International Psychogeriatrics xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Psychogeriatrics

journal homepage: www.sciencedirect.com/journal/inpsyc

Original Research Article

Clinical parameters predicted the progression to dementia in oldest old patients with mild cognitive impairment (MCI)

Nora Molina-Torres[a,b,c,d,1], Carlos Platero[e], Oscar Pérez-Berasategui[b], Pol Andrés-Benito[f], Mónica Povedano[g], Pilar Mesa-Lampré[b], María Abadía-Morales[h], Ana-Cristina Calvo[a,c,d,1], Antonio Lobo[c,1], Concepción De La Cámara-Izquierdo[c,h,1], Rosario Osta[a,d,*,1]

[a] LAGENBIO, Laboratorio de Genética Bioquímica. Facultad de Veterinaria, Universidad de Zaragoza, C/ Miguel Servet 177, 50013 Zaragoza. Spain
[b] Geriatrics Department, Hospital Nuestra Señora de Gracia, C. de Santiago Ramón y Cajal, 60, 50004, Zaragoza, Spain
[c] Instituto de Investigación Sanitaria de Aragón (IIS Aragón). Centro de Investigación Biomédica de Aragón, C. de San Juan Bosco, 13, 50009 Zaragoza, Spain
[d] Centre for Biomedical Research in Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, 28029, Madrid, Spain
[e] Escuela Técnica Superior de Ingeniería y Diseño Industrial Departamento de Ingeniería Eléctrica, Electrónica, Automática y Física Aplicada, Ronda de Valencia 3. C305, 28012 Madrid, Spain
[f] Cognition and Behavior Study Group - Institut de Recerca Biomèdica de Lleida (IRB-Lleida), Avda Alcalde Rovira Roure nº80, 25198 Lleida, Spain
[g] Neurologic Diseases and Neurogenetics Group, Bellvitge Institute for Biomedical Research (IDIBELL), L'Hospitalet de Llobregat, Avinguda de la Granvia de l'Hospitalet, 199, 08908 Barcelona, Spain
[h] Department of Medicine and Psychiatry, Facultad de Medicina, Universidad de Zaragoza, C/ Domingo Miral, s/n, 50009 Zaragoza, Spain

ARTICLE INFO

Keywords:
MCI
Alzheimer disease
MMSE
Oldest old
Disease progression model (DPM)

ABSTRACT

Background: This study intends to assess to what extent instruments commonly used in clinical practice, as well as plasma p-tau-181, can predict the progression from MCI to dementia. The usefulness of a disease progression model (DPM) is also explored.

Methods: A longitudinal, prospective nested case-control study was conducted with patients from the Geriatrics outpatient clinics who met the MCI International Working Group criteria. The patients had a first clinical interview and two follow-ups after 12 and 24 months. Validated Spanish instruments were used for assessment, including the Mini-Mental State Examination (MMSE), the clock test, verbal fluency, the EURO-D depression scale, Barthel's Index, and Lawton's Index. P-tau-181 analysis was performed with SIMOA (Single MOlecule Array). A robust parametric disease progression model (RPDPM) was developed.

Results: Fifty-nine patients fulfilled the inclusion criteria. The median age was 82.7 + /−8.7 years, 93 % had amnestic MCI and 45.8 % progressed to dementia (ICD-11 criteria) in two years. P-tau-181 was not prognostic. An RPDPM with the MMSE, clock test, and Lawton's Index could predict progression to dementia with an AUC of 0.945.

Conclusion: A combination of the MMSE, clock test, and Lawton's Index in a DPM model predicted progression from MCI to dementia best. P-tau and other blood biomarkers did not predict progression. Our results highlight the strength of clinical variables to predict the progression of MCI.

Why does this paper matter?

Our model can forecast a patient's potential progression from MCI to dementia with three tests run in less than 45 min.

Introduction

Mild Cognitive Impairment (MCI) is an intermediate state between dementia and healthy ageing, in which individuals show measurable

* Correspondence to: LAGENBIO, IIS-A, CIBERNED, Universidad de Zaragoza.
E-mail addresses: noramolinat@gmail.com, 646110@unizar.es (N. Molina-Torres), carlos.platero@upm.es (C. Platero), oscarjaizkibel@gmail.com (O. Pérez-Berasategui), pol.andres.benito@gmail.com (P. Andrés-Benito), pmesalamp@gmail.com (M. Povedano), mariaabadiamoraless@gmail.com (M. Abadía-Morales), accalvo@unizar.es (A.-C. Calvo), alobosat@gmail.com (A. Lobo), cdlcamara@salud.aragon.es (C. De La Cámara-Izquierdo), osta@unizar.es (R. Osta).
[1] https://ror.org/012a91z28

https://doi.org/10.1016/j.inpsyc.2025.100129
Received 18 May 2025; Received in revised form 30 July 2025; Accepted 31 July 2025
Available online xxxx

cognitive impairment yet continue to manage their instrumental activities of daily living independently [1]. Although the term MCI has sparked debate, it is widely accepted that, once MCI is diagnosed, the condition must be characterised because modifiable risk factors can delay the onset of dementia [2]. A multidimensional approach is therefore essential: rigorous cognitive testing complemented by biomarkers and demographic and clinical factors such as functional status [3], depression [4] and frailty [5]. Even when the criteria for dementia are not met, MCI still has an impact on the quality of life of patients and caregivers [6]. MCI is heterogeneous in both clinical presentation and aetiology and can be classified into amnestic or non-amnestic (depending on whether memory is impaired) and may affect single or multiple domains. A pattern of multiple-domain amnestic MCI implies a higher risk of progression to dementia [7].

Alzheimer's disease is the most common cause of dementia (about 60 % of cases in a Spanish cohort [8]). Plasma biomarkers such as p-tau181 are emerging as potential diagnostic tools for Alzheimer's Disease (AD) [9]. Plasma p-tau 181 can estimate if there is a high, low or intermediate probability of AD, enabling clinicians to start treatments, rule out the disease or arrange for further tests. It is also useful for screening candidates for clinical trials and population studies. However, its accuracy may be limited in patients over 85 years old. This group can be referred to as "oldest old" [10]. This 'oldest old' group is heterogeneous and understanding how biomarkers and other factors influence the progression from MCI to dementia in this group is a challenge. Evidence is scarce, so work in the specific setting of a geriatric outpatient clinic may be particularly relevant.

Routine early screening for cognitive impairment is recommended in people over 65 years old [11]. Yet there is no consensus on the best clinical tools in primary care settings. The Mini-Mental State Examination (MMSE) alone has limitations [12], whereas the Montreal Cognitive Assessment (MoCA) is more accurate [13], but takes longer to administer. A combination of the MMSE and animals test has shown to improve diagnostic accuracy [12]. The applicability of these instruments in the study of progression from MCI to dementia may be important, particularly if they are used in conjunction with biomarkers and models of disease progression.

