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RESEARCH ARTICLE

Plasma pTau-217 and N-terminal tau (NTA) enhance sensitivity to identify tau PET positivity in amyloid-β positive individuals

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Abstract

INTRODUCTION: We set out to identify tau PET-positive (A+T+) individuals among amyloid-beta (Aβ) positive participants using plasma biomarkers.

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METHODS: In this cross-sectional study we assessed 234 participants across the AD continuum who were evaluated by amyloid PET with [^{18}F]AZD4694 and tau-PET with [^{18}F]MK6240 and measured plasma levels of total tau, pTau-181, pTau-217, pTau-231, and N-terminal tau (NTA-tau). We evaluated the performances of plasma biomarkers to predict tau positivity in Aβ+ individuals.

RESULTS: Highest associations with tau positivity in Aβ+ individuals were found for plasma pTau-217 (AUC [$CI_{95\%}$] = 0.89 [0.82, 0.96]) and NTA-tau (AUC [$CI_{95\%}$] = 0.88 [0.91, 0.95]). Combining pTau-217 and NTA-tau resulted in the strongest agreement (Cohen's Kappa = 0.74, $CI_{95\%}$ = 0.57/0.90, sensitivity = 92%, specificity = 81%) with PET for classifying tau positivity.

DISCUSSION: The potential for identifying tau accumulation in later Braak stages will be useful for patient stratification and prognostication in treatment trials and in clinical practice.

KEYWORDS
blood biomarker, tau accumulation, tau prediction, tau staging

Highlights

- We found that in a cohort without pre-selection pTau-181, pTau-217, and NTA-tau showed the highest association with tau PET positivity.
- We found that in Aβ+ individuals pTau-217 and NTA-tau showed the highest association with tau PET positivity.
- Combining pTau-217 and NTA-tau resulted in the strongest agreement with the tau PET-based classification.

1 | BACKGROUND

Identifying tau-positive individuals, particularly in patients with established amyloid pathology, is crucial for the better screening of patients for clinical trials. These tools can clearly indicate patients with clinically significant tau load and candidates for disease-modifying treatments.

The current clinically available gold standards for quantifying amyloid beta (Aβ) and tau load are based on cerebrospinal fluid (CSF) biomarkers and positron emission tomography (PET) imaging.[1,2] However, the development of novel high-sensitivity technologies to quantify ultra-low protein quantities as well as the discovery of novel tau phosphorylation epitopes has resulted in a variety of new promising biomarkers that can be measured in the plasma.[3–5] Due to their strong association with imaging-based hallmarks of Alzheimer's disease (AD) pathophysiology and disease progression as well as their non-invasive accessibility, they have great translational potential for clinical use.[6] However, phosphorylated tau (pTau) biomarkers are strongly associated with Aβ and tau brain load,[5,7,8] and therefore it is difficult to determine whether increased pTau levels relate to Aβ or tau aggregates. Recently, we reported that N-terminal tau (NTA-tau) is strongly associated with tau pathology.[9] Combining pTau biomarkers with NTA-tau might lead to a better blood-based stratification of the AD continuum.[10]

Recent clinical trials have underscored the importance of targeting both Aβ and tau pathologies for therapeutic success.[11,12] By identifying tau-positive individuals, researchers can develop more precise and effective treatment strategies that address both hallmarks of AD. Moreover, understanding the role of tau in neurodegeneration can facilitate the discovery of novel therapeutic targets and advance the development of new treatments.[13] In addition to guiding therapy, identifying tau-positive individuals can also improve the design and execution of clinical trials.[14] By selecting participants based on their tau status, researchers can better assess the efficacy of potential treatments targeting both Aβ and tau pathologies. Furthermore, a more accurate understanding of the patient population in clinical trials can reduce variability in trial outcomes and increase the chances of success. Additionally, plasma biomarkers are promising non-invasive tools for diagnosing individuals in the AD continuum which could reduce the need for imaging or invasive CSF analyses.[15]

The goal of our study was to identify plasma biomarkers that identify tau PET-positive individuals in Aβ+ participants. Therefore, we performed receiver operating characteristic (ROC) curve analyses to identify tau accumulation and compared the classification into

A+T− and A+T+ of a wide set of plasma biomarkers with PET-based classification of brain amyloidosis and tau load.

