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Clinical value of plasma ALZpath pTau217 immunoassay for assessing mild cognitive impairment

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ABSTRACT

Background Among plasma biomarkers for Alzheimer's disease (AD), pTau181 and pTau217 are the most promising. However, transition from research to routine clinical use will require confirmation of clinical performance in prospective cohorts and evaluation of cofounding factors.

Method pTau181 and pTau217 were quantified using, Quanterix and ALZpath, SIMOA assays in the well-characterised prospective multicentre BALTAZAR (Biomarker of AmyLoid pepTide and AlZheimer's diseAse Risk) cohort of participants with mild cognitive impairment (MCI).

Results Among participants with MCI, 55% were Aβ+ and 29% developed dementia due to AD. pTau181 and pTau217 were higher in the Aβ+ population with fold change of 1.5 and 2.7, respectively. MCI that converted to AD also had higher levels than non-converters, with HRs of 1.38 (1.26 to 1.51) for pTau181 compared with 8.22 (5.45 to 12.39) for pTau217. The area under the curve for predicting Aβ+ was 0.783 (95% CI 0.721 to 0.836; cut-point 2.75 pg/mL) for pTau181 and 0.914 (95% CI 0.868 to 0.948; cut-point 0.44 pg/mL) for pTau217. The high predictive power of pTau217 was not improved by adding age, sex and apolipoprotein E ε4 (APOEε4) status, in a logistic model. Age, APOEε4 and renal dysfunction were associated with pTau levels, but the clinical performance of pTau217 was only marginally altered by these factors. Using a two cut-point approach, a 95% positive predictive value for Aβ+ corresponded to pTau217 >0.8 pg/mL and a 95% negative predictive value at <0.23 pg/mL. At these two cut-points, the percentages of MCI conversion were 56.8% and 9.7%, respectively, while the annual rates of decline in Mini-Mental State Examination were −2.32 versus −0.65.

Conclusions Plasma pTau217 and pTau181 both correlate with AD, but the fold change in pTau217 makes it better to diagnose cerebral amyloidosis, and predict cognitive decline and conversion to AD dementia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Plasma pTau217 is the most promising biomarker for cerebral amyloidosis and Alzheimer's disease. A new immunoassay developed by ALZpath is compatible with routine clinical use. It is important to evaluate its performance on a relevant population of patients with mild cognitive impairment, such as those in the well-characterised prospective multicentre BALTAZAR cohort.

WHAT THIS STUDY ADDS

⇒ Our study shows that this new pTau217 test is highly effective in identifying cerebral amyloidosis, cognitive decline and conversion to Alzheimer's dementia. It also assesses the impact of comorbidities and provides useful thresholds for the clinical application of the test.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The information provided by this study will help optimise the management of patients with Alzheimer's disease, including diagnostic strategy, prevention and access to disease-modifying therapies.

INTRODUCTION

Alzheimer's disease (AD) is a problem that needs close monitoring for better management in an ageing society where it is increasingly prevalent. AD likely follows a trajectory; amyloid build-up is thought to be the preclinical starting point in cognitively unimpaired people. These people start to have cognitive problems in this 'prodromal' stage. This mild cognitive impairment (MCI) is associated with gradual build-up of neuronal Tau tangles and conversion to dementia due to AD. There is an urgent need for the use in clinical practice of biomarkers for these early stages to better manage the disease.

Tau protein is at the heart of AD, and it exists in many post-translationally modified protein isotypes. Tau has many phosphorylation sites, many of which are in the proline-rich region, and some of these have been posited as useful biomarkers.[1] Two of the moieties that have generated the most interest are threonines 181 and 217. Although pTau181 is a useful marker to predict amyloid status and conversion to dementia,[2] many publications in the last 3 years are painting a picture whereby pTau217 is even more promising.[3] For example, in 2020, cerebrospinal fluid (CSF) pTau217 was already found to outperform pTau181 to detect AD.[4 5] A likely crucial factor in this superiority was that the fold

change in CSF was greater for phosphorylation position 217 than for 181.[6]

The brain changes that occur in AD can currently be assessed by two methods: either by positron emission tomography (PET) or by CSF analysis. It is thus essential to find blood biomarkers that mirror these more invasive/expensive/lengthy tests as a prescreen. As mentioned above, many studies have also found plasma pTau217 highly specific in distinguishing AD from normal.[7–10] Indeed, plasma pTau217 is as good as any CSF markers or as PET screening to discriminate AD from other diseases.[11] pTau217 can also distinguish AD from other forms of dementia like frontotemporal lobar degeneration (FTLD).[10] Even more importantly from a clinical perspective, plasma pTau217 can distinguish different stages of the AD trajectory.

