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RESEARCH ARTICLE

Diagnostic performance of plasma p-tau217 and Aβ42/40 biomarkers in the outpatient memory clinic

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Abstract

INTRODUCTION: Plasma biomarkers of Alzheimer's disease (AD) represent accessible alternatives to positron emission tomography (PET) and cerebrospinal fluid (CSF)-based biomarkers in well-characterized cohorts. It remains to be determined whether performance is maintained in outpatient clinics comprised of patients with multiple causes of cognitive impairment.

METHODS: Plasma phosphorylated tau217 (p-tau217) and amyloid beta (Aβ) 42/40 were measured in 509 patients evaluated in a tertiary-care memory clinic. Biomarker performance was compared across diagnoses, referencing established cutpoints for positive and negative biomarkers.

RESULTS: Plasma p-tau217 distinguished patients with diagnoses of symptomatic AD with 95% sensitivity and 82% specificity. Integration of Aβ42 measurements (p-tau217/Aβ42) incrementally improved specificity (86%). Plasma p-tau217 and p-tau217/Aβ42 concentrations closely associated with established CSF biomarkers of AD (area under the curve [AUC]: 0.94 and 0.96, respectively). Reduced kidney function associated with elevated plasma p-tau217 and p-tau217/Aβ42 concentrations in patients without AD (referencing CSF biomarkers).

DISCUSSION: Plasma p-tau217 and p-tau217/Aβ42 concentrations demonstrated robust diagnostic performance in a heterogeneous clinical cohort; interpretation requires consideration of kidney function.

KEYWORDS
Alzheimer's disease, cerebrospinal fluid, dementia, diagnosis, kidney function, memory clinic, plasma biomarker

Highlights

- Plasma phosphorylated tau217 (p-tau217) reliably identified clinic patients with Alzheimer's disease.
- A two-cutpoint strategy yielded definitive results in 86% of patients.

- Integration of plasma amyloid beta (Aβ; p-tau217/Aβ42) minimally improved diagnostic performance.
- Plasma p-tau217 levels were increased in patients with kidney dysfunction.

1 | BACKGROUND

The advent of biomarkers that directly (e.g., amyloid positron emission tomography [PET]) or indirectly (e.g., cerebrospinal fluid [CSF] phosphorylated tau [p-tau] and amyloid beta [Aβ] 42/40) measure cerebral amyloid deposition and accumulation,[1,2] have enabled accurate *ante mortem* diagnosis of symptomatic Alzheimer's disease (AD) in research and clinical settings.[3–5] However, the broad application of these established biomarkers is limited by high costs or perceived invasiveness.[6–9] This limitation emphasizes the need for reliable, accessible, non-invasive, and cost-effective biomarkers that can be broadly applied to support AD diagnoses in clinical settings.

Blood-based biomarkers represent promising alternatives to PET and CSF-based markers of AD neuropathology, with increasingly robust data supporting the ability of plasma Aβ42/40 and p-tau217 to identify cognitively impaired individuals with "positive" amyloid PET scans.[10–12] These biomarkers have been primarily validated in well-characterized cohorts comprised of participants with typical amnestic AD (mild cognitive impairment [MCI] / dementia) and cognitively normal controls,[12–21] with few exceptions.[22,23] There is a need to assess biomarker performance in populations that more closely reflect clinical experience,[24,25] including patients with early- and late-onset cognitive impairment, typical (i.e., amnestic) and atypical (i.e., non-amnestic) presentations of AD, other common neurodegenerative diseases (e.g., Lewy body disease [LBD], frontotemporal lobar degeneration [FTLD]), vascular cognitive impairment, and comorbidities known to influence plasma biomarker concentrations (i.e., kidney disease).[21,26–29] This need is further accentuated by the recent approval of putative disease-modifying therapies (i.e., lecanemab and donanemab) for patients with early-symptomatic AD,[30,31] which is expected to increase clinical demand for reliable and accessible diagnostic measures of AD neuropathology.

We measured plasma Aβ42/40, p-tau217, and p-tau217/Aβ42 in consecutive patients who underwent a diagnostic lumbar puncture for the evaluation of cognitive symptoms in a tertiary care memory disorder clinic. We applied an established "two-cutpoint strategy" to identify individuals with "positive" or "negative" plasma biomarker profiles with high sensitivity and specificity, while flagging individuals with "intermediate" results (i.e., concentrations between two cutpoints) who require additional testing.[11,24,32] We further considered associations between emergent plasma biomarker concentrations (Aβ42/40, p-tau217, and p-tau217/Aβ42) and clinical diagnoses, established CSF biomarkers of AD, and kidney function that may influence the clearance of plasma proteins.[27,29]

2 | METHODS

2.1 | Patient selection

Consecutive patients completed comprehensive clinical evaluations from March 2020 to July 2024 via an outpatient memory clinic at Mayo Clinic in Florida (Jacksonville, FL). Adult participants (≥ 18 years-old) undergoing clinical assessments for cognitive symptoms were invited to participate in this study if a diagnostic lumbar puncture was planned. Participants or their legally authorized representative provided written informed consent, including provisions for research collection and banking of blood and CSF. The study was approved by the Mayo Clinic Institutional Review Board and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2 | Establishing clinical diagnoses

Participants completed one or more clinical evaluations with a behavioral neurologist. Structural neuroimaging (typically brain magnetic resonance imaging [MRI]), neuropsychological testing, CSF analyses (including p-tau181, total tau, and Aβ42 measured via Roche Elecsys assays; Mayo Clinic Laboratories, Rochester, MN), and serum tests (including estimated glomerular filtration rate [eGFR] as a measure of kidney function) were completed per standard-of-care. We applied previously validated CSF p-tau181/Aβ42 cutpoints to identify patients likely to have moderate or greater cerebral amyloid plaque accumulation on amyloid PET.[33] Roche Elecsys Generation 1 assays were used from March 2020 to May 2023, with "positive" p-tau181/Aβ42 ≥ 0.023. Generation 2 assays were implemented June 2023, with "positive" threshold ≥ 0.028.[34] When measurements were outside acceptable ranges (n = 37, p-tau181 < 8.0 or Aβ42 > 1700 [or 2500] pg/mL), CSF ratios were manually calculated using adjusted p-tau181 and Aβ42 values (7.9 and 1701 [or 2501] pg/mL, respectively). Analyses were limited to CSF and blood samples obtained within 1 year of each other (n = 426).

