$).

We divided groups according to median subscores of the domains of NPI-Q, which are mood, psychosis, and frontal domains. High scores of mood, psychosis, and frontal domains were ≥ 2 , ≥ 2 , and ≥ 1 , respectively. Subsequently, three variables were created, namely diagnosis/mood (control, MCI/mood-, MCI/mood+, AD/mood-, and AD/mood+), diagnosis/psychosis (control, MCI/psychosis-, MCI/psychosis+, AD/psychosis-, and AD/psychosis+), and diagnosis/frontal (control, MCI/frontal-, MCI/frontal+, AD/frontal-, and AD/frontal+). A Cox regression model (model III) was created using model I covariates to examine the mortality risks of the aforementioned three variables, and the results showed that only MCI/mood+ (HR = 3.00, 95% CI = 1.00–8.83, $p = 0.046$), AD/mood- (HR = 2.37, 95% CI = 1.29–4.36, $p = 0.005$), and AD/mood+ (HR = 2.72, 95% CI = 1.54–4.79, $p = 0.001$) conferred mortality risks. Table 2 summarizes the results of models I, II, and III.

Discussion

The main findings of this study are as follows: (1) an increased mortality rate was observed in elderly patients with AD, with HR of 2.19 after controlling for covariates, including cognitive function and disability; (2) the incidence rates of death per 1000 person-years were 50.5 and 12.9 for the AD and MCI groups, respectively, and the mean survival durations were 5.5 and 6.4 years for the AD and MCI groups, respectively; (3) NPS increased death risk in both the MCI and AD groups by 2.32- and 2.60-fold, respectively; and (4) among all the domains of NPS, mood domain, but not psychosis or frontal domain, increased mortality risk.

The mean estimate of survival in AD was 5.5 years in this study conducted in Asia. Overall, shortened life expectancy has been noted after first diagnosis at different ages and ranged from approximately 10 years at onset of 60 years to approximately 3 years at onset of 95 years [2]. Our finding of 5.5 years for AD in this population with a mean age of 78 years was compatible with the aforementioned observation. The literature has demonstrated several risk factors for mortality in AD, including age, sex, baseline cognitive function, and functional disabilities [30, 31], which were also noted in our study. Contrary to the general population, with cancer being the most common cause of death, our findings suggested that patients with dementia commonly die of cardiovascular or respiratory diseases, which is in line with a previous finding [32].

Mortality risk in MCI did not reach statistical difference in this study. Various definitions of MCI have been proposed. For instance, Peterson MCI Criteria emphasize the presence of subjective memory complaints and subclinical objective memory performance in the context of relatively intact everyday functioning [33]. Recent consensus criteria for mild neurocognitive disorder have been included in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [34], which specifies a modest decline in one or more cognitive domains but cognitive deficits that do not affect independence in everyday

activities. Increased effort, compensatory strategies, or accommodation may be required to stay independent. In comparison, DSM-5 criteria emphasize objective cognitive impairment and subclinical functional impairment, whereas the Peterson criteria do not. DSM-5 MCI allows for greater compromise in functional independence than Peterson criteria do, indicating a severe form of MCI [35]. One study comparing the mortality risk of MCI using DSM-5 and Peterson criteria found that mortality risk was higher in DSM-5–diagnosed MCI than in Peterson criteria–diagnosed MCI [7]. As Peterson criteria are considered heterogeneous, a considerable proportion of patients do not develop [dementia](#) or may even return to normal cognition [36]. In this study, the case definition of MCI was according to Peterson MCI criteria, which is possibly one of the reasons for the low mortality rate in MCI.

However, we found shortened survival in the MCI group if NPS were considered. Mean survival period of 5.9 years in patients with MCI with significant NPS was similar to that of patients with AD without significant NPS. The relationship between NPS and mortality is complex. Our analyses were adjusted for age, sex, education, APOE, other medical conditions, baseline cognition, and function status, and even then, NPS affected mortality in both the AD and MCI groups. The findings indicate that factors beyond covariates mediate the relationships. A new phenotype, namely mild behavioral impairment (MBI), was proposed and defined as late-onset NPS in the context of predementia [37]. Elderly people with coexisting MBI and MCI have a higher risk of developing dementia than those with MCI alone [38] [39]. Furthermore, biomarker studies have suggested that patients with MBI share similar genetic profiles, brain beta-amyloid imaging, and plasma neurofilament light with those with AD [40-42]. In addition to conversion to AD, our findings highlight the clinical significance of NPS in MCI in terms of mortality and support the MBI concept, which allows for early identification and facilitates new possibilities for therapeutic intervention.