RESEARCH IN CONTEXT

1. **Systematic review**: By reviewing the literature in public databases and search engines, we identified the clinical need to classify patients with tau accumulation through blood biomarkers. No studies have evaluated different blood biomarkers to predict tau PET positivity based on the meta-ROI.
2. **Interpretation**: We find that blood levels of pTau-217 and NTA-tau have the highest associations with tau PET positivity in Aβ+ individuals. When combining pTau-217 and NTA-tau, we observe the highest agreement with PET-based tau classification.
3. **Future directions**: Blood-based identification of tau PET positive individuals across the AD continuum will allow for the selection and risk stratification of more homogeneous study collectives for clinical trials and guide health care professionals in determining appropriate treatment approaches for dementia patients.

2 | METHODS

2.1 | Participants

All assessed participants were enrolled in the Translational Biomarkers in Aging and Dementia (TRIAD) cohort[16] who underwent Aβ PET with [^{18}F]AZD4694, tau PET with [^{18}F]MK6240, and magnetic resonance imaging (MRI). Participants had a detailed clinical and cognitive assessment, including the Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE). Cognitively unimpaired (CU; ages 35 to 82 years) and cognitively unimpaired younger (CUY; ages 20 to 29 years) participants had no objective cognitive impairment, a CDR score of 0, and were asked to report any subjective cognitive decline in a questionnaire given during screening. Individuals with mild cognitive impairment (MCI) had cognitive impairment, relatively preserved activities of daily living, and a CDR score of 0.5. Mild-to-moderate Alzheimer's clinical syndrome patients with dementia had a CDR score between 0.5 and 2 and met the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for probable AD determined by a dementia specialist.[10,16] Exclusion criteria were active substance abuse, recent head trauma, recent major surgery, or MRI/PET safety contraindications.[17]

2.2 | MRI acquisition and processing

Structural MRI data were acquired at the Montreal Neurological Institute (MNI) for all participants on a 3T Siemens Magnetom scanner using a standard head coil. Hippocampal volume was assessed with FreeSurfer version 6.0 using the Desikan–Killiany–Tourville atlas gray matter segmentation.

2.3 | PET acquisition and processing

Study participants had a T1-weighted MRI, and [^{18}F]AZD4694 PET and [^{18}F]MK6240 PET scans were acquired using a brain-dedicated Siemens high-resolution research tomograph. [^{18}F]MK6240 PET images were acquired at 90 to 110 min after the intravenous bolus injection of the radiotracer and reconstructed using an ordered subset expectation maximization algorithm on a 4D volume with four frames (4 × 300 s), as previously described.[18] [^{18}F]AZD4694 PET images were acquired at 40 to 70 min after the intravenous bolus injection of the radiotracer and reconstructed with the same ordered subset expectation maximization algorithm on a 4D volume with three frames (3 × 600 s).[16] A 6 min transmission scan with a rotating ^{137}Cs point source was conducted at the end of each PET acquisition for attenuation correction. Images were corrected for motion, decay, dead time, and random and scattered coincidences. In summary, PET images were linearly registered to T1-weighted image space, and the T1-weighted images were linearly and nonlinearly registered to the Alzheimer's Disease Neuroimaging Initiative (ADNI) reference space. To minimize the influence of meningeal spillover into adjacent brain regions, [^{18}F]MK6240 images were skull-stripped in T1 space before transformations and blurring.[17] The PET images in T1 space were linearly and nonlinearly registered to the ADNI space using transformations from the T1-weighted image to ADNI space. [^{18}F]MK6240 standardized uptake value ratios (SUVRs) were calculated using the cerebellar Crus I gray matter as a reference region,[17,19] as derived from the SUIT cerebellum atlas.[20] [^{18}F]AZD4694 SUVRs were calculated using the whole cerebellum gray matter as the reference region. PET images were spatially smoothed to achieve an 8-mm full-width at half-maximum resolution. The global [^{18}F]AZD4694 SUVR composite included the precuneus, prefrontal, orbitofrontal, parietal, temporal, and cingulate cortices.[20] Participants were assigned according to the amyloid/tau/neurodegeneration (A/T/N) framework by measuring temporal meta-ROI [^{18}F]MK6240 SUVR (cutoff 1.24)[21] and neocortical [^{18}F]AZD4694 SUVR (cutoff 1.55) as previously described.[16]