Syndromic diagnoses were assigned by evaluating clinicians at the time of consent, including subjective cognitive impairment, amnestic MCI or amnestic-predominant dementia (including AD dementia), non-amnestic MCI or non-amnestic dementia (including dementia with Lewy bodies and Parkinson disease dementia), progressive supranuclear palsy, corticobasal syndrome, behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasia, vascular cognitive

impairment, posterior cortical atrophy, normal pressure hydrocephalus (NPH), and "other" diagnoses (e.g., depression). Etiologic diagnoses were assigned by assessing clinicians integrating clinically available data (including CSF biomarker studies and, when available, amyloid [n = 11] and fluorodeoxyglucose [FDG]-PET [n = 117] brain imaging) and referencing established criteria for AD,[35,36] LBD,[37] FTLD (including progressive supranuclear palsy and corticobasal degeneration),[38–40] cerebrovascular disease,[41] NPH,[42] and limbic-predominant age-related TDP-43 encephalopathy (LATE).[43,44] Electronic medical records were reviewed by a second behavioral neurologist who independently assigned syndromic and etiologic diagnoses. Diagnostic disagreements concerning syndrome or etiology were resolved through consensus discussion involving a minimum of three behavioral neurologists. Evaluating clinicians and reviewers were blinded to the results of plasma AD biomarkers.

2.3 | Assessment of kidney function

Electronic medical records were reviewed and laboratory values measured within 1 year of research blood draw were recorded, including creatinine and estimated glomerular filtration rate (eGFR). Normal values were assigned in accordance with clinical laboratory standards (eGFR ≥ 60 mL/min/1.73 m^2; Mayo Clinic Laboratories; Rochester, MN). Participants were stratified by CSF p-tau181/Aβ42 concentrations into patients with and without AD neuropathology, and the associations between kidney function (normal or impaired) and plasma AD biomarkers were assessed.

RESEARCH IN CONTEXT

1. **Systematic review**: Literature review was performed using traditional sources (e.g., PubMed) and meeting abstracts/presentations. The diagnostic applications of plasma phosphorylated tau217 (p-tau217) and amyloid beta (Aβ) 42/40 have been studied in cohorts comprised predominantly of highly characterized individuals with symptomatic Alzheimer's disease (AD). Evaluation is needed in clinically representative populations with diverse cognitive concerns and comorbidities that may affect diagnostic performance.
2. **Interpretation**: Plasma p-tau217 outperformed Aβ42/40 and reliably identified patients with symptomatic AD and CSF biomarkers of AD assessed via a representative outpatient memory clinic. Elevated plasma p-tau217 concentrations were observed in patients with kidney dysfunction, requiring caution when interpretating plasma biomarker results in patients witht kidney disease.
3. **Future directions**: This study validates plasma p-tau217 for AD detection in patients assessed via a subspecialty memory clinic with only a small subset potentially needing additional diagnostic tools. These findings suggest potential utility in primary care settings, where accessible blood testing would be valuable given limited access to established diagnostics and emerging anti-amyloid treatments.

2.4 | Interpretation of plasma AD biomarkers

Blood samples collected for research purposes were processed and divided into 250 µL aliquots within 2 h of collection. Single aliquots of ethylenediaminetetraacetic acid (EDTA) plasma were transferred into 1.5 mL polypropylene tubes and frozen at −80°C. Immediately prior to testing, single aliquots of plasma were defrosted (single freeze-thaw) at room temperature and processed according to established laboratory protocols (i.e., vortex mixing and centrifugation at 4000 × g for 5 min). Plasma biomarker measures were performed via the Fujirebio Lumipulse G1200 automated immunoassay analyzer using Lumipulse G kits for p-tau 217 Plasma (catalog number: 81472, lot number: 4129), β-Amyloid 1-42 Plasma (catalog number: 81301, lot number: 5028), and β-Amyloid 1-40 Plasma (catalog number: 81298, lot number: 5081). Samples with insufficient volume (n = 13) or questionable preanalytic stability (n = 1) were excluded. Plasma p-tau217 concentrations were available for all patients (n = 509); Aβ42/40 concentrations were available for 495 patients (97.3%). Laboratory personnel were blinded to clinical information, including CSF AD biomarker results.