In fact, disease progression can be modelled quantitatively with longitudinal data. Such models can provide long-term predictions of pathological stages. A Disease Progression Model (DPM) is a novel machine-learning approach that uses short-term clinical data to infer long-term pathological trajectories and treats AD progression as a continuous process [14].

In light of these challenges, the aim of this study is to assess whether cognitive, functional and frailty scales used in clinical settings, or a combination of these scales together with plasma p-tau181, can predict progression from MCI to dementia in a cohort of MCI patients in a geriatric outpatient clinic. It also explores to what extent a disease progression model (DPM) can estimate the time of progression to dementia in the oldest cohort (over 80 years [15]).

Methods

Study design

We conducted a longitudinal, prospective, nested case-control study. Each patient had an initial interview (T1) and, two follow-up interviews after 12 and 24 months (T2, T3). The patients completed neuropsychological and functional tests at every visit, and blood samples were collected. All patients were diagnosed with MCI at baseline. After 24 months, patients were classified into pMCI (progression MCI) or sMCI (stable MCI), according to whether or not they had progressed to dementia. Only two patients showed improved cognitive test results by the end of the study, yet self-reported and informant-reported cognitive complaints persisted.

Inclusion criteria

All patients from the Geriatrics outpatient clinics of the Hospital Nuestra Señora de Gracia, Zaragoza, Spain were screened consecutively. Recruitment ran from 1 January 2020 to 1 August 2021 (longer than expected due to the COVID-19 pandemic). Some eligible patients declined hospital visits owing to infection risk, while others already had multiple specialist appointments and were unwilling to attend further medical appointments.

Patients were included in our study if they matched the International Working Group criteria for MCI [16]: the individual is neither normal nor demented; there is evidence of cognitive deterioration documented either through objectively measured decline over time and/or subjective report of decline by the patient and/or informant in conjunction with objective cognitive deficits; and activities of daily living are preserved, with complex instrumental functions either intact or minimally impaired.

Exclusion criteria

Patients with established dementia diagnosis, movement disorders such as Parkinson's disease, acute severe psychiatric disorders, delirium, active cancer or in palliative care were excluded from the study. Chronic depressive disorders were not grounds for exclusion unless patients were experiencing a new active episode. Mild psychiatric disorders were allowed.

Neurocognitive and functional testing

We applied a short, modified version of the ZARADEMP interview, a battery of tests for the epidemiological study of patients with depression and/or dementia in the general population [17]. This battery includes the Spanish versions of Folstein's Mini Mental State Examination (MMSE, scores from 0 to 30) [18], the Clock Drawing Test (CDT) (scores from 0 to 9) [19], semantic verbal fluency (number of animals named in one minute) [20], the EURO-D depression scale (scores from 0 to 12) [21], Barthel's Index (scores from 0 to 100) [22] and Lawton's Index (unified across sexes, scores from 0 to 4) [23].

Frailty [24] was measured using the FRAIL-VIG scale (score 0.1 to 0.7) [25]. This scale is a new frailty index based on the Comprehensive Geriatric Assessment. This simple, rapid tool has discriminative and predictive capacity and was developed based on a cohort of Spanish elderly patients. Thresholds for each scale are provided in the Supplementary Material.

Dementia was diagnosed according to ICD-11 criteria [26]: if patients had impairment in one or more cognitive domains (scores below threshold in the cognitive scales) and cognitive impairment interferes significantly in the instrumental activities of daily living (< 50 % of Lawton's Index items).

Human plasma samples

Plasma was prospectively collected from patients during routine clinical evaluations. For each patient, 12 ± 0.5 mL of blood was collected into tubes with EDTA anticoagulant, centrifuged at 2000 rpm for 20 min at room temperature, and then at 2500 rpm for 10 min to extract plasma. The supernatant was collected and aliquoted in volumes of 2000 μL and stored at -80 °C until use.

The study complied with the Declaration of Helsinki and received prior informed consent and approval from the Regional Clinical Research Ethics Committee (Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón, CEICA, PI 19–455).

Single molecule array (SIMOA) analysis

Plasma P-tau181 concentrations from each patient was measured using the Quanterix SR-X platform and corresponding SIMOA kits, following manufacturer's instructions. The assay was only performed in the 47 patients who completed all three follow-up visits (T1, T2, and T3).

Statistical analysis

R Studio (R 4.3.0), Excel 2016 (Microsoft) and Jamovi (2.2.28) were used to analyse the data. A p value below 0.05 was considered statistically significant.

Normality was tested with the Saphiro Wilk test, and variance homogeneity with the Flinger Killeen test. Repeated-measures ANOVA compared longitudinal outcomes between pMCI and sMCI. Linear regression and binomial logistic regression served as predictive models. To assess the discriminative capacity of p-tau-181, we calculated the area under the curve (AUC), sensitivity, specificity, Youden's Index, and optimal cut-off values within our experimental cohort, representing the results using ROC curves. Additionally, we also used ROC curves to evaluate the prognostic capacity of plasma p-tau181 at baseline. The diagnostic cut-off values were compared with those previously described in the recent literature [10].

We developed a Disease Progression Model (DPM) for our MCI cohort. More specifically, a Robust Parametric Disease Progression Model (RPDPM), tailored to predicting Alzheimer's disease progression [27]. This method performed well despite a more limited sample size compared to alternative methods. DPMs convert individuals' ages into disease progression scores, while simultaneously fitting parametric curves to each biomarkers' longitudinal trajectory. This is an unsupervised learning algorithm that ignores patients' clinical diagnosis. The cohort is divided in two groups: one to train the DPM, and another one to test its validity.

Following this framework, our team developed a RPDPM based on our dataset. The goal of the RPDPM was to identify which variables (or combination of variables) were the best predictors of MCI progression to dementia. Our algorithm selected the combination of variables according to two indicators: first, the highest area under the curve (AUC) for diagnostic accuracy, then the strongest Pearson correlation between the actual conversion times of pMCI individuals and the model's estimations. The final RPDPM, built using the combination of variables, suggests a natural history from cognitive decline to dementia by temporally aligning all markers and the disease progression score. This suggested history of the disease can also estimate future values and the time left to progression to dementia for each patient. Furthermore, the RPDPM can classify the clinical status per subject visit (stable MCI vs dementia) in an independent test set without human supervision.

We have uploaded the algorithm and scripts to a public GitHub repository, accessible to all interested users. They can be found in this link:

https://github.com/cplatero/RPDPM_MCItoDementia.

Results

Demographic and clinical characteristic of our cohort at baseline

Fifty-nine MCI patients were enrolled in the study. The median age was 82.7 + /8.7 years and 40 (67.8 %) were women. Ninety percent of patients showed impairment in multiple cognitive domains (more than one of the three cognitive tests with pathological scores), and 93 % had amnestic MCI. After the three visits, 27 progressed to dementia (45.8 %, pMCI), and 32 remained stable (sMCI). Table 1 compares the demographics, clinical outcomes and medical history of both groups at baseline.