In addition to factors related to cognitive disorders per se, studies have suggested that antipsychotic treatment is one of the possible risk factors [43]. In our study, we added the precise variable of DDD of antipsychotics [29] to the survival analysis. DDD is used for calculating the assumed average maintenance dose per day for a drug used for its main indication. Using DDD allowed us to combine different antipsychotics to compare their mortality risk. However, the analysis did not reveal the mortality risk of DDD of antipsychotics (HR = 2.78, 95% CI = 0.66–11.69, p = 0.16). However, the risk of antipsychotic use in treating NPS for either AD or MCI could not be excluded as the DDD of antipsychotics was only at baseline and not over this study period.

An intriguing result was that the mood domain, but not psychosis or frontal domain, was associated with mortality. Mood domain of NPI-Q comprise anxiety, apathy, and dysphoria. Late-life depression could increase dementia risk [44, 45], and mood dysregulation is often the indicator of neurodegenerative diseases and progressive cognitive change [46]. Studies have suggested that affective symptoms and apathy are associated with early death in AD [47, 48]. Depression itself increases death risk [49]. Depression or apathy in dementia could aggravate failure to thrive and difficulty to manage chronic disease and may lead to social isolation [50, 51]. Therefore, these mood symptoms could accelerate cognitive and functional progression and lead to increased mortality risk. No association was noted

between psychosis and survival time in this study, which is contrary to the finding of a study in community-dwelling elderly people [52]. A possible explanation for the disparity is the study population. This study was hospital-based; thus, treatment for psychosis was provided more actively than in the community. However, further studies are required to explain this discrepancy.

Limitations

Some limitations merit discussion. First, in this study, only baseline NPS were identified, but NPS may change over time. A further study using the NPS change trend will be beneficial. Second, as study participants were enrolled from teaching hospitals, the findings need to be extrapolated cautiously to other populations. Third, although DDD is a delicate measure of antipsychotics dose, we could not exclude the nonlinear association between drug dose and mortality risk. Finally, studies with large study samples are necessary in future to confirm the findings.

Conclusion

In conclusion, in this longitudinal study, high mortality risk was noted in patients with AD or MCI with coexisting NPS. NPS increased death risk in both the MCI and AD groups by 2.32- and 2.60-fold, respectively. Furthermore, the mood domain of NPS increased death risk.

Abbreviations

Neuropsychiatric symptoms (NPS)

Alzheimer's disease (AD)

mild cognitive impairment (MCI)

Neuropsychiatric Inventory Questionnaire (NPI-Q)

hazard ratio (HR)

International Classification of Diseases (ICD-10)

Mini-Mental State Examination (MMSE)

Physical Self-Maintenance Scale (PSMS)

activities of daily living (ADL)

standard deviation (SD)

defined daily dose (DDD)

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

mild behavioral impairment (MBI).

Declarations

Ethics approval and consent to participate:

Completed written consent forms were obtained from all study patients and their caregivers before study initiation. The protocol of the study was approved by the institutional review boards of three hospitals.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

WJL, SJW and JLF designed the study. YSL, HFL, and JLF make contributions to acquisition and interpretation of data. MFH, YCY, YHY and CSC analyzed and interpreted the data. MFH and CSC was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Demographic and clinical data

