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Predicting Disease Progression in Alzheimer's Disease: The Role of Neuropsychiatric Syndromes on Functional and Cognitive Decline

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Abstract. Patients with Alzheimer's disease (AD) have heterogeneous rates of disease progression. The aim of the current study is to investigate whether neuropsychiatric disturbances predict cognitive and functional disease progression in AD, according to failure theory. We longitudinally examined 177 memory-clinic AD outpatients (mean age = 73.1, SD = 8.1; 70.6% women). Neuropsychiatric disturbances at baseline were categorized into five syndromes. Patients were followed for up to two years to detect rapid disease progression defined as a loss of ≥1 abilities in Activities of Daily living (ADL) or a drop of ≥5 points on Mini-Mental State Examination (MMSE). Hazard ratios (HR) were calculated with Gompertz regression, adjusting for sociodemographics, baseline cognitive and functional status, and somatic comorbidities. Most patients (74.6%) exhibited one or more neuropsychiatric syndromes at baseline. The most common neuropsychiatric syndrome was Apathy (63.8%), followed by Affective (37.3%), Psychomotor (8.5%), Manic (7.9%), and Psychotic (5.6%) syndromes. The variance between the observed (Kaplen Meier) and predicted (Gompertz) decline for disease progression in cognition (0.30, CI = 0.26–0.35), was higher than the variance seen for functional decline (0.22, CI = 0.18–0.26). After multiple adjustment, patients with the Affective syndrome had an increased risk of functional decline (HR = 2.0; CI = 1.1–3.6), whereas the risk of cognitive decline was associated with the Manic (HR = 3.2, CI = 1.3–7.5) syndrome. In conclusion, specific neuropsychiatric syndromes are associated with functional and cognitive decline during the progression of AD, which may help with the long-term planning of care and treatment. These results highlight the importance of incorporating a thorough psychiatric examination in the evaluation of AD patients.

Keywords: Activities of daily living, anxiety, apathy, behavioral and psychological symptoms of dementia, failure theory, cognitive impairment, dementia, depression, disease progression, Gompertz

INTRODUCTION

Alzheimer's disease (AD) is characterized by gradual decline of memory and other cognitive functions, in addition to progressive loss of physical functioning and associated neuropsychiatric symptoms [1]. Disease progression is heterogeneous; the rates of decline in cognitive and functional capacities are variable, and there are different rates of institutionalization and death between patients [2].

Research identifying factors that predict AD progression are relevant for the long-term planning of care and treatment of patients. Reports suggest that vascular factors such as hypertension, hyper-cholesterolemia,

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and smoking [3–6] are associated with an increasing rate of cognitive decline in dementia. In addition to cognitive deterioration, loss of independence in daily activities is a clinically relevant marker of disease progression in AD, which contributes to caregiver burden [7] and is a predictor of entering full-time institutional care [8, 9], but little is known concerning predictors of loss of functional independence.

Behavioral disorders and neuropsychiatric symptoms are common in AD, and can be characterized into distinct syndromes [10–13], including Apathy, Affective, Psychomotor, Manic, and Psychotic syndromes [11, 13]. Reports suggest that a large proportion of AD patients (between 78–91%) exhibit one or more neuropsychiatric syndromes [10, 13], but little is known about what role these syndromes play on the progression of the disease. Indeed, these syndromes may be of clinical relevance, since studies investigating individual neuropsychiatric symptoms have suggested that psychotic symptoms [14, 15], wandering, agitation, and restless behavior [9], as well as general behavioral symptoms [9], are associated with an increased risk of functional decline.

When studying the prognosis of AD, a general problem is to define appropriate outcomes that reflect the progression of the disease rather than the effects of other co-occurring pathological conditions. This is important because the health status and comorbidities of AD patients can greatly influence survival as well as cognitive and functional capacities.

One approach is to recognize specific clinical manifestations of AD progression that show a temporal profile coherent with the biological progression of the disease. The incidence of AD increases exponentially with age [16], in a pattern which is similar to the relation between age and mortality. Since death of elderly persons may be regarded as the end point of the aging process, the similarity between AD incidence and mortality has led to suggestions that AD and aging might be a unique phenomenon responding to failure theory [17]. Mortality follows a law, proposed by Gompertz [18], which is unique for all multi-cellular living beings. Incidence refers to the time of appearance of the disease, when AD can be clinically recognized and diagnosed. The time or age of incidence corresponds to the reaching of a threshold of biological damage capable of inducing the clinical manifestations of the disease. A specific clinical outcome of AD such as loss of functioning or cognition, which represents biological damage that induces the manifestation of the outcome, should have a pattern of time appearance similar to disease incidence. In other words, all the specific manifestations of AD progression should follow the Gompertz law, showing an exponential increase with time. Moreover, the greater the adherence of a certain symptom or sign to this exponential distribution with time the higher is the probability that it represents a true manifestation of AD.

