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Agreement between Cerebrospinal Fluid Biomarkers, Brain 18-Fluorodeoxyglucose PET, and Clinical Diagnosis in Older Adults with Cognitive Impairment

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ABSTRACT

Background: Clinical practice has advanced toward a combined diagnostic approach that involves clinical criteria and biological markers for Alzheimer's disease (AD) and other dementias. **Objective:** To establish the level of diagnostic agreement between an initial clinical diagnosis and cerebrospinal fluid (CSF) and [18F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET) biomarkers in a cohort of patients from a memory clinic. **Methods:** This is a observational, retrospective, cohort study conducted at an outpatient memory clinic. Between July 2018 and September 2023, data from adults' ≥ 55 years with a mild cognitive impairment or dementia diagnosis without etiological diagnosis were obtained, complemented with the evaluation of biomarkers in CSF and [18F] FDG-PET biomarker assessment were included. Kappa coefficients (κ) were used to establish the level of agreement between CSF and [18F] FDG-PET results. **Results:** Seventy-seven patients had an available [18F] FDG-PET scan, and 25 (32.5%) had both biomarkers. We observed a fair-to-moderate diagnostic agreement between patients' initial and their final diagnosis in the presence of CSF (κ = 0.233, 95% confidence interval [CI]: −0.099-0.566) and [18F] FDG-PET (κ = 0.451, 95% CI: 0.277-0.625, p < 0.001) results. The Kappa value for diagnostic concordance between [18F] FDG-PET and CSF to differentiate between AD and other dementias was 0.733 (95% CI: 0.425-1.000, p < 0.005). **Conclusion:** This study demonstrates good agreement between the CSF and FDG-PET biomarkers to differentiate AD from other dementias. (REV INVEST CLIN. 2024;76(5):230-7)

Keywords: 18F-Fluorodeoxyglucose-positron emission tomography. Cerebrospinal fluid. Cognitive impairment. Dementia. Alzheimer's disease. Brain aging.

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INTRODUCTION

With an aging population and increased life expectancy, the onset of neurodegenerative diseases such as Alzheimer's and other dementias is expected to increase dramatically by 2050[1]. In Mexico, these conditions are already associated with the highest rates of disability-adjusted life years[2]. Clinical practice has evolved toward a combined diagnostic approach that involves clinical criteria and biological markers[3]. International guidelines recommend the latter as an accurate way of detecting Alzheimer's disease (AD) and other dementias at different stages of the disease process[4-7].

To detect and quantify the accumulation of protein fragments such as amyloid-β (Aβ) and tau in the brain, biomarkers are also often used in cases of diagnostic doubt or atypical presentations[3,8]. With the use of molecular neuroimaging techniques such as positron emission tomography (PET) and specific radiotracers such as 18F-fluorodeoxyglucose ([18F] FDG-PET) or a cerebrospinal fluid (CSF) test, it has been recognized that biomarkers have a role in discriminating between AD and other dementias[9-11]. Given that authors have reported discrepancies between these biomarkers in almost 20% of cases, a need to confirm whether data provided by biomarkers is complementary to clinical diagnosis or equivalent still prevails[12,13].

The objective of this study was to establish concordance between a physician's initial clinical diagnosis and the further determination of CSF and brain [18F] FDG-PET in a cohort of patients from a memory clinic who, in their diagnostic approach, the criteria for the appropriate use of biomarkers.

MATERIALS AND METHODS

Participants

This observational, retrospective, and cohort study was conducted at a university-based outpatient memory clinic. After reviewing 147 clinical records, in the period between July 2018 and September 2023, we included adults 55 years or older with a diagnostic approach that comprised a mild cognitive impairment (MCI) or an all-cause dementia diagnosis, and who also met the criteria for an appropriate use of CSF (Aβ-42/tau proteins) and brain [18F] FDG-PET biomarker assessment were included. In this study, patients with uncontrolled comorbidities and psychiatric disorders such as delirium, treatment-resistant depression, and neurological diseases such as autoimmune encephalitis, rapidly progressive dementia, or space-occupying lesions of the central nervous system were excluded.

This protocol was approved by the local Ethics and Research Committees and received the following registration number: CONBIOETICA-09-CEI-O 11-20160627. All patients had previously signed an informed consent form.