Baseline plasma p-tau-181 levels were not able to predict progression from sMCI to dementia (pMCI)

To better characterize this cohort of patients, we evaluated the prognostic significance of plasma p-tau-181 levels. At baseline (timepoint T1,) no significant differences were observed in plasma p-tau-181 concentrations between sMCI (23.47 ± 2.24 pg/mL) and pMCI (25.49 ± 2.32 pg/mL) ($F = 1.03$, $P = 0.53$) (Fig. 1). Moreover, baseline plasma p-tau-181 levels failed to predict the progression from stable MCI (sMCI) to dementia (pMCI) (binomial regression, $p = 0.4$). In addition, the linear regression between baseline plasma p-tau 181 and MMSE was not significant ($p = 0.38$). When comparing pMCI and sMCI at baseline (T1), the area under the curve (AUC) was 0.57 ± 0.09 (95 % CI 0.39–0.74, $P = 0.47$), with an optimal cut-off of 21.23 pg/mL based on the Youden index (0.24; sensitivity 65 %, specificity 59.1 %). No significant differences in p-tau 181 levels (repeated-measures ANOVA) levels at baseline or any of the follow-up visits were detected. (Fig. 1).

The MMSE score is a prognostic tool for the progression of MCI to dementia

The scores for baseline MMSE ($p = 0.02$) and Clock Drawing Test ($p = 0.022$) were higher in the sMCI group at baseline, indicating a better cognitive state. Conversely, the score for VIG-FRAIL was lower in the sMCI group ($p = 0.029$; indicating less frailty). While the MMSE, the Clock Drawing Test, and the VIG-FRAIL showed differences between groups in the initial visit, the differences remained significant only in the MMSE after Bonferroni's post hoc in a repeated-measures ANOVA test. (Fig. 2).

According to our procedure, the variables that had the best accuracy in estimating the time of progression from MCI to dementia were a combination of Lawton's Index, MMSE and the Clock Drawing Test (AUC 0.95). With this combination of variables, the model suggested a natural history of the progression of MCI towards dementia (Fig. 3). In Fig. 3, the trajectory of each individual patient is represented in a different colour: blue for subjects with stable MCI (sMCI) and red for those with progressive MCI (pMCI). The black line represents the average trajectory of the population. The trend becomes steep near the onset of dementia (year "0"), as the scores of the tests begin to worsen and decrease. When all the individual trajectories (red and blue lines) present low dispersion around the population average (black line), it suggests the marker reflects reliably the proposed natural history of the disease and the progression from cognitive decline to dementia.

The blue and red lines present little dispersion in Lawton's Index (IL), MMSE and the Clock Drawing Test, as they trace this proposed natural history of the clinical symptoms of cognitive decline. There is also little dispersion with Barthel's Index (IB) and verbal fluency (VF). However, the p-tau181 marker shows limitations in reflecting the progression towards dementia, as individual trajectories are notably dispersed, nor did the EURO-D scale follow the progression towards dementia.

As outlined in Methods, we split the dataset into a training set for model fitting and a separate test set for validation. This division let us gauge the DPM's accuracy on pMCI participants who progressed to dementia during follow-up. Fig. 4 charts the accuracy of the model with a Pearson correlation coefficient. Each blue dot marks the actual clinical conversion times from MCI to dementia, while the red line, the regression line, compares the corresponding predictions made by the selected DPM. In Fig. 4A, there is not much dispersion between blue dots and the red line, which indicates high agreement between our model and the actual time of conversion of the pMCI patients of the test cohort (thus Pearson's *r* equals 1). However, in Fig. 4B, blue dots scatter more widely and further away from the red line, indicating less correlation (Pearson's *r* equals 0.8). The time to progression was calculated as the interval between T1 and the midpoint between the last visit with a MCI diagnosis and the first visit with a dementia diagnosis, giving

Table 1
Demographic and clinical characteristic of our cohort at baseline. sMCI = stable MCI. pMCI = progression MCI. MMSE = Mini-Mental State Examination. CSVD = cerebral small vessel disease. Scale and score ranges: MMSE 0 – 30; Clock Drawing Test 0 – 9; semantic verbal fluency = number of animals named in one minute; EURO-D 0 – 12; Barthel Index 0 – 100; Lawton Index 0 – 4 (sex-unified); FRAIL-VIG 0.1 – 0.7. The term "number of patients above/below cut-off" denotes the number of patients whose score falls in the pathological range for that scale (e.g. depression on the EURO-D scale, frailty on the VIG-FRAIL scale).

	32 (sMCI)	27 (pMCI)	P < 0.05
Female	23 (71.8 %)	17 (63 %)	
Age	81.2 + /- 5.7	82.5 + /- 4.5	
Education	7.0 + /- 2.7	7.0 + /- 3.3	
Clinical outcomes			
Barthel's Index	96.1 + /- 2.8	95.0 + /- 5.5	
Lawton's Index	3.4 + /- 0.7	2.9 + /- 0.8	
MMSE	25.2 + /−4	23.6 + /−4.5	0.039
Number of patients below cut-off	14 (43.8 %)	14 (51.9 %)	
Verbal Fluency	11.2 + /- 3.4	10.3 + /- 3.0	
Number of patients below cut-off	23 (71.9 %)	21 (77.8 %)	
Clock Drawing Test	6.4 + /- 2.9	5.3 + /- 2.9	0.022
Number of patients below cut-off	11 (34.4 %)	17 (62.9 %)	
EURO-D	3.0 + /- 2	3.4 + /- 1.9	
Number of patients above cut-off	12 (37.5 %)	10 (37 %)	
VIG-FRAIL	0.17 + /- 0.07	0.21 + /- 0.08	0.029
Number of patients above cut-off	16 (50 %)	21 (77.7 %)	
Medical History			
Hypertension	25 (78.1 %)	14 (51.9 %)	0.03
Diabetes	9 (28.1 %)	7 (25.9 %)	
Dyslipemia	19 (59.4 %)	16 (59.3 %)	
CSVD	20 (62.5 %)	21 (77.8 %)	
Atrophy	14 (43.8 %)	14 (51.9 %)	
Stroke	4 (12.5 %)	4 (14.8 %)	
Heart Attack	1 (3.1 %)	3 (11.1 %)	
Heart Failure	3 (9.4 %)	8 (29.6 %)	0.047

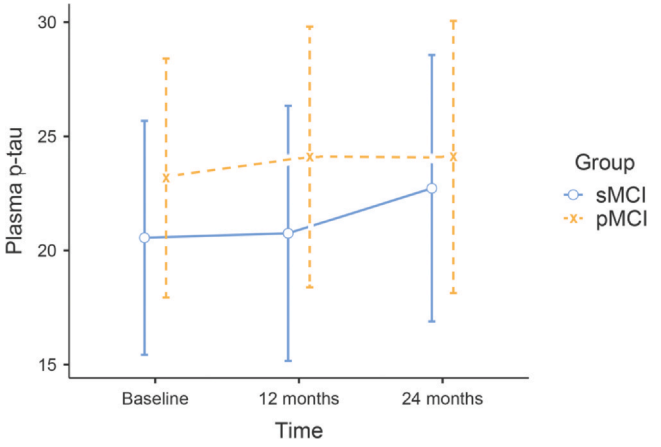

Fig. 1. Mean plasma p-tau 181 values with 95 % confidence intervals at baseline and two follow-up visits. sMCI = stable MCI. pMCI = progression MCI.

