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RESEARCH ARTICLE

Translating NIA-AA criteria into usual practice: Report from the ReDeMa Project

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Abstract

INTRODUCTION: Biomarker-informed criteria were proposed for the diagnosis of Alzheimer's disease (AD) by the National Institute on Aging and the Alzheimer's Association (NIA-AA) in 2011; however, the adequacy of this criteria has not been sufficiently evaluated.

METHODS: ReDeMa (*Red de Demencias de Madrid*) is a regional cohort of patients attending memory and neurology clinics. Core cerebrospinal fluid biomarkers were obtained, NIA-AA diagnostic criteria were considered, and changes in diagnosis and management were evaluated.

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RESULTS: A total of 233 patients were analyzed (mean age 70 years, 50% women, 73% AD). The diagnostic language was modified significantly, with a majority assumption of NIA-AA definitions (69%). Confidence in diagnosis increased from 70% to 92% ($p < 0.0005$) and management was changed in 71% of patient/caregivers. The influence of neurologist's age or expertise on study results was minimal.

DISCUSSION: The NIA-AA criteria are adequate and utile for usual practice in memory and neurology clinics, improving diagnostic confidence and significantly modifying patient management.

KEYWORDS

Alzheimer's disease, CSF biomarkers, clinical impact, NIA-AA diagnostic criteria, diagnostic confidence

HIGHLIGHTS

- Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers increase diagnostic certainty regardless of the neurologist.
- AD CSF biomarkers lead to changes in disease management .
- Biomarker-enriched, 2011 NIA-AA diagnostic criteria are adequate for usual practice.

1 | BACKGROUND

There are nowadays ≈50 million people living with dementia worldwide, mostly due to Alzheimer's disease (AD), and this number is expected to triple by 2050.[1,2] Alzheimer's dementia is typically preceded by a clinical phase of mild cognitive symptoms with none/minimal functional deterioration, which was labeled as mild cognitive impairment (MCI).[3,4] As corresponds to an etiologically heterogeneous syndrome,[5] not every patient with MCI will progress to dementia,[6] which highlights the challenge and importance of early AD detection. The earlier AD is diagnosed, the sooner therapeutic actions can be implemented to prevent neurodegeneration, slow the course of the disease, and keep the patient at the initial clinical stages, that is, those of full autonomy or just mild functional dependence.

Although the definitive diagnosis of AD requires pathological confirmation, early identification has greatly improved in recent years thanks to biomarkers.[7] In particular, the coexistence of low 42/40 amino acid amyloid beta (Aβ) ratio (Aβ_{42}/Aβ_{40}), high phosphorylated tau (p-tau), and high total tau (t-tau) in cerebrospinal fluid (CSF), which represent core AD neuropathological changes,[8,9] is especially useful to predict dementia in people with MCI of unknown etiology.[10] These core biomarkers have replaced the neuropathological study in the research setting,[11,12] but there is no consensus about their use in clinical practice. European guidelines recommended CSF biomarkers in cases of diagnostic uncertainty, atypical presentations, or early onset dementia (i.e., symptom initiation before 65 years).[13–15] However, in the real world, patients present with a high variety of cognitive symptoms, comorbidities, and age, usually adding uncertainty to the etiological diagnosis. In this context, the contribution of CSF biomarkers could be especially valuable, helping clinicians to establish diagnosis and initiate treatment.[16,17]

More than two decades after publication of the seminal AD diagnostic criteria,[18] experts from the National Institute on Aging and the Alzheimer's Association (NIA-AA) initiated a revision process that incorporated atypical clinical manifestations and biomarker information.[19] As a result, diagnostic labels representing different levels of AD pathophysiological likelihood were created to be used in research and academic settings.[20,21] At that time, a lack of standardized procedures for biomarker determination, and of universal cutoff points, was recognized as an obstacle to the application of the new criteria in clinical practice. Nowadays these limitations have been overcome[22,23] and CSF biomarkers are used increasingly, but the evaluation of their usefulness in the usual practice, along with the validation of the NIA-AA criteria, is still pending.

The aim of the study was to assess the impact of Alzheimer's CSF core biomarkers in the diagnosis and treatment of patients with cognitive symptoms, in usual practice conditions. The NIA-AA criteria were introduced to guide the diagnostic process, and their adequacy and usefulness were evaluated. As a secondary objective, the influence of clinician characteristics on the study results was explored.

2 | METHODS

2.1 | Setting and study design

ReDeMa (*Red de Demencias de Madrid*) is a multicenter research group initiated in 2018, formed by professionals of secondary and tertiary

neurology centers in the metropolitan area of Madrid, Spain. The area of influence of the ReDeMa group covers a population of 2.5 million people (38% of the total population living in the community of Madrid: 6.6 million)[24]). The main aim of the initial ReDeMa project was to establish a core protocol for approaching patients presenting with cognitive symptoms in specialized setting, including CSF biomarker determination. Patients were enrolled during usual practice, under a multicentric, observational, prospective design. Every center followed standardized procedures for the collection of demographics, as well as clinical, neuroimaging, blood, and CSF variables. Biological samples (i.e., blood and CSF) were sent to the biobank of the coordinating center (*Hospital General Universitario Gregorio Marañón* [HGUGM]) and CSF core AD biomarkers were analyzed centrally. A study manual was elaborated, investigator meetings were held, and individual feedback was provided to achieve homogeneous and reliable data collection.

2.2 | Participants

The included participants attended neurology or memory clinics due to cognitive symptoms. All participants provided written informed consent to participate in the study and to donate blood and CSF samples for future studies. The study was approved by the HGUGM Ethics Committee. All the participants fulfilled inclusion criteria and did not fulfill any exclusion criteria.

Inclusion criterion were as follows: (1) patients between 50 and 85 years of age; (2) cognitive or behavioral complaints for at least 6 months; (3) reasonable suspicion of neurodegenerative etiology, as per the clinician's judgment; (4) no other priority medical or social interventions; (5) neuroimaging (cranial magnetic resonance imaging [MRI] or computerized tomography [CT]) conducted in the last year, not contraindicating lumbar puncture; (6) follow-up perspective of at least 1 year; (7) a caregiver who would accompany the patient to lumbar puncture and medical visits, and (8) the patient was capable of understanding and signing informed consent.