2.4 | Fluid biomarkers

Plasma samples were collected according to standard procedures in the clinical routine. Samples were then rapidly frozen for permanent storage at −80°C.[22] Plasma levels of pTau variants pTau-181 and pTau-231 were quantified using a custom Single molecule array (Simoa) assay as previously described.[22] pTau-217^{+} was quantified by Janssen R&D.[23] Plasma NTA-tau concentrations were quantified using an in-house–developed Simoa immunoassay using a Simoa HD-X platform

(Quanterix) at the Clinical Neurochemistry Laboratory (Mölndal, Sweden). Development and validation of the NTA assay has been previously described.[9] In brief, plasma NTA assay is comprised by a mouse monoclonal antibody with epitope 6-18aa (Tau12, BioLegend) used as a detector and a mouse monoclonal antibody with epitope 159-163aa (HT7, Thermo Scientific) used as the capture antibody.

2.5 | Statistical analysis

All analyses were performed using *R* within the *R Studio* environment. ROC analyses and estimation of the area under the curve (AUC) and 95% confidence intervals (CIs) were calculated using the *pROC* package.[24] Comparisons between two groups were performed using a non-parametric Mann-Whitney *U* test, and correlations were determined by Spearman correlation analysis. Sensitivity, specificity, and accuracy of continuous biomarker values to evaluate their performances to classify tau positivity in all (T− vs T+) or Aβ+ participants (A+T− vs A+T+) were calculated using Youden's index. Subsequently, we used cutoffs of >0.26 pg/mL for plasma NTA-tau and >0.14 pg/mL for pTau-217 to indicate biomarker positivity. Comparisons between binarization into tau-positive and tau-negative participants' plasma biomarkers or PET as the golden standard were performed using the *vcd* package. The performance of pTau-217, plasma-NTA, and the combination of both to identify tau-positive participants among Aβ+ participants was assessed by sensitivity, specificity, and Cohen's Kappa (0 to 0.2 = weak, 0.23 to 0.39 = minimal, 0.40 to 0.59 = moderate, 0.60 to 0.79 = good, 0.80 to 0.90 = strong, >0.9 = almost perfect agreement).

2.6 | Data availability

All the data that support the findings of the study are available from the corresponding authors upon reasonable request.

3 | RESULTS

3.1 | Study population

We included 234 participants from the TRIAD cohort (n = 31 CUY, n = 120 CU [older], n = 43 with MCI, n = 35 with AD, n = 5 with other neurodegenerative disease) who were separated according to the A/T/N framework by [^{18}F]AZD4694 PET and [^{18}F]MK6240 PET and structural MRI. We identified 145 participants without brain amyloidosis, tau pathology, or neurodegeneration (A−T−N−, 57% female, mean age 58 years), 44 participants with amyloid aggregation without tau PET positivity (A+T−N−, 57% female, mean age 71 years), 11 participants with amyloid and tau accumulation but without hippocampal atrophy (A+T+N−, 36.4% female, mean age 61 years), and 34 participants with hippocampal atrophy (A+T+N+, 62% female, mean age 66 years). The participants' demographics are summarized in Table 1.