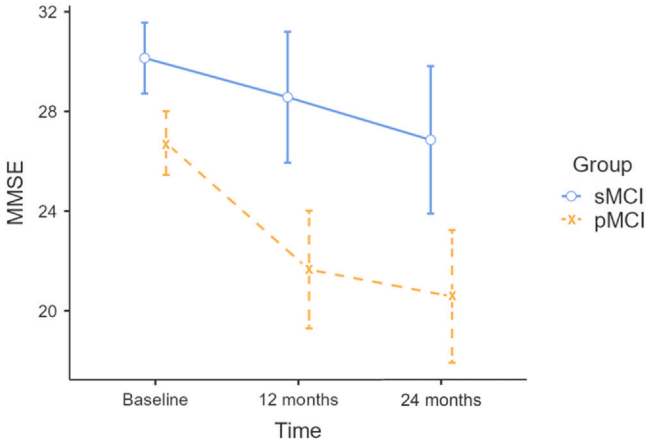

Fig. 2. Mean Mini-Mental State Examination (MMSE) scores with 95 % confidence intervals at baseline and two follow-up visits. sMCI = stable MCI. pMCI = progression MCI. MMSE (scores from 0 to 30).

discrete values of approximately 0.5, 1 or 1.5. years. Beyond validation, the DPM projects the evolution of the biomarker's trajectory up to 10 years beyond the third visit (T3).

Discussion

This article documents that 45.8 % of the oldest individuals with MCI in a cohort of geriatric outpatients progressed to dementia in two years. MMSE, Lawton's Index and the Clock Drawing Test, as well as the frailty index predicted the progress to dementia. Moreover, a combination of the MMSE, Lawton's Index and the Clock Drawing Test in a DPM model accurately estimated the time of progression to dementia. By contrast, plasma p-tau showed little prognostic value in this study.

These findings may be relevant for patients with this clinical phenotype, as the high rate of progression from MCI to dementia in our sample is remarkable, while other studies have found significantly lower rates. Specifically, the rate of progression to dementia was much lower in a representative population sample of individuals aged 65 or more years in our same city in Spain (ZARADEMP) [28]. Espinosa et al. reported a similar high rate of progression in a study (46.7 %), but this cohort was drawn from the highly specialised Alzheimer Centre, and the patients were substantially younger [29]. This team suggested that the risk of dementia increases when additional domains besides memory are impaired. This finding is echoed in the present study, where 90 % of the participants showed impairment in multiple cognitive domains, evidenced by abnormal scores in more than one cognitive test.

Interestingly, at baseline, the scores in both the MMSE and the Clock Drawing Test suggested that, compared with sMCI individuals, pMCI individuals had significantly worse cognitive state; after Bonferroni's post hoc in a repeated-measures ANOVA test, the differences were

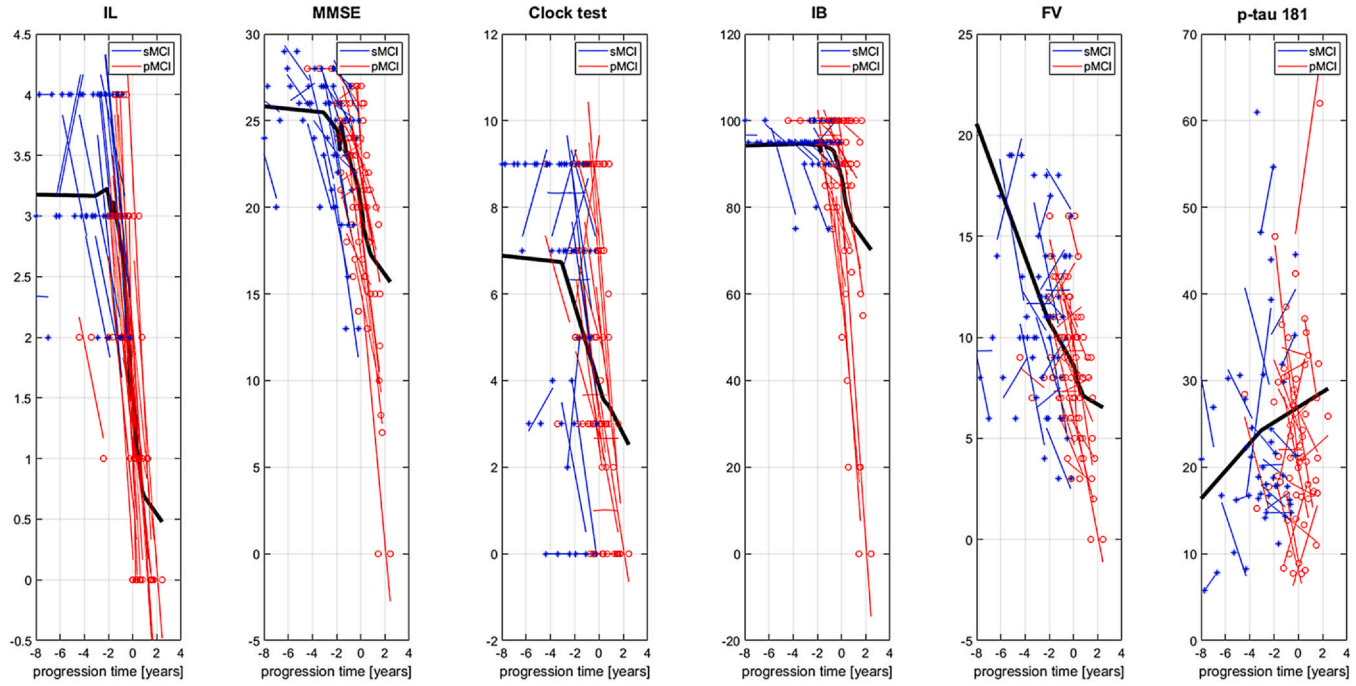

Fig. 3. Trajectories of the neuropsychological measures on the original scale and temporally aligned by the disease-progression model. IB = Barthel's Index, IL = Lawton's Index. MMSE = Mini-Mental State Examination. VF = Verbal fluency. Scale and score ranges: MMSE 0 – 30; Clock Drawing Test 0 – 9; semantic verbal fluency = number of animals named in one minute; Barthel Index 0 – 100; Lawton Index 0 – 4 (sex-unified).