Exclusion criteria were as follows: (1) intellectual disability; (2) major depression, schizophrenia, obsessive compulsive disorder, or bipolar disorder[25]; (3) substance-related and addictive disorders[25] ; and (4) lumbar puncture contraindication (<50,000 platelet count, other bleeding disorder, anticoagulant therapy, etc.).

2.3 | Demographic and clinical variables

A common protocol was administered to all patients at the initial and annual follow-up visits. At the initial visit, demographic and clinical variables were collected, including age, sex, education degree, comorbidities, medications, and family history of dementia. Cognitive complaints (type and duration) and neuropsychiatric symptoms[26] were obtained through semi-structured interview with the patient and informant. A systematic assessment of the different cognitive domains was conducted using Spanish-validated versions of the following brief cognitive tests (BCTs): Mini-Mental State Examination (MMSE),[27] semantic fluency task (number of animals in 1 min), Clock Drawing Test,[28] and Memory Impairment Screen (MIS).[29] To characterize functional alterations in instrumental activities of daily living the 11-item version of the Functional Activity Questionnaire (FAQ)[30] and the Clinical Dementia Rating (CDR) scale[31] were used. Depressive symptoms were assessed using the 15-item version of the Geriatric Depression Scale (GDS).[32]

RESEARCH IN CONTEXT

Systematic Review: The authors reviewed the literature mainly through PubMed, Google Scholar, and bibliographies of relevant papers. Core Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers are used increasingly in clinical practice, and their utility in terms of diagnosis and treatment has been reported. The National Institute on Aging and the Alzheimer's Association (NIA-AA) established AD diagnostic criteria in 2011, based on clinical features and biomarkers. Although frequently referred, very few studies have evaluated the suitability of these criteria for clinical practice, nor their impact on the management of the disease.
Interpretation: Our findings demonstrate that the NIA-AA criteria can be recommended for use in neurology and memory clinics. They confirm and homogenize AD etiological diagnosis, and improve diagnostic confidence, regardless of the clinician's level of expertise.
Future Directions: The 2011 NIA-AA criteria are expected to be updated in the near future, possibly including plasma biomarkers. The ReDeMa cohort will help to validate blood biomarkers in a real-world scenario. Access to accurate and timely diagnosis of AD should be a reality for everybody in the forthcoming years.

2.4 | Blood tests

A complete blood count was obtained for all patients, as well as levels of blood glucose, creatinine, ion, transaminase, lipid, vitamin B12, folate, and thyroid-stimulating hormone, to rule out secondary causes of dementia. Other analytical determinations (e.g., serological tests) were conducted if necessary, depending on the patient's characteristics and the etiological suspicion.

2.5 | Neuroimaging

Every patient underwent a cranial neuroimaging study in the year prior to the first visit at the recruiting center. Cranial CT or, preferably, MRI study, was permitted. Independent neuroradiologists evaluated white matter lesions and mesial temporal atrophy using Wahlund[33]

and Scheltens[34] scales, respectively. Additional neuroimaging studies, for example, 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET), single photon emission computed tomography (SPECT), or dopamine transporter scan were conducted, if needed.

2.6 | CSF biomarkers

Lumbar punction was conducted between 9:00 a.m. and 12:00 p.m. to obtain CSF via gravity drip, at the recruiting centers. After obtaining 0.5 mL for basic study, 5 mL of CSF was collected in polypropylene tubes (Sarstedt, Ref# 62.610.201) and centrifuged (2000 *g* x 10 min) at room temperature within the first 2 h after acquisition. Volumes of 0.5 mL of CSF were aliquoted into polypropylene vials (Sarstedt, Ref# 72.694.007) and stored at −80°C until analysis. The storage centers processed and stored their CSF samples, whereas the non-storage centers sent the samples to the coordinating center for processing and storage immediately after extraction.

All the CSF biomarker tests were conducted in the HGUGM Laboratory. Samples were analyzed for total tau, p-tau181, Aβ_{42}, and Aβ_{40}) using the Lumipulse G600II automated platform (Fujirebio Europe, Ghent, Belgium) and following the manufacturer´s instructions. For the day of the analysis, samples were thawed at room temperature and vortexed for 5–10 s. Only aliquots that had not been thawed previously were used. Each patient's four study biomarkers were measured using the same aliquot, in the same run. Quality control testing was performed at the beginning of each set of biomarker determination to ensure that all measured values of each control level (low, medium, and high) were within the target ranges.

2.7 | Blood and plasma samples

Blood samples were collected the same morning that CSF were collected, after overnight fasting. Three milliliters of complete blood was extracted for future genetic studies and 6 mL of plasma was obtained for future blood biomarker determinations. These samples were processed within 3 h after acquisition. Plasma samples were centrifuged (1500 *g* x 15 min) at room temperature, aliquoted into polypropylene vials (Sarstedt, Ref# 72.694.007), and stored at −80°C. The storage centers processed and stored their samples, whereas the non-storage centers sent the blood to the coordinating center for processing and storage immediately after extraction.

2.8 | Cognitive and etiological diagnosis

Clinicians filled out a two-part questionnaire for every patient. The first part had to be completed before lumbar puncture, at the first study visit. The clinicians in charge of the patient established a syndromic cognitive diagnosis, as well as an etiological diagnosis, based on all the available information (i.e., clinical, neuropsychological, and neuroimaging information, as well as other ancillary tests). For the cognitive diagnosis, the following categories were utilized: normal cognition (NC), amnestic MCI (aMCI), non-amnestic MCI (naMCI), mixed MCI (mMCI),[35] and dementia.[21] For the etiological diagnosis, National Institute of Neurological and Communicative Disorders and Stroke -Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) categories were used for AD,[18] whereas international consensus criteria were used for other etiologies.[36–39] At the time of etiological diagnosis, clinicians rated their diagnostic confidence using a five-point, interval scale ranging from 0% to 100% (diagnostic confidence was not requested in the case of NC or uncertain etiological diagnosis).