Clinical diagnosis

A geriatric and neurology specialist performed a cognitive assessment during the patients' initial clinical evaluation. Respectively, criteria by Petersen and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), were used to allocate patients into three clinical diagnosis groups: MCI, AD, and other dementias (non-AD) clinical diagnosis groups[14,15]. Data, standardized by age and education, obtained from the Montreal Cognitive Assessment (MoCA)[16,17] and the Mini–Mental State Examination (MMSE) were also considered[18]. The Katz Index of Independence in Activities of Daily Living (ADL) and the Lawton Instrumental ADL Index were used to assess functional status. In the latter scales, lower scores indicated greater dependence[19,20].

Biomarkers were requested in two scenarios: an atypical clinical presentation or cases where a diagnostic doubt persisted despite a conventional clinical and neuroimaging characteristic (e.g., magnetic resonance imaging [MRI]) cognition-oriented evaluation. The maximum time CSF biomarkers and [18F] FDG-PET were obtained was 6 months from the initial evaluation. In this study, all patients underwent a second clinical evaluation at a maximum of 18 months between the first and second evaluations (average time in months, 9.6), in which the treating specialist established the final or probable diagnosis.

CSF biomarkers

Patients' CSF samples were obtained from patients through lumbar puncture performed by a neurologist

and/or geriatric neurology fellow. Samples were collected according to standard CSF analysis[21]. The specimen was sent for processing and enzyme-linked immunosorbent assay analysis to Labco Noûs laboratory[22], to determine pathological (Aβ-42) and neurodegeneration (p-Tau and t-Tau) CSF biomarkers. According to established cutoff values provided by the laboratory/manufacturer, a positive result for probable AD was considered when the values of Aβ-42 CSF, t-Tau, and p-Tau were < 550 pg/mL, > 375 pg/mL, and > 60 pg/mL, respectively, the sensitivity of 83%, specificity of 71%, positive predictive value (PPV) of 77%, and negative predictive value (NPV) of 79%; total tau protein has a sensitivity of 71%, specificity of 79%, PPV of 79%, and NPV of 70%; phosphorylated tau has 81%, 76%, 80%, and 78%, respectively[23].

Cerebral [18F] FDG-PET

According to institutional protocol, each patient underwent a brain [18F] FDG-PET procedure[24]. Image reconstruction was performed using Vue Point HD (VPHD), which is an ordered subset expectation maximization algorithm that can be combined with point spread function (PSF), correction (VPHD-S), and true-time of flight ability. The images were processed using three iterative reconstructions and 48 subsets, a 5 mm full width at half maximum PSF (SharpIR) modeling with a matrix size of 192 × 192; a field of view = 30 cm, and a voxel size of 3.3 mm/pixel.

Commercial software CortexID (GE® Healthcare) was used for brain [18F] FDG-PET analysis. Activity values were normalized using the pons as a reference region. Z-score 3D-stereotactic surface projection surface maps were created for each patient. These maps were obtained by comparing results with an external normative FDG-PET database containing data from healthy individuals.

A nuclear medicine specialist and a medical imaging specialist examined the images. An AD [18F] FDG-PET pattern was suggested in the presence of parietal, posterior cingulate, and precuneus cortex hypometabolism was considered a Z value in the ID cortex of −1 (unilateral or bilateral) with or without frontal involvement. A non-AD pattern was considered when observing an anterior or a non-specific distribution of hypometabolism. The sensitivity of [18F] FDG-PET has been reported to be 76% and specificity of 82%, with a PPV of 4.03 (95% CI: 2.97-5.47) and NPV of 0.34 (95% CI: 0.15-0.75)[25].