The aim of the current study is to investigate the progression of AD, according to Gompertz law, and identify predictors of disease progression. Specifically, the aims are: 1) to investigate whether specific neuropsychiatric syndromes (Psychotic, Psychomotor, Affective, Manic, and Apathetic) are related to an increased risk of cognitive or functional decline in patients with AD; 2) to examine whether the neuropsychiatric syndromes that predict future functional decline are the same syndromes that predict cognitive decline; and 3) to investigate whether cognitive or functional decline are consistent with the time profile expected from specific manifestation of AD according to Gompertz' and failure theory. To answer these questions we longitudinally followed newly-diagnosed AD outpatients from an Italian memory clinic to assess predictors of disease progression over two years.

METHOD

Study sample

We followed a cohort of 177 patients with AD, diagnosed by neurologists according to DSM-IV and NINCDS-ADRDA criteria [19]. Patients were consecutively admitted as memory clinic outpatients at Fondazione Santa Lucia, Rome, Italy between November 1998 to December 2007. Patients underwent a complete neurological examination by a neurologist and comprehensive cognitive assessment by neuropsychologists. The extensive cognitive examination included a battery assessing verbal memory, short term visual memory, logical reasoning, language, simple constructional praxis, long-term visual memory, complex constructional praxis, and attentive shifting and control. A total of 1026 patients were consecutively admitted to the clinic. At first visit, 39 (3.8%) patients were normal, 167 (16.3%) had mild cognitive deficits without dementia, 226 (22.0%) had mixed dementia, vascular dementia, or other dementia types, 217 patients (21.2%) were diagnosed with other diseases including Parkinson's disease, depression, and primary progressive aphasia. The remaining

377 patients had a diagnosis of "pure" AD and were eligible for the study. We excluded 200 (53.1%) AD patients who only attended the clinic once or had severe cognitive impairment, defined as scoring <10 on the Mini-Mental State Examination (MMSE) [20]. Thus, the current study population consisted of 177 patients with AD with MMSE > 9, who had at least two or more follow-up visits. All patients had a relevant caregiver or next-of-kin (spouse, child, or friend). Patients were examined on average every six months; the mean number of follow-up visits was 3.5 (SD = 1.7, range 2–9 visits). At first visit, all AD patients initiated a treatment with an acetylcholinesterase inhibitor; donepezil, rivastigmine, or galantamine.

Baseline sociodemographic variables and evaluation of comorbid diseases

Sociodemographic characteristics (age, gender, education) were taken from the patient and next-of-kin at the first visit. Education was assessed as the number of years of formal schooling/university. Drug treatments were recorded at each visit, including baseline and all follow-up examinations. Use of anxiolytics, neuroleptics, and antidepressive medications were categorized as no treatment versus treatment.

Comorbidity was evaluated with the Cumulative Illness Rating Scale (CIRS) [21]. CIRS is a scale for assessing comorbidity in geriatric patients, and consists of fourteen items for classifying somatic conditions in the following categories: hypertension, cardiological pathologies, vascular pathologies, respiratory disease, superior and inferior gastrointestinal disease, malignancies, liver and renal pathologies, genital-urinary disorders, muscular-skeletal problems, systemic and nervous system disorders, endocrine and metabolic diseases and, psychiatric and behavioral disorders. Severity, frequency, and duration of the pathologies are used to calculate an overall comorbidity score [21]. We also assessed three specific categories of comorbidity using the CIRS sub-scores: i) cardiological pathologies; ii) metabolic/endocrine disorders; and iii) vascular disease (including hypertension and vascular pathologies).

Assessment of neuropsychiatric syndromes

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI) [22], which was administered through structured interview with the next-of-kin. Symptoms were categorized into five syndromes that are relevant to AD patients and have been established and validated through previous research [13]. These include: Psychotic syndrome (comprised of delusions and hallucinations); Psychomotor syndrome (agitation, irritability, and aberrant motor behavior); Affective syndrome (anxiety and depression); Manic syndrome (euphoria and disinhibition); and Apathy syndrome (apathy).

Assessment of cognition and basic ADL functioning

General cognitive functioning was assessed with the MMSE, with adjustment for age and education [23]. Functioning at baseline and follow-ups was assessed with Katz' basic ADL scale which measures the patient's autonomy for elementary activities of daily life (score range 0–6).