Once the results of the biomarkers were obtained, a second visit was scheduled. This could be in-person or a telephone visit and was usually carried out 1–3 months after the first visit. At the second visit, the CSF results were disclosed to the patient and the caregiver, the case was re-evaluated, new etiological diagnoses (and diagnostic confidence) were established, and possible treatment modifications were considered. At this step, the NIA-AA diagnostic criteria were incorporated.[20,21] The first and second visits were performed by the same neurologist, who did not have information regarding prior diagnostic confidence.

2.9 | Biomarker cutoff points

Cutoffs of CSF biomarkers were obtained by Parnetti et al. (unpublished data) and provided by the manufacturer. According to maximum Youden's index, the following values were recommended: <599 pg/mL (Aβ_{42}), <0.069 (Aβ_{42}/ Aβ_{40}), >404 pg/mL (total tau), and >56.5 pg/mL (p-tau). In addition, values of best clinical-biological concordance (overall percentage agreement) were provided for Aβ_{42} (<726 pg/mL) and total tau (>392). Following previous studies and expert recommendations, low Aβ_{42}/Aβ_{40} ratio and high p-tau were considered as the most specific biomarkers. In the case of indeterminate values, the clinical phenotype was prioritized.[11]

2.10 | Changes in patient management

As mentioned above, the treatment plan was revised in the second study visit, once biomarker results were available. Treatment modifications at this visit were categorized according to the following domains: patient pharmacological treatment, patient non-pharmacological treatment, caregiver/social interventions, and pre-selection for clinical trial.

2.11 | Follow-up visits

Annual follow-up visits were conducted, which included data collection regarding cognitive evolution, neuropsychiatric symptoms, and medications, as well as performance of BCT, FAQ, GDS, and CDR scales. Two different versions of the MMSE and MIS were alternated each year to avoid a learning effect. Cognitive and etiological diagnoses were

updated, along with diagnostic confidence. Finally,, the therapeutic plan was evaluated and modified, according to the needs of the patients and caregivers.

2.12 | Neurologists' characteristics

Data regarding physician's age, sex, special dedication to dementia, and biomarker experience were collected as potential predictors of etiological diagnosis, diagnostic confidence, and biomarker-derived treatment modifications. Special dedication to dementia was defined as at least one monographic dementia consultation per week, during the study period. Biomarker experience was measured as time of use of Alzheimer's CSF biomarkers in clinical practice, in the middle of the study period.

2.13 | Statistical analysis

Demographic and clinical variables were reported as mean, standard deviation (SD), number, median, interquartile range, and/or percentage, as appropriate. Baseline differences between the study groups were assessed using analysis of variance (ANOVA) for quantitative variables and nonparametric tests for categorical variables. Change in diagnostic confidence was analyzed using Wilcoxon test, whereas chi-square test and Spearman *r* coefficient were utilized to investigate the influence of biomarkers and physician's characteristics on etiological diagnosis. For this analysis, three groups of interest were created, namely AD, non-AD, and uncertain etiology. Convenience categories were created post hoc for the analysis of the influence of neurologist characteristics on the study results.

3 | RESULTS

3.1 | Patient and neurologists' characteristics

A total of 245 patients signed informed consent, but CSF was not obtained in 5 patients, and clinical data were not provided for 7 patients. Hence, data of 233 patients from 10 (8 public, 2 private) centers are presented and analyzed (Figure 1). Patients were recruited by 15 (7 male, 8 female) neurologists of 30–39 ($n = 7$), 40–49 ($n = 4$), and 50–59 ($n = 4$) years of age. The experience of neurologists in the use of Alzheimer CSF biomarkers was of 0–3 ($n = 5$), 3–6 ($n = 5$), and 6–9 ($n = 5$) years and 11 (73.3%) of them had special dedication to dementia.

Mean age (SD, range) of the patients was 69.9 (7.5, 50–85) years and 117 (50.2%) were women. The educational level was basic, primary, and superior in, respectively, 31 (13.7%), 90 (39.6%), and 106 (46.7%) of the participants. As per study protocol, blood tests (i.e., hemogram and biochemical analytes) and cranial structural imaging study (MRI [78.1%] or CT scan [21.9%]) were conducted in all the patients. The cognitive diagnoses were as follows: NC (13 patients, 5.6%), aMCI (74 patients, 31.8%), naMCI (35 patients, 15.0%), mMCI (58 patients, 24.9%), and dementia (53 patients, 22.7%). Demographic and clinical characteristics of the patients are presented in Table 1 and the biomarker results are presented in Table 2.

3.2 | Impact of biomarkers on etiological diagnosis

AD was largely the most prevalent cause of cognitive deterioration, including 160 of 233 patients (68.7%) before and 169 of 233 patients (72.5%) after biomarker information. Considering Alzheimer's versus non-Alzheimer's diagnosis, biomarkers led to a diagnosis change in 76 of 233 (32.6%) of patients (39/187 [20.9%] if uncertain diagnoses were not considered). Non-Alzheimer's to Alzheimer's was the most frequent switch (25/45 [55.6%] patients vs 14/160 [8.8%] patients opposite change) (Table 3).

Looking at more granular diagnostic labels, pre-biomarker etiologies were as follows: probable/possible AD (63.0%), frontotemporal lobar degeneration (9.4%), AD with vascular disease (5.6%), Lewy body disease (2.6%), other neurodegenerative disease (2.1%), vascular cognitive impairment (1.3%), other type of secondary cognitive deterioration (3.9%), and NC/uncertain etiology (12.0%). After biomarker information, the diagnostic label was changed in 192 patients (82.4%), mostly due to the adoption of two of the NIA-AA categories, namely, "MCI due to AD–high likelihood" (MCI-AD) and "probable AD dementia with evidence of AD pathophysiological process" (AD-EPP) (two additional patients received diagnosis of "MCI unlikely due to AD," which will be included in the group of uncertain etiology for result presentation and analysis). The NINCDS-ADRDA categories became anecdotal, due to the assumption of the NIA-AA criteria. Specifically, 139 of 147 diagnoses (94.6%) of possible/probable AD were switched to AD-EPP (47.5%), MCI-AD (35.3%), frontotemporal lobar degeneration (FTLD) (3.6%), uncertain (10.8%), and other etiology (2.9%) (Figure 2).

