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Neuropsychological Contribution to Predict Conversion to Dementia in Patients with Mild Cognitive Impairment Due to Alzheimer's Disease

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Abstract.
Background: Diagnosis of Alzheimer's disease (AD) confirmed by biomarkers allows the patient to make important life decisions. However, doubt about the fleetness of symptoms progression and future cognitive decline remains. Neuropsychological measures were extensively studied in prediction of time to conversion to dementia for mild cognitive impairment (MCI) patients in the absence of biomarker information. Similar neuropsychological measures might also be useful to predict the progression to dementia in patients with MCI due to AD.
Objective: To study the contribution of neuropsychological measures to predict time to conversion to dementia in patients with MCI due to AD.
Methods: Patients with MCI due to AD were enrolled from a clinical cohort and the effect of neuropsychological performance on time to conversion to dementia was analyzed.
Results: At baseline, converters scored lower than non-converters at measures of verbal initiative, non-verbal reasoning, and episodic memory. The test of non-verbal reasoning was the only statistically significant predictor in a multivariate Cox regression model. A decrease of one standard deviation was associated with 29% of increase in the risk of conversion to dementia. Approximately 50% of patients with more than one standard deviation below the mean in the z score of that test had converted to dementia after 3 years of follow-up.

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Conclusion: In MCI due to AD, lower performance in a test of non-verbal reasoning was associated with time to conversion to dementia. This test, that reveals little decline in the earlier phases of AD, appears to convey important information concerning conversion to dementia.

Keywords: Alzheimer's disease (AD), amyloid-β, cognitive impairment, dementia, mild cognitive impairment due to AD, neuropsychological assessment, prodromal AD, Raven Coloured Progressive Matrices

INTRODUCTION

Nowadays, the development and clinical application of biomarkers has dramatically changed the framework of Alzheimer's disease (AD) diagnosis. It is now possible to diagnose AD at an early pre-dementia stage, that is, before the patient has symptoms severe enough to be considered demented [1, 2]. Different diagnostic criteria with slight differences were advanced, namely prodromal AD [3–5] and mild cognitive impairment (MCI) due to AD [6], that rely on biomarkers reflecting pathological alterations in the brain typical of AD, namely: 1) decline in episodic memory, confirmed by neuropsychological testing, 2) atrophy of the hippocampus and other medial temporal lobe structures shown by magnetic resonance imaging, 3) detection of abnormal cerebrospinal fluid (CSF) biomarkers, namely low amyloid amyloid-β ($A\beta)_{42}$ concentrations, increased phosphorylated tau or total tau concentrations, 4) abnormal brain deposits of Aβ and tau, as well as reduced glucose metabolism in temporoparietal regions, by positron emission tomography (PET scan). The use of biomarkers for diagnosis of MCI due to AD quickly spread to AD reference centers [7] and more sluggishly to routine clinical practice.

Uncertainties remain about the possible benefits and disadvantages of obtaining and communicating a specific diagnosis of prodromal AD, or MCI due to AD, to an individual patient. On the one hand, it should be relevant for the patient to make life decisions and prepare the near future, engage in a cognitive rehabilitation program, start appropriate pharmacological therapy, and eventually participate in a clinical trial. On the other hand, it might upset patients and caregivers, leading to emotional distress and concerns about progression of symptoms and the fleetness of future cognitive decline [8]. One important present limitation of obtaining and communicating a specific diagnosis of MCI due to AD is that the actual pace of disease progression, attainment of important clinical milestones, and in particular conversion to dementia, are presently impossible to predict in an individual basis. This point could not be made more clearly than by the patient's sentence when receiving the diagnosis of MCI due to AD: *Yes, I hope for the best. It will definitely evolve. I don't think it will stay like that, but is that within 5 years?* [8].

