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Impact of amyloid-PET in daily clinical management of patients with cognitive impairment fulfilling appropriate use criteria

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Abstract

To evaluate the use of amyloid-positron emission tomography (PET) in routine clinical practice, in a selected population with cognitive impairment that meets appropriate use criteria (AUC).

A multicenter, observational, prospective case-series study of 211patients from 2 level-3 hospitals who fulfilled clinical AUC for amyloid-PET scan in a naturalistic setting. Certainty degree was evaluated using a 5-point Likert scale: 0 (very low probability); 1 (low probability); 2 (intermediate probability); 3 (high probability); and 4 (practically sure), before and after amyloid PET. The treatment plan was considered as cognition-specific or noncognition-specific.

Amyloid-PET was positive in 118 patients (55.9%) and negative in 93 patients (44.1%). Diagnostic prescan confidence according amyloid-PET results showed that in both, negative and positive-PET subgroup, the most frequent category was intermediate probability (45.7% and 55.1%, respectively). After the amyloid-PET, the diagnostic confidence showed a very different distribution, that was, in the negative-PET group the most frequent categories are very unlikely (70.7%) and unlikely (29.3%), while in the positive-PET group were very probable (57.6%) and practically sure (39%). Only in 14/211 patients (6.6%) the result of the amyloid-PET did not influence the diagnostic confidence, while in 194 patients (93.4%), the diagnostic confidence improved significantly after amyloid-PET results. The therapeutic intention was modified in 93 patients (44.1%). Specific treatment for Alzheimer disease was started, before amyloid-PET, in 80 patients (37.9%).

This naturalistic study provides evidence that the implementation of amyloid-PET is associated with a significant improvement in diagnostic confidence and has a high impact on the therapeutic management of patients with mild cognitive impairment fulfilled clinical AUC.

Abbreviations: AD = Alzheimer disease, AIT = amyloid imaging taskforce, AUC = appropriate use criteria, CBNU = cognitive behavioral neurology unit, CSF-B = cerebrospinal fluid biomarkers, FBB = F-18-florbetaben, MCI = mild cognitive impairment, MRI = magnetic resonance imaging, PET &EQUALS; positron emission tomography.

Keywords: Alzheimer's disease, amyloid PET, appropriate use criteria, florbetaben PET, mild cognitive impairment

1. Introduction

In the epidemiologic context of the progressive population aging, the early diagnosis of Alzheimer disease (AD) is an emerging problem of growing magnitude. The clinical approach to the cognitive impairment and the AD, which is its most prevalent form,[1,2] has undergone a change in recent years since the definition of NINCD-ADRDA criteria for the clinical diagnosis of AD in 1984.[3] The incorporation of the theory of biomarkers[4] within the classic hypothesis of the amyloid cascade[5] has radically modified the diagnostic approach of AD during the life of the patients, trying to solve the clinical problem of a reliable and early diagnosis of the disease as a continuum.[6]

Nuclear medicine has contributed to the management of dementias and particularly AD, not only by allowing the identification of neurodegeneration before the macroscopic deterioration of the gray matter with positron emission tomography (PET) with F-18-2-fluoro-2-deoxy-D-glucose (FDG), but also by the contribution of amyloid-PET, as a biomarker in vivo with proven analytical validity.[7]

Since its introduction in a research context C-11-PiB[8] has demonstrated to be a useful tool to obtain "in vivo" imaging of the amyloid plaque, one of the hallmarks of AD. It uses, restricted

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to centers with onsite cyclotron has been overcome with the availability of fluorinated compounds (as F-18-florbetaben [FBB]), which allow a widespread clinical use.[9] Despite progress, amyloid-PET is considered an expensive, complicated and scarcely available procedure, without studies that support it. In general terms, there is not enough evidence to recommend the use in the clinic[10] and some clinical problems remain unresolved, such as the assessment of the validity and reliability of this diagnostic test in clinical practice.[10–14] This situation leads to a vicious circle: its use is not recommended because there is no evidence and there is no evidence because it is not recommended its use.