3.2 | Plasma pTau-217 and NTA-tau identify tau PET positivity

The goal of this study was to identify plasma biomarkers that separate PET-confirmed A+T− from A+T+ individuals. We initially performed ROC analysis in all participants (Figure 1A) and in Aβ+ individuals (Figure 1B) with established tau and pTau plasma biomarkers. Within all participants, pTau-181 (AUC = 0.91), pTau-217 (AUC = 0.95), and NTA-tau (AUC = 0.88) showed the highest performance for discriminating tau-positive from tau-negative participants. However, in Aβ+ individuals only pTau-217 (AUC = 0.89) and NTA-tau (AUC = 0.88) reliably separated the two groups with an AUC of >85% for distinguishing A+T+ from A+T− (AUCs and $CI_{95\%}$ are provided in Table 2), which was significantly higher than pTau-231 (AUC = 0.74; vs pTau-217, p = 0.02; vs NTA-tau, p = 0.03) and total Tau (tTau; AUC = 0.65; vs pTau-217, p = 0.001; vs NTA-tau, p = 0.002; all p-values of AUC comparisons are shown in Table 3). Next, we analyzed the diagnostic accuracies of plasma pTau-217 and NTA-tau to detect tau PET positivity. First, we confirmed that the plasma levels of pTau-217 were increased in A+T+ in comparison with A+T− and A−T−, and in A+T− as compared to A−T− (Figure 2A). Of note, pTau-217 was slightly increased in CU in comparison to CUY and correlated with the common AD scores on the MMSE and CDR (Figure S1A-C). By using Youden's index, we calculated that within all participants (Figure 2B), pTau-217 levels above 0.09 pg/mL (sensitivity = 0.91, specificity = 0.9, accuracy = 0.91), and in Aβ+ individuals (Figure 2C), levels above 0.14 pg/mL (sensitivity = 0.90, specificity = 0.72, accuracy = 0.79), indicate tau positivity by PET (performance values are provided in Table 4). Next, we calculated the plasma NTA-tau performance to distinguish tau status (performance values are provided in Table 4). First, we validated that the plasma NTA-tau levels were increased in A+T+ in comparison to A+T− and A−T−. In contrast to pTau-217, NTA-tau levels in A+T− were not increased in comparison to A−T− (Figure 2D) and were not significantly increased in CU in comparison to CUY (Figure S1D). Similar to pTau-217, NTA-tau also significantly correlated with MMSE and CDR scores (Figure S1E,F). We calculated that within all participants (Figure 2E), plasma NTA-tau levels above 0.26 pg/mL (sensitivity = 0.87, specificity = 0.78, accuracy = 0.80), and in Aβ+ individuals (Figure 2F), levels above 0.54 pg/mL (sensitivity = 0.89, specificity = 0.77, accuracy = 0.82), indicate tau positivity assessed by PET.

3.3 | Combined plasma pTau-217 and NTA-tau shows the highest sensitivity to detect tau PET positivity

Next, we asked whether combining plasma pTau-217 and NTA-tau improves the performance to detect tau PET positivity across Aβ+ individuals. First, we performed correlation analysis between pTau-217 and NTA-tau. We identified a strong correlation (Figure 2G; r = 0.68, p < 0.001), and also that A+T+ participants have high pTau217 and NTA-tau plasma levels. Finally, we compared the accuracy for separating A+T− from A+T+ by plasma pTau-217 and NTA-tau using

TABLE 1 Patient demographics.

	A−T−	A+T−	A+T+
N (% female)	145 (57.2)	44 (56.8)	45 (55.6)
APOE ε4 carriers, *N* (%)	42 (29)	16 (36.4)	33 (73.3)
Age, mean (SD)	57.7 (20.3)	71 (8.3)	64.7 (9)
MMSE, mean (SD)	29.1 (1.1)	28.5 (2.1)	21.7 (5.8)
Educational years, mean (SD)	15.4 (3.3)	14.9 (3.6)	14.1 (3.3)
Meta-ROI [^{18}F]MK6240 SUVR, mean (SD)	0.9 (0.1)	0.9 (0.1)	2.2 (0.8)
Total [^{18}F]AZD4694 SUVR, mean (SD)	1.3 (0.1)	2.1 (0.4)	2.5 (0.4)
Hippocampal volume, mean (SD)	3.7 (0.4)	3.6 (0.3)	2.9 (0.5)

Abbreviations: A, amyloid; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; SUVR, standardized uptake value ratio; T, tau positron emission tomography.