Plasma p-tau217 cutpoints were previously established referencing amyloid status determined by amyloid PET.[11] Using the same research dataset, which included concurrent measurements of Aβ42, Aβ40, and p-tau217, we calculated cutpoints for p-tau217/Aβ42 and Aβ42/40 ratios. Consistent with established p-tau217 cutpoints, we used the same performance criteria: a fixed sensitivity of 92% at the lower cutpoint and specificity of 96% at the upper cutpoint. This level of fixed sensitivity and specificity at the lower and upper cutpoints was chosen to support comparisons of plasma biomarkers at the same level of overall accuracy, expecting that the proportion of intermediate results would differ between the assays. Plasma AD biomarker cutoffs were applied to classify patients as "positive" (p-tau217 ≥ 0.325 pg/mL; Aβ42/40 ≤ 0.0777; p-tau217/Aβ42 ≥ 0.0132), "negative" (p-tau217 ≤ 0.185 pg/mL; Aβ42/40 ≥ 0.0997; p-tau217/Aβ42 ≤ 0.0074), or "intermediate" (p-tau217 = 0.186–0.324 pg/mL; Aβ42/40 = 0.0778–0.0996, p-tau217/Aβ42 = 0.0075–0.0131).[11]

2.5 | Statistical analyses

Demographics, clinical presentation, test results, and diagnoses were summarized using descriptive statistics. The distribution of continuous variables were compared using independent t-tests; categorical variables distributions were analyzed using chi-squared tests and reported as odds ratios (with 95% confidence intervals [CI]). Inter-rater reliability was assessed using the kappa coefficient. The sensitivity, specificity,

and positive and negative predictive values of plasma AD biomarkers were assessed referencing established clinical diagnoses and (separately) CSF AD biomarkers. Patients with "intermediate" biomarker concentrations were withheld from these analyses, asserting that an "intermediate" test result implies the need for further evaluation (i.e., amyloid PET or CSF biomarkers). Receiver operating characteristic analyses assessed the accuracy of individual biomarkers referencing clinical diagnoses of AD (vs. non-AD) and the presence/absence of AD neuropathology, established via CSF p-tau181/Aβ42. Associations between kidney dysfunction (reduced eGFR; [normal vs. 45 $\leq$ eGFR $<$ 60 or $<$ 45 mL/min/1.73 m^2]), and plasma AD biomarkers concentrations were assessed using independent *t*-tests. Finally, we considered the correlation between AD plasma biomarkers and CSF p-tau181/Aβ42 using Spearman correlation coefficients.

Estimates, 95% CI, and figures were produced using Analyse-it, version 6.15 for Microsoft Excel; Stata MP, version 18; and the R language and environment for statistical computing, version 4.4.2 (R Foundation for Statistical Computing), or the ggplot2 package for data visualization. Other analyses were conducted using SPSS (version 28.0, IBM Corp, Armonk, NY)

3 | RESULTS

3.1 | Patient characteristics

Table 1 outlines patient characteristics, clinical syndromes, and presumed causes of cognitive impairment in 509 patients who completed memory clinic assessments. Patient ages spanned the adult life course (range: 32.7–89.4 years-old), with mean age-at-symptom onset of 65.5 ± 9.8 years. Twelve patients were younger than 50 years-old (2.4%). Most patients were non-Hispanic White (*n* = 465, 91.3%) individuals. Sex-distribution was balanced (53.0% male). Memory concerns predominated in this clinic-based cohort, with 274 (53.8%) patients diagnosed with amnestic-predominant cognitive impairment. NPH (*n* = 64, 12.6%) and non-amnestic cognitive impairment (*n* = 51, 10.0%) were the next most common clinical syndromes.

In 285 patients (56.0%), AD was determined to be the underlying cause of cognitive symptoms, including 237 patients (83.2%) with an amnestic presentation, 23 patients (8.1%) with primary progressive aphasia, 13 patients (4.5%) with visual variant (i.e., posterior cortical atrophy), 7 patients (2.4%) with another non-amnestic syndrome, 3 patients (1.1%) with a motor-predominant presentation (i.e., corticobasal syndrome), and 1 patient each (0.35%) with cerebral amyloid angiopathy (incidentally discovered on MRI performed for another indication) and preclinical/prodromal AD (subjective cognitive impairment). The remaining patients (224, 44.0%) had primary etiologies that broadly reflected the spectrum of disorders associated with age-related cognitive decline. Patients with NPH were overrepresented (*n* = 66, 29.5%), reflecting our center's expertise and the priority placed on large-volume lumbar punctures in the diagnostic evaluation of patients with suspected CSF flow dynamic disorders. In patients with typical neurodegenerative diseases, LBD (*n* = 30, 13.4%) and

TABLE 1 Patient characteristics, clinical syndromes, and causes of cognitive impairment.

	n = 509
Demographics	
Age at symptom onset, mean (SD)	65.5 (9.8)
Age at lumbar puncture, mean (SD)	68.5 (9.2)
Age at blood draw, mean (SD)	68.6 (9.3)
Female, *n* (%)	239 (47.0)
Race, *n* (%):	
Black/African American	17 (3.3)
White	471 (92.5)
Other	21 (4.1)
Hispanic ethnicity, *n* (%):	12 (2.4)
Clinical syndrome, *n* (%)	
Amnestic MCI/dementia	274 (53.8)
Normal pressure hydrocephalus	64 (12.6)
Non-amnestic MCI/dementia	51 (10.0)
Subjective cognitive decline	51 (10.0)
Primary progressive aphasia	30 (5.9)
Logopenic	22 (73.4)
Non fluent/agrammatic	4 (13.3)
Semantic	3 (10.0)
Other (apraxia of speech)	1 (3.3)
Posterior cortical atrophy	14 (2.8)
Corticobasal syndrome	8 (1.6)
Progressive supranuclear palsy	5 (1.0)
Behavioral variant FTD	4 (0.8)
Vascular MCI/dementia	1 (0.2)
Other*	7 (1.3)
Etiology, *n* (%)	
Alzheimer's disease	285 (56.0)
Normal pressure hydrocephalus	66 (13.0)
Lewy body disease	30 (5.9)
Frontotemporal lobar degeneration	28 (5.5)
Vascular cognitive impairment	9 (1.8)
Hippocampal sclerosis/LATE	6 (1.2)
Other	85 (16.7)
Degenerative†	6 (7.1)
Non-degenerative‡	61 (70.9)
Unknown/no clear etiology	18 (20.9)