Regarding patients with initial uncertain etiological diagnosis, biomarkers promoted diagnostic definition in 19 of 28 (67.9%) of cases, being post-biomarker diagnoses as follows: MCI-AD (13 patients), FTLD (3 patients), vascular cognitive impairment (1 patient), and other secondary etiology (2 patients). However, 18 of 205 patients (8.8%) with non-uncertain initial diagnosis were switched to uncertain diagnosis after biomarker information. The pre-biomarker diagnoses of those patients were as follows: possible AD (14 patients), probable AD (1 patient), vascular cognitive impairment (1 patient), and other secondary etiology (2 patients). Hence, despite the diagnostic changes produced by the biomarkers, the final proportion of patients with uncertain diagnosis remained virtually unchanged (≈12%) (Figure 2).

For those patients who did not receive uncertain etiological diagnosis, diagnostic confidence was significantly increased, from median (interquartile range [IQR]) value of 70 (54, 80) to 92 (87, 97) ($p < 0.0005$) (Figure 3). As expected, confidence was greater when the final diagnosis was AD. Pre- and post-biomarker confidence were 70 (60, 82) and 95 (89, 97) for patients with final AD diagnosis ($n = 156$), whereas the corresponding values for patients with non-AD final diagnosis were 62 (52, 82) and 80 (63, 88).

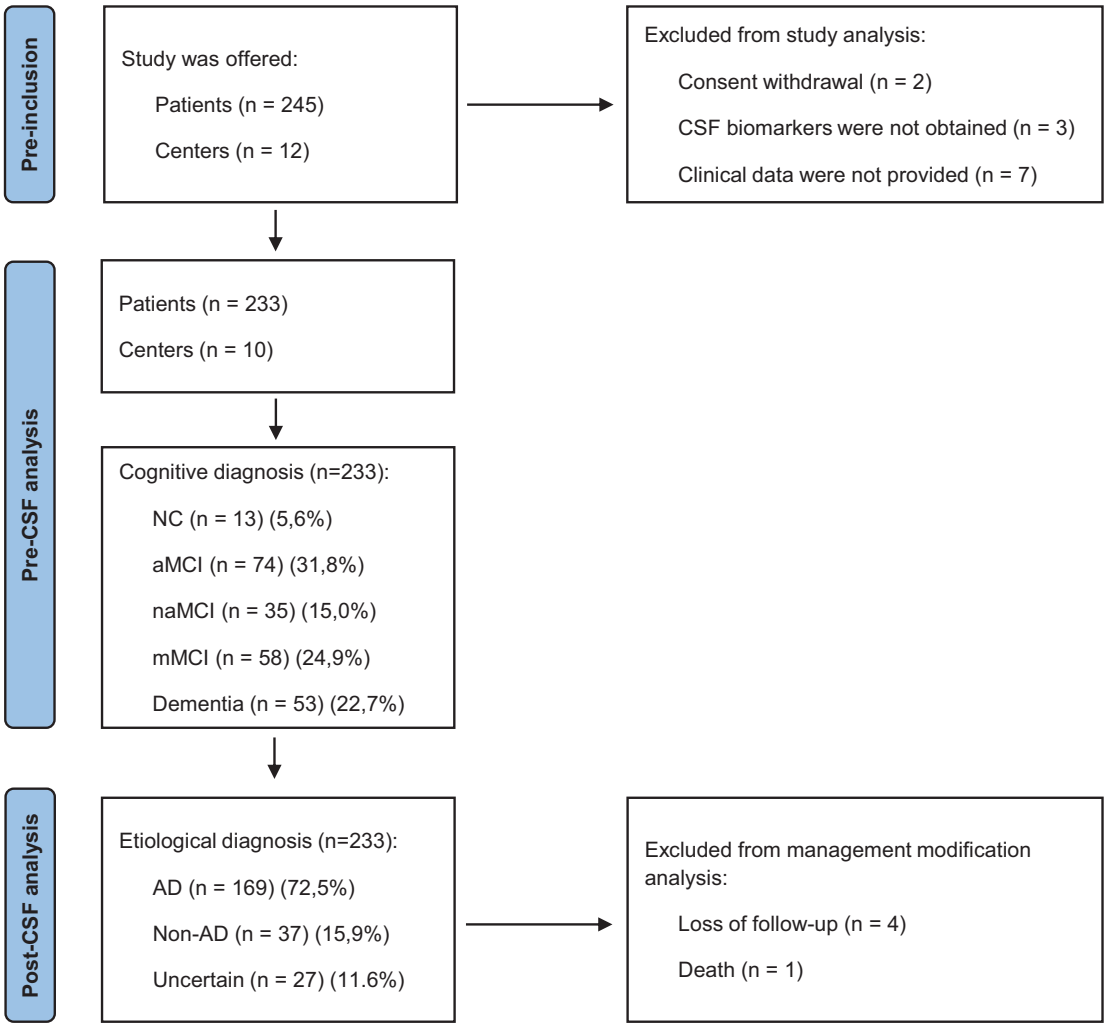

FIGURE 1 Patient disposition. AD, Alzheimer's disease; CSF, cerebrospinal fluid; aMCI, amnestic MCI, naMCI, non-amnestic MCI; mMCI, mixed MCI; MCI, mild cognitive impairment; NC, normal cognition.

TABLE 1 Demographic and clinical characteristics of the study participants by cognitive diagnosis.

	NC ($n = 13$)	aMCI ($n = 74$)	naMCI ($n = 35$)	mMCI ($n = 58$)	Dementia ($n = 53$)	p
Age	68.6 (9.1)	71.2 (6.4)[1]	70.2 (6.6)	70.8 (8.1)	67.4 (8.0)[1]	0.051
Sex (% women)	15.4	55.4	57.1	44.8	52.8	0.072
Education degree (%)*						0.081
-Basic	7.7	14.9	9.1	16.1	14.0	
-Primary	23.1	37.8	66.7	35.7	32.0	
-Intermediate	23.1	27.0	9.1	16.1	22.0	
-Superior	46.2	20.3	15.2	32.1	32.0	
MMSE	27.5 (1.7)[2,3]	24.7 (3.2)[4,5]	24.6 (2.9)[6]	22.3 (4.1)[2,4,7]	18.6 (5.7)[3,5-7]	0.000
CDRsb	0.8 (0.5)[3]	2.6 (1.7)[5]	2.2 (1.7)[6]	2.6 (1.3)[7]	6.6 (3.0)[3,5-7]	0.000

Note: Figures represent mean (SD) value, unless % is indicated; *education degree was missed for seven patients; [1-7]superscript numbers indicate between-group statistically significant differences ([1,4]$p < 0.05$, [2]$p < 0.005$, [3,5-7]$p < 0.0005$, Bonferroni test).

