RESEARCH ARTICLE

Diagnosis, Assessment & Disease Monitoring

Diagnosing Alzheimer's disease: Which dementia screening test to use in elderly Puerto Ricans with mild cognitive impairment and early Alzheimer's disease?

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Abstract

Typically, Alzheimer's disease (AD) diagnosis is not made at its earliest period, for instance, at mild cognitive impairment (MCI) and early AD (E-AD). Our study aims to demonstrate a correlation between the screening tools, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Clinical Dementia Rating (CDR), and the biological biomarkers in the cerebrospinal fluid (CSF) amyloid beta 1-42 ($A\beta42$), phosphorylated tau (p-tau) proteins and total tau (t-tau)/$A\beta42$ ratio in Puerto Ricans > 55 years old with MCI and E-AD. We evaluated 30 participants, including demographics, memory scales, and CSF biomarkers. Twenty-eight CSF biomarkers ($A\beta42$, p-tau protein, and t-tau/$A\beta42$ ratio) were analyzed using the Meso Scale Discovery Platform (MSD). Associations between memory scales (MoCA, MMSE, CDR) and CSF markers were performed using Spearman rho correlation. Our study revealed a statistical association favoring a direct relationship between MMSE and MoCA with t-tau/$A\beta42$ ratio in CSF ($P = 0.022$, $P = 0.035$, respectively). We found a trend toward significance with an inverse relationship with MMSE and $A\beta42$ ($P = 0.069$) and a direct relationship with MMSE and p-tau ($P = 0.098$). MMSE and MoCA screening tests were identified with a statistically significant association with the CSF biomarkers, specifically t-tau/$A\beta42$ ratio, in elderly Puerto Ricans with MCI and E-AD. Puerto Ricans > 55 years old with MCI and E-AD could be screened confidently with MMSE and MoCA for a higher likelihood of earlier detection and, thus, initiation of disease-modifying treatment and prompt non-pharmacological interventions.

KEYWORDS
cerebrospinal fluid, Clinical Dementia Rating, early Alzheimer's disease, mild cognitive impairment, Mini-Mental State Examination, Montreal Cognitive Assessment

1 | INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia and the fourth cause of death in Puerto Rico.[1] As life expectancy increases, the number of people suffering from cognitive impairment will grow significantly, causing an increasing burden on society, the economy, and health care throughout the world. According to the US Census Bureau, the nation's older population, fueled by "baby boomers," will double in the next 20 years. By 2030, all baby boomers will be ≥ 65 years old, comprising nearly 20% of US residents. The Latino population, already the nation's largest minority group, will triple in size and will account for most of the nation's population growth from 2005 through 2050. Hispanics will comprise 29% of the US population in 2050, compared to 14% in 2005. Puerto Rico's 2020 census revealed that even though the population decreased by 11.8% compared to the 2010 census, an increase of 35% of 3,285,874 million people was evident in persons > 65 years old. This population group represents 731,899 people, comprising 22.3% of all Puerto Ricans.[2] All of the above represent upcoming challenges in developing a strategic plan to encompass people's needs and those of their caretakers.

Most of the time, AD diagnosis is not made at its earliest periods and prodromal stages, for instance, at mild cognitive impairment (MCI) and early AD (E-AD) stages. Commonly, the diagnosis of AD is made when significant impairment interferes with customary daily activities.[1] One of the most neuropathological hallmarks of AD is the "amyloid cascade hypothesis," in which amyloid protein precursor (APP) is cleaved mainly by β-secretase instead of α-secretase, leading to the amyloidogenic cascade and the formation of the insoluble Aβ 1-42 (Aβ42) fibrils in the brain inducing impairment of synaptic plasticity, especially in the hippocampal area.[3] The retention of Aβ42 plaque in the brain leads to a biochemical decrease in Aβ42 in the cerebrospinal fluid (CSF).[4] The second mechanism of AD is the dysregulation of tau protein phosphorylation, generating insoluble tau protein aggregates in the brain and CSF.[3] Tau protein is a microtubule-associated protein (MAP) with a native predominant unfolded conformation, which usually has a very low tendency toward aggregation and buildup in the intracellular or extracellular space.[5] Hyperphosphorylation and Aβ may potentiate a tendency of tau protein self-aggregation, forming a β-sheet–like structure, further leading to neurofibrillary tangles (NFTs).[5] Cellular internalization of abnormal tau occurs through the endocytic mechanism, which serves as a transcellular transfer, inducing the seeding of normal soluble tau and converting it to aggregated tau.[6] The load of these NFTs is associated with disease severity, and thus, in vivo studies with tau protein as a biomarker may advocate for accurate diagnostic and prognostic information. One of the most studied biomarkers is the CSF's phosphorylated tau (p-tau).[7] Our study evaluates p-tau and the ratio of total tau (t-tau)/Aβ42.