Statistical analysis

Categorical variables were described as frequencies and proportions, and the χ^2 test was used for comparison. According to distribution, quantitative variables were expressed as means and standard deviations (SD). The analysis of variance and Kruskal-Wallis tests were used accordingly for intergroup comparison. CSF, [18F] FDG-PET, and clinical test results were dichotomously categorized according to their compatibility with an AD or non-AD diagnostic profile. With a 95% confidence interval (CI), diagnostic concordance analysis among physicians' initial versus their final clinical diagnosis when considering a biomarker AD or non-AD pattern was calculated with Cohen's Kappa Index (κ). The diagnostic agreement was considered fair, moderate, good, and excellent when Kappa scores were 0.21-0.40, 0.41-0.60, 0.61-0.80, and > 0.81, respectively[26]. Aβ-42 and tau protein quantitative value distributions were represented in a scatter plot according to [18F] FDG-PET's hypometabolism pattern. Finally, the longitudinal change description after biomarker implementation was illustrated with a Sankey diagram. Associations were considered significant at the 0.05 level. Analyses were performed using the Statistical Package for the Social Sciences version 22 for Windows® (Chicago, IL, USA).

RESULTS

Patients' data were obtained from a total of 77 clinical records. Individuals had a mean age of 71 (SD ± 10.1) years, most (53.2%) were men, and the mean educational level was 11.7 (SD ± 5.6) years. All patients had an available [18F] FDG-PET scan, and 25 (32.5%) had both biomarkers. Table 1 shows patients' sociodemographic and clinical characteristics according to their initial cognitive diagnosis. Twenty-one patients (28%) were diagnosed with MCI, 33 (42.8%) with AD, and 23 (29.8%) with another dementia diagnosis. Depression was the most prevalent comorbidity in all groups. Patients diagnosed with AD or other presented lower MMSE and MoCA scores when compared to the MCI group.

Table 1. Patients' sociodemographic characteristics according to the initial diagnostic group

Variable	MCI (n = 21)	AD (n = 33)	Other dementias (n = 23)	p-value
Age, years mean (SD)	67.6 (11.5)	71.9 (65-79)	74.1 (67-79)	0.140
Male (%)	33.3	48.4	78.2	0.009
Education, years mean (SD)	12.2 (3.6)	11.4 (6.6)	10.7 (5.5)	0.932
Hypertension (%)	33.3	36.1	30.0	0.570
DM (%)	23.8	27.7	35.0	0.493
Depression (%)	47.6	44.4	35.0	0.835
CVD history (%)	14.2	13.8	20.0	0.974
MMSE, mean (IQR)	25.7 (1.5)	17.6 (6.4)	19.5 (7.5)	0.002
MOCA mean (IQR)	21.7 (3.9)	11.1 (6.8)	14.5 (8.2)	0.001

MCI: mild cognitive impairment, AD: Alzheimer's disease, DM: type 2 diabetes mellitus, IQR: interquartile range, CVD: cerebrovascular disease, MMSE: Mini–Mental State Examination, MoCA: Montreal cognitive assessment.

Table 2. Contingency tables representing the diagnostic concordance between initial clinical diagnosis, 18FDG-PET hypometabolism pattern, and CSF profile

	18-FDG PET (n = 77)				
Initial clinical diagnosis	Variable	AD pattern	Non-AD pattern	Subtotal	
	AD	23	20	43	k = 0.451* (95% CI: 0.277-0.625)
	Non-AD	2	32	34	
	Subtotal	25	52	77	
	CSF (n = 25)				
	Variable	AD pattern	Non-AD pattern	Subtotal	
	AD	6	8	14	k = 0.233 (95% CI: −0.099-0.566)
	Non-AD	2	9	11	
	Subtotal	8	17	25	

*p < 0.005. FDG: fluorodeoxyglucose, PET: positron emission tomography, AD: Alzheimer's disease.

We observed a fair-to-moderate diagnostic agreement between physicians' initial clinical and their final diagnosis in the presence of CSF (κ = 0.233, 95% CI: −0.099-0.566) and [18F] FDG-PET hypometabolism (κ = 0.451, 95% CI: 0.277-0.625, p < 0.001) results (Table 2). The Kappa value for diagnostic concordance between [18F] FDG-PET and CSF to differentiate between AD and other dementias was 0.733 (95% CI: 0.425-1.000, p < 0.005), which shows a good level of agreement (Table 3).

After analyzing CSF quantitative values and their distribution according to 18[F] FDG-PET metabolism, patients with a suggestive initial AD pattern presented lower Aβ-42 values and higher t-Tau (Fig. 1).