Several studies have demonstrated a link between pTau217 and cerebral amyloidosis (Aβ+). pTau217 has the power to detect Aβ+ MCI[12] and Aβ+ can be detected with an area under the curve (AUC) of 0.91.[13] For example, Doré *et al* found that preclinical subjects that are Aβ+ had twice the level of pTau217, rising to 3.5× in cognitive impairment.[14] The Hansson group have shown that pTau217 correlates with clinical deterioration, cognitive decline and brain atrophy and can detect the difference between cognitively unimpaired Aβ+ and Aβ-, making it a surrogate marker for preclinical and prodromal AD.[3 15–17] In fact, plasma pTau217 is a predictor of poor cognitive trajectory[8 18] and conversion to AD.[19 20] Plasma pTau217 builds up for two decades before the onset of symptoms[21] and plasma pTau217 and 231 build-up earlier than Aβ PET can detect changes.[22]

Two different plasma pTau217 immunoassays: p-tau217Lilly (run on a Meso Scale Discovery (MSD) platform) and p-tau-217Janssen (run on a Simoa plateform) were compared with similar results by Groot *et al*[23] and Janelidze *et al*.[12] These assays were developed with proprietary antibodies. These results were further confirmed although with some doubts about their sensitivity to detect pTau217 all the time.[24 25] More recently, novel pTau217 assays (University of Gothenburg) run on Simoa using commercially available tau12, and tau-441 antibodies gave very good results.[13]

Not all the pTau217 assays used in these studies are available off-the-shelf to all investigators. Indeed, the ALZpath plasma pTau217 assay, which we evaluate below, is in fact the first scalable commercially available test. An article preprint has already suggested that it is accurate in detecting AD pathology.[26] In our results presented below, this assay is comparable to other pTau217 assays in identifying cerebral amyloidosis, cognitive decline and conversion to AD dementia. Moreover, our study integrates the evaluation of comorbidities since the BALTAZAR cohort includes biomarkers designed to monitor metabolism, nutrition, diabetes and cardiovascular risk. Importantly, unlike for pTau181, the impact of comorbidities on performance seems to be limited probably in relation with the high fold change observed between normal and pathological groups. We therefore propose useful thresholds to confirm or rule out the presence of cerebral amyloidosis, information that can be used to stratify patients to select those who will benefit from the last line of antiamyloid treatment.

MATERIALS AND METHODS

Study population

This study included participants with MCI of the BALTAZAR multicentre prospective cohort (ClinicalTrials.gov Identifier #NCT01315639).[27] All participants had clinical, neuropsychological, brain MRI and biological assessments (see next). Right and left hippocampal volumes were obtained for each participant using virtual segmentation of the hippocampus. APOE was genotyped in a single-centralised laboratory. MCI subjects were selected according to the Petersen criteria.[28] Participants were assessed for conversion to dementia every 6 months for 3 years.[27] The progression from MCI to dementia was defined by evaluation of the following parameters: (1) decline in cognitive function measured by Mini-Mental State Examination (MMSE), (2) disability in activities of daily living and (3) clinical dementia rating sum of boxes. Conversions from MCI to AD dementia were reviewed by an adjudication committee. Conversion to AD accounted for 95% of conversions to dementia, and was assessed on the basis of clinical, imaging and neuropsychological evaluation and follow-up. Participants were categorised, as amyloid-positive (Aβ+) or negative (Aβ−), based on their CSF Aβ42/Aβ40 (ratio below 10% as measured with Euroimmun ELISA assays). Blood and CSF samples were taken on the same day, and to minimise preanalytical and analytical problems, identical plasma collection tubes were used across centres. Plasma aliquots were stored at −80°C until testing.

Plasma pTau measurement

Plasma pTau level was determined, using the Quanterix method that is based on ultrasensitive Simoa technology,[29] on an HD-X analytical platform. Plasma pTau181 was measured with a commercial Advantage V1 kit (#104111). This assay has a low limit of detection at 0.019 pg/mL and a low limit of quantification at 0.085 pg/mL. Quality controls, with low (QC 1 with mean concentration of 3.82 pg/mL) or high (QC 2–52.4 pg/mL) assigned pTau181 concentrations, are provided in the kits. Inter-assay coefficients of variation for QC 1 and QC 2 were 7% and 5%, respectively. Plasma pTau217 was detected using a novel immunoassay developed by ALZpath, using a proprietary monoclonal pTau217-specific antibody. For this assay, the low limit of detection was 0.0052 pg/mL and the limit of quantification was 0.06 pg/mL. Intrarun and inter-run precision were 11.4% and 14.6%, respectively.

Biological biomarker measurements

Blood samples, taken at baseline, were used for determination of routine parameters in ISO15189-certified laboratories: fasting glycaemia, triglycerides, cholesterol (total, high-density lipoproteins, low-density lipoproteins), creatinine, prealbumin, albumin, total protein, C reactive protein (CRP), haemoglobin, vitamin B_{12}, thyroid stimulating hormone, folate and red-cell folate.[27] Estimated glomerular filtration rate (eGFR) based on creatinine, age and sex was calculated using the CKD Epidemiology Collaboration equation, revised in 2021 without inclusion of race.[30] High molecular weight adiponectin was measured on stored samples using the LUMIPULSE G platform.

Statistical analyses

General characteristics were analysed in the MCI sample overall and in converter and non-converter MCI subsets. Categorical variables were analysed as percentage and counts (% (N)), continuous variables as mean and SD (M (SD)) or median (25–75 percentile IQR) and comparisons were made by χ^2 test, t-test, Mann-Whitney U test or analysis of variance (Kruskal-Wallis test). Cox proportional hazards regression models for conversion, with time to dementia as a dependent variable, were computed, with adjustment for age at blood draw, sex, and APOEε4 allele carrier status. We additionally plotted Kaplan-Meier curves for the different pTau tertiles and differences between tertiles

were calculated by Log-rank test. For all analyses, a two-sided α-level of 0.05 was used for significance testing. Receiving operator characteristic (ROC) curves, using conversion as a dependent variable, were also used. The corresponding AUCs were compared using the Delong method.[31] For each comparison, the size of the different groups is indicated in the tables. Missing data have not been imputed. All analyses were performed using MedCalc (20·118) and R (R Core Team (2019)) software.