In Puerto Rico, AD remains mainly a clinical diagnosis, although neuroimaging techniques provide information regarding areas of focal or generalized atrophy, hypoperfusion, or hypometabolism. CSF biomarkers continue to be the most accurate test to support the diagnosis of AD, particularly useful in detecting preclinical stages, early onset dementia, and atypical presentations of AD.[8] However, they are only

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the current literature regarding the correlation between memory test scores and underlying Alzheimer's disease (AD) biological biomarkers in the cerebrospinal fluid (CSF) of patients with mild cognitive impairment (MCI) and early AD (E-AD). Cerebrospinal fluid (CSF) biomarkers as a tool for AD diagnosis are mainly used for research due to scarcity of standardization and limited data regarding predictability.

2. **Interpretation**: Our discovery led to the hypothesis that older Puerto Ricans with MCI and E-AD with a positive dementia screening tests would have pathological AD CSF biomarkers: low amyloid beta(Aβ), high p-tau proteins, and high tau/Aβ ratio.

3. **Future directions**: The article advises Mini-Mental State Examination and Montreal Cognitive Assessment as the screening tests to be used in elderly Puerto Ricans with MCI and E-AD based on the CSF correlation. Further understanding of (a) the validity of screening tests in Puerto Ricans, (b) diagnostic pathways in patients with E-AD and MCI, and (c) the role of screenings test is needed for the initiation of disease-modifying treatment.

routinely obtained for diagnosis in some memory clinics. In Puerto Rico, CSF analysis is used for research purposes rather than routinely by physicians due to limited access to lumbar puncture outpatient procedures, equipment, availability of experts, and specialized laboratories to analyze the samples.

Our pilot study aims to assess whether there is any correlation between the screening tools, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Clinical Dementia Rating (CDR), and the biological biomarkers in the CSF, Aβ42 (pg/mL), p-tau (pg/mL), and the ratio of t-tau/Aβ42 in Puerto Ricans > 55 years old with MCI and E-AD. To our knowledge, this is the first study to examine the correlation between memory test scores and underlying AD pathology measured by CSF biomarkers in elderly Puerto Ricans.

We hypothesized that Puerto Ricans 55 years old with MCI and E-AD with a positive screening test, including MMSE, MoCA, and CDR, will have a low Aβ42 (pg/mL), high p-tau (pg/mL) and high t-tau/Aβ42 ratio.

2 | METHODS

2.1 | Population sampling

The institutional review board (IRB) of the Medical Sciences Campus, University of Puerto Rico, approved this study on June 7, 2012. IRB approval number is 1330312.

We conducted a cross-sectional study based on a convenience sample recruiting process of 30 Puerto Rican patients. The participants were not randomized; they were subjectively selected after being evaluated in the Geriatrics and Neurology Clinics of the University of Puerto Rico, School of Medicine in San Juan, Puerto Rico, from January 2013 to November 2015. If the patient met the inclusion criteria, they were asked to participate in the study and recruited after consent. They must fulfill the inclusion criteria, as follows: male or female, >55 years old, of Puerto Rican ethnicity (parents should be Puerto Ricans), with MCI or E-AD defined by the National Institute on Aging (NIA) and the Alzheimer's Association (AA), and who consented to undergo lumbar puncture procedure for CSF analysis. CSF was obtained from 28 of 30 participants due to dry tap in two of them. Therefore, the final sample was a total of 28 participants. The cutoff values for participation were MMSE > 24, MoCA > 17, and CDR ≤ 0.5 plus the ability to consent to participate.[9,10] Subjects needed to have normal laboratory tests (practice parameters) of Vitamin B12, thyroid function tests, chemistry, cell blood count, and venereal disease research laboratory (VDRL). Participants were excluded from the study if: they refused lumbar puncture or blood tests; had been using anticoagulants; or had uncontrolled blood pressure (BP), active psychotic or depressive disorders, delirium, or schizophrenia and other neurologic, metabolic, or systemic conditions present at the time of the evaluation.