In the past years the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging convened the Amyloid Imaging Taskforce (AIT), aimed to identify the circumstances under amyloid-PET would have clinical utility, setting its recommendations in the appropriate use criteria (AUC). The AIT considered several situations in which the added certainty of amyloid-PET could be useful to patients and caregivers altering the management of the disease.[11] The AUC from AIT could be considered as restrictive,[11,15] but support the basis for the national consensus.[16] As the authors refers in its report, its suggestions proceed from a literature revision and the interpretation of the previous knowledge in precise clinical settings, but " . . . *empirical evidence of impact on clinical outcomes is not yet available*."[11]

In this scenario, some reports are emerging describing the clinical utility of the amyloid-PET in a clinical naturalistic setting.[17–19] All of them reported relevant changes in the diagnosis, level of diagnostic uncertainty and treatment.

The objective of the present study is located exclusively in patients fulfilling AUC for amyloid-PET and aimed to provide information about the potential benefits of the amyloid-PET in daily clinical management.

2. Methods

2.1. Participants

This case series included patients from 2 level-3 hospitals (A: 1.75×10^6 inhabitants; B: 1.5×10^6 inhabitants) who fulfilled clinical AUC for PET-amyloid scan in agreement with international[11] and national[16] consensuses. According recruitment could be considered as ambispective (in center A in 12 cases and in center B in 6 cases, data were collected retrospectively; in the rest of the cases the information were collected prospectively). The population included in this study corresponds to the total number of patients scanned during the recruitment period between January 2014 and June 2018 without randomization, in a clinical setting: the inclusion in this work does not interfere with the natural clinical workup. This series does not include patients under specific clinical trials.

Four subgroups of these patients were considered for investigation of their beta-amyloid burden to guide clinical management and according to AUC[11,16]:

1. patients with persistent or progressive unexplained mild cognitive impairment (MCI), defined by revised Petersen criteria[20];
2. patients fulfilling core clinical criteria for possible AD but an atypical clinical course with no documented progression in the patient's records;
3. those with progressive cognitive impairment or dementia and atypically early age of onset ($\leq$65 years) and
4. patients fulfilling these core clinical criteria but with cerebrovascular comorbidity, concomitant pharmacologic, neurologic, or cognitive components (mixed etiology).

Exclusion criteria were: the presence of a metabolic disorder (hypothyroidism, vitamin B12, or folic acid deficiencies), psychiatric pathology (schizophrenia or depression), magnetic resonance imaging (MRI) diagnosed cerebrovascular disease (infarction or hemorrhage), neurologic disease affecting gnosis (Parkinsonian syndrome, epilepsy, etc), pregnancy, glycaemia >160 mg/dL, history of substance abuse, or age <18 years. In summary, the selected cases correspond only to patients attended by a cognition trained neurologist, visit at a specific Cognitive Behavioral Neurology Unit, and fulfilling consensual appropriate criteria for amyloid-PET exploration.

All participants gave their written informed consent to participation in the study, which complied with the principles of the Helsinki Declaration and had formal institutional review board approval of each respective Hospital.

2.2. Clinical protocol

All participants were evaluated in a Cognitive Behavioral Neurology Unit (CBNU) by experienced neurologists sharing homogeneous practices in cognitive-behavioral disorders.

2.2.1. Initial assessment. Initial evaluation at CBNU included a medical interview, informant-based history, biochemical panel, and physical and neurological examinations using standardized tests for neuropsychological examination of the domains of orientation, attention, memory, executive function, language, visual and constructive functions, and behavior. Cognition was globally evaluated with the mini-mental estate examination[21] in the Center A and with the FotoTest[22] in the Center B. Brain imaging includes MRI or computed tomography.

In this first visit the potential eligibility was assessed. With the information provided by this first evaluation the neurologist was asked to estimate the probability of AD (vs Non-AD) as responsible of symptomatology. Certainty degree was evaluated using a 5-point Likert scale: 0 (very low probability; 0%–20%); 1 (low probability; 21%–40%); 2 (intermediate probability; 41%–60%); 3 (high probability; 61%–80%); and 4 (practically sure; 81%–100%). At this visit the treatment plan was considered as cognition-specific (eg, acetylcholinesterase inhibitors or memantine hydrochloride); or non-cognition-specific (eg, anxiolytics, hypnotics, antidepressants, antipsychotics, or anticonvulsants).

2.2.2. Specific assessment. If this initial evaluation is inconclusive or insufficient for diagnosis, the patient is transferred to a more specifics procedures, usually in the first line cerebrospinal fluid by spinal puncture biomarkers (CSF-B) and in the second line: amyloid-PET.