Abbreviations: aMCI, amnesic mild cognitive impairment; CDRsb, Clinical Dementia Rating sum of boxes; mMCI, mixed MCI; MMSE, Mini-Mental State Examination; naMCI, non-amnesic MCI; NC, normal cognition.

TABLE 2 Results of CSF biomarkers in the different study groups ($n = 233$).

	Cognitive diagnosis						Etiological diagnosis[a]			
	NC ($n = 13$)	aMCI ($n = 74$)	naMCI (n = 35)	mMCI (n = 58)	Dementia (n = 53)	*P*	Alzheimer (n = 169)	Non-Alzheimer (n = 37)	Uncertain (n = 27)	*p*
$A\beta_{40}$	13,283.1 (4969.2)	11,797.3 (3810.3)	11,515.9 (4245.9)	11,366.8 (3295.5)	10,632.3 (3780.5)	0.199	11,674.4 (3766.5)	10,956.8 (3963.1)	10,857.5 (4133.5)	0.403
$A\beta_{42}$	694.1 (400.9)	581.6 (278.6)	752.5 (411.4)	619.0 (315.6)	561.0 (260.8)	0.050	501.6 (151.3)[2,3]	961.5 (422.4)[2]	877.3 (454.2)[3]	0.000
$A\beta_{42}/A\beta_{40}$	0.055 (0.025)	0.050 (0.017)[1]	0.066 (0.028)[1]	0.054 (0.019)	0.055 (0.023)	0.005	0.044 (0.009)[2,3]	0.086 (0.018)[2]	0.079 (0.022)[3]	0.000
tau	544.6 (260.6)	601.2 (317.8)	567.5 (484.2)	606.3 (301.6)	664.7 (415.9)	0.713	730.5 (350.9)[2,3]	293.8 (114.6)[2]	287.1 (148.9)[3]	0.000
p-tau	83.2 (46.0)	98.0 (51.8)	90.0 (89.6)	103.4 (56.6)	107.0 (70.0)	0.628	121.9 (60.6)[2,3]	38.9 (12.5)[2]	41.9 (19.2)[3]	0.000

Note: Figures represent mean (SD) value (pg/mL).
[a]After biomarker information; [1-3]superscript numbers indicate between-group statistically significant differences ([1]$p < 0.005$, [2,3]$p < 0.0005$, Bonferroni test).
Abbreviations: aMCI, amnesic mild cognitive impairment; mMCI, mixed MCI; naMCI, non-amnesic MCI; NC, normal cognition.

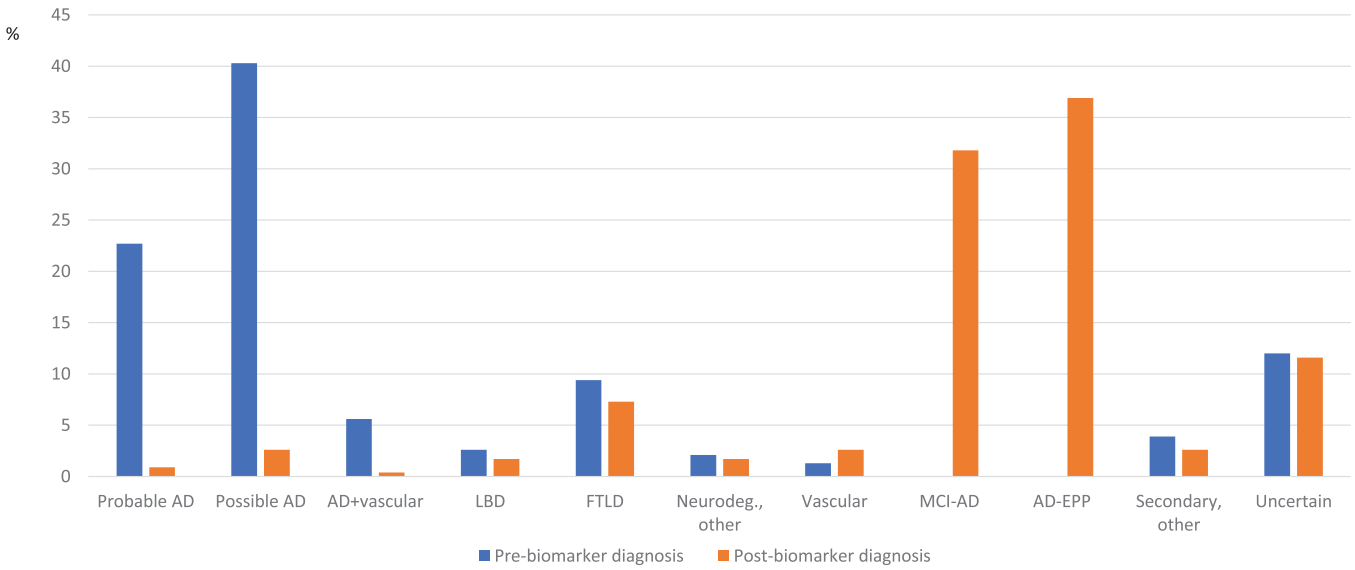

FIGURE 2 Etiological diagnosis before and after CSF biomarker information ($n = 233$). AD, Alzheimer disease; AD-EPP, probable AD dementia with evidence of AD pathophysiological process; CSF, cerebrospinal fluid; FTLD, frontotemporal lobar degeneration; LBD, Lewy body disease; MCI, mild cognitive impairment; MCI-AD, MCI due to AD—high likelihood; Neurodeg., neurodegenerative dementia.