Abbreviations: MCI, mild cognitive impairment; FTD, frontotemporal dementia; LATE, limbic-predominant amnestic TDP-43 encephalopathy.
Other*: Parkinson disease (*n* = 3), epilepsy (*n* = 2), and undefined clinical syndrome (*n* = 2).
†Chronic traumatic encephalopathy (*n* = 2), multiple system atrophy (*n* = 2), cerebral amyloid angiopathy (*n* = 1), primary lateral sclerosis (*n* = 1).
‡Depression/anxiety (*n* = 28), no pathology/healthy (*n* = 14), obstructive sleep apnea (*n* = 5), encephalitis (*n* = 4), traumatic brain injury (*n* = 3), congenital hydrocephalus (*n* = 2), epilepsy (*n* = 2), space occupying lesion (*n* = 2), Wernicke encephalopathy (*n* = 1).

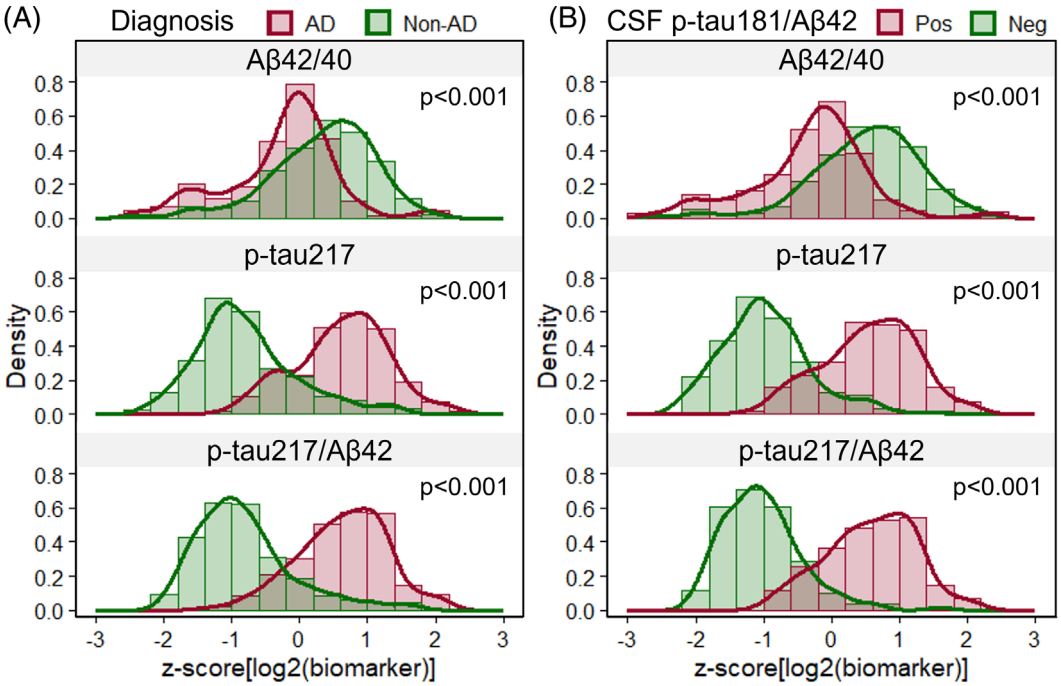


FIGURE 1 Distribution of plasma AD biomarkers by diagnosis and CSF p-tau181/Aβ42. Density plots showing the distribution of plasma AD biomarkers: Aβ42/40 (top), p-tau217 (middle), and p-tau217/Aβ42 (bottom). (A) Plasma biomarker values in patients with (red) and without a clinical diagnosis of AD (green). (B) Plasma AD biomarkers in patients with (red) and without (green) CSF p-tau181/Aβ42 consistent with AD. The x-axis represents z-scores of log2-transformed biomarker values; the y-axis shows density (i.e., proportion of patients). Histograms with fitted normal distribution curves demonstrate the separation between groups for each biomarker. Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.

FTLD were the next most common diagnoses ($n = 28$, 12.5%). Patients with non-degenerative causes of cognitive complaints (e.g., depression) comprised 27.2% of patients ($n = 61$).

3.2 | Diagnostic performance of plasma AD biomarkers

Plasma Aβ42/40 concentrations were lower in patients with AD versus without AD (mean difference 0.0094, 95% CI: 0.0065, 0.0123; $p < 0.001$). Plasma p-tau217 concentrations (mean difference 0.572 pg/mL, 95% CI: 0.492, 0.651; $p < 0.001$) and p-tau217/Aβ42 (mean difference 0.0234, 95% CI: 0.0200, 0.0267; $p < 0.001$) were increased in patients with AD versus without AD (Figure 1A). Similar patterns were observed when comparing between patients with and without AD neuropathology, determined by established CSF biomarkers (Figure 1B; Aβ42/40: mean difference -0.0096, 95% CI: -0.0065, -0.0127; $p < 0.001$; p-tau217: mean difference 0.566 pg/mL, 95%CI: 0.481, 0.650; $p < 0.001$; p-tau217/Aβ42: mean difference 0.0230, 95%CI: 0.0195, 0.0264; $p < 0.001$).