RESULTS

Baseline characteristics of participant with MCI

Here, we present data from 473 patients with MCI from the BALTAZAR cohort[27] (table 1). Mean age at baseline was 77.7 (SD 5.5) years. 28.5% of the subjects (135/473) converted to AD dementia during the 3-year period.[32] Subjects who converted to AD dementia (MCI converters) did not differ from non-converters regarding their age, sex distribution, body mass index (BMI) or educational levels (table 1). 39.1% (184/470) of the participants with MCI were APOE ε4 carriers. The average MMSE score at baseline was 26.4 (SD 2.5) and MCI converters had lower MMSE at baseline and a much higher MMSE decline per year, at −3.45 (SD 4.26) on average versus −0.42 (SD 1.89) for the non-converter population. Hippocampal volume (R+L) (cm^3) was also lower in converters than in non-converters. Hippocampal volume was not correlated to plasma pTau levels (online supplemental figure 1). All these differences remained significant after adjustment for age, sex, APOE ε4 and the educational status. pTau217 levels were always lower than pTau181 levels; respective mean plasma levels in the MCI population were 0.49 (SD 0.34) versus 3.18 (SD 1.49) pg/mL. The two sets of values were however correlated (Pearson correlation coefficient 0.73 (95% CI 0.68 to 0.77), significance level p <0.0001).

Plasma pTau217 and pTau181 in Aβ– and Aβ+ participants

In the subgroup of MCI with available CSF amyloid measurements, participants could be stratified as Aβ− or Aβ+ according to their CSF Aβ42/Ab40 ratio. Both plasma pTau217 and pTau181 levels were higher in Aβ+ MCI than in Aβ− (n=116, 0.75 (SD 0.34) vs n=97, 0.28 (SD 0.19) pg/mL for pTau217 and 3.87 (SD 1.38) vs 2.6 (SD 1.42) pg/mL for pTau181) (figure 1A,B, table 1). This was also the case for CSF pTau181 (Aβ− 51.9 (SD 16.0) vs Aβ+ 79.1 (SD 32.3) pg/mL). CSF pTau181 correlated better with plasma pTau217 than with pTau181 (online supplemental figure 2). However, fold change was much higher for plasma pTau217 than for plasma pTau181 (2.67 vs 1.48) as well as for CSF pTau181 (2.67 vs 1.52) (online supplemental table 1). The AUC for Aβ+ detection was significantly higher for pTau217 (0.914 (95% CI 0.868 to 0.948)) than for pTau181 (0.783 (95% CI 0.721 to 0.836)) (figure 1, table 2). Optimal cut-points were determined, by Youden index, at 0.44 pg/mL and 2.75 pg/mL for pTau217 and pTau181, respectively. The AUCs increased non-significantly in a logistic regression model with age, sex and APOEε4 status (figure 1C,D, table 2). Conversely, the predictive power of age, sex and APOEε4 status was significantly improved by adding pTau217, with the AUC rising from 0.750 (95% CI 0.686 to 0807) to 0.931 (95% CI 0.889 to 0961). Regarding blood biomarker comorbidities, folate and CRP concentrations were slightly lower in the Aβ+ population (online supplemental table 2). However, Bonferroni adjustment linked to the multiple comparison of comorbidities did not reach significance (p >0.001).

Plasma pTau217 and pTau181 predict cognitive decline and conversion to AD dementia

For participants with MCI that converted to AD (n=135) versus those that did not (n=331), the respective values were 0.69

Table 1 Patient characteristics

	Total n MCI	Value (mean (SD))	Aβ−	Value (mean (SD))	Aβ+	Value (mean (SD))	Aβ− versus Aβ+ (p)	Adjusted age, sex, APOE ε4, education	N MCI Non converter	Value (mean (SD))	N MCI converter	Value (mean (SD))	Converter versus non-converter (p)	Adjusted age, sex, APOE ε4, education
Age (years)	473	77.7 (5.5)	97	76.6 (5.1)	116	78 (5.9)	0.0780	/	338	77.4 (5.4)	135	78.4 (5.7)	0.0918	/
Men (%)	473	38.7	97	45.4	116	36.2	0.1782	/	338	38.4	135	39.4	0.7135	/
BMI (kg/m^2)	466	25 (3.8)	97	25.4 (3.7)	112	24.2 (3.6)	0.0207	0.2558	334	25.1 (3.8)	132	24.7 (3.7)	0.3021	0.8348
MMSE (/30)	462	26.4 (2.5)	94	27.1 (2)	113	25.8 (2.5)	<0.0001	0.0003	328	26.7 (2.5)	134	25.6 (2.5)	<0.0001	0.0003
MMSE/year	417	−1.38 (3.18)	89	−1.2 (2.87)	105	−1.87 (4.24)	0.1902	0.1061	285	−0.42 (1.9)	132	−3.45 (4.26)	<0.0001	<0.0001
1 or 2 APOE4 alleles (%)	470	39.1	97	15.5	116	53.4	<0.0001	/	335	31.9	135	57.0	<0.0001	/
Hippocampal volume (R+L) (cm3)	383	4.55 (1.12)	82	4.64 (1.23)	98	4.52 (0.95)	0.4677	0.9674	271	4.79 (1.06)	112	3.99 (1.06)	<0.0001	<0.0001
Educational level (years)	472	5.2 (1.6)	97	5.3 (1.5)	115	5.4 (1.6)	0.0277	/	337	5.2 (1.6)	135	5.2 (1.6)	0.6877	/
pTau217 (pg/mL)	473	0.49 (0.34)	97	0.28 (0.19)	116	0.75 (0.34)	<0.0001	<0.0001	338	0.41 (0.29)	135	0.69 (0.37)	<0.0001	<0.0001
pTau181 (pg/mL)	473	3.18 (1.49)	97	2.60 (1.42)	116	3.87 (1.38)	<0.0001	<0.0001	338	2.93 (1.39)	135	3.81 (1.54)	<0.0001	<0.0001