Disease progression: Cognitive and functional decline

We considered two outcomes as indicators of disease progression. Functional decline over follow-up was defined as a loss of one or more functional abilities; a drop of 1 or more points since baseline on ADL. Cognitive decline over follow-up was defined as a decrease of 5 points or more on the MMSE since baseline, based on previous research [24]. A five-point decrease is considered to be a clinically relevant worsening and is too large a change to be attributed to the intrinsic limits of test reliability [25]. Time of disease progression was calculated as the date of the visit when a patient first reduced $\geq$5 MMSE points or lost 1 or more ADL abilities, respectively.

Missing data

At baseline, we were unable to calculate the CIRS total score for some patients ($n = 43$, 24.3%). There were no significant differences between patients with missing data and those with complete CIRS data in gender, age, education, baseline ADL, baseline MMSE, or future decline in MMSE, at the 0.05 significance level. Further, 26 persons (14.7%) had incomplete ADL data. There were no significant differences between patients with missing or complete ADL data in gender, age, education, CIRS score, baseline MMSE, or future decline in MMSE, at the 0.05 significance level.

Statistical analysis

The presence of neuropsychiatric syndromes [13] at baseline was calculated using data from the NPI. Statistical significance of the differences in baseline characteristics between patients with and without neuropsychiatric syndromes were assessed with chi-square for dichotomous variables, and student *t*-tests for continuous variables.

We analyzed which of the two outcomes was the most reliable indicator of disease progression: functional (ADL) decline or cognitive (MMSE) decline. The observed probabilities of occurrence of the outcome were calculated with the Kaplan-Meier method, considering that this method makes no assumption about the time dependent distribution of the outcome. The probabilities were also calculated according to the Gompertz distribution that assumes an exponential increase of the cumulative probability of occurrence with time. The goodness of fit of the Gompertz model was calculated quantifying the error of prediction as mean quadratic difference between the individual predicted probability of occurrence of the outcome and the value of 0 or 1 respectively for the patients not showing or showing the outcome of interest.

For the current analysis, a maximum follow-up time of two years was taken for the outcome. This time limitation was adopted to better recognize those patients with a fast disease progression, considering that AD is a progressive disease and that all the patients would have shown one or more of the considered outcomes during a more prolonged follow-up. Time in study was considered as the time between baseline examination and a) the date of clinical examination when the outcome was observed, or b) the date of last clinical examination or c) two years for those patients with follow up of more than 24 months not showing the outcome during this period of time.

To assess whether patients with specific baseline neuropsychiatric syndromes had a higher risk of functional or cognitive decline, we calculated relative hazards using Gompertz regression based on Gompertz law [17, 18]. The relative hazard ratios (HR) of disease progression with 95% confidence intervals were calculated with Gompertz regression using STATA 11 [26]. The risk of functional/cognitive decline in patients exhibiting a specific syndrome (e.g., Affective syndrome) was compared with one group consisting of patients who either had no syndromes present or who exhibited one of the other syndromes (i.e., any other syndrome except the Affective syndrome). Crude HRs were calculated, as well adjusted HRs considering three different models. The first model used baseline ADL (impaired versus no impairment) or baseline MMSE (continuous) as covariates for evaluating the risk of functional or cognitive decline, respectively. The second model considered comorbitity (CIRS score). The third model considered multiple potential confounders: age, gender, education, baseline MMSE, ADL and, comorbidity (CIRS score).

Following this, the hazard ratios of progression for a specific syndrome were recalculated with further adjustment for the number of neuropsychiatric syndromes present. Finally, all analyses were run with additional adjustment for specific comorbidities, including vascular disease, cardio pathologies, and metabolic/endocrine disorders.

RESULTS

Baseline characteristics and presence of neuropsychiatric syndromes

The mean age of the 177 AD patients was 73.1 years (SD = 8.1), and 125 (70.6%) were female. The mean baseline MMSE score at enrolment was 19.4 (SD = 3.3), which is comparable to scores for AD patients at first-diagnosis in clinical settings [27, 28]. The majority of AD patients ($n = 132$, 74.6%) exhibited one or more neuropsychiatric syndromes at baseline. Ten (5.6%) patients had the Psychotic syndrome, 15 (8.5%) exhibited the Psychomotor syndrome, 66 (37.3%) had the Affective syndrome, 14 (7.9%) had the Manic syndrome, and 113 (63.8%) had the Apathetic syndrome. These five syndromes were not mutually exclusive, as some syndromes co-occur in the same individuals. Table 1 shows the baseline characteristics of patients, according to the presence of the five neuropsychiatric syndromes. We assessed whether there were any differences in baseline characteristics of the 45 patients without a neuropsychiatric syndrome and the 132 patients who exhibited one or more neuropsychiatric syndromes. There were no differences in gender ($\chi^2 = 1.489$, $p = 0.222$), age ($t = -0.643$, $p = 0.52$), education ($t = 0.447$, $p = 0.656$), CIRS total score ($t = 0.737$, $p = 0.462$) or specific comorbidities including cardiological pathologies ($\chi^2 = 0.511$, $p = 0.475$), hypertension ($\chi^2 = 0.927$, $p = 0.336$), vascular pathologies ($\chi^2 = 0.060$, $p = 0.807$), or metabolic and endocrine disorders ($\chi^2 = 0.257$, $p = 0.612$). The baseline cognitive and functional status was similar between patient with and without neuropsychiatric syndromes, as we detected no significant differences