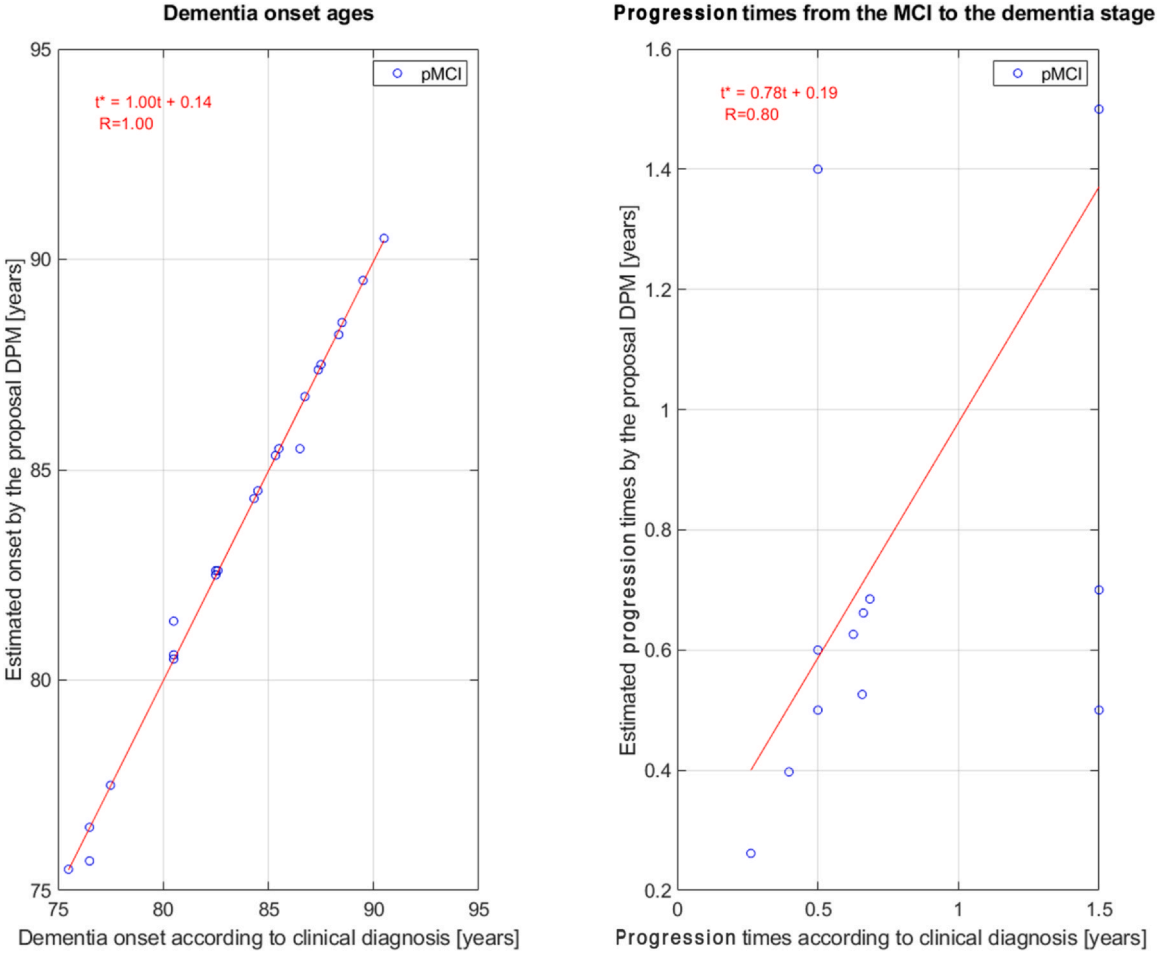

Fig. 4. Correlation between the age of the pMCI (progression MCI) patient at onset of dementia and the time estimated by disease-progression model (left side), and the estimated progression times (right side).

significant only in the MMSE. The utility of the MMSE has been highlighted in studies in representative population samples of the oldest old, with links to incident dementia [30] and mortality [31]. Specifically, Zuliani et al. [32] in 2021 reported that the MMSE was independently associated with progression to dementia in MCI patients. However, their sample was drawn from the specific setting of a memory clinic, from individuals 65 years old or older, with a mean age considerably younger than the individuals in our study. Moreover, the relevance of studying the MMSE more than once in periods of three or more years to gain validity, as we did, has been underscored in previous reports [33]. We found that three longitudinal MMSE scores retained significant differences across all three visits in repeated-measures ANOVA (Bonferroni's post hoc), confirming their strong prognostic value.

In terms of frailty, we found a high prevalence in our sample at baseline —50 % in sMCI individuals and 77.7 % among pMCI individuals—and the patients who would later progress to dementia had significantly higher VIG-FRAIL scores (*t*-test, p = 0.029). This is consistent with meta-analytic results that frail older adults were at higher risk of incident cognitive disorders than their non-frail peers. Even though the VIG-FRAIL scale is a useful clinical tool with documented predictive validity [25], it did not pass the sphericity test in this study, so repeated-measures ANOVA could not be applied. Even so, our data suggests that frailty is a factor that may influence patients with MCI and the progression to dementia. Moreover, the new concept of cognitive frailty could well describe our patients, offering a useful lens for these findings [34]. This emerging entity, defined by concurrent physical frailty and cognitive impairment that does not meet the threshold for dementia, has been associated with executive and attentional deficits consistent with a subcortical-frontal profile, distinct from the cortical patterns observed in Alzheimer's disease or in non-frail cognitively impaired individuals. Although diagnostic consensus is lacking, evidence suggests that the co-occurrence of physical and cognitive deficits confers a significantly elevated risk for progression to dementia. Given that most of our patients met frailty criteria and exhibited multi-domain cognitive dysfunction, particularly in executive function, it is plausible they fall within this phenotype.

Regarding depression, it is remarkable that it affected 37.5 % of sMCI patients and 37 % of pMCI patients. The role of depression as a risk factor for dementia has been described in several studies in the literature [4]. Therefore, we might expect that depression in this study would be a predictor of progression from MCI to dementia, but neither the results of regression models, nor the scores of the proposed natural history of the disease support this conjecture. While EURO-D is a robust test for detecting depression in older adults [21], we cannot rule out the possibility that specific symptoms of depression such as anhedonia might predict the progression [35], rather than a general screening.