3.3 | Influence of neurologists' characteristics

A mild correlation was found between neurologist's age and AD diagnosis ($r = 0.136$, $p = 0.038$), which disappeared when the diagnosis was informed by biomarkers ($r = 0.081$, $p = 0.218$). Before biomarker determination, younger neurologists established AD diagnosis less frequently than did senior neurologists (60.3% young, 74.2% senior, $p = 0.012$), but that difference disappeared after biomarker information (67.9% young, 75.8% senior, $p = 0.757$) (Table 4). In addition, pre-biomarker diagnosis of uncertain etiology was less frequently established by young clinicians (11.5% young, 14.5% senior), whereas the opposite trend occurred after biomarker information (14.1% young, 10.5% senior). As mentioned, biomarkers produced an increase in the clinician's diagnostic confidence, which did not depend significantly on any of the neurologists' characteristics, although a trend toward less benefit from biomarkers (final diagnostic confidence <90%) was observed among neurologists who did not have special dedication to dementia or had a shorter period of experience in biomarker use (Table 4).

3.4 | Consequences for patient management

Case review with patient and family could not be conducted in five instances, due to death (1 patient) and loss of follow-up (4 patients). Biomarkers brought consequences for management to 163 of 228

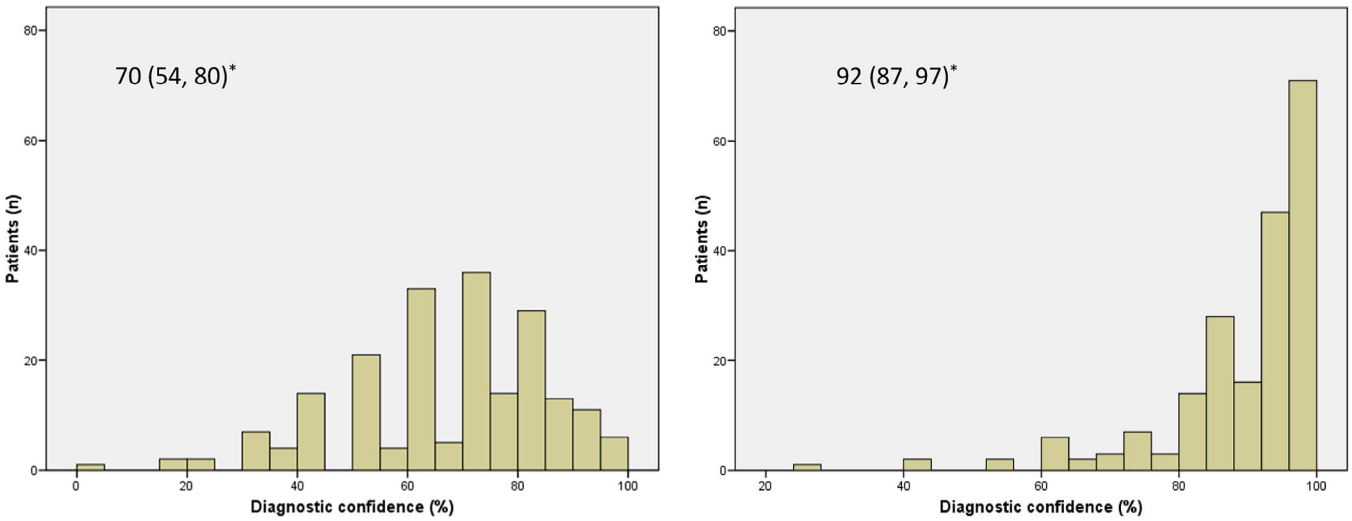

FIGURE 3 Clinician's confidence in etiological diagnosis before ($n = 205$, left) and after ($n = 206$, right) biomarker information. *Median value (interquartile range); $p < 0.0005$ for pre-post difference.

TABLE 3 Impact of CSF biomarkers on etiological diagnosis ($n = 233$).

	Post-biomarker diagnosis		
Pre-biomarker diagnosis	**Alzheimer ($n = 169$)**	**Non-Alzheimer ($n = 37$)**	**Uncertain ($n = 27$)**
Alzheimer's ($n = 160$)	131 (81.9%)	14 (8.8%)	15 (9.4%)
Non-Alzheimer's ($n = 45$)	25 (55.6%)	17 (37.8%)	3 (6.7%)
Uncertain ($n = 28$)	13 (46.4%)	6 (21.4%)	9 (32.1%)

Abbreviation: CSF, cerebrospinal fluid.

(71.5%) of patients. Specifically, pharmacological treatment was modified in 140 of 228 patients (61.4%), nonpharmacological treatment was modified in 84 of 228 patients (36.8%), and caregiver/social interventions were recommended in 28/228 cases (12.3%). In addition, drug clinical trial was offered to 19 of 228 patients (8.3%). A more detailed description of treatment and care modifications indicated by neurologists, after biomarker-informed case review and use of NIA-AA criteria, is provided in Table 5.

Cholinesterase inhibitor (CEI) initiation was the most frequent pharmacological change, occurring in 76 of 227 patients (33.5%) (additional patients [21.8%] were taking CEI at study inception). The frequency of CEI initiation in the different cognitive groups was as follows: NC 3.9%, aMCI 47.4%, naMCI 11.8%, mMCI 25.0%, and dementia 11.8% ($p < 0.005$) (39.5% of additional patients from the dementia group were taking CEI at study inception). Nevertheless, the global impact of biomarkers on treatment and care was similar across the different cognitive groups (p-values of 0.404, 0.300, and 0.172 for pharmacological treatment, non-pharmacological treatment, and caregiver/social interventions, respectively) (Figure 4).

4 | DISCUSSION

We prospectively evaluated the impact of core AD CSF biomarkers and the adequacy of the 2011 NIA-AA criteria in a regional cohort of patients who were recruited and studied in memory and neurology clinics during usual practice. Accompanied by clinical profiles, the NIA-AA criteria provided biomarker-enriched definitions which, in terms of probability, would identify or rule out the pathological substrate of AD.[20,21] Hence, a pragmatical study was designed in which patient inclusion was essentially driven by the presence of persistent cognitive symptoms, the absence of important comorbidities, and the agreement between patient and physician about the convenience of early AD identification.