Clinical utility of 18[F] FDG-PET

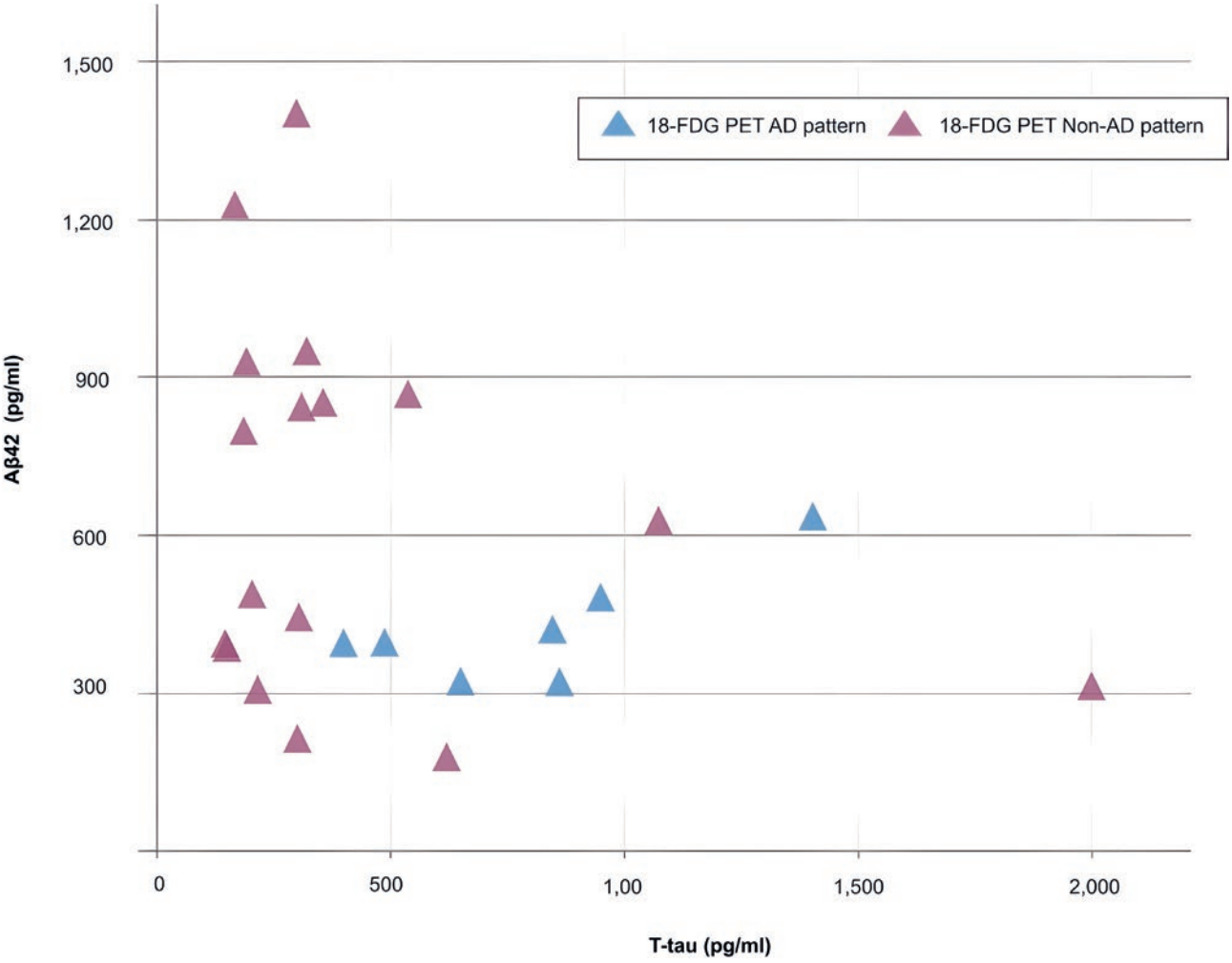
Almost half (46%) of physicians changed their initial versus their final diagnosis after 18[F] FDG-PET analyses (Fig. 2). The highest proportion of change was found in the MCI 11/21 (52%) and the other dementias 13/23 (56%) groups. In the MCI group, the diagnosis changed mainly to AD 5/11 (44.4%), followed by vascular cognitive impairment 2/11 (22.2%). On initial evaluation, the most frequently established diagnosis

Table 3. Contingency table representing the diagnostic concordance between CSF and 18 FDG-PET biomarkers (n = 25)

		18 FDG-PET			
	Variable	AD pattern	Other dementias pattern	Subtotal	
CSF	AD pattern	7	1	8	k = 0.733* (95% CI: 0.452-1.000)
	Other dementias pattern	2	15	17	
	Subtotal	9	16	25	

*p < 0.005. FDG: fluorodeoxyglucose, PET: positron emission tomography, AD: Alzheimer's disease, CSF: cerebrospinal fluid.