Values in the number (n) of participants with MCI for which different data types were available and comparison between non-converter and converters, with Student's t-test or χ2 and linear regression adjusted for age, sex and the presence of the APOE ε4 allele; numbers were used to describe categorical variables. mean±SD for continuous variables.
APOE, apolipoprotein E; BMI, body mass index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

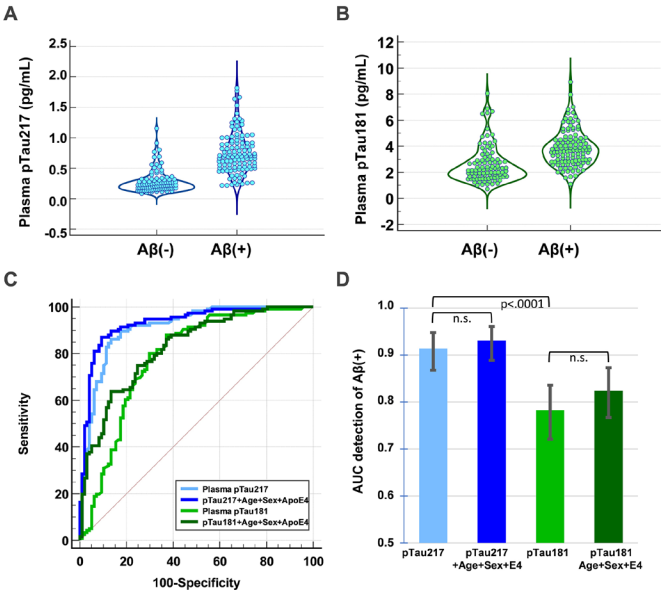

Figure 1 Plasma pTau217 and pTau181 in mild cognitive impairment according to amyloid status. Distribution of (A) pTau217 and (B) pTau181 in pg/mL is represented in the Aβ− and Aβ+ populations. (C) Receiving operator characteristic curves for the same data. Both biomarkers were significantly different between these two populations and a logistic regression model combining pTau values with age, sex and APOEε4 status gave slightly higher AUCs. (D) Area under the curve (AUC) with 95% CIs.

(SD 0.37) versus 0.41 (SD 0.29) pg/mL for pTau217 and 3.81 (SD 1.53) versus 2.93 (SD 1.39) pg/mL for pTau181, that is, converters had 70% more pTau217 and only 30% more pTau218 (table 1, online supplemental figure 3A,B). The AUC for conversion to AD were significant, but they were lower than they were for the detection of cerebral amyloidosis: (0.746 (95% CI 0.704 to 0.785)) for pTau217 and (0.677 (95% CI 0.633 to 0.719)) for pTau181 (online supplemental figure 3C). AUC for conversion, of CSF pTau181, was 0.712 (95% CI 0.646 to 0.771), and CSF Aβ42/40: 0.733 (95% CI 0.668 to 0.791). Participants who converted to AD were 78.3% Aβ+, whereas only 43.1% of non-converters were Aβ+. After adjustment for age, sex and APOE ε4 status, in a Cox proportional hazard model, conversion to AD dementia, within 3 years, showed a significant risk for age, MMSE, APOE ε4, hippocampal volume, pTau181 and pTau217 (table 3). pTau217 had a higher HR at 8.30 (5.46 to 12.61), compared with 1.38 (1.26 to 1.52) for pTau181. Importantly, none of the comorbidity biomarkers were independently associated with an increased risk of conversion (online supplemental table 3). The relative risks of conversion to AD dementia, as predicted by high plasma pTau217 and pTau181, are illustrated by Kaplan-Meier curves of pTau tertiles (figure 2A,B). The HRs between the first and the third tertile were 7.37 (95% CI 4.86 to 11.16) and 3.83 (95% CI 2.54 to 5.79) for plasma pTau217 and pTau181, respectively. We also tracked changes in MMSE over 18 months (figure 2C,D) and found the steepest decline for the p217-high (third) tertile. The three p217 tertiles each predicted distinct cognitive decline trajectories. The differences were less significant for pTau181 with a smaller difference between low and medium and no further effect in the third pTau181 tertile.