When lumbar puncture was not possible (rejected by the patient; not feasible: anticoagulants, spinal problems, and brain or spinal mass) or CSF-B offered nondiagnostic results (technical problems; results near the reference threshold; only 1 or 2 positive result and when result was inconsistent with clinical information),[18] amyloid-PET was performed.

2.2.3. Third (final) diagnosis approach. When amyloid-PET results are available, the neurologist made a re-evaluation of the possible etiological diagnosis (and his confidence level) and about

Table 1

Amyloid-PET protocol details.

	CENTER A		CENTER B
Camera	GE Discovery STE		Siemens Biograph 16
Patient position		Resting; closed eyes	
Operation		3D mode	
Filtering		*Z*-Axis standard	
Dose		300 MBq (8 mCi)	
Acquisition start		90 min post injection	
Acquisition duration		20 min	
Matrix size		168 × 168	
Number of slices		70	
Slice thickness	4.01 mm		4.06 mm
Voxel size	16.08 (mm3)		16.48 (mm3)
Reconstruction	VUE Point Iterative (5 it/35 sub)		Gaussian + OS − OM (6it/21 sub)
CT Parameters	Low-dose, 80 mAs, 120 kV		Low-dose, 50 mAs, 120 kV
CT Matrix size		512 × 512	
CT Slice thickness		1 mm	
Corrections	Scatter; CT attenuation; well counter sensitivity and activity; delayed event subtraction and normalization		Scatter; CT attenuation; slice coincidence location with CT

CT = computed tomography, PET = positron emission tomography.

treatment plan, using the same methodology as for prescan evaluation.

In order to assess the incremental diagnostic value of amyloid-PET the outcome variables were diagnostic confidence and treatment plan.

2.3. Amyloid-PET imaging (FBB-PET)

The imaging protocol in both centers complied with international guidelines[9] according supplier recommendations.[23] Extended information is available in Table 1. The FBB was reported blinded to the clinical information by a nuclear medicine physician as positive (loss of grey-white matter contrast; regional cortical tracer uptake at any of the cortical target regions: lateral temporal, frontal, posterior cingulate-precuneus, and parietal), negative (good grey-white matter contrast; no tracer uptake at target regions), or inconclusive for amyloid plaque presence.[23]

2.4. Statistical analysis

Mean ± standard deviation values and frequency distributions are reported. We assessed differences in baseline characteristics between groups using analysis of variance, Kruskal–Wallis tests, and Pearson χ^2 tests when appropriate. We compare the initial and final diagnostics confidence levels using a paired sample test (Wilcoxon sign rank and McNemar–Bowker tests). We used χ^2 tests to assess differences between negative and positive amyloid PET in the treatment plan. We set the level of significance at $P < .05$. Statistical analyses were performed using SPSS version 15. (IBM, Chicago, IL).

3. Results

3.1. Diagnostic evaluation and treatment before amyloid-pet

A total of 211 patients (115 women and 96 men) with a mean age of 63.54 ± 6.43 years were included. The baseline characteristics of the patients are shown in Table 2. The study of routine dementias, before the amyloid-PET, was completed in 208/211 patients (98.6%), being inconclusive in 201 cases (99.5%). According to the AUC criteria 86 patients (40.7%) had a progressive early-onset dementia (≤65 years); 55 patients (26.1%) shown atypical presentation and/or atypical course;

Table 2

Baseline characteristics of the overall study population and according to the origin center.

	CENTER 'A' (n = 112)	CENTER 'B' (n = 99)	TOTAL (n = 211)	*P*
Age	61.81 ± 6.54 [60.59–63.04]	65.48 ± 5.73 [64.34–66.63]	63.54 ± 6.43 [62.66–64.41]	.000
Sex	Male: 55 (49%) Female: 57 (51%)	Male: 41 (41%) Female: 58 (59%)	Male: 96 (45%) Female: 115 (55%)	.163
Patiens CBNU*	7200	6300		
AUC				.000
Persistent or progressive unexplained MCI	17 (15.2%)	33 (33.3%)	50 (23.7%)	
Clinical criteria for possible AD but atypical clinical onset or course	22 (19.6%)	33 (33.3%)	55 (26.1%)	
Early age onset (≤ 65 yr) of progressive cognitive impairment or dementia	58 (51.8%)	28 (28.3%)	86 (40.7%)	
Mixed etiology	15 (13.4%)	5 (5.1%)	20 (9.5%)	

In cells: mean ± typical deviation [confidence interval].