Other neuropsychiatric symptoms, including the diagnosis of Mild Behavioral Impairment (MBI), were not analyzed here. The reported prevalence of MBI ranges from 29 % [36] to 85.3 % among patients with MCI [37], suggesting that different methodologies were used. MBI has been proposed as a phenotypic marker for individuals at risk of dementia [38] and as a risk factor for faster progression of cognitive decline [39]. Therefore, its omission from our model constitutes a limitation.

Sex was not a prognostic factor of progression to dementia in our sample. This sample was heterogeneous regarding aetiology, which may have influenced the results. While female sex is often cited as a risk factor for Alzheimer's disease, vascular dementia and mixed dementia are more frequent in men [40].

From a molecular perspective, prior work studying the plasma levels of p-tau 181 in older healthy individuals has produced inconsistent findings [41], [42], and there even seems to be an overlap of plasma p-tau levels between healthy individuals and Alzheimer's patients beyond 85 years [10]. In our study, no significant differences were observed at baseline between plasma p-tau 181 concentrations in sMCI and pMCI individuals. Moreover, baseline plasma p-tau-181 levels did not predict the progression from MCI to dementia. While the results of our study related to p-tau 181 were not positive, the fact that using a cut-off point of 23.2 pg/mL for plasma p-tau shows promise; the proportion of patients with levels above the cut-off was substantially higher among pMCI individuals (52 %) than in sMCI individuals (29 %). This cut-off was the mean in patients with Alzheimer's Disease reported in a relevant study [10].

Although blood biomarkers may be good hallmarks of the underlying pathology of dementia, they alone are unable to predict dementia progression in MCI. In large cohorts such as MEMENTO, it is suggested that p-tau181 alone has a moderate prognostic value in MCI patients (AUC 0.74), and it needs to be combined with other markers to become robust [43]. In other studies, predictive models achieve acceptable robustness once molecular markers are integrated with clinical parameters [44], New studies in larger samples of the oldest old may clarify the potential of p-tau 181 as a biomarker.

Based on the previous findings, our team proposed a disease-progression model that combined the Lawton Index, MMSE and Clock Drawing Test. The model achieved an AUC of 0.95 and produced a coherent timeline of decline from MCI to dementia. In this validation cohort, the age of progression to dementia that the model predicted had a strong linear relationship with the actual progression age of pMCI patients (Pearson correlation coefficient of 1). When estimating the onset of dementia in 0.5, 1 or 1.5 years after the first visit, the correlation declined (Pearson correlation coefficient of 0.8).

In connection with this, the work by Gazhi et al. [27] proposed a model of Alzheimer's disease progression, called Robust Parametric Disease Progression Modeling (RPDPM). This approach addresses potential curve-fitting problems such as outliers or missing data by combining different estimators and logistic functions across the data from ADNI. The data included measurements from volumetric magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF) and cognitive tests. Another study by Platero et al. [14] built a DPM based on 633 MCI patients and 145 dementia cases over 15 years in ADNI and showed that predictions of whether MCI will progress into dementia and timelines can be derived from neuropsychological data alone. In this study, 30 % of the MCI population converted to dementia within four years. It is difficult to compare the results of both studies with ours, as our cohort included older patients, which is characteristic of a geriatric setting. Moreover, our model relies on simpler clinical tests that are easy to administer in a primary care setting.

One of the strengths of our study is the longitudinal design, in a cohort in which most patients are over 80 ("oldest old"). These patients, characteristic of geriatric settings, are under-represented in the literature. Every patient underwent a full geriatric assessment that offers a multidimensional, holistic view of the individual in real clinical practice. All clinical tests can be completed in less than 45 min and could be administered even in a primary care setting. Multiple disease progression models have been created for Alzheimer's disease, but these models typically use magnetic resonance imaging, positron emission tomography, cerebrospinal fluid and blood biomarkers [9]. It is remarkable, having clinical implications, that a combination of clinical variables—the MMSE, the Clock Drawing Test and Lawton's Index—had the strongest predictive value in our study. On the other hand, the disease progression model (DPM) implemented in this study demonstrated the highest accuracy in estimating the time to dementia onset and enabled a detailed characterisation of the natural history of MCI progression and its specific chronological milestones.

Limitations, such as our small sample size, remain. A larger cohort, and thus a larger validation group, would help build a more robust DPM. There is also a high loss of patients to follow-up, close to 20 %. However, this is a familiar problem in cohort studies of the oldest old, often through death of study participants before outcomes can be measured [45]. In particular, the COVID-19 pandemic impacted this study since hospital outpatient clinic services were limited and

mortality and morbidity were higher in patients over 70. Data specific to subtypes of dementia could not be provided due to the heterogeneity of the sample. It is worth mentioning that a DPM and its RPDPM variant are novel statistical procedures that require further testing and validation in larger cohorts.

Conclusions

This study supports the idea that progression from MCI to dementia is particularly high among the oldest old in a geriatric clinical setting. The MMSE, Lawton's Index and the Clock Drawing Test combined estimated the time of progression to dementia in a DPM model, whereas plasma p-tau 181 added little predictive value in this study.

Funding sources

This work was funded by Instituto de Salud Carlos III and Fondo Europeo de Desarrollo Regional (FEDER) 'Una manera de hacer Europa' from the European Union, coordinated projects PI21/00372 and PI21/00286, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED, CB18/05/0037), Consolidated Groups from Gobierno de Aragón (A19_23R).

Nora Molina Torres has received the grant Apoyo Post-FSE I: Ayuda de Investigación Traslacional IIS Aragón, de la Convocatoria Intramural del IIS Aragón 2022.

Pol Andrés Benito has received support from the Instituto de Salud Carlos III (ISCIII), through the Sara Borrell contract (CD23/00097).

CRediT authorship contribution statement

Mónica Povedano: Methodology. **Mesa-Lampre Pilar:** Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Abadia-Morales Maria:** Methodology, Investigation. **Calvo Ana Cristina:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Antonio Lobo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **De-la-Cámara Concepción:** Validation, Supervision, Resources, Conceptualization. **Osta Rosario:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nora Molina-Torres:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carlos Platero:** Writing – review & editing, Validation, Software, Methodology, Investigation, Data curation. **Oscar P é rez-Berasategui:** Supervision, Resources, Methodology, Investigation. **Pol Andrés-Benito:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis.

Declaration of Competing Interest

Lobo, A reports a relationship with Eli Lilly, Bial, and Janssen that includes: consulting or advisory and travel reimbursement. Concepcion De-La-Camara reports a relationship with Almirall, Esteve, Eli Lilly, Astrazeneca, Lundbeck, Rovi, Novartis, Casen Recordati and Janssen-Cilag that includes: travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

I affirm that I have listed everyone who contributed significantly to this work.