Table 3 Risk factors associated with conversion to dementia during follow-up

Factors	N	HR conversion (95%CI)	P value	P adjusted (age, sex, APOE ε4)
Age	473	1.03 (1 to 1.07)	0.0443	/
Sex	473	0.87 (0.62 to 1.23)	0.4256	/
BMI	466	0.99 (0.95 to 1.04)	0.7878	0.5496
MMSE	462	0.84 (0.79 to 0.89)	<0.0001	<0.0001
APOE ε4	470	2.34 (1.67 to 3.3)	<0.0001	/
Hippocampal volume	383	0.58 (0.5 to 0.67)	<0.0001	<0.0001
Educational level	472	0.95 (0.85 to 1.05)	0.3032	0.3014
pTau217	473	8.30 (5.46 to 12.61)	<0.0001	<0.0001
pTau181	473	1.38 (1.26 to 1.52)	<0.0001	<0.0001

Cox proportional hazard model of conversion to dementia in follow-up before and after adjustment for age, sex, educational level and the APOE ε4 status.
APOE, apolipoprotein E; BMI, body mass index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Association of plasma pTau217 and pTau181 levels with different biomarkers and cohort characteristics

The relationships, between plasma pTau concentrations and demographic or biological factors, collected at baseline in the BALTAZAR cohort, were studied using a linear regression approach. Plasma pTau217 and pTau181 were associated with BMI and APOE status (figure 3A). The presence of APOE ε4 alleles was associated with significantly higher pTau values (t-test between APOE ε4 negative and positive population: $p < 0.0001$). Levels of both pTau isoforms were also strongly related to renal function parameters: creatinine and eGFR (panel B). The only other biomarkers clearly associated with pTau levels were CRP for both isoforms and total protein for pTau181. The association between clinical chemistry analytes and plasma pTau levels was confirmed by calculation of Pearson correlations (online supplemental table 4). To further assess the impact of renal function on pTau performance, participants were stratified, using eGFR values, between those having normal, slightly reduced or impaired renal function (figure 3C,D). Impaired renal function was associated with increased pTau values in both the Aβ− and Aβ+ MCI populations. However, renal function had a significant confounding impact on the performance of pTau181, with the optimal cut-point not separating the two populations well. On the other hand, renal parameters had little effect on plasma pTau217 performance, likely because this biomarker had a much

Table 2 AUCs of ROC curves for Aβ+ detection

ROC analysis for of Aβ+	AUC in total population (95% CI)	Cut-point (Youden index)	Sensitivity (%)	Specificity (%)
pTau217	0.914 (95% CI 0.868 to 0.948)	>0.44 (pg/mL)	86.21	86.60
pTau 181	0.783 (95% CI 0.721 to 0.836)	>2.75 (pg/mL)	80.17	68.04
pTau217 with age sex APOE ε4	0.913 (95% CI 0.889 to 0.961)	>10.8	87.1	90.7
pTau181 with age sex APOE ε4	0.824 (95% CI 0.767 to 0.873)	>6.7	75.86	72.16

AUC, area under the curve; ROC, receiver operation curve.

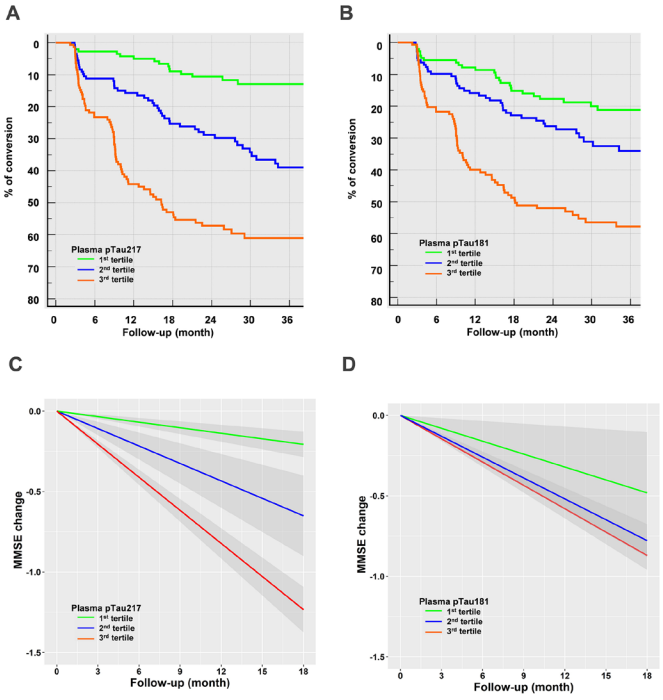

Figure 2 Conversion to Alzheimer's disease (AD) dementia and Mini-Mental State Examination (MMSE) evolution according to pTau181 or pTau217 tertiles. Plasma pTau217 and pTau181 measurements were separated into tertiles and conversion to AD dementia determined at 6-month intervals over 3 years (panels A, B). A very significant overall difference was observed for both pTau217 and pTau181 (Log-rank test (overall difference) 76.1 and 46.7, respectively, both p <0.0001). HR between first versus third tertile was 7.37 (4.86 to 11.16) compared with just 3.83 (2.54 to 5.79) for plasma pTau217 and pTau181, respectively. The average slopes of MMSE decline per year in pTau terciles are plotted in panels C, D. Grey shadows show the CI. Lower lines show increasing tertile: first tertiles are green, second tertiles, blue and third tertiles are orange.