	Controls (N=365)	MCI (N=338)	AD (N=984)	Total (N=1687)	Statistics
Sex					
Male	161 (44.4%)	172 (50.3%)	491 (50.0%)	824 (48.8%)	P=0.16
Female	203 (55.6%)	168 (49.7%)	492 (50.0%)	863 (51.2%)	
Age, y	71.9 (7.8)	72.4 (8.8)	78.2 (7.9)	75.7 (8.6)	P<0.001
Education, y	11.9 (4.6)	10.8 (4.4)	9.3 (4.7)	10.3 (4.7)	P<0.001
MMSE	28.1 (1.9)	26.1 (2.5)	18.3 (5.7)	22.0 (6.4)	P<0.001
ADL	0.1 (0.4)	0.3 (0.9)	3.2 (4.8)	2.4 (4.3)	P<0.001
NPI-Q	2.1 (2.9)	2.6 (3.8)	6.8 (6.7)	5.6 (6.3)	P<0.001
CDR					
0	365 (100%)	-	-	365 (21.9%)	P<0.001
0.5	-	338 (100%)	180 (18.6%)	518 (31.0%)	
1	-	-	567 (58.7%)	567 (34.0%)	
2	-	-	177 (18.3%)	177 (10.6%)	
3	-	-	42 (4.3%)	42 (2.5%)	
APOE					
E2E2	4 (1.1%)	3 (0.9%)	3 (0.3%)	10 (0.6%)	P<0.001
E2E3	51 (14.1%)	37 (11.0%)	88 (9.0%)	176 (10.5%)	
E2E4	11 (3.0%)	5 (1.5%)	24 (2.5%)	40 (2.4%)	
E3E3	240 (66.3%)	223 (66.0%)	518 (53.2%)	981 (58.6%)	
E3E4	52 (14.4%)	59 (17.5%)	306 (31.5%)	417 (24.9%)	
E4E4	4 (1.1%)	11 (3.3%)	34 (3.5%)	49 (2.9%)	
Diseases					
CV diseases	60 (19.1)	81 (24.5%)	218 (22.2%)	359 (22.1%)	P=0.25
Stroke	8 (2.5%)	14 (4.2%)	46 (4.7%)	68 (4.2%)	P=0.26
Hypertension	183 (58.3%)	174 (52.6%)	586 (60.0%)	943 (58.1%)	P=0.06
Dyslipidemia	69 (22.1%)	79 (24.2%)	213 (22.0%)	361 (22.5%)	P=0.69
Diabetes	69 (22.0%)	71 (21.5%)	266 (27.3%)	406 (25.1%)	P=0.04

Mortality	21 (5.8%)	22 (6.5%)	248 (25.2%)	291 (17.2%)	P<0.001
CNS	1 (0.3%)	0	15 (1.5%)	16 (0.9%)	
Cancer	5 (1.4%)	8 (2.4%)	47 (4.8%)	60 (3.6%)	
CV disease	5 (1.4%)	2 (0.6%)	59 (6.0%)	66 (3.9%)	
Respiratory	2 (0.5%)	4 (1.2%)	47 (4.8%)	53 (3.1%)	
Others	8 (2.2%)	8 (2.4%)	80 (8.1%)	96 (5.7%)	

Abbreviations: MCI: mild cognitive impairment; AD: Alzheimer disease; MMSE: Mini-Mental State Examination; ADL: activities of daily living; NPI-Q: Neuropsychiatric Inventory Questionnaire; CDR: Clinical Dementia Rating; CV: cardiovascular; CNS: central nervous system

Table 2 Cox regression models investigating cognitive diagnosis and neuropsychiatric symptoms predicting mortality

	B (SE)	Wald	Significance	HR (95% CI)
Model I (for cognitive diagnosis)				
Diagnosis		10.95	0.004	
Control				1
MCI	0.15 (0.34)	0.20	0.66	1.16 (0.60-2.24)
AD	0.76 (0.27)	7.85	0.005	2.14 (1.26-3.64)
Model II (for diagnosis and NPS)				
Diagnosis/NPS		22.29	0.001	
Control				1
MCI/NPS -	-0.29 (0.43)	0.46	0.50	0.75 (0.33-1.73)
MCI/NPS +	0.84 (0.40)	4.44	0.035	2.30 (1.06-5.01)
AD/NPS -	0.55 (0.29)	3.72	0.05	1.74 (1.00-3.04)
AD/NPS +	0.95 (0.28)	11.50	0.001	2.58 (1.49-4.46)
Model III (for diagnosis and domains of NPS)				
Diagnosis/mood		16.05	0.003	
Control				1
MCI/mood -	0.04 (0.84)	0.002	0.96	1.04 (0.20-5.44)
MCI/mood +	1.10 (0.55)	3.97	0.046	3.00 (1.02-8.83)
AD/mood -	0.86 (0.31)	7.74	0.005	2.37 (1.29-4.36)
AD/mood +	1.00 (0.29)	11.93	0.001	2.72 (1.54-4.79)
Diagnosis/psychosis		1.90	0.39	
Diagnosis/frontal		3.17	0.21	