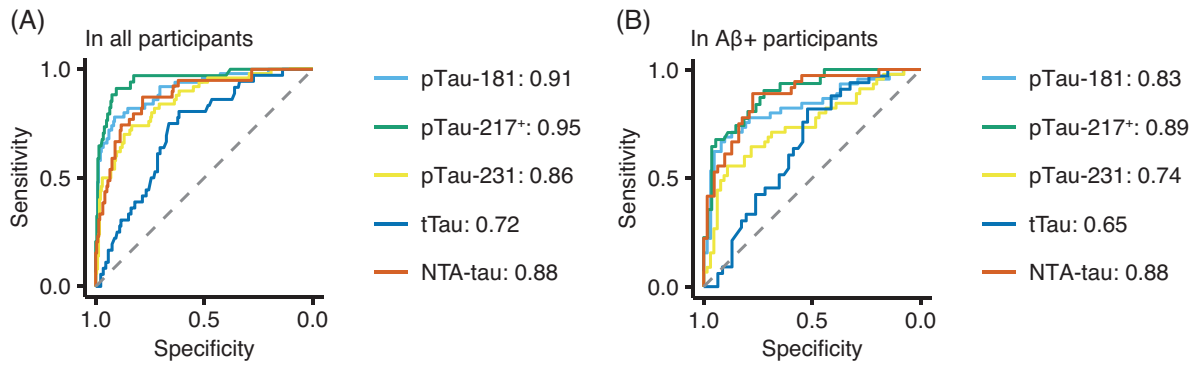

FIGURE 1 Plasma pTau-217 and NTA-tau identify tau PET positivity in Aβ+ individuals. (A) ROC analyses to discriminate tau positivity determined by [^{18}F]MK6240 PET in all included participants. AUCs are provided in the figure. (B) ROC analyses to discriminate tau positivity determined by [^{18}F]MK6240 PET in Aβ-positive participants. AUCs are provided in the figure. Aβ, amyloid beta; AUC, area under the curve; NTA-tau, N-terminal tau; PET, positron emission tomography; pTau, phosphorylated tau; ROC, receiver operating characteristic; tTau, total tau.

TABLE 2 ROC analysis to discriminate tau PET positivity.

Biomarker	Groups	AUC	95% CI down	95% CI up
tTau	All participants	0.72	0.63	0.8
tTau	Aβ+ participants	0.65	0.53	0.77
pTau-181	All participants	0.91	0.86	0.96
pTau-181	Aβ+ participants	0.83	0.75	0.91
pTau-217	All participants	0.95	0.91	0.99
pTau-217	Aβ+ participants	0.89	0.82	0.96
pTau-231	All participants	0.86	0.8	0.92
pTau-231	Aβ+ participants	0.74	0.65	0.84
NTA-tau	All participants	0.88	0.82	0.94
NTA-tau	Aβ+ participants	0.88	0.81	0.95

Abbreviations: Aβ, amyloid beta; AUC, area under the curve; CI, confidence interval; NTA, N-terminal; PET, positron emission tomography; pTau, phosphorylated tau; ROC, receiver operating characteristic; tTau, total tau.

TABLE 3 Comparisons of (p)Tau variants to identify tau PET positivity.

Comparison	All participants, *p*-value	Aβ+, *p*-value
pTau-181 vs pTau-217	0.159	0.254
pTau-181 vs pTau-231	0.197	0.189
pTau-181 vs tTau	<0.001	0.018
pTau-181 vs NTA-tau	0.454	0.403
pTau-217 vs pTau-231	0.008	0.015
pTau-217 vs tTau	<0.001	0.001
pTau-217 vs NTA-tau	0.04	0.744
pTau-231 vs tTau	0.006	0.245
pTau-231 vs NTA-tau	0.627	0.031
tTau vs NTA-tau	0.002	0.002

Abbreviations: Aβ, amyloid beta; NTA, N-terminal; PET, positron emission tomography; pTau, phosphorylated tau; tTau, total tau.

our previously determined cutoffs with the PET-based classification as ground truth (Figure 3A). Plasma NTA-tau and pTau-217 together (Figure 3B) identified A+T+ with a sensitivity of 92% and specificity of 81% (Cohen's Kappa = 0.74, $CI_{95\%}$ = 0.57/0.90). Using only pTau-217 (Figure 3C) resulted in a sensitivity of 78% and specificity of 84% (Cohen's Kappa = 0.62, $CI_{95\%}$ = 0.43/0.80), and only NTA-tau (Figure 3D) in a sensitivity of 50% and specificity of 85% (Cohen's Kappa = 0.68, 95% $CI_{95\%}$ = 0.50/0.85), showing that the highest agree-