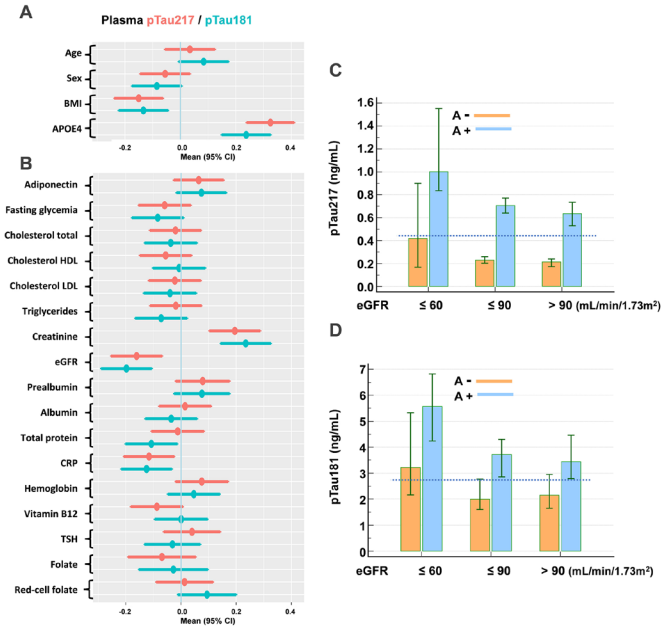

Figure 3 Association of plasma pTau217 and pTau181 levels with different biomarkers and cohort characteristics Forest plots of associations between demographic (panel A) and comorbidity (panel B) biomarkers and plasma pTau217(red) or pTau181(blue), using linear regression of z-scores. Means and 95% CIs are provided. The concentrations of plasma pTau217 (panel C) or pTau181(panel D), in Aβ− (orange) and Aβ+ (blue) participants, are represented in participants stratified by their estimated glomerular filtration rate (eGFR) (eGFR ≤60: impaired renal function; 60–90 mildly reduced renal function, >90 normal renal function). The value corresponding to the optimal cut-points for Aβ+ detection (Youden index) in all the population is represented by a dotted line. Note that the line separates the Aβ− and Aβ+ population for pTau217 only. APOE, apolipoprotein E; BMI, body mass index; CRP, C reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; TSH, thyroid stimulating hormone.

higher fold change between the Aβ− and Aβ+ populations than pTau181.

Definition of pTau217 cut-point to detect cerebral amyloidosis

At the optimal threshold of 0.44 pg/mL, deduced from the ROC analysis, the positive predictive value (PPV) for Aβ+ detection was 88.5% and the negative predictive value (NPV) was 84.0% (table 2). To achieve a PPV of 95%, plasma pTau217 had to be above 0.8 pg/mL, while to achieve an NPV of over 95%, pTau217 must be below 0.23 pg/mL. At these two cut-points, the percentages of MCI converting to AD dementia, over the 3 years, were 56.8% and 9.7%, respectively, while the annual rates of decline in MMSE were −2.32 and −0.65 (table 4).

DISCUSSION

Here, we examined the performance of plasma pTau181 and pTau217 in monitoring AD parameters, in the BALTAZAR cohort.[27] This included data on 473 participants with MCI over a 3-year period, with regular assessments and biological fluid tests. Our main finding was that plasma pTau217 can accurately assess the presence of cerebral amyloidosis, with a confidence level above 95%. There was no relationship with hippocampal atrophy. Moreover, this biomarker predicts cognitive decline and the conversion of MCI to Alzheimer's-type dementia. Plasma ALZpath pTau217 performs significantly better than the plasma pTau181 Advantage Simoa assay and overall, our results confirm previous observations of the superiority of pTau217 in other large cohorts.[3 18 25] In our hands, plasma pTau217 matches CSF biomarkers for the prediction of conversion to AD and is even more effective than CSF pTau181 in identifying cerebral amyloidosis, consistent with recent work.[33] This suggests that blood tests are comparable to or may even be more accurate than CSF tests.

However, before pTau217 assays can move to the clinic, they will to have proven accuracy and they will also need to be made available for purchase and installation at a reasonable cost. Most published studies on pTau217 had one drawback; the tests were not available to standard clinical laboratories. These studies used in-house or proprietary assays that were not commercially available. With the growing interest in pTau217, this picture is set to evolve rapidly. Our data therefore represent a step forward in the deployment of clinical tests, which will eventually comply with the ISO15189 standard.

As well as clinical reproducibility, interpreting plasma pTau217 levels will require knowledge of the medical context, to be useful. An important factor for real-life use of assays in large populations is knowledge of the confounding factors that induce bias in the measurements. Indeed, it has been established that certain comorbidities, and in particular impaired renal function, can significantly modify the predictive value of plasma biomarkers.

Table 4 Characteristics of participants with MCI at different pTau217 cutpoints

pTau217 cut-points (pg/mL)	% of population with MCI	PPV of Aβ+ (%)	NPV of Aβ+ (%)	% AD dementia conversion	MMSE/year
>0.44	53.1	88.5 (95% CI 82.2 to 92.8)	84.0 (95% CI 76.8 to 89.3)	46.3	−2.07
>0.80	20.3	95.3 (95% CI 83.6 to 98.8)	55.9 (95% CI 52.5 to 59.2)	56.8	−2.32
<0.23	24.4	70.8 (95% CI 66.4 to 74.9)	96.2 (95% CI 86.2 to 99.0)	9.7	−0.65

MMSE, Mini-Mental State Examination ; PPV, NPV, Positive and negative predictive values.