2.2 | Data recompilation

Participants were studied regarding demographics, education level, smoking prevalence, and past medical history of cardiovascular diseases. Clinical data included past and current medical history, as well as medications. Participants were also evaluated for depressive disorders, as participants underwent the Geriatric Depression Scale (GDS) short version.[11] The GDS short version is a 15-item scale in which the patient is interviewed for symptoms of depression. Physical examination included height, weight, body mass index (BMI), and waist circumference. Assessment for the presence of metabolic syndrome (MetS) was also performed. Each cardiometabolic parameter of the MetS was considered present if the participant used medication for that same underlying disease. If BMI was ≥ 30 kg/m^2, central obesity was assumed.[12]

Participants were clinically evaluated by a geriatrician and a neurologist to determine baseline cognitive disorders. According to the NIA-AA, MCI is defined as non-amnestic cognitive performance decline but able to perform daily life activities independently. E-AD has a clear functional impact on daily life, affecting mainly instrumental activities, and requiresthe patients to receive occasional assistance with daily life activities.[13] In our case, patients were categorized with MCI if the participant themselves or caretakers referred minimal impairment in functional activities with intact social or occupational functions, and did not meet dementia criteria on screening dementia tests.[14] E-AD was defined as having at least one positive screening dementia scale test, which included the MMSE,[15] MoCA,[16] and the CDR,[17] and/or

unable to perform occasional assistance performing activities of daily living (ADLs).

The MMSE is a 30-item scale that evaluates orientation, registration, attention, recall, and comprehension. A cut-off value of > 24 was used to define E-AD, while a cutoff of ≥ 28 was used to distinguish MCI from E-AD.[18] The MoCA test is a one-page 30-point test that also assesses several cognitive domains: orientation, short-term and working memory, visuospatial abilities, executive function, attention, concentration, and language. A cut-off value of > 17 was used to define E-AD, while a cutoff of ≥ 23 was used to distinguish MCI from E-AD.[18] The CDR is a six-category scale that evaluates cognitive and functional domains. A cutoff of ≤ 0.5 was determined to define MCI.[10]

2.3 | Laboratory analysis

A lumbar puncture for 20 mL of CSF collection was performed on each evaluated participant. Samples were sent to Massachusetts General Hospital for the analyses of CSF Aβ42 (pg/mL), p-tau (pg/mL), and t-tau/Aβ42 ratio, using the Meso Scale Discovery (MSD) Platform. MSD technology is a multiplexed immunoassay platform that allows for the quantification of proteins in a biological sample.[19] CSF analyses of Aβ42, p-tau, t-tau/Aβ42 ratio was performed using an enzyme-linked immunosorbent assay. Positivity criteria were: Aβ42 < 190 (pg/mL), p-tau > 470 (pg/mL), and t-tau/Aβ42 ratio > 2.75.[19]

2.4 | Statistical analysis

Associations between memory scales (MoCA, MMSE, CDR) and CSF markers were performed using Spearman's rho correlation. A p-value of less than 0.05 was considered statistically significant.

3 | RESULTS

Thirty participants were evaluated by obtaining a history of present illness (HPI) and performing a physical examination. The population was divided into 66.7% self-identified females and 33.3% self-identified males. The average age was 66.4 years old and 56.67% were ≥ 65 years. The average BMI was 27.2 kg/m^2 with 27% approximately meeting criteria for BMI ≥ 30 kg/m^2, and 83.3% not meeting the criteria for MetS (Table 1). Fifty-three percent of the participants were found to be hypertensive.