AD = Alzheimer, AUC = appropriate use criteria (see text), CBNU = cognitive behavioral neurology unit, MCI = mild cognitive impairment.

* Estimation of total of patients attended at cognitive behavioral neurology unit (CBNU) during recruitment period (January/2014–June/2018).

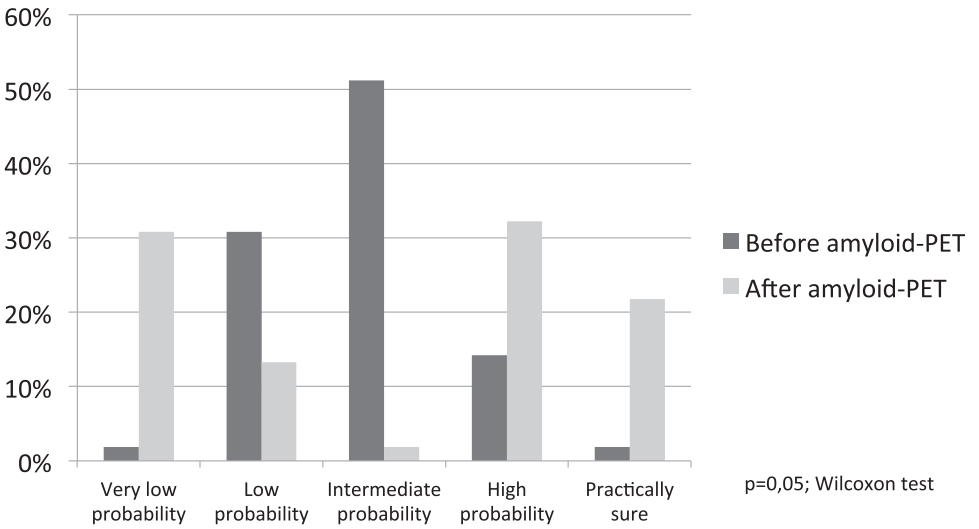


Figure 1. Diagnostic confidence before and after amyloid-PET. PET = positron emission tomography.

50 patients (23.7%) suffer persistent or progressive unexplained MCI and in 20 patients (9.5%) a mixed etiology was considered. After this first diagnostic evaluation, the most frequent degree of diagnostic confidence of AD was intermediate probability (category 2) in 108 patients (51.2%); followed by low probability (category 1) in 65 patients (30.8%) and high probability (category 3) in 30 patients (14.2%); in only 4 patients (1.9%) the diagnosis was practically sure (category 4) or very low probability (category 0).

Specific treatment for AD was started, before amyloid-PET, in 80 patients (37.9%).

Amyloid-PET was positive in 118 patients (55.9%) and negative in 93 patients (44.1%).

3.2. Diagnostic confidence before and after amyloid pet

After amyloid-PET, the diagnostic confidence showed that the most frequent category was high probability (category 3) in 68 patients (32.2%); followed by the category very low probability (category 0) in 65 patients (30.8%); practically sure (category 4) in 46 patients (21.8%); low probability (category 1) in 28 patients (13.3%); and only 4 patients (1.9%) in intermediate probability (category 2). Consequently, there was a significant increase in categories of greater diagnostic confidence, what is 28.9% in very low probability (category 0), 18% in high probability (category 3) and 19.9% in practically sure (category 4) ($P = .05$, Wilcoxon test) (Fig. 1).

Analysis of the diagnostic prescan confidence according to amyloid-PET results showed that in both, negative and positive-PET subgroup, the most frequent category was intermediate probability (45.7% and 55.1%, respectively) (Fig. 2). After the amyloid-PET, the diagnostic post-scan confidence showed a very different distribution, that was, in the negative-PET group the most frequent categories are very low probability (70.7%) and low probability (29.3%); while in the positive-PET group were high probability (57.6%) and practically sure (39%) (Fig. 3). Figure 4 shows the change in diagnostic confidence before and after amyloid-PET. Only in 14/211 patients (6.6%) the result of the amyloid-PET did not influence the diagnostic confidence, while in most of the sample, 194 patients (93.4%), the diagnostic confidence improved significantly after amyloid-PET results.