Other parameters such as age or BMI can also confound the value of AD prognostic biomarkers. For pTau181, we previously found that impaired renal function likely undermines diagnostic performance.[34] In the same cohort, we observed here that renal function and other potential confounding factors have a minimal effect on the performance of pTau217. This is likely due to the high fold difference observed between normal and pathological situations. These results pave the way for wider, independent use of this marker. Note that none of the other factors we tested, such as age, sex, BMI, level of education or ApoE Ɛ4 genoytpe, either separately or together, significantly improve the independent predictive value of plasma pTau217, by more than an AUC of 0.02.

We are therefore in a situation where pTau217 alone can provide significant information for patient management, not only with regard to the presence of cerebral amyloidosis, which is important when selecting an antiamyloid treatment and for diagnostic strategy,[35] but also, for prognosis. Indeed, we demonstrate that high plasma pTau217 levels are associated with a high risk of conversion to AD dementia within 3 years. We can also see that cognitive evolution can be stratified with this marker, which is important information for the clinician.

For clinical use, it is also necessary to define one or more pathological cut-points, and recent papers have proposed for pTau217 different approaches depending on the medical need.[3 26 36 37] A universally applicable plasma pTau217 cutpoint would therefore be useful for the management of patients presenting cognitive disorders. General practitioners would greatly appreciate a threshold 'diagnosing' cerebral amyloidosis with a 95% confidence level. In our cohort, the cut-point of >0.44 pg/mL is a useful combination of sensitivity and specificity (>85%) and the cut-point of >0.8 pg/mL gives a 95% PPV for cerebral amyloidosis. Conversely, it is also very useful for patient management to be able to exclude the presence of cerebral amyloidosis with a high confidence (>95%). In our case, this low cut-point value is <0.23 pg/mL. The intermediate zone of our study, or grey zone, between these two thresholds, represents 55% of the population. This percentage seems higher than in previous studies.[3] The explanation certainly lies in our study population, which includes only participants with MCI, and in the methods for detecting Aβ+ and pTau217.

The present study has some limitations. To increase the likelihood of conversion to AD, we excluded participants with Lewy Body, Parkinson, frontotemporal or vascular MCI disorders. Therefore, 77% of subjects had amnestic MCI and 28% of participants developed AD dementia. Amyloid status was available in only a part of the population, since the BALTAZAR study focused on conversion, and it was defined using CSF biomarkers rather than with PET amyloid. Conversion to AD was assessed using clinical, imaging and neuropsychological data, which represents a risk of error but avoids circular thinking about the use of biomarkers. The main strengths of the study lie in the large sample size of participants with MCI that are well described, the controlled preanalytical conditions, the use of a commercially available plasma pTau217 assays and the consideration of clinical chemistry analyte measurements realised at baseline.

CONCLUSION

These data place us at the dawn of a major change in the management of AD. This is linked to the clinical use of the plasma marker pTau217, whose performance, using commercially available assays, is exceptional, both in terms of identifying cerebral amyloidosis and, as we have shown in this article, in predicting progression to Alzheimer's dementia and accelerated cognitive decline. This information is essential for optimal patient management, including diagnostic strategy, prevention and access to disease-modifying therapy.