We further considered diagnostic applications of plasma AD biomarkers. Plasma Aβ42/40 concentrations were "positive" (≤ 0.0777) in 47/495 (9.5%) patients and "negative" (≥ 0.0997) in 235/495 (47.5%) patients. Results were "intermediate" (0.0778-0.0996) in 213/495 patients (43.0%), implying the need for further testing to inform the likelihood of AD neuropathologic change. Limiting analyses to patients with definitive results, Aβ42/40 concentrations were "positive" in 38/129 patients with cognitive impairment attributed to AD (sensitivity, 29%; Table 2). "Positive" results were also reported in 9/153 patients with alternate (non-AD) diagnoses (specificity, 94%), including patients with NPH (5/66, 7.6%), LBD (1/30, 3.3%), and "other" conditions (3/80, 3.8%; Table 3). "Positive" results were associated with a clinical diagnosis of AD in 38/47 patients (positive predictive value [PPV], 81%). A "negative" value excluded AD as the cause for cognitive concerns in 144/235 patients (negative predictive value [NPV], 61%).

Plasma p-tau217 concentrations were "positive" (≥ 0.325 pg/mL) in 267/509 (52.4%) patients, "negative" (≤ 0.185 pg/mL) in 172/509 (33.8%) patients, and "intermediate" (0.186–0.324 pg/mL) in 70/509 (13.8%) patients. Limiting analyses to patients with definitive results, p-tau217 concentrations were "positive" in 233/246 patients with cognitive impairment attributed to AD (sensitivity, 95%), and 34/193 patients with alternate (non-AD) diagnoses (specificity, 82%), including LATE (3/6, 50%), LBD (10/30, 33.3%), vascular cognitive impairment (2/9, 22.2%), NPH (8/66, 12.1%), FTLD (1/28, 3.6%), and "other" causes (10/85, 11.8%). "Positive" values were associated with a diagnosis of AD in 233/267 patients (PPV, 87%); "negative" values excluded the diagnosis in 159/172 patients (NPV, 92%).

TABLE 2 Diagnostic performance of plasma AD biomarkers, referencing consensus clinical diagnoses (AD vs non-AD) and results of established CSF AD biomarkers.

Plasma biomarkers, *n* (%)	AD	Non-AD
Aβ42/Aβ40*	277	218
Positive	38 (13.7)	9 (4.1)
Negative	91 (32.9)	144 (66.1)
Intermediate	148 (53.4)	65 (29.8)
p-tau217	285	224
Positive	233 (81.7)	34 (15.2)
Negative	13 (4.6)	159 (71.0)
Intermediate	39 (13.7)	31 (13.8)
p-tau217/Aβ42*	277	218
Positive	224 (80.9)	26 (11.9)
Negative	13 (4.7)	165 (75.5)
Intermediate	40 (14.4)	27 (12.7)
	CSF p-tau181/Aβ42 (+)	**CSF p-tau181/Aβ42 (–)**
Aβ42/Aβ40†	263	149
Positive	26 (9.9)	4 (2.7)
Negative	86 (32.7)	111 (74.5)
Intermediate	151 (57.4)	34 (22.8)
p-tau217	270	156
Positive	218 (80.7)	14 (9.0)
Negative	18 (6.7)	118 (75.6)
Intermediate	34 (12.6)	24 (15.4)
p-tau217/Aβ42†	263	149
Positive	208 (79.1)	7 (4.7)
Negative	16 (6.1)	124 (83.2)
Intermediate	39 (14.8)	18 (12.1)

Note: Measures performed in 495/509 (97.3%)* and 412/426 (96.7%)† of patients. Fourteen samples were excluded: thirteen had insufficient volume for measurement and one due to preanalytic Aβ instability. CSF p-tau181/Aβ42 considered positive ≥ 0.0023 (March 2020-May 2023); ≥ 0.0028 (after May 31, 2023), Mayo Clinic Laboratories (Rochester, MN).
Abbreviations: Aβ, amyloid-beta; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.

The ratio of p-tau217/Aβ42 was "positive" (≥ 0.0132) in 250/495 (50.5%) patients, "negative" (≤ 0.0074) in 178/495 (36.0%) patients, and "intermediate" (0.0075-0.0131) in 67/495 (13.5%) patients. Limiting analyses to patients with definitive results, p-tau217/Aβ42 was "positive" in 224/237 patients with cognitive impairment attributed to AD (sensitivity, 95%), and "positive" in 26/191 with alternate diagnoses (specificity, 86%), including LBD (10/30, 33.3%), LATE (1/6, 16.7%), vascular cognitive impairment (1/9, 11.1%), NPH (5/66, 7.6%), and "other" causes (9/80, 11.3%). "Positive" values were associated with AD diagnoses in 224/250 (PPV, 90%); "negative" values excluded the diagnosis in 165/178 patients (NPV, 93%).

3.3 | Diagnostic performance of plasma AD biomarkers stratified by age

The diagnostic performances of plasma AD biomarkers were compared in patients younger ($n = 186$, 36.5%) and older than 65 years ($n = 323$, 63.5%; Table S1). Definitive plasma biomarker results ("positive" or "negative") were reported in a higher proportion of younger versus older patients for Aβ42/40 (64.2% vs. 52.8%; $p = 0.010$), p-tau217 (92.5% vs. 82.7%; $p = 0.002$), and p-tau217/Aβ42 (92.2% vs 83.2%; $p = 0.006$); that is, "intermediate" results were more common in older patients. The sensitivities (Aβ42/40: 34% vs. 25%, $p = 0.332$; p-tau217: 97% vs. 93%, $p = 0.252$; p-tau217/Aβ42: 98% vs. 92%, $p = 0.079$) and specificities (Aβ42/40: 95% vs. 94%, $p > 0.99$; p-tau217: 84% vs. 82%, $p = 0.846$; p-tau217/Aβ42: 83% vs. 88%, $p = 0.283$) of plasma biomarkers were similar in younger and older patients.