Importantly, prediction of time to conversion to dementia has already been extensively studied in MCI without the information of biomarkers, namely using neuropsychological assessments. These studies showed that memory tests, as well as executive function and verbal fluency tests, are able to predict with accuracy the time to conversion to dementia [9–25]. We hypothesize that similar neuropsychological measures may also be useful to predict the progression to dementia in MCI due to AD. It should be very important to provide the individual patient diagnosed with MCI due to AD with reliable information on the prediction of stability or conversion to dementia at a clinically relevant time window.

METHODS

Participants

A cohort of 232 patients who attended neurologic consultation in a private memory clinic in Lisbon (Memoclínica) and Coimbra University Hospital, in Coimbra, from 2006 to 2017, performed a comprehensive neuropsychological evaluation and were tested for biomarkers of brain amyloidosis and neuronal injury. From these, 127 had the diagnosis of MCI due to AD and were included in the present study. Patients had to have associated follow-up information and to be followed for at least one year, thus only 110 patients were analyzed for the present study (Fig. 1).

Ethical guidelines

The study was conducted in accordance with the Declaration of Helsinki, and the local ethics committee approved the study. All patients provided their written informed consent before any procedure.

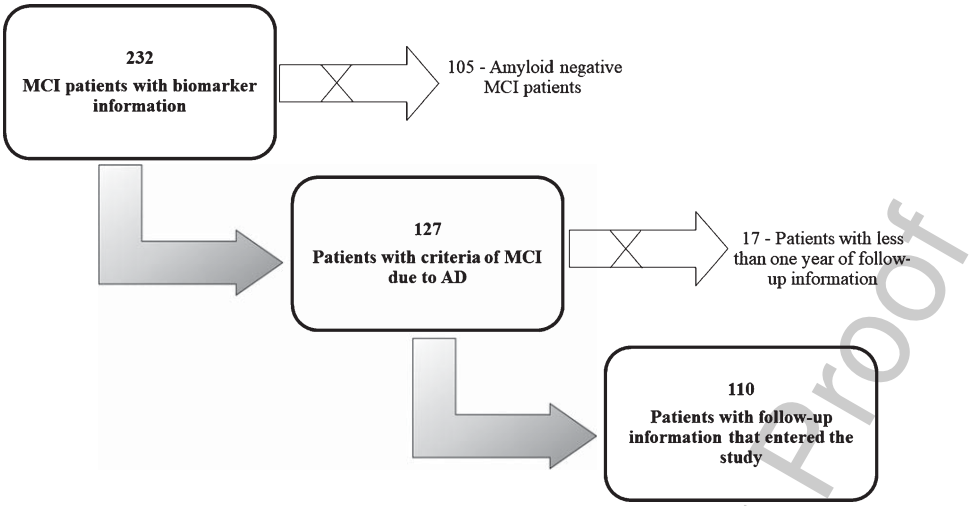


Fig. 1. Flow-chart of patient selection for the study.

Diagnostic criteria

The diagnostic criteria of MCI due to AD, as proposed by the National Institute on Aging - Alzheimer's Association workgroups [6], offer the most accurate prognosis in clinical settings [26]. Specifically, the criteria of MCI due to AD–High Likelihood [6] were considered in the present study since they provide the highest degree of certainty that the patient will progress to AD dementia:

1. Clinical and cognitive criteria
   a. Cognitive concern reflecting a change in cognition reported by patient, informant, or clinician
   b. Objective evidence of impairment in one or more cognitive domains, typically including memory
   c. Preservation of independence in functional abilities
   d. Not demented
2. Etiology of MCI consistent with AD pathophysiological process
   a. Vascular, traumatic and medical causes of cognitive decline were ruled out
   b. Evidence of longitudinal decline in cognition (when feasible)
3. Biomarkers of Aβ deposition
   a. Low CSF $A\beta_{42}$ and/or
   b. Positive amyloid PiB-PET imaging.
4. Biomarkers of neuronal injury (at least one present)
   a. High CSF total tau or hyperphosphorylated tau, and/or
   b. Medial temporal atrophy by volumetric measures or visual rating, and/or
   c. Temporoparietal hypometabolism by FDG-PET imaging