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REFERENCES

1 Wesseling H, Mair W, Kumar M, *et al*. Tau PTM profiles identify patient heterogeneity and stages of Alzheimer's disease. *Cell* 2020;183:1699–713.
2 Lehmann S, Schraen-Maschke S, Vidal J-S, *et al*. Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function. *J Neurol Neurosurg Psychiatry* 2023;94:411–9.
3 Mattsson-Carlgren N, Salvadó G, Ashton NJ, *et al*. Prediction of longitudinal cognitive decline in preclinical Alzheimer disease using plasma biomarkers. *JAMA Neurol* 2023;80:360–9.
4 Janelidze S, Stomrud E, Smith R, *et al*. Cerebrospinal fluid P-Tau217 performs better than P-Tau181 as a biomarker of Alzheimer's disease. *Nat Commun* 2020;11:1683.
5 Barthélemy NR, Bateman RJ, Hirtz C, *et al*. Cerebrospinal fluid Phospho-Tau T217 outperforms T181 as a biomarker for the differential diagnosis of Alzheimer's disease and PET amyloid-positive patient identification. *Alzheimers Res Ther* 2020;12:26.
6 Leuzy A, Janelidze S, Mattsson-Carlgren N, *et al*. Comparing the clinical utility and diagnostic performance of CSF P-Tau181, P-Tau217, and P-Tau231 assays. *Neurology* 2021;97:e1681–94.
7 Brickman AM, Manly JJ, Honig LS, *et al*. Plasma P-Tau181, P-Tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimers Dement* 2021;17:1353–64.
8 Pereira JB, Janelidze S, Stomrud E, *et al*. Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects. *Brain* 2021;144:2826–36.
9 Chen L, Niu X, Wang Y, *et al*. Plasma Tau proteins for the diagnosis of mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *Front Aging Neurosci* 2022;14:942629.
10 Thijssen EH, La Joie R, Strom A, *et al*. Plasma phosphorylated Tau 217 and phosphorylated Tau 181 as biomarkers in Alzheimer's disease and frontotemporal Lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol* 2021;20:739–52.
11 Palmqvist S, Janelidze S, Quiroz YT, *et al*. Discriminative accuracy of plasma Phospho-Tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA* 2020;324:772–81.
12 Janelidze S, Bali D, Ashton NJ, *et al*. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain* 2023;146:1592–601.
13 Gonzalez-Ortiz F, Ferreira PCL, González-Escalante A, *et al*. A novel ultrasensitive assay for plasma P-Tau217: performance in individuals with subjective cognitive decline and early Alzheimer's disease. *Alzheimers Dement* 2024;20:1239–49.
14 Doré V, Doecke JD, Saad ZS, *et al*. Plasma P217+Tau versus Nav4694 amyloid and Mk6240 Tau PET across the Alzheimer's continuum. *Alzheimers Dement (Amst)* 2022;14:e12307.
15 Ashton NJ, Janelidze S, Mattsson-Carlgren N, *et al*. Differential roles of Abeta42/40, P-Tau231 and P-Tau217 for Alzheimer's trial selection and disease monitoring. *Nat Med* 2022;28:2555–62.
16 Mattsson-Carlgren N, Janelidze S, Palmqvist S, *et al*. Longitudinal plasma P-Tau217 is increased in early stages of Alzheimer's disease. *Brain* 2020;143:3234–41.
17 Janelidze S, Berron D, Smith R, *et al*. Associations of plasma phospho-Tau217 levels with Tau positron emission tomography in early Alzheimer disease. *JAMA Neurol* 2021;78:149–56.
18 Jonaitis EM, Janelidze S, Cody KA, *et al*. Plasma phosphorylated Tau 217 in preclinical Alzheimer's disease. *Brain Commun* 2023;5:fcad057.
19 Palmqvist S, Tideman P, Cullen N, *et al*. Prediction of future Alzheimer's disease dementia using plasma Phospho-Tau combined with other accessible measures. *Nat Med* 2021;27:1034–42.
20 Groot C, Cicognola C, Bali D, *et al*. Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma P-Tau217. *Alzheimers Res Ther* 2022;14:67.
21 Barthélemy NR, Li Y, Joseph-Mathurin N, *et al*. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat Med* 2020;26:398–407.
22 Milà-Alomà M, Ashton NJ, Shekari M, *et al*. Plasma P-Tau231 and P-Tau217 as state markers of amyloid-beta pathology in preclinical Alzheimer's disease. *Nat Med* 2022;28:1797–801.
23 Groot C, Smith R, Stomrud E, *et al*. Phospho-Tau with subthreshold Tau-PET predicts increased Tau accumulation rates in amyloid-positive individuals. *Brain* 2023;146:1580–91.
24 Bayoumy S, Verberk IMW, den Dulk B, *et al*. Clinical and analytical comparison of six Simoa assays for plasma P-Tau Isoforms P-Tau181, P-Tau217, and P-Tau231. *Alzheimers Res Ther* 2021;13:198.
25 Palmqvist S, Stomrud E, Cullen N, *et al*. An accurate fully automated panel of plasma biomarkers for Alzheimer's disease. *Alzheimers Dement* 2023;19:1204–15.
26 Ashton NJ, Brum WS, Di Molfetta G, *et al*. Diagnostic accuracy of the plasma Alzpath Ptau217 immunoassay to identify Alzheimer's disease pathology. *medRxiv* 2023;2023:2023.07.11.23292493.
27 Hanon O, Vidal J-S, Lehmann S, *et al*. Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers. *Alzheimers Dement* 2018;14:858–68.
28 Petersen RC, Smith GE, Waring SC, *et al*. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
29 Rissin DM, Walt DR. Digital concentration readout of single enzyme molecules using Femtoliter arrays and poisson Statistics. *Nano Lett* 2006;6:520–3.
30 Inker LA, Eneanya ND, Coresh J, *et al*. New creatinine- and Cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;385:1737–49.
31 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
32 Hanon O, Vidal J-S, Lehmann S, *et al*. Plasma Amyloid beta predicts conversion to dementia in subjects with mild cognitive impairment: the BALTAZAR study. *Alzheimers Dement* 2022;18:2537–50.
33 Barthélemy NR, Salvadó G, Schindler SE, *et al*. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med* 2024. 10.1038/s41591-024-02869-z. [Epub ahead of print 21 Feb 2021].
34 Lehmann S, Schraen-Maschke S, Vidal J-S, *et al*. Plasma phosphorylated Tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function. *J Neurol Neurosurg Psychiatry* 2023;94:411–9.
35 Delaby C, Alcolea D, Hirtz C, *et al*. Blood amyloid and tau biomarkers as predictors of cerebrospinal fluid profiles. *J Neural Transm (Vienna)* 2022;129:231–7.
36 Brum WS, Cullen NC, Janelidze S, *et al*. A two-step workflow based on plasma P-Tau217 to screen for amyloid beta positivity with further confirmatory testing only in uncertain cases. *Nat Aging* 2023;3:1079–90.
37 Mattsson-Carlgren N, Collij LE, Stomrud E, *et al*. Plasma biomarker strategy for selecting patients with Alzheimer disease for antiamyloid immunotherapies. *JAMA Neurol* 2024;81:69.