3.4 | Plasma versus CSF AD biomarkers

Correlations between plasma and CSF AD biomarkers were considered in the 426/468 patients (88.2%) with paired samples, including 412/426 (96.7%) patients with plasma Aβ42/40 and 426/426 (100%) patients with plasma p-tau217 results (Figures 2, 3). Plasma Aβ42/40 concentrations were negatively correlated (rho = -0.4) with CSF p-tau181/Aβ42 (i.e., lower concentrations of plasma Aβ42/40 associated with higher [i.e., more positive] CSF p-tau181/Aβ42concentrations). Plasma p-tau217 concentrations were positively associated with CSF AD biomarkers, with increases in plasma p-tau217 (rho = 0.742) and p-tau217/Aβ42 (rho = 0.761) associated with higher CSF p-tau181/Aβ42 concentrations.

We further evaluated the concordance between definitive (i.e., "positive" and "negative"; see the Methods section) plasma AD biomarkers and established CSF measures of AD neuropathology (Table 2), stratified by etiologic diagnoses (Table S2). There was poor overall agreement between binarized (i.e., "positive" ≤ 0.0777 pg/mL vs. "negative" ≥ 0.0997) plasma Aβ42/40 and CSF p-tau181/Aβ42 results. Plasma and CSF AD biomarker results were concordant in 137/227 patients (accuracy 60%; $\kappa = 0.199$, $p < 0.001$), including 26/263 (9.9%) patients with and 111/149 (74.5%) patients without AD neuropathology (defined by CSF AD biomarkers). Agreement was highest in patients with "other" causes of cognitive impairment (accuracy 98%; $\kappa = 0.791$, $p < 0.001$) and lowest in patients with symptomatic AD (accuracy 27%, $\kappa = 0.009$, $p = 0.707$).

Agreement was substantially higher for plasma results incorporating measures of p-tau217. When p-tau217 was considered in isolation, results were concordant in 336/368 patients (91% accuracy; $\kappa = 0.812$, $p < 0.001$), including 218/236 (93%) patients with AD neuropathology and 118/132 (89%) patients without AD neuropathology (defined by CSF AD biomarkers). Agreement was highest in patients with AD as the cause of cognitive impairment (96% accuracy; k = 0.479, $p < 0.001$) and lowest in patients with presumed hippocampal sclerosis/LATE (60% accuracy; $\kappa = 0.286$, $p = 0.361$). Integration of plasma Aβ42

TABLE 3 Plasma AD biomarkers stratified by etiologic diagnosis.

Etiology, *n* (%)	AD	LBD	FTLD	Vascular	NPH	Hippocampal sclerosis/LATE	Other†
Plasma Aβ42/40, *n* (%)*	277	30	27	9	66	6	80
Positive	38 (13.7)	1 (3.3)	0 (/)	0 (/)	5 (7.6)	0 (/)	3 (3.8)
Negative	91 (32.9)	14 (46.7)	19 (70.4)	6 (66.7)	40 (60.6)	3 (50.0)	62 (77.6)
Intermediate	148 (53.4)	15 (50.0)	8 (29.6)	3 (33.3)	21 (31.8)	3 (50.0)	15 (18.6)
Plasma p-tau217, *n* (%)	285	30	28	9	66	6	85
Positive	233 (81.8)	10 (33.3)	1 (3.6)	2 (22.2)	8 (12.1)	3 (50.0)	10 (11.8)
Negative	13 (4.6)	17 (56.7)	23 (82.1)	4 (44.5)	44 (66.7)	2 (33.3)	69 (81.2)
Intermediate	39 (13.6)	3 (10.0)	4 (14.3)	3 (33.3)	14 (21.2)	1 (16.7)	6 (7.0)
Plasma p-tau217/Aβ42, *n* (%)*	277	30	27	9	66	6	80
Positive	224 (80.9)	10 (33.3)	0 (/)	1 (11.1)	5 (7.6)	1 (16.7)	9 (11.3)
Negative	13 (4.3)	18 (60.0)	24 (88.9)	6 (66.7)	48 (72.7)	3 (50.0)	66 (82.5)
Intermediate	40 (14.4)	2 (6.7)	3 (11.1)	2 (22.2)	13 (19.7)	2 (33.3)	5 (6.)

Abbreviations: AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; LBD, Lewy body disease; NPH, normal pressure hydrocephalus; LATE, limbic-predominant age-related TDP-43 encephalopathy.

*Biomarker measures performed in 495/509 (97.2%) patients. Fourteen samples were excluded: thirteen had insufficient volume for measurement and one due to preanalytic Aβ instability.

Other† = depression/anxiety ($n = 28$), no pathology/healthy ($n = 14$), obstructive sleep apnea ($n = 5$), encephalitis ($n = 4$), traumatic brain injury ($n = 3$), chronic traumatic encephalopathy ($n = 2$), multiple system atrophy ($n = 2$), congenital hydrocephalus ($n = 2$), epilepsy ($n = 2$), space occupying lesion ($n = 2$) cerebral amyloid angiopathy ($n = 1$), primary lateral sclerosis ($n = 1$), Wernicke encephalopathy ($n = 1$), unknown/no clear etiology ($n = 18$).