Both sources of amyloid status (CSF and PiB-PET) were considered interchangeable since a high agreement between $A\beta_{42}$ concentrations in the CSF and amyloid PiB-PET scan results in MCI and AD patients was confirmed by previous studies [27]. All procedures were performed according to the established protocols on participating centers [28–32]. The levels of $A\beta_{42}$, total tau (t-tau), and hyperphosphorylated tau (p-tau) were measured using commercially available enzyme-linked immunosorbent assays (INNOTEST® Aβ42, INNOTEST hTAU Ag and INNOTEST PHOSPHO-TAU(181P); Innogenetics, Ghent, Belgium). The expected site assay variability present in multicenter studies was acknowledged [33] and positivity was determined using locally available cut-off values. Amyloid PET scans used the Pittsburgh Compound B (^{11}C-PIB) and were performed in the same scanner (Philips PET/CT Gemini GXL), preceded by a low-dose brain computed tomography (CT) acquisition for attenuation correction (Institute of Nuclear Science Applied to Health, ICNAS, University of Coimbra). PiB-PET images were classified as amyloid positive or negative based on a support vector machines (SVM) local classifier, which uses the voxel wise brain grey matter standardized uptake value ratio

(SUVR) and the cerebellar grey matter as reference region [31].

Conversion to dementia

At follow-up, the patients were classified as "non-converter" if the diagnosis persisted until last assessment or "converter" in the presence of a dementia diagnosis established according to the DSM-IV-TR [34] criteria, in a consensus meeting with the team of neurologists and neuropsychologists that followed the patients.

Neuropsychological assessment

The baseline and follow-up comprehensive neuropsychological assessment was carried out by the same team of trained neuropsychologists, following a standard protocol and comprised the following instruments and scales:

- Mini-Mental State Examination (MMSE) [35, 36] - the MMSE is a brief screening instrument to assess global cognitive performance. The Portuguese version was applied, and normative data was >27 for more than 11 years of education and >22 for 11 or less years of education [36].
- Battery of Lisbon for the Assessment of Dementia (BLAD) [37, 38] - the BLAD is a comprehensive neuropsychological battery that includes some tests from the Wechsler Memory Scale [39] and has been validated for the Portuguese population. This battery includes tests for the following cognitive domains: attention (Cancellation Task); verbal initiative (Semantic Fluency), motor and graphomotor initiatives; verbal comprehension (a modified version of the Token Test); verbal and non-verbal reasoning (Interpretation of Proverbs and the Raven's Coloured Progressive Matrices – Ab series); orientation (Personal, Spatial, and Temporal Orientation); visuo-constructional abilities (Cube Copy); planning and visuospatial/praxis abilities (Clock Draw); calculation (Basic Written Calculation); immediate memory (Digit Span Forward); visual memory (Visual Reproduction Test); working memory (Digit Span Backward); learning and verbal memory (Verbal Paired-Associate Learning, Logical Memory and Word Recall).
- California Verbal Learning Test (CVLT) [40, 41] - the CVLT measures verbal learning and assesses constructs such as repetition learning, serial position effects, semantic organization, intrusion, and proactive interference. The word lists (List A and List B) are made up of 16 items from 4 different categories of "shopping list" items. The trial of interest (better discriminating ability for different stages of cognitive decline) [42] considered for the present study was the total number of words from List A correctly recalled on the first 5 learning trials (CVLT 5 Trials Total Recall).
- Trail Making Test (part A and part B) [43, 44] - the TMT task measures sustained attention, visuomotor processing speed (part A), visuospatial working memory and cognitive flexibility (part B). The part A consists of 25 circles numbered 1–25 distributed over a sheet of paper and the patient should draw lines to connect the numbers in ascending order. In Part B there are 25 circles as well, but the circles include both numbers (1–13) and letters (A–M) and the patient has to draw lines to connect them all in an ascending pattern with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.).
- Geriatric Depression Rating Scale (GDS) [45–47] - the GDS is a self-report instrument used specifically to identify depressive symptomatology in the elderly. For this study, a Portuguese version of a short form (15 items) was applied [47].
- Subjective Memory Complaints Scale (SMC) [48, 49] - the SMC scale comprises 10 individual questions for the assessment of subjective memory complaints, with total scores ranging from 0 (absence of complaints) to 21 (maximal complaints score).
- Blessed Dementia Rating Scale (BDRS) [50, 51] - the BDRS is a brief behavioral scale based on the interview of a close informant. This scale is composed of 22 items that address daily life activities, habits and changes in personality.