Our study revealed statistical association in favor of a positive direct relationship between MMSE and t-tau/Aβ42 ratio in CSF (P = 0.022, 95% confidence interval [CI] = [−0.69, −0.07]; Table 2C and Figure 1C). The correlation between the MMSE and CSF protein was statistically significant with t-tau/Aβ42 ratio (P = 0.022) meaning that the higher the MMSE score, the lower t-tau/Aβ42 ratio. We found a trend toward statistical significance with a direct relationship with MMSE and Aβ42 (P = 0.069); the higher the MMSE score, the higher the concentration of Aβ42 (Table 2A and Figure 1A). Also, there was

TABLE 1 Characteristics of participants with E-AD and MCI.

Variable	n	%
Age		
≥ 65	17	56.67
< 65	13	43.33
Sex		
Male	10	33.33
Female	20	66.67
Area of living		
No metropolitan area	17	56.67
Metropolitan area	13	43.33
Education level		
≥ High school	22	73.33
< High school	6	20.00
Unknown	2	6.67
BMI ≥30 (kg/m^2)		
No	22	73.33
Yes	8	26.67
Waist circumference (WC; women > 35 inches; men > 40 inches)		
Normal WC	21	70.00
High WC	8	26.67
Not measured	1	3.33
Antihypertensives agents		
No	14	46.67
Yes	16	53.33
Antihyperlipidemic agents		
Yes	12	40.00
No	18	60.00
Metabolic syndrome		
No	25	83.33
Yes	5	16.67

Abbreviations: BMI, body mass index; E-AD, early Alzheimer's disease; MCI, mild cognitive impairment.

a trend toward statistical significance with an inverse relationship between MMSE and p-tau (*P* = 0.098; Table 2B and Figure 1B). The higher the MMSE score, the less concentration of p-tau was observed.

MoCA and t-tau/Aβ42 ratio had a statistically significant relationship (*P* = 0.035; Table 3C and Figure 2C) meaning the higher the MoCA, the lower the t-tau/Aβ42 ratio. On the contrary, MoCA and Aβ42 (pg/mL; *P* = 0.103), and MoCA and p-tau (pg/mL; *P* = 0.243) had no statistical association seen in Table 3A and Figure 2A, Table 3B and Figure 2B, respectively.

Finally, there was no significant statistical association between CDR with CSF biomarkers including Aβ42 (pg/mL), p-tau (pg/mL), and t-tau/Aβ42 ratio in elderly Puerto Ricans evaluated in this pilot (Table 4 and Figure 3).

4 | DISCUSSION

In 2011, the NIA-AA guidelines included in the definition of AD the pathologic processes found in *post mortem* or in vivo markers and not only the clinical consequences or symptoms.[20] Then, in 2018, guidelines were updated by the NIA-AA to refine diagnosis criteria and encourage research on AD aiming for earlier disease detection, thus cast as a "Research Framework." In 2018, the diagnosis of AD not only includes the severity of the clinical impairment but also the biomarker profile: moving forward the hypothesis of AD as a "biological disease" established that AD should be defined biologically and not based on a clinical syndrome.[20] Especially in these so-called "preclinical stages" when there is uncertainty about the diagnosis, the NIA recommends the use of biomarkers in one of four possible forms: levels of the 42-amino-acid form of Aβ, levels of protein tau and p-tau in the CSF, positive amyloid positron emission tomography (PET) imaging, characteristic pattern of glucose hypometabolism in fluorodeoxyglucose PET (FDG-PET) or temporal lobe atrophy in brain magnetic resonance imaging (MRI) considered to be equivalent.[21]

This study aims to demonstrate correlations between the cognitive screening tools, including the MMSE, MoCA, and CDR, and the biological biomarkers in CSF Aβ42 (pg/mL), p-tau (pg/mL), and t-tau/Aβ42 ratio in Puerto Ricans > 55 years old with MCI and E-AD. Our study evaluates the combination of cognitive tests and compares them to the CSF biomarkers, looking for the most statistically significant correlation for this population. It is a pilot project that marks the beginning of a new era incorporating biomarkers in AD diagnosis. Puerto Ricans relay the diagnosis of AD mainly on screening tests because diagnostic testing with CSF biomarkers and amyloid PET scans are limited due to resources. Therefore, cognitive screening tools are used as diagnostic strategies until additional studies, such as brain MRI or FDG-PET scan, can be performed to support AD diagnosis. For this reason, inquiring about the correlation between CSF and cognitive screening tools is essential for our population.