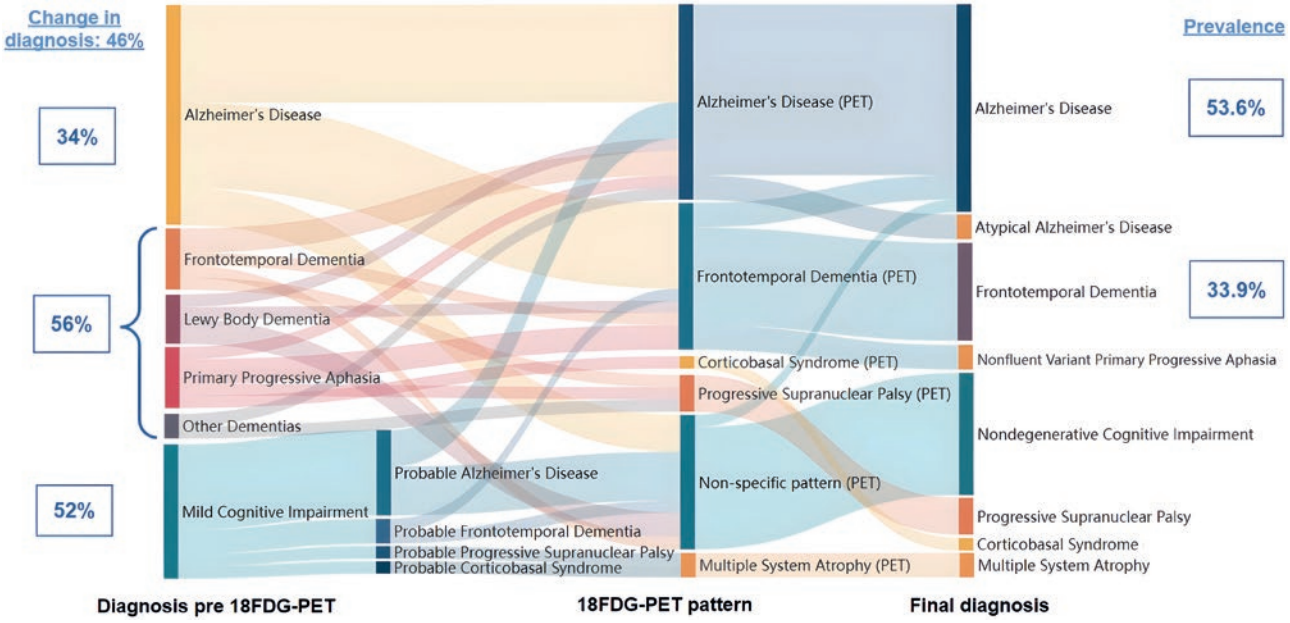
Figure 1. Scatter plot diagram of CSF Aβ-42 and t-Tau values according to FDG-PET hypometabolism pattern (n = 25).
Aβ-42: amyloid-β-42; t-Tau: total Tau; FDG-PET: fluorodeoxyglucose positron emission tomography; AD: Alzheimer's disease.



in the other dementias group was frontotemporal dementia (FTD), which was diagnosed in 9/23 (40.7%) of cases. Changes in the latter group occurred in 4/9 (45.4%) cases, mainly toward an AD diagnosis. The most prevalent final diagnosis was AD (53.6%), and the second most frequent was FTD (33.9%).

Figure 2. Change in diagnosis during follow-up after [18F] FDG-PET biomarker determination (n = 77).

AD: Alzheimer's disease, [18F] FDG-PET: 18-fluorodeoxyglucose-positron emission tomography; FTD: frontotemporal dementia; PPA: primary progressive aphasia; CBD: corticobasal degeneration; MSA: multiple system atrophy.