Statistical analysis

For baseline comparison of demographic and clinical data between groups the Student's t test and Pearson's χ^2 test were used, for numerical and nominal data, respectively. All tests were 2-tailed and a p-value <0.05 was assumed to be statistically significant. The neuropsychological assessments were standardized according to the age and education

norms for the Portuguese population [37, 38] and z scores were calculated. The comparison of neuropsychological results between the group that progressed to dementia during follow-up and the group that remained with MCI was conducted using Student's t test. To explore the effect of impairment in neuropsychological tests on the time to conversion to dementia during follow-up, first the proportional hazards assumption for neuropsychological predictors was tested by adding time dependent covariates (interaction of predictors and a function of survival time) and then a Cox Proportional Hazards Regression model was conducted. The hazard or risk of conversion to dementia for the neuropsychological tests that were significantly different between converter and non-converter groups was computed. Time to event was calculated as the interval from the initial baseline evaluation to the diagnosis of dementia. For cases that remained non-demented, time was censored at the date of the last clinical/neuropsychological assessment. Kaplan-Meier curves analyzing the incidence of dementia according to the z scores of the lowest and the highest tercile were depicted. For comparison of curves, we opted for the Gehan-Breslow test since one group had a higher risk of conversion due to the significantly lower cognitive performance at baseline.

Statistical analyses were performed using IBM SPSS Statistics 25 for Windows (2017 SPSS Inc., an IBM Company) package.

RESULTS

One hundred and ten patients with MCI due to AD were enrolled. During the follow-up period (2.69 ± 1.56 years for converters and 2.67 ± 1.39 for non-converters), 63 patients (56%) progressed to dementia and 50 (44%) did not. Demographic and clinical data are reported in Table 1. The converters at the baseline assessment were younger than the non-converters; however, for mean follow-up time, education level, gender, depressive symptomatology, cognitive complaints, and independence at daily activities, no statistically significant differences were found (Table 1).

The results of a comprehensive neuropsychological assessment showed the presence of impairment (z score<–1) in measures of attention and executive functions (Trail Making Test A and B), orientation, verbal learning and episodic memory (Word Recall; Logical Memory immediate recall; Logical Memory delayed recall; Verbal Paired-Associate Learning; California Verbal Learning Test 5 Trials Total Recall) for both groups. In a measure of language comprehension (Token Test), only the converters showed impairment. Moreover, converters scored significantly lower than non-converters at measures of verbal initiative (Semantic Fluency), non-verbal reasoning (Raven's Coloured Progressive Matrices), and episodic memory (Logical Memory immediate recall). Noteworthy, a trend toward statistical significance was found for the delayed recall condition of the Logical Memory test with converters scoring lower than non-converters at baseline assessment (Table 2).

A multivariate Cox proportional hazards regression model was applied to identify the independent predictors associated with time to conversion. The proportional hazards assumption was tested for each predictor (Age: Hazard Ratio [HR] = 1.020, CI: 0.990–1.052, $p = 0.192$; Semantic Fluency: HR = 0.965, CI: 0.804–1.159, $p = 0.704$; Logical Memory (immediate recall): HR = 0.981, CI: 0.834–1.155, $p = 0.821$; Raven Coloured Progressive

Table 1
Baseline demographic and clinical characteristics of non-converters and converters