As expected, our patients were relatively young (mean age, 70 years) and AD etiology was diagnosed in almost three of four cases (73%), in contrast with previous studies which showed predominance of non-AD etiologies.[40–42] Although former study results reflect traditional recommendations of CSF study in the case of atypical presentation, rapid deterioration, or young age,[14,40] our study would respond to the current need of more inclusive, timely AD diagnosis, with the spotlight on present and near future treatments.[43] In this context, our study could be considered essentially confirmatory. Not surprisingly, the NIA-AA categories of high diagnostic probability were adopted in most cases, whereas confidence in the diagnosis was increased.

Although studies of AD CSF biomarkers are abundant, investigations addressing the adequacy of the NIA-AA criteria are scarce. In a retrospective study of patients with early onset cognitive symptoms, the category of "MCI due to AD–high likelihood" was highly predictive of dementia development, whereas the opposite occurred in patients bearing diagnosis of "MCI probably not due to AD." Moreover, the addition of CSF biomarkers to clinical criteria was reportedly determinant to attain the level of high probability of AD pathophysiology. Like our results, high concordance between AD clinical profile and

TABLE 4 Etiological diagnosis and confidence, by neurologist's characteristics.[a]

		Etiological diagnosis (%)				Confidence (median, IQR)	
		Alzheimer (n = 160/169)	Non-Alzheimer (n = 45/37)	Uncertain (n = 28/27)	p[b]		p[c]
Sex	-Male	69.7	18.4	11.8	0.876	70 (54, 80)	0.000
	(*n* = 7)	75.0	14.5	10.5	0.513	95 (87, 97)	
	-Female	66.7	21.0	12.3		70 (53, 82)	0.000
	(*n* = 8)	67.9	18.5	13.6		91 (87, 97)	
Age (years)	-30–39	60.3	28.2	11.5	0.012	72 (52, 82)	0.000
	(*n* = 7)	67.9	17.9	14.1	0.757	92 (87, 97)	
	-40–49	67.7	29.0	3.2		73 (58, 82)	0.000
	(*n* = 4)	71.0	19.4	9.7		97 (87, 97)	
	-50–59	74.2	11.3	14.5		62 (54, 80)	0.000
	(*n* = 4)	75.8	13.7	10.5		95 (85, 98)	
Special dedication to dementia	-Yes	69.5	19.5	11.5	0.768	70 (52, 82)	0.000
	(*n* = 11)	74.5	15.0	10.5	0.236	92 (87, 97)	
	-No	63.6	21.2	15.2		70 (60, 80)	
	(*n* = 4)	60.6	21.2	18.2		88 (85, 97)	
Years of experience in the use of AD CSF biomarkers	-0–3	68.6	17.1	14.3	0.517	68 (60, 72)	0.000
	(*n* = 5)	67.1	18.6	14.3	0.734	87 (83, 92)	
	-3–6	63.2	28.9	7.9		72 (52, 82)	0.000
	(*n* = 5)	71.1	18.4	10.5		92 (87, 97)	
	-6–9	70.4	17.6	12.0		70 (52, 82)	0.000
	(*n* = 5)	76.0	13.6	10.4		95 (90, 97)	

[a]Pre-biomarker diagnosis up, post-biomarker diagnosis down.
[b]Chi-square test.
[c]Wilcoxon test.
Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; IQR, interquartile range.

TABLE 5 Treatment and management modifications after biomarker-informed case review (*n* = 228).

Pharmacological treatment	%	Non-pharmacological treatment	%	Caregiver/social interventions	%
CEI initiation	24.6	Cognitive stimulation/training	17.1	Guardianship/power of attorney	3.9
Medical food initiation	13.1	Day care center	3.5	Caregiver education/counseling/support	2.2
CEI and medical food/supplement initiation	7.0	Speech therapy	2.2	Other interventions	3.5
Increase of CEI dose	3.5	Social activities	1.3	Not specified	2.6
Memantine initiation	2.2	Physical activity	0.9	Caregiver/social interventions were not recommended	87.7
Psychotropic medication initiation/modification	2.6	Other/combination of the former	11.4		
CEI withdrawal	0.9	Not specified	0.4		
Ginkgo biloba initiation	0.4	Non-pharmacological treatment was not recommended	63.2		
Combination of the former	6.7				
Not specified	0.4				
Pharmacological treatment was not modified	38.6				

Abbreviation: CEI, cholinesterase inhibitor.

CSF biomarkers was observed, and the categories of "intermediate likelihood" of AD pathophysiology were not utilized.[44]

Despite this being an AD-oriented study, there was significant diagnostic change (i.e., AD to non-AD or vice versa) after biomarker information in 21% of patients, and 12% additional patients remained etiologically uncertain, also in agreement with previous investigations.[45] These results underscore the need for CSF biomarker confirmation, even in cases of typical clinical presentation and congruent neuroimaging study, as well as the necessity of non-AD biomarkers and prospective follow-up to clarify the underlying pathophysiology in those patients with negative or inconclusive AD biomarker results.[46]

For those patients who received specific etiological diagnosis, biomarkers raised diagnostic confidence from 70% to 92%, which is greater than previously reported results.[41,42,47] Given that the characteristics of the neurologists did not influence diagnostic confidence, possible explanations for our results could be the predominance of AD etiology and the addition of $A\beta_{40}$, and subsequent $A\beta_{42}/A\beta_{40}$ ratio, determination to the traditionally conducted biomarkers (i.e., $A\beta_{42}$, total tau, and p-tau).[48] Combined with elevated p-tau, low $A\beta_{42}/A\beta_{40}$ ratio provides firm AD diagnosis of AD in patients who present $A\beta_{42}$ and total tau values in the gray zone.[49]