The population in our study was mainly composed of females (66.67%) with a higher level of education (73.3%). The cutoff age was > 55 years old, with the intent to avoid the exclusion of MCI or E-AD, which can be seen in younger participants. We evaluated three cognitive tests: MMSE, MoCA, and CDR. The correlation between the MMSE and CSF protein was statistically significant, with a lower t-tau/Aβ42 ratio related to a higher MMSE score. In addition, the MoCA test also had a statistically significant correlation with the CSF biomarker, specifically t-tau/Aβ42 ratio (*P* = 0.035). Our findings fit with prior studies which have shown that CSF biomarker ratios were superior to individual CSF biomarkers when compared to PET imaging analogs. Using ratios appears to be more reliable because it mitigates the effect of incorrect handling and disruption of CSF and compensates for individual differences in APP, leading to a falsely low Aβ42.[22] On the contrary to our analysis, other studies have reported that Aβ42 is the best CSF biomarker correlating with MoCA as a tool to predict the conversion of MCI to dementia, especially in highly educated subjects.[23] This divergence might be secondary to discrepancies in immunoassay method or limited replicability of Aβ42 in Puerto Rican MCI patients.

TABLE 2 Spearman correlation results among MMSE and CSF biomarkers, including (A) Aβ42 (pg/mL), (B) p-tau (pg/mL), and (C) t-tau/Aβ42 ratio.

Combination	r	95% CI	n	P
A. MMSE and Aβ42 (pg/mL)	0.35	[−0.03, 0.64]	28	0.069
B. MMSE and p-tau (pg/mL)	−0.32	[−0.62, 0.06]	28	0.098
C. MMSE and t-tau/Aβ42 ratio	−0.43	[−0.69, −0.07]	28	0.022

Abbreviations: Aβ, amyloid beta; CI, confidence interval; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; t-tau, total tau.
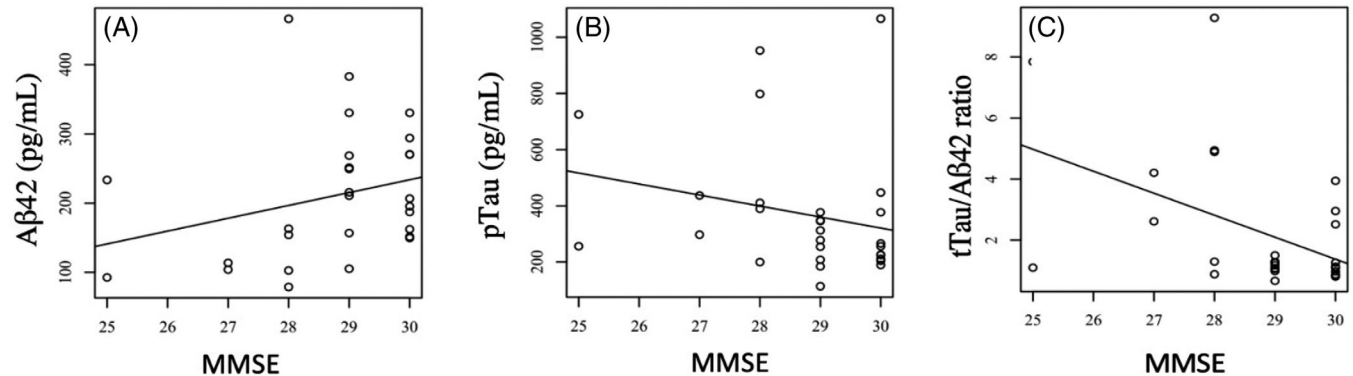
FIGURE 1 Spearman correlation between MMSE and CSF biomarkers and CSF biomarkers. A, Direct correlation between MMSE and Aβ42 (pg/mL; $P = 0.069$). B, Inversely proportional correlation between MMSE and p-tau (pg/mL; $P = 0.098$). C, Inversely proportional correlation between MMSE and t-tau/Aβ42 ratio ($P = 0.022$). Statistical significance was found in the correlation between MMSE and t-tau/Aβ42 ratio. Aβ, amyloid beta; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; t-tau, total tau