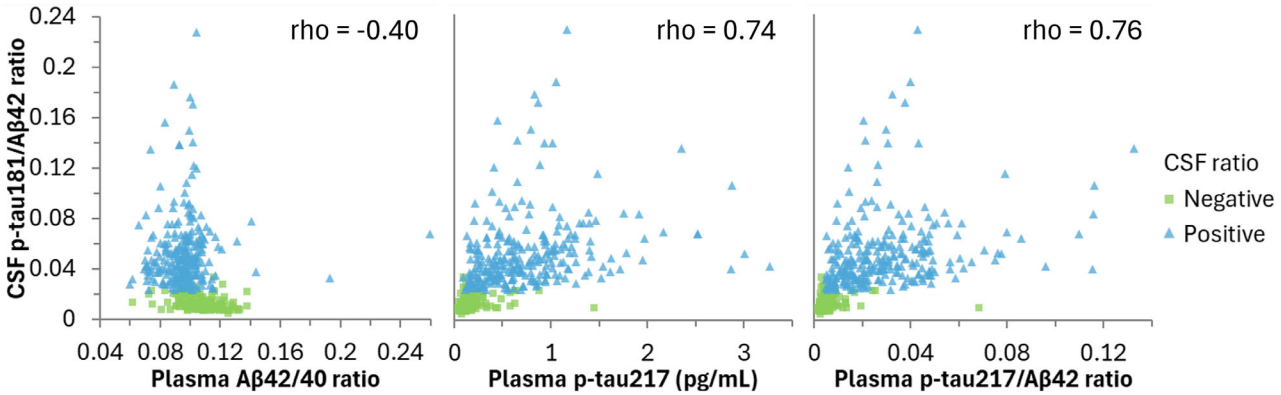


FIGURE 2 Correlation between plasma and CSF AD biomarker concentrations. Spearman's correlation coefficients (rho) are shown between CSF ratio values (y-axis) and plasma measures of Aβ42/40 (A), p-tau217 (B), and p-tau217/Aβ42 (C). Results are stratified by the presence (blue triangles) and absence (green squares) of AD neuropathology, defined by CSF p-tau181/Aβ42 concentrations. Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.

marginally improved agreement. Plasma p-tau217/Aβ42 (≥ 0.0132) and CSF AD biomarkers results were concordant in 332/355 patients (93% accuracy; $\kappa = 0.863$, $p < 0.001$).

3.5 | Comparative diagnostic performance of plasma AD biomarkers

The diagnostic performances of plasma AD biomarkers were compared using receiver operating characteristics (Figure 4), referencing clinical diagnoses (AD vs. non-AD; panel A) and established CSF AD biomarkers (panel B). Although all plasma biomarkers identified patients with AD at frequencies greater than chance, the performance of plasma biomarkers incorporating p-tau217 were superior to isolated measures of plasma Aβ42/40. Plasma Aβ42/40 measures exhibited fair ability to distinguish patients with symptomatic AD (area under the curve [AUC] = 0.73, 95% CI: 0.68, 0.77). Plasma p-tau217 concentrations, by comparison, reliably identified patients with symptomatic AD (AUC = 0.91, 95% CI: 0.88, 0.93); results were incrementally improved when combining measures (p-tau217/Aβ42, AUC = 0.92, 95% CI: 0.89, 0.94). Results were similar when assessing the ability of plasma biomarkers to discern patients with and without AD neuropathology

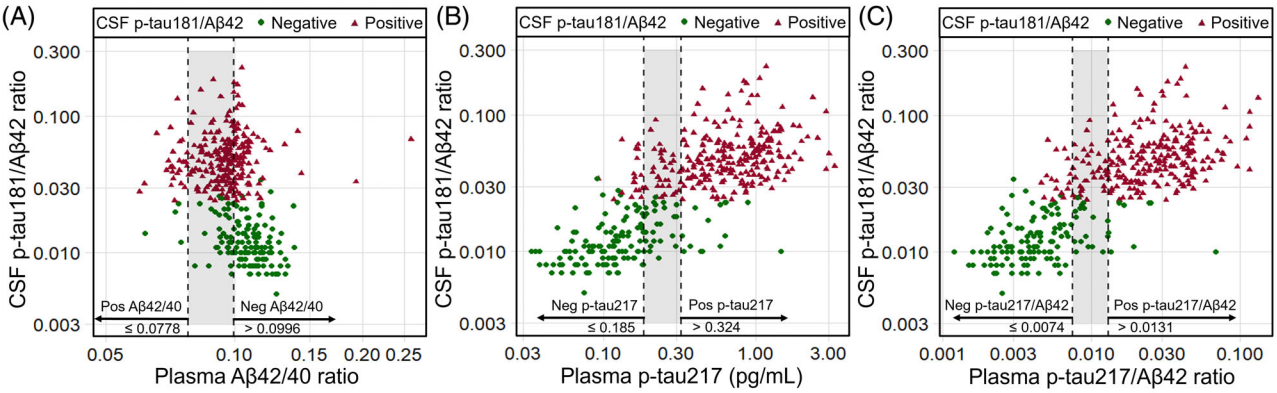
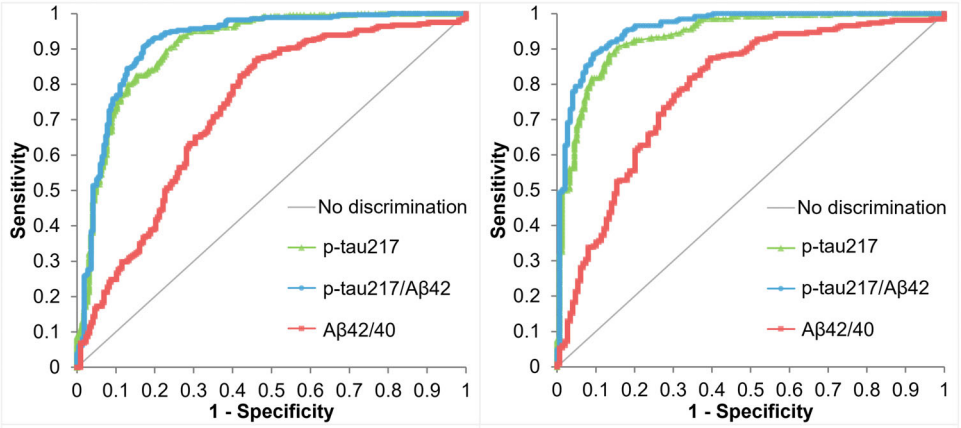


FIGURE 3 Distribution of plasma versus CSF AD biomarkers concentrations stratified by CSF p-tau181/Aβ42 status. Scatterplots show the relationship between CSF p-tau181/Aβ42 ratio (y-axis) and plasma Aβ42/40 ratio (A), p-tau217 concentrations (B) or p-tau217/Aβ42ratio (C). Green circles and red triangles represent CSF-negative and CSF-positive cases, respectively. Gray areas indicate intermediate zones between established cutoff values for plasma biomarkers (Aβ42/40: 0.0778–0.0996; p-tau217: 0.186–0.324 pg/mL; p-tau217/Aβ42: 0.0075–0.0131). Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.