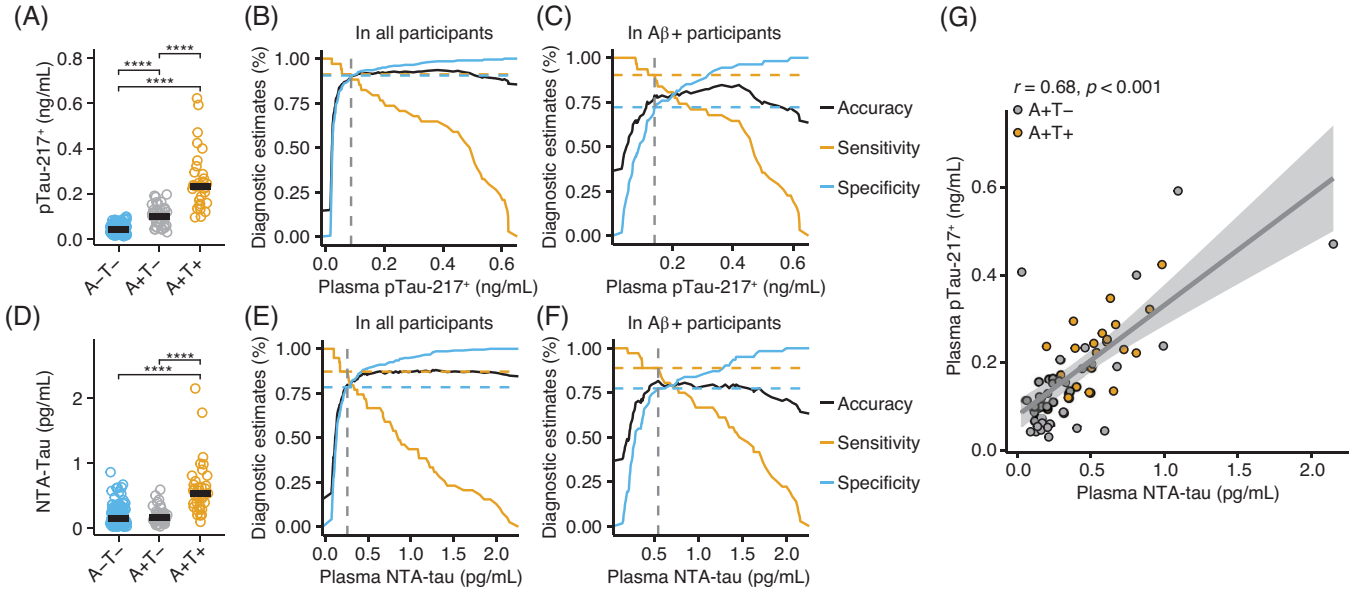

FIGURE 2 Diagnostic accuracy testing of pTau-217 and NTA-tau to discriminate tau PET positivity. (A) pTau-217 levels (ng/mL) in A−T−, A+T−, and A+T+ participants. The Mann-Whitney *U* test was used. (B,C) Accuracy, sensitivity, and specificity of pTau-217 in all participants (B) and Aβ+ participants (C) to identify tau PET positivity. Cutoffs according to Youden's index are shown as dashed lines. (D) NTA-tau levels (pg/mL) in A−T−, A+T−, and A+T+ participants. The Mann-Whitney *U* test was used. (E,F) Accuracy, sensitivity, and specificity of NTA-tau in all participants (E) and Aβ-positive participants (F) to identify tau accumulation. Cutoffs according to Youden's index are shown as dashed lines. (G) Spearman correlation of plasma pTau-217 and NTA-tau of Aβ-positive participants. A, amyloid; Aβ, amyloid beta; NTA-tau, N-terminal tau; PET, positron emission tomography; pTau, phosphorylated tau; T, tau. **** $p < 0.0001$.