Table 1
Baseline characteristics of the patients, according to the presence of neuropsychiatric syndromes*

	No syndrome ($n=45$)		Apathetic ($n=113$)		Affective ($n=66$)		Psychomotor ($n=15$)		Manic ($n=14$)		Psychotic ($n=10$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, years	72.4	8.2	73.6	7.2	72.7	8.4	76.6	4.9	71.6	7.5	77.9	3.7
MMSE[1]	19.5	3.2	18.8	3.3	19.2	3.8	18.2	4.0	18.5	3.5	17.0	3.7
Education, years	8.7	4.3	8.0	4.4	8.4	4.2	8.0	3.5	8.2	3.9	8.0	4.6
ADL[3] score	5.6	0.9	5.4	1.1	5.4	0.09	4.5	1.5	4.9	1.7	4.9	1.8
Comorbidities (CIRS)[2]												
Comorbidity total score	0.97	0.98	1.3	0.99	1.3	0.98	1.4	1.1	1.0	0.7	1.2	0.8
CIRS[2] sub-scores	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Cardiological	7	15.6	23	20.4	19	28.8	5	33.3	2	14.3	2	20.0
Hypertension	12	26.7	44	38.9	25	37.9	2	13.3	3	21.4	3	30.0
Vascular	2	4.4	6	5.3	4	6.1	1	6.7	1	7.1	0	0.0
Metabolic/Endocrine	13	28.9	36	31.9	18	27.3	2	13.3	3	21.4	1	10.0
Gender female	35	77.8	76	67.3	51	77.3	11	73.3	10	71.4	8	80.0

* Syndromes are not mutually exclusive.
[1] MMSE: Mini-Mental State Examination.
[2] CIRS: Cumulative Illness Rating Scale; data missing for 43 persons.
[3] ADL: Activities of daily living.

in baseline MMSE ($t=0.874$, $p=0.383$) or ADL ($t=-1.720$, $p=0.088$).

Disease progression over two years

Patients were followed for two years to detect a drop in cognition (a loss of five or more MMSE points), or functioning (a loss in one or more ADL functions). When the observation period was censored at 24 months, the median follow-up time from baseline until last examination or date of disease progression was about one year (median = 361 days). Over 24 months 42 (23.7%) patients did not decline in either cognition or ADL functioning. Forty-seven patients (26.6%) had a decline both in cognition and functioning whereas 76 (42.9%) only declined in MMSE with no loss in ADL functioning. A small percentage of patients ($n=12$, 6.8%) declined only in ADL functioning.

Predictors of disease progression: decline in ADL functioning

Figure 1 shows the Kaplan-Meier survival curves over two years for functional decline and the predictions according to Gompertz function. The variance between the observed and predicted decline was 0.22 (95% CI = 0.18–0.26). We then examined whether any specific neuropsychiatric syndrome at baseline was related to an increased risk of functional decline over two-year follow-up using Gompertz regression modelling. Table 2 shows the relative hazard of disease progression defined as a decline in ADL functioning, in patients with a specific syndrome at baseline compared to patients without the respective syndrome. Crude and adjusted estimates were calculated including a model fully adjusted for age, gender, education, baseline ADL, baseline MMSE, and comorbidity (CIRS score). There was no increased risk of functional decline in patients with the Apathy, Psychomotor, or Psychotic syndrome, but for the Affective and Manic syndromes there was an increased crude risk of ADL decline. After full adjustment, only the Affective syndrome predicted decline in ADL over follow-up; almost half the patients with the Affective syndrome declined in ADL functioning, with a twofold increased risk compared to patients without the Affective syndrome, even after multiple adjustment. The high risk of functional decline in patients with the Manic syndrome was mostly due to the confounding effect of baseline comorbidity; although two-thirds of patients with the

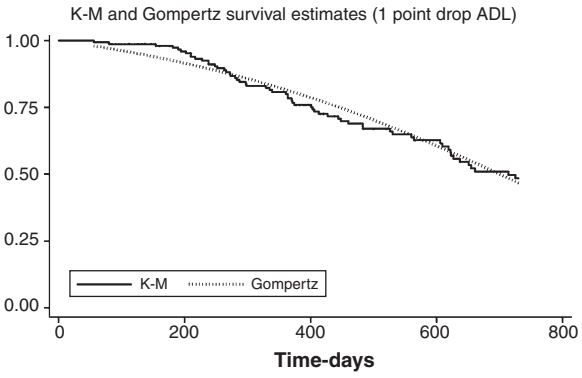

Fig. 1. Kaplan Meier (K-M) observed rates and Gompertz estimates of functional decline.