TABLE 3 Spearman correlation results among MoCA and (A) Aβ42 (pg/mL), (B) p-tau (pg/mL), and (C) t-tau/Aβ42 ratio.

Combination	r	95% CI	n	P
A. MoCA and Aβ42 (pg/mL)	0.31	[−0.07, 0.62]	28	0.103
B. MoCA and p-tau (pg/mL)	−0.23	[−0.55, 0.16]	28	0.243
C. MoCA and t-tau/Aβ42 ratio	−0.40	[−0.67, −0.03]	28	0.035

Abbreviations: Aβ, amyloid beta; CI, confidence interval; CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment; p-tau, phosphorylated tau; t-tau, total tau.
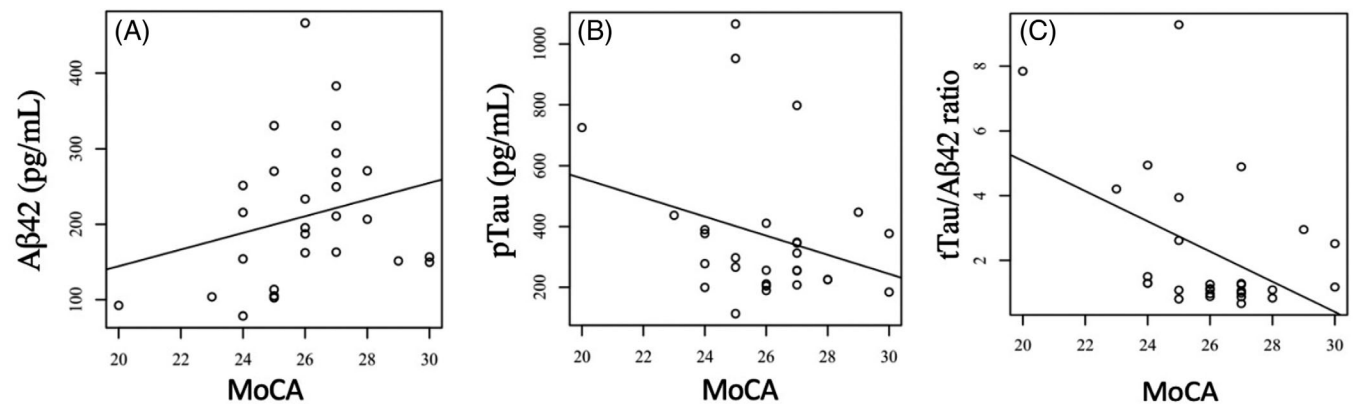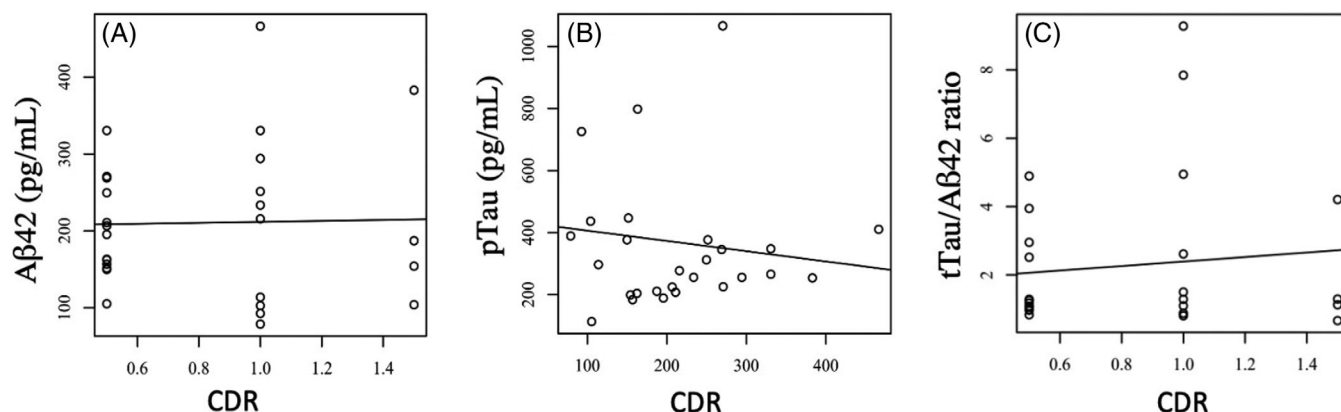