	Non-converter $n = 49$ mean ($n = 24$)	Converter $n = 61$	p
Age at first assessment, y, mean (SD)	70.1 (6.2)	65.4 (7.3)	**<0.001***
Formal education, y, mean (SD)	10.7 (4.6)	10.2 (4.8)	0.591
Gender, female/male, n	28/22	35/27	1.000#
Follow-up time, y, mean (SD)	2.7 (1.4)	2.7 (1.6)	0.921
Time between onset of symptoms and first neuropsychological assessment, mean (SD)	2.4 (1.5)	2.2 (1.2)	0.576
Geriatric Depression Scale, mean (SD)	5.1 (3.4)	5.8 (4.5)	0.420
Subjective Memory Complaints Scale, mean (SD)	10.3 (4.6)	10.2 (4.1)	0.959
Blessed Dementia Rating Scale, mean (SD)	3.1 (1.9)	3.4 (2.0)	0.528
Mini-Mental State Examination, mean (SD)	26.4 (2.2)	25.6 (2.4)	0.084

Group comparisons were performed with parametric Student's t test (or χ^2 Pearson test when appropriate#); *Statistically significant $p < 0.05$; SD, standard deviation.

Table 2
Baseline neuropsychological performances of non-converters and converters

Cognitive domain Neuropsychological test	Non-converter ($n=49$)	Converter ($n=61$)	p	Cohen's d
• **attention and executive functions**				
Cancellation Task	0.26 (1.17)	0.04 (1.37)	0.406	0.14
Digit Span Backward	0.06 (0.90)	–0.09 (1.20)	0.488	0.12
Clock Draw	0.05 (1.49)	–0.37 (1.53)	0.216	0.28
Trail Making Test A	–1.31 (1.70)#	–1.36 (1.85)#	0.896	0.02
Trail Making Test B	–1.97 (1.84)#	–1.63 (1.79)#	0.413	–0.18
• **initiative**				
Semantic Fluency	–0.07 (1.33)	–0.86 (1.48)	**0.004***	0.54
Motor Initiative	–0.27 (1.80)	–0.70 (1.90)	0.238	0.23
Graphomotor Initiative	0.05 (0.76)	–0.13 (1.00)	0.319	0.21
• **reasoning**				
Raven Coloured Progressive Matrices	0.05 (1.06)	–0.60 (1.43)	**0.009***	0.48
Interpretation of Proverbs	0.73 (1.23)	0.34 (1.82)	0.211	0.21
• **orientation**				
Personal, Spatial and Temporal Orientation	–2.32 (2.45)#	–2.23 (2.35)#	0.846	–0.04
• **calculation**				
Basic Written Calculation	–0.47 (1.00)	–0.59 (1.17)	0.582	0.08
• **visuo-constructional abilities**				
Cube Copy	1.54 (1.95)	1.33 (2.37)	0.656	0.11
• **language**				
Token Test	–0.59 (1.11)	–1.17 (1.83)#	0.113	0.36
• **memory and learning**				
Visual Reproduction	1.45 (1.30)	0.58 (0.99)	0.150	0.77
Digit Span Forward	0.55 (1.30)	0.42 (1.34)	0.622	0.08
Word Recall	–1.25 (1.44)#	–1.77 (1.57)#	0.093	0.35
Logical Memory (immediate recall)	–1.17 (1.13)#	–1.92 (1.53)#	**0.005***	0.53
Logical Memory (delayed recall)	–1.99 (1.40)#	–2.64 (0.93)#	0.056	0.53
Forgetting Index (1)	–1.23 (2.38)#	–1.79 (2.78)#	0.266	0.26
Verbal Paired-Associate Learning	–1.18 (1.20)#	–1.58 (1.54)#	0.139	0.25
CVLT 5 Trials Total Recall	–3.14 (1.36)#	–3.69 (0.95)#	0.077	0.42

Means of z scores calculated according to the equation [$z=(x$–mean)/SD]; Group comparisons were performed with independent samples Student's t test. *Statistically significant $p<0.05$. #Presence of impairment (z score<–1). (1)Forgetting Index = [(LM delayed recall –LM immediate)/LM immediate)]*100. CVLT, California Verbal Learning Test.