We grouped the categories of greater diagnostic confidence (very low probability and practically sure) and those of less confidence (low, intermediate, and high probability). We found that the diagnostic confidence was not modified for the all cases (8 patients) with a greater prescan diagnostic confidence; however, in 50.7% of cases with less diagnostic confidence prescan, amyloid-PET results conditioned an increase in the degree of confidence diagnostic ($P < .001$, McNemar test).

3.3. Changes in management

Before amyloid-PET, 80 patients (37.9%) had specific treatment for AD and 131 patients (62.1%) had not initiated treatment.

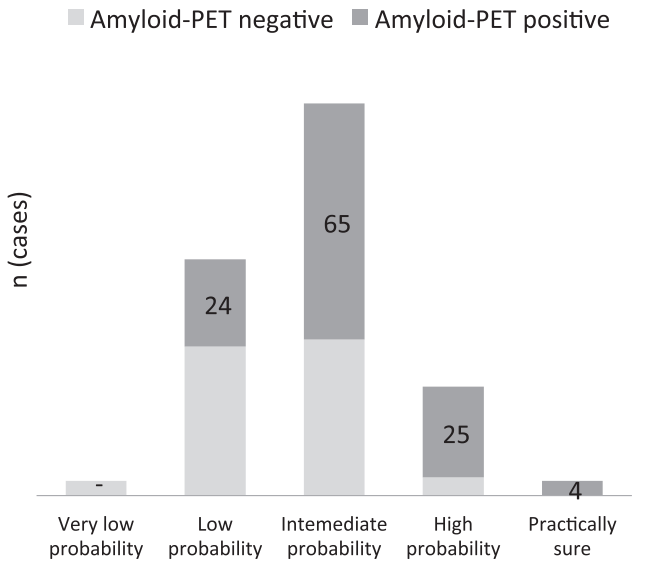


Figure 2. Diagnostic pre-scan confidence according amyloid-PET results. PET = positron emission tomography.

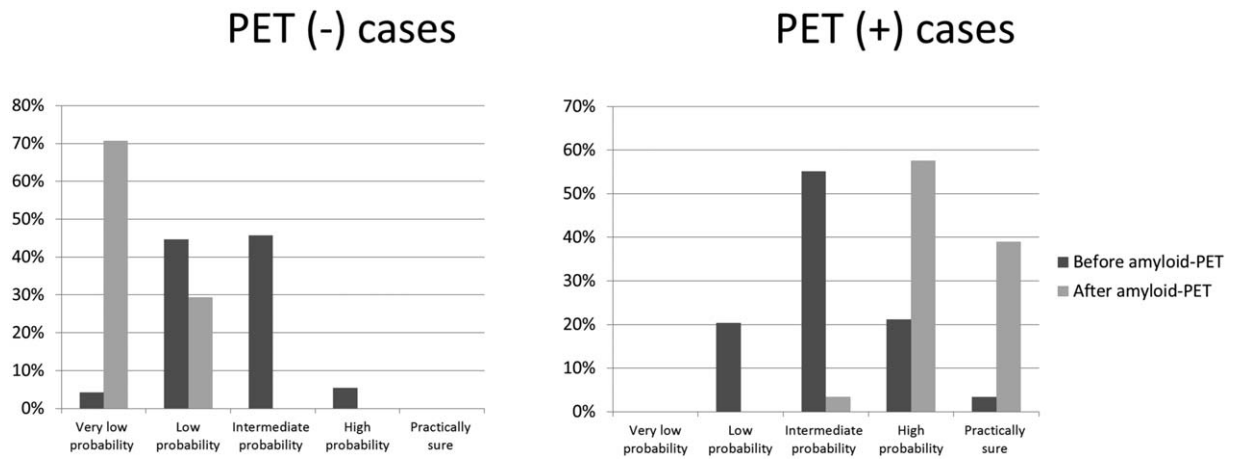
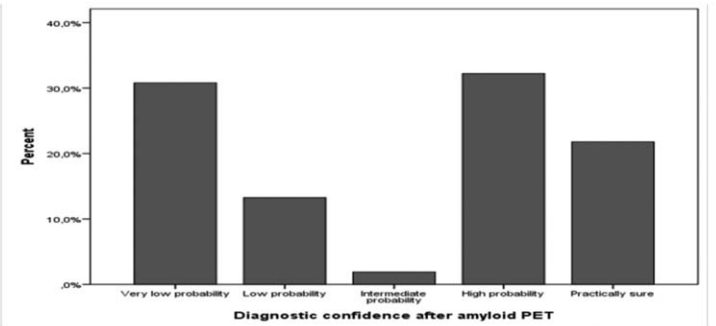
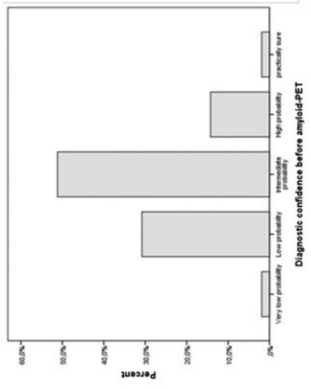