Author's contributions

1. Molina Torres Nora: Geriatrics consultant in the Hospital Nuestra Señora de Gracia (Zaragoza, Spain). Post-FSE Grant by the Instituto de Investigación Sanitaria de Aragón (Zaragoza, Spain). Study design, ethics committee protocol, clinical interview design, patient recruitment, successive clinical interviews and clinical testing, analysis and interpretation of data, and preparation of manuscript.
2. Platero, Carlos: Professor in the Health Science Technology Group, Technical University of Madrid, Madrid, Spain. Design of a disease progression model, based on all the data. Analysis and interpretation of data, and preparation of manuscript.
3. Oscar: Geriatrics specialized nurse in the Hospital Nuestra Señora de Gracia (Zaragoza, Spain). Blood extraction of patients, clinical testing, patient recruitment.
4. Andrés-Benito Pol: Post-doctoral researcher - Sara Borrell. IRBLleida Institute of Biomedical Research. (Lleida, Spain). Single Molecule Array (SIMOA) analysis in blood samples. Analysis and interpretation of data, and preparation of manuscript.
5. Povedano Mónica: MD, Neurology consultant. Neurologic Diseases and Neurogenetics Group, Bellvitge Institute for Biomedical Research (IDIBELL), Barcelona (Spain). Analysis and interpretation of data, and preparation of manuscript.
6. Mesa-Lampré Pilar: MD, Geriatrics consultant in the Hospital Nuestra Señora de Gracia (Zaragoza, Spain). Acquisition of subjects, clinical support as consultant.
7. Abadía-Morales María: Medical graduate. Analysis and interpretation of data.
8. Calvo Ana-Cristina: Genetics professor in Department of Anatomy, Embryology and Animal Genetics, University of Zaragoza (Spain). Study design, ethics committee protocol, analysis and interpretation of data, preparation of manuscript
9. Lobo Antonio: MD; Emeritus Professor. Psychiatry consultant. Clinical interview design, ethics committee protocol, preparation of manuscript
10. De La Cámara-Izquierdo Concepción: MD; Psychiatry consultant in the Psychiatry Department, Hospital Universitario Lozano Blesa in Zaragoza (Spain). Ethics committee protocol redaction, clinical interview design.
11. Osta Rosario: Genetics full professor in Department of Anatomy, Embryology and Animal Genetics, University of Zaragoza (Spain). Study design, analysis and interpretation of data, and preparation of manuscript.

Financial conflict

C. De-la-Cámara has received financial support to attend scientific meetings from Almirall, Esteve, Eli Lilly, Astrazeneca, Lundbeck, Rovi, Novartis, Casen Recordati and Janssen-Cilag, outside the submitted work.

A. Lobo had a consultancy with Janssen and received financial support to attend scientific meetings from Eli Lilly, Bial, and Janssen. None of these activities were related to the current project.

For the remaining authors, none was declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.inpsyc.2025.100129.

References

[1] Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment – beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. J Intern Med 2004;256(3):240–6. https://doi.org/10.1111/j.1365-2796.2004.01380.x.

[2] Mateos R. Mild cognitive impairment: some steps forward. Int Psychogeriatr 1 De Oct De 2018;30(10):1427–9.