Matrices: HR = 1.217, CI: 1.005–1.475, $p=0.045$). Only the clinical and neuropsychological measures that differentiate the groups were included as predictors. In the first model, only the clinical predictor (age) by the method enter was included. Age at baseline was not associated with time to event (conversion to dementia). Neuropsychological predictors were subsequently subjected to multivariate Cox proportional hazards regression analysis (Table 3). The Semantic Fluency was added to the model and was a significant predictor (HR = 0.762, CI: 0.634–0.916, $p=0.004$), whereas the Logical Memory (immediate recall) in the presence of Semantic Fluency did not reach significance as predictor (HR = 0.852, CI: 0.704–1.031, $p=0.099$) (Table 3). However, the Logical Memory (immediate recall) was a significant predictor if entered first in the model (data not shown in Table 3; HR = 0.797, CI: 0.663–0.957, $p=0.015$). When the Raven Coloured Progressive Matrices was added to the model, the other predictors lost their significance (Semantic Fluency: HR = 0.835, CI: 0.691–1.009, $p=0.062$; Logical Memory (immediate recall): HR = 0.898, CI: 0.738–1.092, $p=0.281$). In the final model, only the Raven Coloured Progressive Matrices, a test of non-verbal reasoning, remained significant as a predictor of time to conversion to dementia (HR = 0.712, CI: 0.566–0.894, $p=0.004$). A decrease of one unit (z score) in Raven Coloured Progressive Matrices was associated with a 29% increase in the risk of conversion to dementia (Table 3).

For the Kaplan-Meier curves, the comparison was between the highest and the lowest terciles of the Raven Coloured Progressive Matrices scores to assess the differences in time to conversion to dementia. Because at baseline both groups showed normative results, the presentation of Kaplan-Meier curves comprised the lowest and the highest terciles, instead of impaired and unimpaired z scores, to offer a more balanced sample size curves (Fig. 2).

Table 3
Multivariate Cox proportional-hazard regression models for predictors of conversion to dementia

Predictors ($n = 110$; event/conversion to dementia = 61; censured = 49)	HR	95%CI	p
Multivariate analysis			
Model 1 – demographic variable (enter method)			
Age (mean, y)	0.984	0.950–1.019	0.376
Model 2 – cognitive predictors (enter method)			
Semantic Fluency (mean, z score)	0.762	0.634–0.916	**0.004***
Model 3 – cognitive predictors (enter method)			
Semantic Fluency (mean, z score)	0.804	0.664–0.974	**0.026***
Logical Memory (immediate recall) (mean, z score)	0.852	0.704–1.031	0.099
Model 4 – cognitive predictors (enter method)			
Semantic Fluency (mean, z score)	0.835	0.691–1.009	0.062
Logical Memory (immediate recall) (mean, z score)	0.898	0.738–1.092	0.281
Raven's Coloured Progressive Matrices (mean, z score)	0.712	0.566–0.894	**0.004***

CI, Confidence Interval; HR, Hazard Ratio; *Statistically significant ($p < 0.05$).

According to the Kaplan-Meier curves, for z scores in the lowest tercile (z score range: –2.88 to –0.96) after 3 years of follow-up approximately 50% of patients had converted to dementia, whereas for the highest tercile (z score range: 0.59 to 1.82) the conversion of approximately 50% of patients occurred later, after 4 years of follow-up. Accordingly, a significant difference between Kaplan-Meier curves was found ($\chi^2(1) = 6.131$; $p = 0.013$).