Controlled for age, sex, education, Mini-Mental State Examination, activities of daily living, and medical diseases (cardiovascular disease, stroke, hypertension, diabetes, and dyslipidemia)

HR: hazard ratio; CI: confidence interval; MCI: mild cognitive impairment; AD: Alzheimer disease; NPS: neuropsychiatric symptoms

Figures

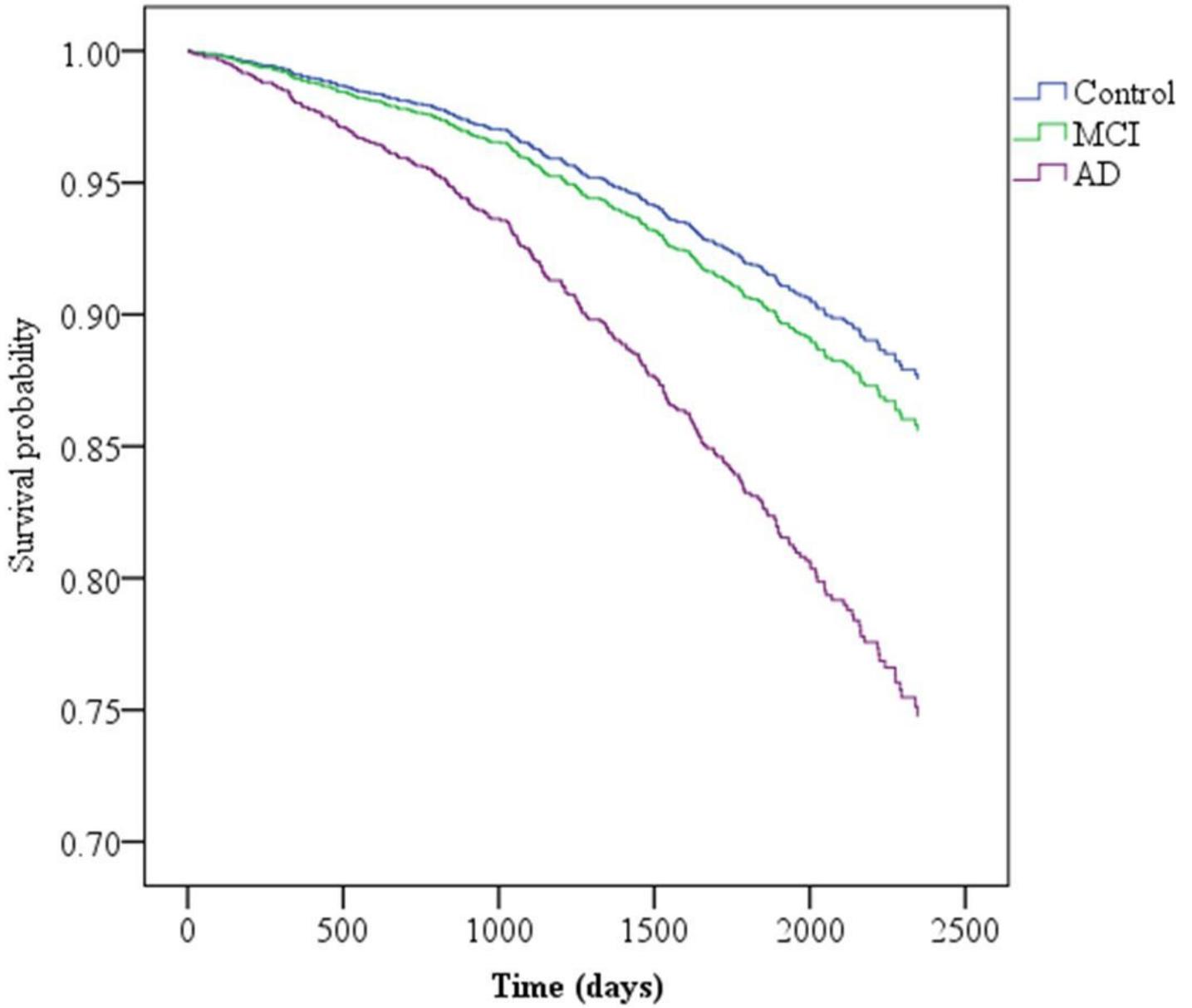


Figure 1

Survival curves for people with dementia due to Alzheimer's disease(AD) and mild cognitive impairment(MCI)