[3] Reppermund S, Brodaty H, Crawford JD, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. Psychol Med 2013;43(11):2437–45. https://doi.org/10.1017/S003329171200308X.
[4] Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, Diniz BS. Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis. Int J Geriat Psychiatry 2016;31(8):905–11. https://doi.org/10.1002/gps.4406.
[5] Borges MK, Canevelli M, Cesari M, Aprahamian I. Frailty as a predictor of cognitive disorders: a systematic review and Meta-Analysis. Front Med 2019;6 Accessed February 19, 2024 ⟨https://www.frontiersin.org/articles/10.3389/fmed.2019.00026⟩.
[6] Frank L, Lloyd A, Flynn JA, Kleinman L, Matza LS, Margolis MK, et al. Impact of cognitive impairment on mild dementia patients and mild cognitive impairment patients and their informants 1 de marzo de Int Psychogeriatr 2006;18(1):151–62.
[7] Forlenza OV, Diniz BS, Nunes PV, Memória CM, Yassuda MS, Gattaz WF. Diagnostic transitions in mild cognitive impairment subtypes 1 de diciembre de Int Psychogeriatr 2009;21(6):1088–95.
[8] Calvo-Perxas L, Osuna MT, Gich J, et al. Clinical and demographic characteristics of the cases of dementia diagnosed in the health district of girona throughout the period 2007-2010: data from the girona dementia registry (ReDeGi). Rev Neurol 2012;54(7):399–406.
[9] Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for alzheimer's disease in clinical practice and trials. Nat Aging 2023 May;3(5):506–19. https://doi.org/10.1038/s43587-023-00403-3. Epub 2023 May 18. PMID: 37202517; PMCID: PMC10979350.
[10] Hazan J, Alston D, Fox NC, Howard R. Practical application of alzheimer's disease neuroimaging initiative plasma P-tau181 reference data to support diagnosis of alzheimer's disease. Int J Geriat Psychiatry 2022;37(2):gps.5670. https://doi.org/10.1002/gps.5670.
[11] Nguyen AT, Lee GJ. Cognitive screening for early detection of mild cognitive impairment. Int Psychogeriatr September 1 2020;32(9):1015–7.
[12] McDonnell M, Dill L, Panos S, Amano S, Brown W, Giurgius S, et al. Verbal fluency as a screening tool for mild cognitive impairment 1 de septiembre de Int Psychogeriatr 2020;32(9):1055–62.
[13] Pinto TCC, Machado L, Bulgacov TM, et al. Is the Montreal cognitive assessment (MoCA) screening superior to the Mini-Mental state examination (MMSE) in the detection of mild cognitive impairment (MCI) and alzheimer's disease (AD) in the elderly? Int Psychogeriatr 2019;31(4):491–504. https://doi.org/10.1017/S1041610218001370.
[14] Platero C, Tohka J, Strange B. Estimating dementia onset: AT(N) profiles and predictive modeling inmild cognitive impairment patients (noviembre de). CAR 2023;20(11):778–90.
[15] United Nations. World Population Prospects 2019: Data Booklet. UN; 2019. doi:10.18356/3e9d869f-en.
[16] Dunne RA, Aarsland D, O'Brien JT, et al. Mild cognitive impairment: the manchester consensus. Age Ageing 2020;50(1):72–80. https://doi.org/10.1093/ageing/afaa228.
[17] Lobo A, Saz P, Marcos G, et al. Prevalence of dementia in a Southern european population in two different time periods: the ZARADEMP project. Acta Psychiatr Scand 2007;116(4):299–307. https://doi.org/10.1111/j.1600-0447.2007.01006.x.
[18] Crum RM, Folstein MF. Population-Based norms for the Mini-Mental state examination by age and educational level. JAMA 1993 May 12;269(18):2386–91.
[19] Tuokko H, Hadjistavropoulos T, Miller JA, Beattie BL. The clock test: a sensitive measure to differentiate normal elderly from those with alzheimer disease. J Am Geriatr Soc 1992;40(6):579–84. https://doi.org/10.1111/j.1532-5415.1992.tb02106.x.
[20] García-Herranz S, Díaz-Mardomingo MC, Venero C, Peraita H. Accuracy of verbal fluency tests in the discrimination of mild cognitive impairment and probable alzheimer's disease in older spanish monolingual individuals. Aging Neuropsychol Cogn 2020;27(6):826–40. https://doi.org/10.1080/13825585.2019.1698710.
[21] Larraga L, Saz P, Dewey ME, Marcos G, Lobo A. Validation of the spanish version of the EURO-D scale: an instrument for detecting depression in older people. Int J Geriatr Psychiatry 2006;21(12):1199–205. https://doi.org/10.1002/gps.1642.
[22] Jj Baztan, Perez Del Molino J, Alarcon T, San Cristobal E, Izquierdo G, Manzarbeitia J. Indice de barthel: instrumento válido para la valoración funcional de pacientes con enfermedad cerebrovascular. Rev Esp Geriatr Gerontol 1993;28(1):32–40.
[23] Lawton MP, Brody EM. Assessment of older people: Self-Maintaining and instrumental activities of daily living. Gerontologist 1969;9(3):179–86. (Autumn).
[24] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol Ser A 2001;56(3):M146–57. https://doi.org/10.1093/gerona/56.3.M146.
[25] Amblàs-Novellas J, Martori JC, Molist Brunet N, Oller R, Gómez-Batiste X, Espaulella Panicot J. Frail-VIG index: design and evaluation of a new frailty index based on the comprehensive geriatric assessment. Rev Esp Geriatr Gerontol 2017;52(3):119–27. https://doi.org/10.1016/j.regg.2016.09.003.
[26] International Classification of Diseases, Eleventh Revision (ICD-11), World Health Organization (WHO) 2019/2021 ⟨https://icd.who.int/browse11⟩.
[27] Ghazi MM, Nielsen M, Pai A, et al. Robust parametric modeling of alzheimer's disease progression. Neuroimage 2021;225:117460. https://doi.org/10.1016/j.neuroimage.2020.117460.
[28] Marcos G, Santabárbara J, Lopez-Anton R, et al. Conversion to dementia in mild cognitive impairment diagnosed with DSM -5 criteria and with petersen's criteria. Acta Psychiatr Scand 2016;133(5):378–85. https://doi.org/10.1111/acps.12543.
[29] Espinosa A, Alegret M, Valero S, et al. A longitudinal Follow-Up of 550 mild cognitive impairment patients: evidence for large conversion to dementia rates and detection of major risk factors involved. J Alzheimer's Dis 2013;34(3):769–80. https://doi.org/10.3233/JAD-122002.
[30] Santabárbara J, Lopez-Anton R, Gracia-García P, et al. Staging cognitive impairment and incidence of dementia. Epidemiol Psychiatr Sci 2015;25(6):562–72. https://doi.org/10.1017/S2045796015000918.
[31] Santabárbara J, Lopez-Anton R, Marcos G, et al. Degree of cognitive impairment and mortality: a 17-year follow-up in a community study. Epidemiol Psychiatr Sci 2014;24(6):503–11. https://doi.org/10.1017/S2045796014000390.
[32] Zuliani G, Polastri M, Romagnoli T, et al. Clinical and demographic parameters predict the progression from mild cognitive impairment to dementia in elderly patients. Aging Clin Exp Res 2021;33(7):1895–902. https://doi.org/10.1007/s40520-020-01697-8.
[33] Clark CM, Sheppard L, Fillenbaum GG, et al. Variability in annual Mini-Mental state examination score in patients with probable alzheimer disease: a clinical perspective of data from the consortium to establish a registry for alzheimer's disease. Arch Neurol 1999;56(7):857–62. https://doi.org/10.1001/archneur.56.7.857.
[34] Nader MM, Cosardereliogluc, Miao E, Whitson H, Xue QL, Grodstein F, et al. Navigating and diagnosing cognitive frailty in research and clinical domains (noviembre de). Nat Aging 2023;3(11):1325–33.
[35] Vaquero-Puyuelo D, De-la-Cámara C, Olaya B, et al. Anhedonia as a potential risk factor of alzheimer's disease in a Community-Dwelling elderly sample: results from the ZARADEMP project. Int J Environ Res Public Health 2021;18(4):1370. https://doi.org/10.3390/ijerph18041370.
[36] Rouse HJ, Small BJ, Schinka JA, Loewenstein DA, Duara R, Potter H. Mild behavioral impairment as a predictor of cognitive functioning in older adults 1 de marzo de Int Psychogeriatr 2021;33(3):285–93.
[37] Sheikh F, Ismail Z, Mortby ME, Barber P, Cieslak A, Fischer K, et al. Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden (febrero de). Int Psychogeriatr 2018;30(2):233–44.
[38] Gracia-García P, López-Antón R, de la Cámara C, Santabárbara J, Lobo E, Lobo A. Mild behavioral impairment in the general population aged 55+ and its association with incident dementia. Alzheimers Dement (Amst 2024;16(4):e12610.
[39] Mortby ME. Mild behavioral impairment: challenges facing a quickly developing evidence base 1 de marzo de Int Psychogeriatr 2021;33(3):209–12.
[40] Cao Q, Tan CC, Xu W, et al. The prevalence of dementia: a systematic review and Meta-Analysis. J Alzheimers Dis 2020;73(3):1157–66. https://doi.org/10.3233/JAD-191092.
[41] Chiu MJ, Fan LY, Chen TF, Chen YF, Chieh JJ, Horng HE. Plasma tau levels in cognitively normal Middle-Aged and older adults. Front Aging Neurosci 2017;9:51. https://doi.org/10.3389/fnagi.2017.00051.
[42] Kumar P, Vanbrabant J, Encarnacion M, et al. The effects of age and sex on plasma p-tau181 concentrations in alzheimer's disease. Alzheimer's Dement 2022;18(S5):e068159. https://doi.org/10.1002/alz.068159.
[43] Planche V, Bouteloup V, Pellegrin I, et al. Validity and performance of blood biomarkers for alzheimer disease to predict dementia risk in a large Clinic-Based cohort. Neurology 2023;100(5):e473–84. https://doi.org/10.1212/WNL.0000000000201479.
[44] Shen XN, Huang YY, Chen SD, et al. Plasma phosphorylated-tau181 as a predictive biomarker for alzheimer's amyloid, tau and FDG PET status. Transl Psychiatry 2021;11(1):1–10. https://doi.org/10.1038/s41398-021-01709-9.
[45] Kingston A, Jagger C. Review of methodologies of cohort studies of older people. Age Ageing 2018;47(2):215–9. https://doi.org/10.1093/ageing/afx183.