Figure 3. Diagnostic confidence in positive and negative amyloid-PET. PET = positron emission tomography.

After performing the amyloid-PET, 119 patients (56.4%) had specific AD treatment, while 92 patients (43.6%) had no treatment. That is, 27/80 (33.8%) patients with specific treatment before amyloid-PET stopped receiving it after amyloid-PET study, while in 66/131 (50.4%) patients who did not receive specific treatment before amyloid-PET, started a treatment based on the results of amyloid-PET. Therefore, the therapeutic intention was modified in 93 patients (44.1%). Of these, 66 patients (71%) had a positive amyloid-PET study, while the remaining 27 (29%) had a negative amyloid-PET. In the rest (118 cases; 55.9%) the treatment was not modified, 52/118 (44.1%) with positive amyloid-PET and 66/118 (55.9%) with negative amyloid-PET. A positive result in the amyloid-PET conditioned changes in management in 66/118 patients (55.9%), whereas a negative result in 27/93 (29%) patients ($P < .001$, χ^2 test).

Treatment in the intermediate probability subgroup of the diagnostic confidence prescan was modified in 56/108 patients (51.9%); of these, 42 patients (75%) had a positive amyloid-PET,





	Very low probability	Low probability	Intermediate probability	High probability	Practically sure
Very low probability	4	0	0	0	0
Low probability	38	3	3	20	1
Intermediate probability	19	24	1	48	16
High probability	4	1	0	0	25
Practically sure	0	0	0	0	4

Modified of Ceccaldi et al (18).

Figure 4. Change in diagnostic confidence.

while in the remaining 14 patients (25%) was negative. In 52/108 patients (48.1%) the management was not modified, 23 patients (44.2%) with positive amyloid-PET and 29 patients (55.8%) negative amyloid-PET.

4. Discussion

In this naturalistic study, we have attempted to estimate the impact of amyloid-PET on the diagnostic certainty and therapeutic approach of AD, added to the routine diagnostic procedures, in a subgroup of patients in which AUC recommend the investigation of their beta-amyloid burden to assess clinical management.[11,16] The population from which patients were recruited is representative of the population of eastern and southern Spain, asking for specialized help in the study of cognitive impairment, when the initial clinical evaluation is insufficient for diagnosis.

The clinical diagnosis suffers from limitations in the actual clinic context.[24] The use of consensual criteria improves this setting, but, even for dementia (not only for MCI), the misdiagnosed rate is high.[25] Final diagnosis is not possible "in vivo" and its approach on basis follow-up of patient could delay the correct treatment. This study arises from this scenario, in which the neurologist cannot wait the clinical evolution, but need to reduce the uncertainty in the diagnosis. Ancillary procedures as CSF-B or amyloid-PET (mandatory for investigation)[4] are now available for clinical use.