FIGURE 2 Spearman correlation between MoCA and CSF biomarkers. A, Direct correlation between MoCA and Aβ42 (pg/mL; $P = 0.103$). B, Inversely proportional correlation between MoCA and p-tau (pg/mL; $P = 0.243$). C, Inversely proportional correlation between MMSE and t-tau/Aβ42 ratio ($P = 0.035$). Statistical significance was found in the correlation between MoCA and t-tau/Aβ42 ratio. Aβ, amyloid beta; CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment; p-tau, phosphorylated tau; t-tau, total tau

TABLE 4 Spearman correlation results among CDR and (A) Aβ42 (pg/mL), (B) p-tau (pg/mL), and (C) t-tau/Aβ42 ratio.

Combination	r	95% CI	n	P
A. CDR and Aβ42 (pg/mL)	−0.06	[−0.43, 0.32]	28	0.745
B. CDR and p-tau (pg/mL)	0.09	[−0.29, 0.45]	28	0.639
C, CDR and t-tau/Aβ42 ratio	0.07	[−0.31, 0.44]	28	0.708

Abbreviations: Aβ, amyloid beta; CDR, Clinical Dementia Rating; CI, confidence interval; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau.

FIGURE 3 Spearman correlation between CDR and CSF components found no statistically significant association. A, Correlation between CDR and Aβ42 (pg/mL; $P = 0.745$). B, Correlation between CDR and p-tau (pg/mL; $P = 0.639$) and (C) CDR and t-tau/Aβ42 ratio ($P = 0.708$). Aβ, amyloid beta; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; t-tau, total tau

A pattern toward statistical significance was seen with higher Aβ42, lower p-tau, and higher MMSE score. This finding was anticipated because Aβ42 is expected to be at low concentrations in CSF due to cortical amyloid deposition. At the same time, there is a high t-tau due to neuronal loss in CSF in patients who have dementia.[24] A higher MMSE score in the screening test suggests no dementia, and thus the correlation of low p-tau proteins and high Aβ42 on the CSF. On the contrary, the CDR scale showed no statistical significance with CSF biomarkers. According to Álvarez-Sanchez et al., CDR only had a positive correlation with neurofilament light chain (NfL), a non-specific AD biomarker molecule which can also be found in the CSF; nonetheless no other correlation between CSF biomarkers was evidenced.[25] Although these biomarkers represent the pathological hallmark of AD, there are no concrete guidelines on how to interpret or apply CFS biomarkers in patients with dementia.[21] It is for this reason that, as of this day, CFS biomarkers are almost exclusively used in the research setting rather than in the clinical one despite their high diagnostic accuracy with a sensitivity and a specificity of 85% to 90%, respectively in patients with MCI.[24]

Using these biomarkers in the primary clinical setting for screening and/or diagnosing early AD is challenging because it is not cost effective and is an invasive procedure. Nonetheless, a correlation between cognitive performance and CSF protein biomarkers has been reported, especially in patients with MCI.[26] Radanovic et al. tested the correlation of CSF biomarkers and MMSE in 208 subjects and found lower levels of Aβ42 ($P = 0.030$) and higher levels of t-tau ($P = 0.036$) comparing control and MCI.[26] Even more, studies have shown decreased cognitive performance in patients with MCI despite treatment with acetylcholinesterase inhibitors when found with lower levels of Aβ42 and higher t-tau.[27] Ideally, the combination of CSF biomarkers analysis, brain functional imaging, and cognitive screening tests would provide more information for an accurate diagnosis. Unfortunately, the feasibility and access of these tests are not realistic in the Puerto Rican population. That is why we suggest cost-effective alternatives that indirectly provide pertinent information identifying which cognitive screening tests, compared to its CSF analog, have the highest sensitivity to making an early diagnosis.