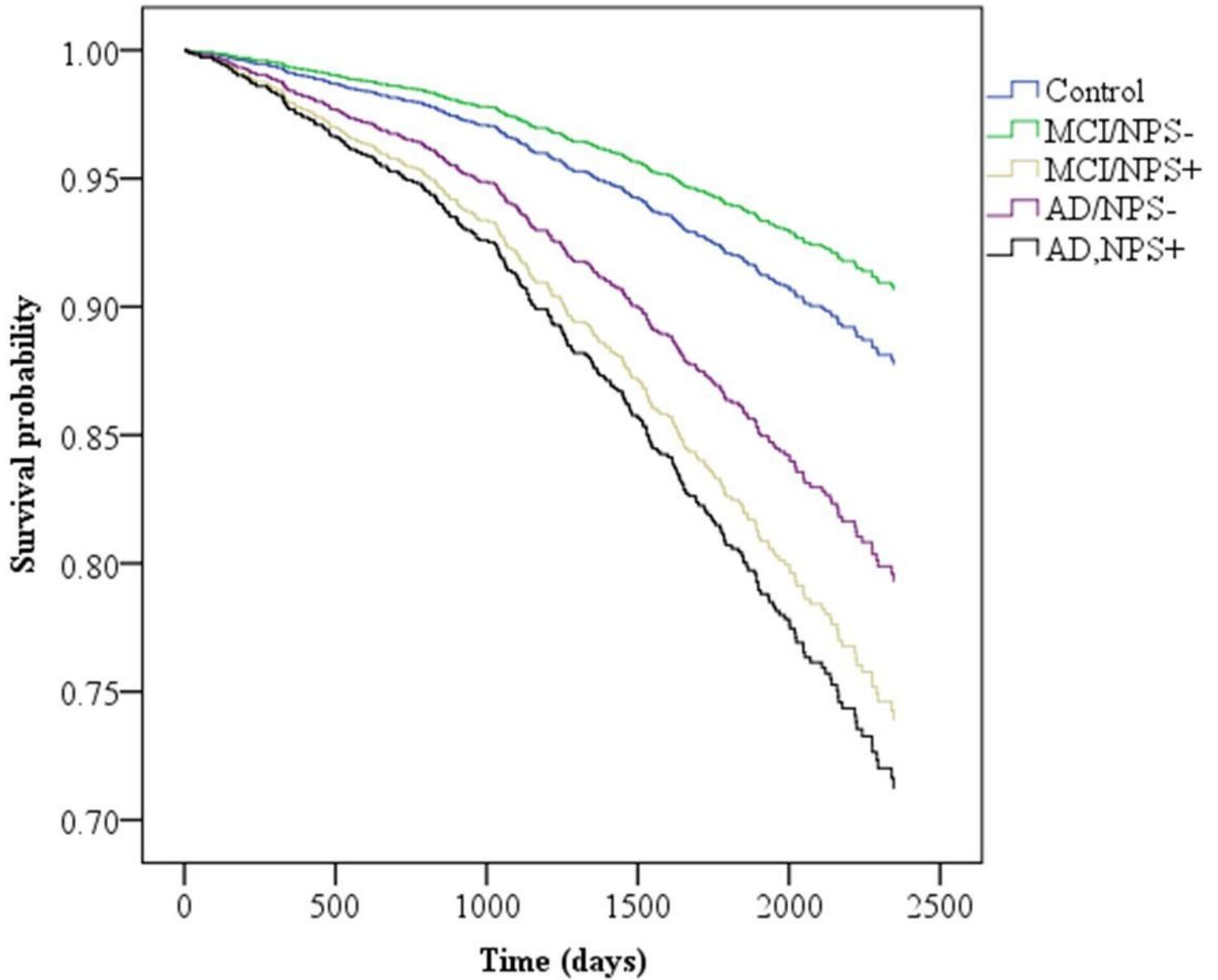


Figure 2

Survival curves for neuropsychiatric symptoms(NPS) among people with Alzheimer's disease(AD) and mild cognitive impairment(MCI)