Table 2
Risk of functional decline over two-year follow-up in AD patients with baseline neuropsychiatric syndromes

		ADL decline		Crude risk of ADL decline		Adjusted for baseline ADL		Adjusted for comorbidity		Fully adjusted model[3]	
		n	%	HR[1]	(95% CI)	HR[1]	(95% CI)	HR[1]	(95% CI)	HR[1]	(95% CI)
Apathy syndrome	No[2]	15	34.1	1.0		1.0		1.0		1.0	
	Yes	44	41.1	1.0	(0.5–1.7)	0.9	(0.5–1.7)	1.0	(0.5–2.1)	0.9	(0.4–1.8)
Affective syndrome	No[2]	29	33.0	1.0		1.0		1.0		1.0	
	Yes	30	47.6	1.8	(1.1–3.0)	1.7	(1.0–2.9)[a]	1.8	(1.0–3.2)[b]	2.0	(1.1–3.6)
Psychomotor syndrome	No[2]	50	36.8	1.0		1.0		1.0		1.0	
	Yes	9	60.0	1.0	(0.4–2.6)	0.9	(0.3–2.4)	1.6	(0.5–4.9)	1.6	(0.5–5.1)
Manic syndrome	No[2]	51	36.7	1.0		1.0		1.0		1.0	
	Yes	8	66.7	2.3	(1.0–5.6)[c]	2.3	(0.9–5.8)	2.1	(0.7–6.1)	2.3	(0.8–6.9)
Psychotic syndrome	No[2]	53	37.3	1.0		1.0		1.0		1.0	
	Yes	6	66.7	2.5	(0.9–6.9)	2.4	(0.8–6.8)	2.4	(0.7–8.4)	1.4	(0.3–5.8)

[1] Hazard ratios calculated with Gompertz regression, with 95% confidence intervals.
[2] Reference category includes patients with any other syndrome and patients with no syndromes.
[3] Adjusted for age, gender, education, baseline ADL, baseline MMSE, and comorbidity (CIRS).
[a] $p = 0.046$; [b] $p = 0.042$; [c] $p = 0.062$.

Manic syndrome declined in ADL over follow-up, the increased risk of decline was no longer statistically significant after adjustment for comorbidity.

Predictors of disease progression: decline in cognitive functioning

Figure 2 shows the Kaplan-Meier survival curves over two years for cognitive decline and the predictions according to Gompertz function. The variance between the observed and predicted decline was 0.30 (95% CI = 0.26–0.35), which was higher than the variance seen for functional decline (Fig. 1).

Table 3 shows the hazard ratios of disease progression for a decline in cognitive functioning in patients with a specific syndrome at baseline compared to patients without the respective syndrome, using Gompertz regression modeling. Almost two-thirds of patients with the Apathy syndrome declined in cognition over two-year follow-up, but this figure was less than the comparison group of patients without Apathy. Consequently, we observed a slight decrease in the risk of cognitive decline in these patients, but this association was only borderline significant after adjustment for comorbidity or multiple adjustment. There was no increased risk of cognitive decline in patients with the Affective syndrome or in patients with the Psychotic syndrome.

Patients with the Psychomotor syndrome had more than a double increased risk of cognitive decline compared to patient without this syndrome, even after adjustment for comorbidity. However, after fully adjusting for multiple variables, the risk was no longer statistically significant.

Cognitive decline was predicted by baseline presence of Mania; patients with the Manic syndrome had an approximately threefold increased risk of cognitive decline compared to patients without this syndrome at baseline. This association remained significant even after adjustment for sociodemographic variables, baseline MMSE, ADL, and comorbidity. However, it is noteworthy that a large number of patients with the Manic syndrome (85.7%) also had another neuropsychiatric syndrome. Consequently, it is possible that the increased risk of cognitive decline in these patients was due to the number of syndromes present (i.e., a proxy for the severity of the neuropsychiatric disturbances). Thus, to investigate whether the increased risk of cognitive decline in patients with the Manic syndrome was due to the confounding effect of other syndromes, rather than an association between the specific syndrome and cognitive decline, we ran the