Amyloid-PET is a neuroimaging modality that is been increasingly used to assess patients with AD.[11] Several past and present studies investigated the cumulative utility of amyloid imaging on the routine clinical diagnostic assessment of large sets of patients evaluated for cognitive impairment.[19,26–29] This work uses the AUC to select amyloid-PET candidates because there is evidence-based consensus that benefit in decrease diagnostic uncertainty and improve treatment suitability.[18] The AUC could help the neurologist to request an amyloid-PET in an appropriate context, when the evaluation of the dementia supposes a dilemma.[30] This is important because amyloid-PET can also identify amyloid deposition in healthy subjects, who will not necessarily develop the disease as it occurs in a large number of normal elderly[11] or in multiple etiologies such as Lewy bodies or cerebral amyloid angiopathy[4] increasing the false positive rate. On the other hand, the negative predictive value of PET is very important, especially in a disease with high (and growing) prevalence,[17] but always bearing in mind that the rare forms of AD[11] can generate false negatives. In addition, the application of the AUC could help to select amyloid-PET resources rationally justified, due to the low availability of the test or its cost, relevant in health systems.[31]

In the present study, the diagnostic accuracy of amyloid PET was not addressed because does not have final histopathological results. This estimation has been reported in previous works confirmed by final histology[32–34] or supported by clinical follow-up.[7,35] A preliminary and indirect approach of diagnostic accuracy in this series is available in a previous study.[36]

As set above, this work aims to evaluating the clinical usefulness of amyloid-PET as a biomarker of AD, in a naturalistic context. Our results show that amyloid images have an additional value in routine clinical practice. Overall, the amyloid PET study improved the diagnostic confidence in 93.4% patients. Our results are in line with those published by Ceccaldi et al[18] reporting an increase in diagnostic confidence in 81.5% of the subjects after the performance of amyloid-PET. These authors justify this proportion of change as consequence of the high level of pre-test diagnostic uncertainty, which in turn reflects the complexity of the population. At this respect, our population has some peculiarities: is younger, predominantly early onset disease ($\leq$65 years) and lower proportion of atypical forms. In our opinion, although our subpopulations are different, they guarantee the whole spectrum of possibilities found in clinical practice (external validity). In general terms our results are in agreement with others works[17,35,37,38] using a different methodology to estimate diagnostic confidence as the percentage of increase in diagnostic confidence, reporting modifications from 16% to 26% (the modification in 1 step in the 5-point scale used in this work or in Ceccaldi et al,[18] implies a 20%), and in a population not restricted to AUC.[19]

According to the modification of confidence our sample could not be considered as homogeneous. Starting from a clinical setting of inconclusive or insufficient diagnostic, it seems logical to find that after this first evaluation, the categories of diagnostic certainty with the highest proportion of patients are the intermediate categories (specifically in our study, 50% of the patients were classified with an intermediate probability of AD). When the categories are grouped: higher diagnostic confidence (very unlikely and practically sure) and those of less confidence (unlikely, intermediate probably and very probable), we found that the diagnostic confidence was not modified in any cases with a high diagnostic confidence before the scan (8 patients). However, in 50.7% of the cases with less previous diagnostic confidence, PET results conditioned an increase in the degree of diagnostic confidence. These results are closed with those previously published, reporting that the change in diagnosis and the increase in diagnostic confidence were lower in cases with greater pre-PET diagnostic confidence,[7,35,39] therefore, it would support the hypothesis that amyloid PET can have greater impact in situations with significant diagnostic problems, with greater diagnostic uncertainty after a first line protocol for the study of AD has been completed.

Our results show significant changes in diagnostic confidence between positive and negative amyloid-PET subgroups, probably because they represent 2 different scenarios.

On the one hand, in the subgroup of patients with a positive result of amyloid-PET, in respect pre-PET categories there was a relevant migration from intermediate stages to the categories very probable (57.6%) and practically sure (39%). PET with amyloid also showed a clinical utility for cases with more certain diagnosis of AD and a positive result of amyloid-PET was also useful, increasing confidence levels. These results (similar to previously recognized for the CSF-B)[40] support its usefulness available to establish the diagnosis of AD in combination with clinical parameters.

On the other hand in the PET-amyloid negative subgroup, the categories with the highest proportion of patients were very unlikely (70.7%) and unlikely (29.3%). These results are not surprising and come to highlight previous evidence reporting the high negative predictive value of amyloid images in histopathological studies,[33] and indicates that dementia experts generally use a negative amyloid scan as a validated method to exclude a diagnosis of AD in the majority of complex cases; this high negative predictive value is even more valuable when the disease prevalence increases in the general population.

In view of our results, in consonance with other works, amyloid-PET improves diagnostic confidence[18,41] and clinical

management.[39,41] Our results support that the use of amyloid-PET should be implemented as a biomarker, not only in a research framework as suggested by the AT (N) system,[42] but also in the study of cognitive impairment in a clinical context.