DISCUSSION

This study shows a fair-to-moderate agreement between the initial clinical diagnosis and CSF and [18F] FDG-PET's results in a cohort of patients with cognitive impairment. Moreover, a good diagnostic concordance was found between both pathophysiologic biomarkers to differentiate between AD and other dementias. An early and accurate diagnosis has therapeutic, ethical, and social implications in this context. A timely differential diagnosis of AD and other dementias is essential to determine specific disease-modifying treatments and selecting participants for relevant clinical trials[27].

Previous studies have reported an improvement in diagnostic certainty when combining biomarkers[28,29]. Shaffer et al. demonstrated that the classification error in patients who progressed from MCI to AD decreased from 27% to 9% when incorporating [18F] FDG-PET, CSF, and MRI evaluations[30]. Mónica Quispialaya et al. demonstrated that [18F] FDG-PET discriminated patients with an AD-positive CSF profile from patients with an AD-negative profile with a sensitivity and specificity > 80%[13]. Perini et al. reported a 31% change in diagnosis after FDG-PET determination among patients with an uncertain diagnosis[31].

In this study, as in other previously reported studies, an agreement of 88% between biomarkers to differentiate between AD and other dementias was found[13,32,33]. In 12% of our study population, we found a discrepancy between the patients' FDG-PET hypometabolism pattern and their CSF profile. In these patients, a positive biomarker was considered the reference for the final diagnosis. These cases could represent atypical presentations in which, even though a positive CSF-AD profile was present, the FDG-PET uptake pattern did not correspond to the involvement of typical areas. Therefore, mixed neurodegeneration etiologies could be considered.

Another important finding is that a change in diagnosis occurred in a high proportion of patients. Various studies have shown a 30-55% influence of biomarkers on the definitive diagnosis. To date, the diagnosis of AD is still based on a complete clinical evaluation, including neuropsychological testing and brain imaging as diagnostic tools. Within a selected clinical population, FDG-PET has a significant clinical impact, both in the early and differential diagnosis of uncertain dementia. FDG-PET provides significant incremental value in detecting AD and other dementias compared to a clinical diagnosis of uncertain dementia. When a physician must discriminate AD from non-AD dementia based on

clinical (non-biomarker-based) diagnostic criteria, 16% are misdiagnosed and 16% of patients have a doubtful diagnosis of AD versus non-AD[31,34,35].

In this study, the fair-moderate agreement between clinical diagnosis, CSF, and FDG-PET hypometabolism patterns could be attributed to an insufficient sample, heterogeneity of FDG-PET reference criteria, or an unsubstantiated initial diagnosis. In this study, in patients with an FDG-PET-positive AD pattern, Aβ values were lower whereas tau protein was higher.

The average time of clinical course before cognitive assessment was 3.9 years, which is longer than that reported in another study[36]. Regarding the severity of dementia at the time of care initiation, 40% of patients were diagnosed in a mild stage and 40% in a moderate stage of the disease. Patients with early-onset presentation had a longer time to diagnosis (4.9 years) than those with a late-onset presentation (3.2 years). The latter phenomenon could be related to the fact that early-onset cognitive impairment is usually accompanied by an atypical clinical presentation, which could delay a timely diagnostic approach. These findings are similar to those reported in a position document by a group of experts on dementia care in Latin America[37].

This study has some limitations. Time for biomarker determination took, in some patients, as long as 9 months, which is longer than what is reported in other studies[33,38] The latter could represent a source of bias when determining the agreement between biomarker availability and clinical diagnosis. Furthermore, the average time for patients to complete the study protocol and receive a final diagnosis was 7 months or more. One of the main causes of this delay was the loss of follow-up during the COVID-19 pandemic, which decreased the number of patients who underwent biomarker evaluation.

To our knowledge, this is the first study in Mexico that describes the agreement between AD and other dementia biomarkers. An agreement between biomarker determination, which further demonstrates their clinical usefulness, was found. Another of the study's strengths is the longitudinal follow-up, which made it possible to determine diagnostic trajectories and confirm the need for biomarker use in dementia's definitive diagnosis in cases of low clinical diagnostic certainty.

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