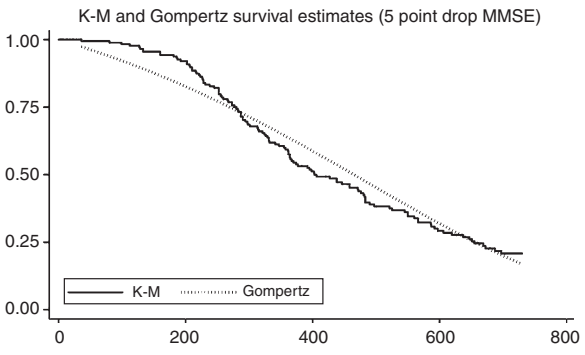

Fig. 2. Kaplan Meier (K-M) observed rates and Gompertz estimates of cognitive decline.

Table 3
Risk of cognitive decline over two-year follow-up in AD patients with baseline neuropsychiatric syndromes

		MMSE decline		Crude risk of MMSE decline		Adjusted for baseline MMSE		Adjusted for comorbidity		Fully adjusted model[3]	
		n	%	HR[1]	(95% CI)	HR[1]	(95% CI)	HR[1]	(95% CI)	HR[1]	(95% CI)
Apathy syndrome	No[2]	51	79.7	1.0		1.0		1.0		1.0	
	Yes	72	63.7	0.6	(0.4–0.9)	0.6	(0.4–0.9)	0.6	(0.4–1.0)[a]	0.6	(0.4–1.0)[b]
Affective syndrome	No[2]	79	71.2	1.0		1.0		1.0		1.0	
	Yes	44	66.7	0.9	(0.6–1.4)	0.9	(0.6–1.4)	0.8	(0.5–1.2)	0.7	(0.5–1.2)
Psychomotor syndrome	No[2]	110	67.9	1.0		1.0		1.0		1.0	
	Yes	13	86.7	2.4	(1.2–4.5)	2.6	(1.3–5.2)	3.5	(1.5–8.3)	2.3	(0.8–6.5)
Manic syndrome	No[2]	110	67.5	1.0		1.0		1.0		1.0	
	Yes	13	92.9	2.7	(1.4–5.2)	2.6	(1.3–5.0)	2.7	(1.2–5.8)	3.2	(1.3–7.5)
Psychotic syndrome	No[2]	116	69.5	1.0		1.0		1.0		1.0	
	Yes	7	70.0	0.6	(0.2–1.4)	0.6	(0.2–1.5)	0.3	(0.1–1.1)	1.0	(0.2–5.0)

[1] Hazard ratios calculated with Gompertz regression, with 95% confidence intervals.
[2] Reference category includes patients with any other syndrome and patients with no syndromes. All models are adjusted for the presence of other syndromes.
[3] Adjusted for age, gender, education, baseline ADL, baseline MMSE, and comorbidity (CIRS).
[a] $p = 0.030$; [b] $p = 0.049$.

analyses with a further adjustment for the number of syndromes present. Interestingly, after adjustment for all confounders plus the number of syndromes present, there was still an increase risk of cognitive decline in patients with the Manic syndrome (HR = 4.8, 95% CI = 1.9–12.3).

Although our analyses were adjusted for an overall comorbidity score, it is possible that specific comorbid conditions, such as vascular disease or metabolic disorders might act as confounders, as they may be related both to certain neuropsychiatric syndromes as well as ADL functioning. The mean item scores on the CIRS for vascular, cardio, and metabolic disorders are presented in Table 1 for each of the five neuropsychiatric syndromes. Although there were no clear differences in these subscores between the different syndromes, a final survival analyses was conducted with an adjustment for specific comorbidities from the CIRS subscore: 1) Vascular (including vascular disease and hypertension); 2) metabolic and endocrine diseases; and 3) cardiological pathologies. The results remained the same; there was no change in either statistical significance or point estimate for any of the hazard ratios (data not shown).

Finally, as patients with neuropsychiatric syndromes might be more likely to be prescribed anxiolytic, neuroleptic, or antidepressive medications, we investigated whether these drug treatments played a role on disease progression. Disease progression in functioning and cognition did not differ according to the use of anxiolytic medications (no drugs $n = 41$, 27.0% versus drug use $n = 6$, 24.0%; $\chi^2 = 0.097$, $p = 0.755$), neuroleptics (no drugs $n = 3$, 27.3% versus drug use $n = 44$, 26.5%; $\chi^2 = 0.003$, $p = 0.956$), or antidepressive treatment (no drugs $n = 15$, 34.1% versus drug use $n = 32$, 24.1%; $\chi^2 = 1.706$, $p = 0.192$).