Regarding changes in the management after amyloid-PET (ie, new medication initiated, medication withdrawn), in our series changing were reported in 44.1% of patients. These results are in agreement with previous studies that used similar criteria, which report changes in treatment from 37% to 68%.[38,43] However, our results are lower than those described by Ceccaldi et al,[18] which reported changes in management for 80.0% of cases; but in this series only are considerate changes in management presuming to have a substantial impact on management (ie, a new drug started, a drug withdrawn, additional diagnostic tests, referred to another specialist), this percentage is reduced to 50.7% of patients, closer to that found in our population. This discrepancy suggests variability in clinical practice: some neurologists indicate a specific treatment before knowing the results of amyloid-PET, while others expect them to indicate the treatment. We believe that this fact reproduces what really happens in the daily clinic. Other diverse factors, such as differences in methodological definitions, selected variables of patient management and diagnostic uncertainty before amyloid-PET, may have contributed to the differences in the findings.

Changes in management were more common in patients with higher diagnostic uncertainty, (the intermediate probability subgroup of AD pre-PET) and the treatment was modified in more than half of the patients (51.9%). This result is not surprisingly and is in the same direction as those previously described by Ceccaldi et al, who report that changes in management were more common in patients with low pre-PET diagnostic confidence.[18]

Interestingly, changes in management were more frequent in patients with positive amyloid-PET compared to negative. In our study a positive result in the amyloid-PET changes therapeutic intention in 55.9% patients, whereas a negative result in 29%. These results are inconsistent with those previously published by other series, in which the treatment changes were similar in patients with positive or negative PET amyloid.[18] As set above, these discrepancies support the variability in clinical practice regarding the time to start specific treatment of AD respect to amyloid-PET report.

This study is not specifically a cost-analysis and our contribution cannot be more than speculative but could not be indifferent to this aspect. The prognostic and preventive implications of an early and clear diagnosis of AD have direct repercussions in the health systems,[44] patients[6,19] and caregivers.[27] Cannot ignore the intangible costs and the fact that an early diagnosis allows to make decisions that the illness must face. New therapies are addressed to stop the progression of disease and it is desirable to be effective in early stages of process.[45] Evidently, the implementation of specific early therapies could be more cost-effective than the costs generated by the delay in the application of a treatment, when only secondary or tertiary prevention can be done.[6]

This study has some limitations. First, in our work postmortem verification was not available and the main outcome measure was the change in diagnostic confidence, and this outcome reflects the beliefs of clinicians. However, the proportional change observed in diagnostic confidence is in agreement with others previous studies[18,27,35,37] with a similar methodological approach. Could be desirable that a long clinical follow-up of the population provides information on the relation of amyloid-PET results with the parameters of diagnosis certainty and treatment optimization. Second, the cases were recruited in a clinical frame setting, without randomization, which may have led to an overestimation or underestimation of the effect of amyloid-PET in diagnostic confidence, but this naturalistic study provides evidence that the interpretation of amyloid-PET is associated with a significant improvement in diagnostic confidence, and it is worthy of clinical promotion and application. Third, most patients were included in a tertiary referral center, with a high proportion of early-onset and atypical clinical presentations. This can hinder translation to primary and secondary-care levels, where the populations tend to be older, more advanced or less complex. However, in our opinion amyloid-PET should only be performed after exhaustive standardized protocols applied by trained staff.[11] Finally, amyloid-PET scans have been reported only by visual analysis, grounded in the subjective criteria of qualified specialists. Semiquantitative procedures could be of interest in inconclusive studies (none in our series) and provide complementary objective information. In the project phase of this work, the investigation team decides does not modify the standardized protocol used in daily practice based only in visual analysis to maximize the external validity of our results to any other center.

5. Conclusions

In conclusion, this naturalistic study provides evidence that the performance of amyloid-PET is associated with a significant improvement in diagnostic confidence and has a high impact on the therapeutic management of patients with MCI, fulfilling clinical AUC, who usually present uncertain clinical features as early-onsets, atypical, mixed and rapid progressing presentations. Consequently we strongly recommend, based on existing evidence and our results, to implement amyloid PET in AUC in daily clinical practice.

Author contributions

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