TABLE 4 Diagnostic performances of plasma pTau-217 and NTA-tau.

Biomarker	Groups	Threshold (relative)	Threshold (absolute)	Sensitivity (%)	Specificity (%)	Accuracy (%)
pTau-217 (pg/mL)	All participants	0.12	0.09	91	90	91
pTau-217 (pg/mL)	Aβ+ participants	0.21	0.14	90	72	79
NTA-Tau (pg/mL)	All participants	0.11	0.26	87	78	80
NTA-Tau (pg/mL)	Aβ+ participants	0.24	0.54	89	77	82

Abbreviations: Aβ, amyloid beta; NTA, N-terminal; pTau, phosphorylated tau.

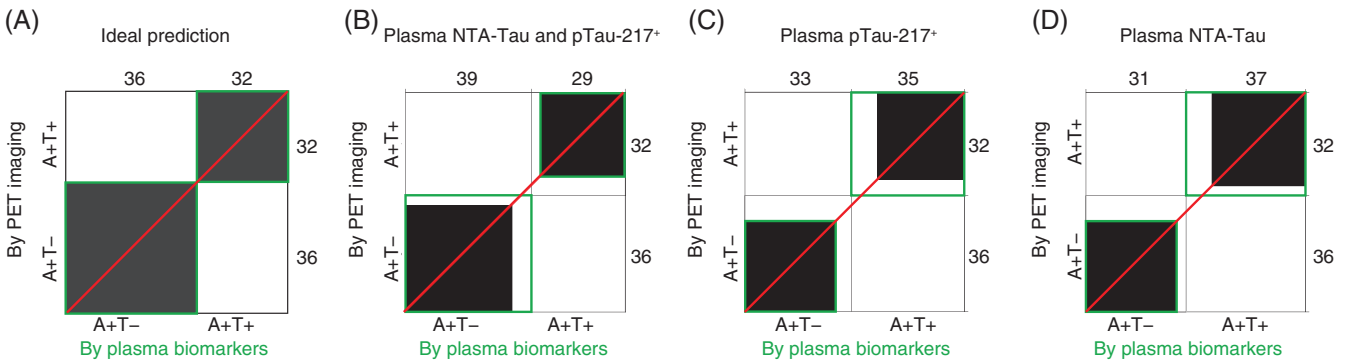

FIGURE 3 Agreement analyses of plasma- and PET-based identification of tau positivity. (A–D) Bangdiwala's Observer Agreement Charts of ideal prediction with full agreement (A), plasma NTA-tau and pTau-217 together (B; Cohen's Kappa = 0.74, 95% CI = 0.57/0.90, sensitivity = 92%, specificity = 81%), pTau-217 alone (C; Cohen's Kappa = 0.62, 95% CI = 0.43/0.80, sensitivity = 78%, specificity = 84%), and NTA-tau alone (D; Cohen's Kappa = 0.68, 95% CI = 0.50/0.85, sensitivity = 78%, specificity = 90%) to identify A+T+ participants in Aβ+ participants. A, amyloid; Aβ, amyloid beta; PET, positron emission tomography; pTau, phosphorylated tau; NTA-tau, N-terminal tau; T, tau.

ment with PET-based staging was achieved by combining pTau-217 and NTA-tau.

Here, we report a prevalence of 47% PET-based A+T+ in Aβ+ individuals, which is similar to the prevalence observed in other studies (53% in,[25] 29% in[26]). Using pTau-217 and NTA-tau together, we calculated a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 85%. pTau-217 alone scored a similar PPV of 84% but a lower NPV of 77%. NTA-tau similarly showed a lower NPV of 78% but an increased PPV of 90% in comparison to the combined classification.

4 | DISCUSSION

We identified that the combination of plasma pTau-217 and NTA-tau differentiates tau PET positive individuals in Aβ+ populations with a high performance. Traditional methods for detecting tau pathology, such as CSF analysis and PET scans, are invasive, expensive, and not universally accessible.[15] The utilization of plasma biomarkers, on the other hand, offers a more practical and cost-effective approach that can be easily implemented in clinical settings.[27] We identified A+T+ with a high sensitivity of 92%, but a lower specificity of 81%. Therefore, pTau-217 and NTA-tau may be eligible biomarkers for the triage of patients with early cognitive symptoms who should receive subsequent diagnostic testing, which could help screen out patients with low likelihood of having AD and thereby strongly reduce the number of needed confirmatory PET or CSF measurements to determine tau positivity.