DISCUSSION

In this clinical sample of Italian AD patients, we investigated the predictive role of five neuropsychiatric syndromes on disease progression over a period of two years with Gomperz regression. We discovered different predictors of functional and cognitive decline; patients with a Manic syndrome had a higher risk of cognitive decline, whereas functional decline was predicted by the Affective syndrome. Our results suggest that specific neuropsychiatric syndromes have a role in disease progression in AD patients.

A major finding of our study was that AD patients with the Manic syndrome at baseline had a threefold increased risk of cognitive decline, even after adjustment for potential confounders, including other concurrent neuropsychiatric syndromes and somatic comorbidity. The Manic syndrome is characterized by symptoms of euphoria and disinhibition, and an essential point is that this syndrome was infrequent, occurring in less than ten percent of our patients, similar to previous research [13]. Thus, although the Manic syndrome predicted disease progression, the prognostic relevance of this syndrome is limited, as it will not have a high sensitivity to predict change in a large number of patients. However, these results suggest that at the individual level, physicians should be aware of the potentially rapid decline of cognition and dis-

ease progression in AD patients with symptoms of Mania.

Differences in functional and cognitive decline were identified, because each outcome was predicted by different syndromes. The presence of the Manic syndrome in AD patients was associated with future cognitive decline, whereas functional decline was associated with the Affective syndrome. The Affective syndrome is comprised of neuropsychiatric symptoms of anxiety and depression, and was associated with an almost twofold risk of functional decline, but was not related to future cognitive decline. Research suggests that loss of ADL independence in AD is associated with decreased gray matter volume in the medial frontal and temporal-parietal cortices [29]. Previous studies have shown that anxiety is associated with loss of independence and social functioning in AD, independently from age and dementia severity [30], and that loss in functional ability precedes the onset of depressive symptoms [31]. The presence of an Affective syndrome may reflect neuropathological changes in the AD brain that are associated with subsequent disease progression. Neuropathological and imaging studies support this hypothesis; patients with comorbid depression have higher neurofibrillary tangle burden in the hippocampus [32], and patients with depressive symptoms have increased hypoperfusion in the prefrontal cortex [33]. Depression in AD is associated with a reduced cerebral blood metabolism in frontal, temporal, and parietal regions [33]. Thus, emotional and affective reactions associated with the neuropathological changes may manifest as an Affective syndrome, signaling an impending decline in functional abilities.

It is also possible that both the Affective syndrome and functional decline in AD are related to a confounder such as somatic comorbidities. Depressive and anxiety symptoms are associated with vascular factors such as stroke and hypertension in AD patients [34], and vascular factors are related to faster AD progression [5]. Further, symptoms of anxiety are associated with increased white matter hyperintensities in AD patients [35]. This previous research suggests that the Affective syndrome symptoms are related to AD progression via vascular-related events. On the contrary, our data support an independent contribution of the Affective syndrome on AD progression. We included an extensive somatic examination in all patients to assess the frequency and severity of comorbidities. After adjustment both for overall comorbidity and specifically vascular comorbidities, the association between the Affective syndrome and functional decline still remained significant, suggesting an independent role of this syndrome on disease progression.

It is worth noting that the Affective syndrome comprised symptoms of depression and anxiety, which both might influence performance during cognitive testing. Supplementary analysis investigating the differential role of depression and anxiety respectively, showed that neither symptom alone was responsible for the reported association with functional decline (data not shown). However, it will be interesting for future studies to focus on specifically examining the role of each separate symptom on disease progression, and for research to identify whether the testing procedures are directly influenced by the presence of an affective symptom.

Our study also identified an important confounding effect of somatic comorbidity on the associations between neuropsychiatric syndromes and functional decline. For example, although Mania was associated with an increased risk of ADL decline in crude regression analyses, the associations were no longer statistically significant after adjustment for CIRS score. This suggests that the faster functional decline in patients with Mania is due to co-occurring somatic disturbances which influence a patient's functional ability. This result highlights the importance of including a comprehensive examination of AD patients that considers the neurological, psychiatric, and somatic status of the patients, which may all play a role in the physical functioning of an individual.

Interestingly, the Psychomotor syndrome, characterized by symptoms of agitation, irritability, and psychomotor disturbances, was associated with an increased risk of cognitive decline after adjustment for baseline cognitive functioning or comorbidity, but this association lost significance after multiple adjustment. Previous studies showed a relationship with these symptoms and functional outcomes; agitation predicts institutionalization in AD [36], and agitation and restlessness predict faster functional decline [9]. There is evidence supporting the specific link between symptoms of the Psychomotor syndrome with cognitive functioning in AD, as aberrant motor behaviors are linked to executive dysfunction and attention [37]. The association between the Psychomotor syndrome and cognitive decline may indicate pathological changes associated with disease progression, as studies have demonstrated an increase in neurofibrillary tangles in the orbitofrontal cortex in patients with agitation [38]. Thus, these symptoms may be a marker of pathological changes in AD that precede disease progression characterized by cognitive decline. Interestingly, research

has also reported increased white matter hyperintensities in AD patients with aberrant motor behaviors [35, 39].