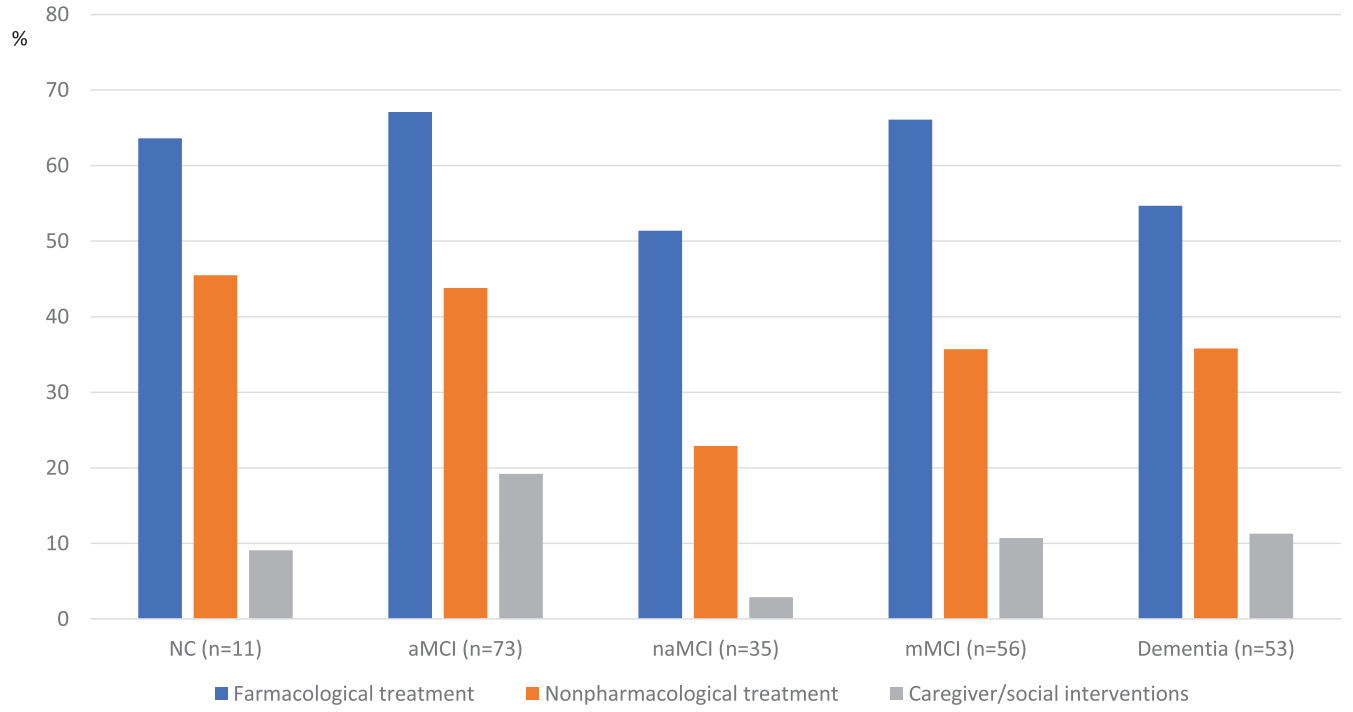

FIGURE 4 Frequency of treatment and care modifications after biomarker information in the different cognitive groups. MCI, mild cognitive impairment; aMCI, amnesic MCI; mMCI, mixed MCI; naMCI, non-amnesic MCI; NC, normal cognition.

The NIA-AA criteria were remarkably well accepted by the study neurologists, who displayed high variability in terms of age and dementia expertise. In addition, the characteristics of the neurologist did not modify the study results substantially. Significant increase in diagnostic confidence was observed, regardless of neurologist age, sex, or dementia expertise. Furthermore, small age-related differences observed in the initial etiological diagnosis, presumably due to seniority, disappeared after CSF biomarker information. To the authors' knowledge, this is the first report on the influence of clinician's characteristics on biomarker-enriched dementia diagnosis. In this regard, our results should be confirmed and extended, including to non-specialized professionals and settings. This type of study may help to adapt the available material and human resources to a foreseeable need for mass detection of AD pathophysiology.[50]

Patient or caregiver management was modified after CSF biomarker information in 71% of patient/caregiver dyads, which is higher than previously reported. In a meta-analysis of five studies (n = 918), the overall proportion of patients whose management changed was 31%, falling the proportions of the individual studies between 13% and 47%.[45] Although previous studies were focused mainly on CEI inhibitor initiation, we displayed a global treatment approach, which included medical food/supplement initiation, modifications in psychotropic medications, implementation of non-pharmacological interventions, and caregiver counseling. Certainly the consequences of AD diagnosis go far beyond pharmacological treatment. In this regard, our results further confirm and expand the utility of AD CSF biomarkers in usual practice, which affected patients regardless of clinical stage or cognitive profile.

Our study had several limitations. First, structural neuroimaging was conducted and considered for diagnosis, and functional neuroimaging was also performed in some instances, but those studies were only qualitatively evaluated and were not analyzed. In a previous investigation of patients with early-onset cognitive symptoms, MRI and FDG-PET/SPECT contributed to the category of "intermediate likelihood" of AD pathology, but clinical criteria and CSF biomarkers were sufficient to attain high likelihood level in all the instances.[44] In another study conducted by the same researchers, CSF biomarkers and PET amyloid increased diagnostic confidence, whereas MRI and PET did not.[47] In a retrospective study of AD-suspected patients, PET and CSF showed similar confirmatory value when added to clinical features, but CSF biomarkers had a higher impact on diagnostic confidence and reduced the use of ancillary tests[51] Certainly molecular biomarkers may be sufficient to established AD pathophysiology, but that should not be accomplished by means of CSF study only.[52,53] Patients in whom lumbar puncture was contraindicated were not offered the study, which might be the case in one of four candidates,[47] thus limiting the generalizability of the results.

In conclusion, the NIA-AA diagnostic criteria were adequate and useful in an AD-oriented cohort of patients who attended memory or neurology clinics due to cognitive complaints and received neuroimaging and CSF study. In this setting, our results were satisfactory for both patients and clinicians, which encourages the use of these criteria to confirm or rule out AD diagnosis. Nevertheless, in this rapidly evolving field, as disease-modifying therapies advance, further NIA-AA diagnosis and staging criteria definition are expected [https://aaic.alz.org/diagnostic-criteria.asp], including plasma biomarkers and,

hopefully, emerging predictors of treatment response.[54–56] Clearly, a continuous review of AD diagnostic criteria will serve to promote research and to build the bridge between basic science and patient care.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflicts of interest in relation to this study. 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.

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