Historically, cognitive assessment was mainly designed for the English-speaking and White populations.[28] Nonetheless, our pilot study showed a statistically significant correlation between cognitive tests with positive screening for E-AD, mainly with MMSE and MoCA tests, and CSF biomarkers in a Hispanic population. These results stand by the meta-analysis by Arévalo et al., which revealed an excellent diagnostic accuracy of the MMSE for Hispanics and Latinos in the United States, reaching sensitivities from 75% to 100%.[28] This study is clinically relevant because, based on this pilot study, we recommend using the MMSE and the MoCA tests in combination in Puerto Ricans > 55 years old to screen for dementia. In particular, we use the version validated in Puerto Rico by Bird et al.[29] In Latinos, dementia diagnosis and treatment could be delayed nearly 5 years, mainly

due to personal belief, economic status, and language proficiency.[30] Through this study, it is evidenced that patients screening positive in the MMSE, for even MCI, may have changes in CSF biomarkers consistent with dementia disease. Patients who score ≤ 27 are 10 times more likely to have dementia compared to patients who score higher.[31] This groundbreaking information will encourage primary care physicians and geriatricians to be aware of underrecognized dementia and consider the importance of early diagnosis (mostly at preclinical stages) that will lead to prompt therapeutic interventions.

Some of the limitations of our study include a limited sample size, as we observed that people in Puerto Rico resist being evaluated routinely with a lumbar puncture. The authors did not look for the influence of age, sex, or BMI as possible confounding variables due to the small population and lack of randomization. Future studies comparing CSF biomarkers of participants with advanced AD to our population (E-AD and MCI), stipulated as the control group, will contribute to assessing a direct or inverse proportional relationship with disease severity and CSF biomarkers. This objective will promote participant recruitment and expansion of population size. Also, a 10- to 15-year follow-up screening test for cognitive impairment of these participants is under consideration. The strength of this study is that it has served as a stepping stone for future studies because analyzing CSF biomarkers and its correlation with cognitive screening tests in a Puerto Rican population offers cultural specificity, potentially exposing unique factors influencing cognitive health. This study provided insight into population-specific variations, contributing to the study of targeted health-care strategies for this demographic.

5 | CONCLUSION

The MMSE and the MoCA were the dementia screening tests consistently identifying a statistical significance, specifically with the t-tau/Aβ42 ratio associated with the CSF AD biomarkers in elderly Puerto Ricans with MCI and E-AD. Consequently, Puerto Ricans > 55 years old who screened positive in the MMSE, even for MCI, may have changes in CSF biomarkers consistent with AD. Our findings support that Puerto Ricans > 55 years old will benefit from being screened for MCI and E-AD using the MMSE and MoCA. According to the Facts and Figures published by the Alzheimer's Association in 2019, despite that 82% of seniors expressed that having their memory examined is essential, only 16% received regular cognitive assessment.[32] Hence, the importance of studies like ours, which can encourage physicians to screen their patients for a higher likelihood of prompt detection and, thus, early initiation of disease-modifying treatment. Cognitive screening tests, including the MMSE, MoCA, and CDR, are currently used in these individuals during the initial clinical work-up of dementia. Due to the limited access to "advanced" testing such as functional imaging, CSF biomarkers, and biomarkers (amyloid/tau) PET scans, we rely on screening tests, clinical presentation, and neuroimaging to diagnose precisely. Evaluating whether there is any correlation between CSF biomarkers and cognitive screening tests is of utmost importance, as it provides a description of the most sensitive screening tests in the Puerto Rican population.

CONSENT STATEMENT

All human subjects provided informed consent and voluntarily agreed to take part in this study.

CONFLICTS OF INTEREST STATEMENT

The authors of this study have no conflict of interest to report. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.