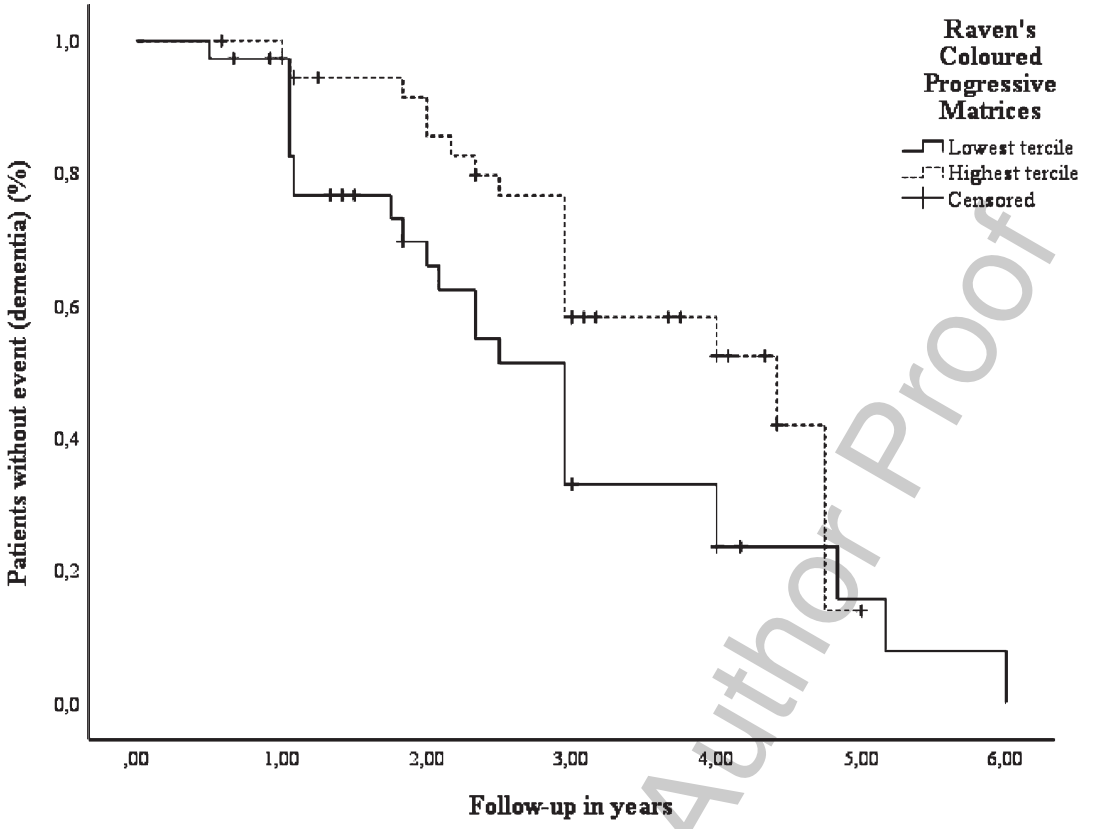
DISCUSSION

Patients with MCI due to AD that converted to dementia during the follow-up period were more impaired at the baseline in neuropsychological tests assessing verbal fluency, non-verbal reasoning, and episodic memory, as compared to non-converters. An interesting result is that only non-verbal reasoning, assessed through Raven Coloured Progressive Matrices, remained significant as a predictor of time to conversion to dementia in a multivariate model.

Several studies have previously evidenced the predictive value of neuropsychological measures to assess time to conversion to dementia in MCI patients with unknown biomarker status [22, 52–54]. Noteworthy, some studies highlighted that not only episodic memory performance but also other cognitive areas, namely executive functions and language tests, are associated with a higher likelihood of progression from MCI to dementia during follow-up [14, 21, 55–57]. Thus, it would be plausible to expect a similar contribution of neuropsychological testing for patients with MCI due to AD.