Another important result from the current study concerned the variance between predicted and observed disease progression between the two outcomes. The variance between the Gompertz prediction and the Kaplen Meier observed disease progression was less for functional decline as an outcome than cognitive decline. This suggests that ADL might be a better measure of disease progression than MMSE. This could be because the ADL is less sensitive to conditions other than AD, and thus loss of functioning is a more stable outcome of dementia. Cognitive functioning and performance on the MMSE can be affected by many factors, some of which we controlled for such as age, education, and comorbid disease. However, there were a number of factors that may affect cognition that we were unable to control for in our study, for example, fatigue, vitamin deficiency, or drug use. Cognitive performance may fluctuate over time, whereas functional decline is more progressive and stable, which may be why functional decline is a better measure of disease progression according to the Gomperz predictions than cognition. Our study was not designed to answer this question in detail, and there is a need for future research to identify and compare different measures and patterns of disease progression.

Our findings have relevance for the treatment and management of patients. Neuropsychiatric syndromes can be used by clinicians for prognostic planning, and clinical decision making on intervention and treatment strategies. The progression of behavioral symptoms decreases the quality of life of AD patients [40]. Neuropsychiatric disturbances, cognitive decline, and loss in ADL abilities predict institutionalization in AD and are associated with caregiver burden [7, 8, 15, 41]. Thus, they have relevance for the long-term planning and care for patients and caregivers. Although there is limited knowledge concerning the benefits of treating neuropsychiatric disturbances in AD, donezepil has been suggested to reduce delusions and depression in AD patients [42]. As we considered neuropsychiatric syndromes instead of single symptoms, our results are more clinically relevant, as the disturbance can be regarded in a more coherent way, as it reduces the problems associated with situations where patients have mild symptoms with uncertain clinical relevance. Further, previous studies provide evidence concerning the neuropathological relationship between AD and behavioral symptoms [32, 33, 38]. Together our findings may help to target future research on understanding disease mechanisms and developing intervention and prevention strategies in AD.

Some limitations deserve mention. First, as we included a group of people attending memory clinic outpatient services, our results may not be generalizable to the general population. Second, the definition of our two outcomes, cognitive and functional decline may be questioned. There are different techniques for measuring disease progression in AD. Our aim was to focus on clinical changes that may have important prognostic relevance to the patient; for example, functional decline is related to institutionalization [8]. A follow-up of two-years was chosen to increase the clinical relevance of the findings, and to highlight differences in rate of disease progression over a clinically meaningful, limited time period. Third, it is likely that there is some heterogeneity in our patients at first visit due to differences in care seeking patterns. Studies on AD patients have shown a large variation in the time between the onset of first symptoms and first physician consultation, and some patients only seek medical care when the disease has already reached a severe stage [28, 43, 44]. For this reason we adjusted all our analyses for baseline cognitive and functional status, included only patients with a new diagnosis of AD, and measured disease progression at the individual level as a decline from each patient's previous level of functioning. However, it is worth noting that the mean baseline MMSE score of our sample was similar to the performance of AD patients at first diagnosis in clinical settings [28, 45], and that all our patients had only mild to moderate AD. Another limitation is that there may be uncontrolled confounding in our results. For example, although genetic risk factors, such as Apolipoprotein E, might be related both to neuropsychiatric syndromes and disease progression, unfortunately we were unable to control for this as we did not have genetic information available on our participants. Finally, we did not take into account previous psychiatric disturbances occurring over the lifespan, which might influence disease progression. A major strength of our study is the multiple adjustment for potential confounders. In particular, we took into account comorbidities of the patients, to reduce the risk of confounding from other diseases. We also evaluated the risk of both functional and cognitive decline using a syndromic approach for characterizing neuropsychiatric disturbances in AD. Another major strength is the use of Gompertz regression, based on failure theory, to investigate factors associated with an increased risk of disease progression, which has

been proposed as an appropriate statistical theory to investigate disease progression in AD [17]. Finally, our study included a comprehensive assessment of all patients, comprising neurological, somatic, psychiatric, and cognitive assessment with regular follow-up examinations.

In conclusion, specific neuropsychiatric syndromes have an important role in predicting functional and cognitive decline during the progression of AD. Neuropsychiatric syndromes might be useful as markers to predict functional and cognitive decline in AD patients, which may help with the long-term planning of care and treatment in AD.

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