We found that the plasma levels of pTau-217 and NTA-tau showed the highest accuracy for separating A+T+ and A+T−. At the group level, pTau-217 is already elevated in the CSF[28] and blood in cognitively unimpaired individuals who have Aβ pathology. However, previous studies showed that pTau-217 correlates more strongly with Aβ brain load than tau accumulation measured by PET.[3,7,8] This is of high relevance when considering the relatively small observed reduction in pTau levels in response to anti-Aβ antibodies in comparison to the strong reduction in PET-reported Aβ brain load. For example, during the main study period of the TRAILBLAZER-ALZ 2[29] trial that evaluated the Aβ-targeting antibody donanemab, pTau-217 was significantly reduced by 23% in the treatment arm whereas the Aβ load was reduced by 85 centiloids.[30] This might be explained by Aβ oligomers that are not detected by PET and are still present after monoclonal antibody treatment, or by further ongoing Aβ-independent tau accumulation. To evaluate this Aβ-independent performance of fluid biomarkers to predict PET-based tau staging, further longitudinal studies are required. These should focus on differentiating responders from non-responders to Aβ-targeting antibodies and analyzing the associations between fluid biomarkers and tau accumulation independent of brain Aβ load.

The application of this biomarker combination may also lead to a more precise stratification of patients according to the A/T/N framework using plasma biomarkers.[31,32] This in turn can improve diagnostic accuracy and enable clinicians to better predict disease progression. By accurately identifying tau PET-positive individuals among those already positive for Aβ PET, physicians can tailor treatment strategies to target both amyloid[12,29] and tau pathologies,[33] potentially improving therapeutic outcomes. Furthermore, our findings have the potential to enhance the design and execution of clinical trials by excluding tau-positive individuals for Aβ-targeting strategies to obtain a more homogeneous study population, given that targeting earlier stage disease should have the greatest impact. This more accurate representation of the patient population could reduce variability in trial outcomes and increase the chances of success.[34] As a result, the development and evaluation of novel therapeutics targeting both amyloid and tau pathologies may be accelerated, ultimately benefiting patients afflicted with these debilitating diseases.

Here, we identified tau-positive individuals in an Aβ-enriched population. Therefore, the thresholds for pTau-217 and NTA-tau are specific to this goal and cannot be generalized for AD diagnosis. Furthermore, the absolute thresholds depend on the assay platform and are likely to vary between different platforms and methods as recently shown.[35] However, the cutoff we identified by Youden's index for pTau-217 for detecting tau positivity was similar to a recently published cutoff for identifying PET-based tau positivity in different cognitive states.[36] Although we reached a high sensitivity, we only achieved a specificity of 81%. Therefore, pTau-217 and NTA-tau are suited for screening to identify Aβ+ individuals who should receive subsequent PET imaging to assess tau accumulation.

In summary, we found that the combination of plasma pTau-217 and NTA-tau identifies tau PET positivity in Aβ+ individuals with a high sensitivity. This discovery has the potential to improve diagnostic accuracy using plasma biomarkers, which may enhance treatment outcomes and better stratify patients for clinical trials.

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CONFLICT OF INTEREST STATEMENT

Henrik Zetterberg has served at scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, NervGen, Novo Nordisk, OptoCeutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, AlzeCure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. Kaj Blennow has served as a consultant and at advisory boards for Acumen, ALZPath, BioArctic, Biogen, Eisai, Julius Clinical, Lilly, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials, and participated in educational programs for Biogen, Eisai, and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. Hartmuth C. Kolb and Gallen Triana-Baltzer receive salary and stock from Janssen R&D. All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was approved by the Montreal Neurological Institute (MNI) PET working committee and the Douglas Mental Health University Institute Research Ethics Board. Written informed consent was obtained for all participants.

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SUPPORTING INFORMATION

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