According to our results, cognitive areas associated with reasoning and fluid intelligence, that reveal little decline until more advanced phases of AD, as can be seen in the normative results of our MCI patients, can contribute significantly to predict time to conversion. As previously mentioned, only non-verbal reasoning, assessed through Raven Coloured Progressive Matrices, remained significant as a predictor of time to conversion to dementia in a multivariate model. For each standard deviation reduction in the z score of Raven Coloured Progressive Matrices score the risk of conversion to dementia increased approximately 30%. This test is a measure of fluid intelligence that demands several abilities as visual-perceptual, process integration, logical reasoning, and cognitive flexibility [58]. The contribution of the Raven Coloured Progressive Matrices to predict time to conversion to dementia has been, to the best of our knowledge, largely neglected in the literature. Fluid intelligence has been addressed as a proxy of cognitive reserve [59]. In AD patients, a higher cognitive reserve was associated with slower clinical progression in predementia stages, but after the onset of dementia it appears to have the opposite effect and accelerate the cognitive decline [60]. Interestingly, in a different cohort study from the same memory clinic in Lisbon, in amnestic MCI patients without amyloid status information, an association of performance in Raven Coloured Progressive Matrices with long-term (10 years) diagnostic stability was also found [61]. Likewise, a large community-based study with non-demented subjects, the Framingham cohort prospective study, showed that a test of abstract reasoning was a strong predictor of long-term (22 years) conversion to dementia [62]. In the present study, the Raven Coloured Progressive Matrices test was found to be the stronger predictor of conversion to dementia at a shorter (3 years) term in patients with MCI due to AD.

As foreseeable, most of the MCI due to AD patients converted during the follow-up period. Remarkably



Number at risk						
	1 year	2 years	3 years	4 years	5 years	6 years
Lowest tercile (n=37)	33	18	8	6	1	0
Highest tercile (n=37)	35	30	18	9	0	0

Fig. 2. Kaplan-Meier analysis of the incidence of dementia among patients in the lowest and in the highest tercile of the *z* scores.

patients that converted to dementia during follow-up were younger at baseline than patients that did not convert, with no differences being found in duration of symptoms, presence of depressive symptoms, and years of formal education. This result seems to be in contradiction to longitudinal studies of conversion from MCI to AD that commonly report higher risk of conversion to dementia for the older patients [63, 64]. However, the influence of age in cognitive decline for AD patients is not straightforward and some studies have revealed that AD patients starting the symptoms earlier had a less benign course with higher rate of cognitive decline [65]. Notwithstanding the difference at baseline, age was not a significant predictor of time to conversion.

The present study has some limitations that might be addressed in future studies. Obtaining a longer follow-up would be important. Replication of the present findings in other studies recruiting patients at a similar clinical stage would be needed. The genotyping of Apolipoprotein E (*APOE*) $\varepsilon 4$ is not recommended in a clinical context [66] and for that reason was not available, and this is a limitation of the present study. Patients did not undergo all neuronal injury biomarkers, so it was not possible to assess their predictive value on time to future conversion to

dementia. Not all patients with MCI undergo the diagnostic procedures with biomarkers, which are costly and invasive, thus the patients diagnosed with MCI due to AD are not representative of the AD population in a memory clinic.

The major strengths of the present study are the sample high likelihood of having AD neurodegeneration according to the diagnostic criteria and the minor loss to follow-up of the cohort. As future perspectives, predicting conversion of MCI due to AD to dementia might be improved by machine learning techniques, namely by a feature selection ensemble approach to automatically choose the best neuropsychological predictors of future conversion, as was already done for MCI patients without amyloid status information [67]. Anticipating a precision medicine approach, it would important to refine risk models that can provide reliable prognostic information to the individual patient with MCI due to AD [68].

It has been an extraordinary recent advance being able to diagnose AD at an early clinical stage. Still, after being diagnosed with MCI due to AD, patients and families need to make important life decisions and future planning, and expectedly wish to get a reliable estimation of the disease progression. To the best of our knowledge, the present study is the first to explore the differential contribution of routine neuropsychological tests to predict time to conversion to dementia among patients diagnosed with MCI due to AD. Neuropsychological tests, namely assessing verbal fluency, episodic memory, and particularly non-verbal reasoning assessed with the Raven Coloured Progressive Matrices, may contribute to predict stability or conversion to dementia at a clinically meaningful time window.

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