Test	AUC	95% CI
p-tau217	0.91	0.88 to 0.93
p-tau217/Aβ42	0.92	0.89 to 0.94
Aβ42/Aβ40	0.73	0.68 to 0.77

Test	AUC	95% CI
p-tau217	0.94	0.91 to 0.96
p-tau217/Aβ42	0.96	0.94 to 0.98
Aβ42/Aβ40	0.78	0.74 to 0.83

FIGURE 4 Comparative diagnostic performance of plasma AD biomarkers. Receiver operating characteristic curves compare the relative diagnostic performance of plasma AD biomarkers, referencing clinical consensus diagnoses (A) and established CSF AD biomarkers ("positive" CSF p-tau181/Aβ42; B). Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.

established via CSF AD biomarkers (plasma Aβ42/40, AUC = 0.78, 95% CI: 0.74, 0.83; plasma p-tau217, AUC = 0.94, 95% CI: 0.91, 0.96; plasma p-tau217/Aβ42, AUC = 0.96, 95% CI: 0.94, 0.98).

3.6 | Influence of kidney function on diagnostic performance of plasma AD biomarkers

The association between plasma AD biomarkers and kidney dysfunction (i.e., decreased creatinine clearance) was assessed using eGFR (Table S3). CSF AD biomarkers were used to stratify patients into groups with and without AD neuropathology. Analyses were constrained to patients with eGFR measures completed within 1 year of the date of plasma collection for AD biomarkers (median 1.6 months between measures, range 0.0–12.0). Data were available from 340/426 (79.8%) patients.

Plasma Aβ42/40 concentrations were not influenced by decreased creatinine clearance (Figure 5A-C). In patients without AD neuropathology (131/156, 84.0%), modest declines in creatinine clearance (eGFR < 60 mL/min/1.73 m^2; n = 28, 21.4%) were associated with elevations in p-tau217 (mean difference: 0.142 pg/mL, 95%CI: 0.072, 0.212; p < 0.001) and p-tau217/Aβ42 (mean difference: 0.0038, 95%CI: 0.0008, 0.0066; p = 0.012). Greater impairments in creatinine clearance (eGFR < 45 mL/min/1.73 m^2; n = 7, 5.3%) were associated with greater elevations in plasma p-tau217 (mean difference 0.156, 95% CI: 0.022, 0.289; p = 0.022). A similar association was noted in patients with AD neuropathology (209/270, 77.4%) and decreased creatinine clearance (eGFR < 45 mL/min/1.73 m^2; n = 8, 3.8%), with

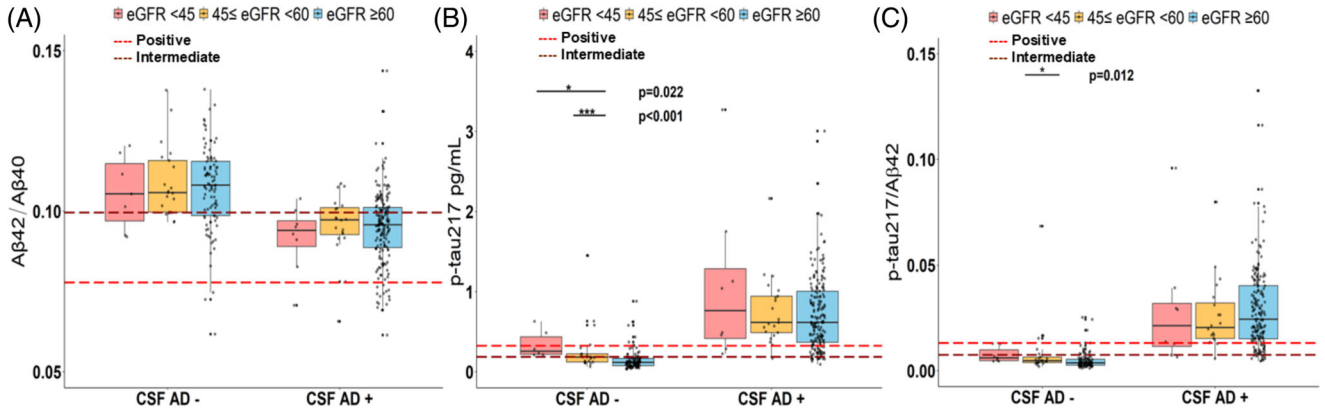


FIGURE 5 The association between creatinine clearance and plasma AD biomarker concentrations. Box and scatter plots depict plasma concentrations of Aβ42/40 (A), p-tau217 (B), and p-tau217/Aβ42 (C) in patients with normal creatine clearance (eGFR ≥ 60 mL/min/1.73 m^2, blue), and mild (45 ≤ eGFR < 60 mL/min/1.73 m^2, yellow) and severe kidney dysfunction (eGFR < 45 mL/min/1.73 m^2, red). Analyses are stratified by the presence (CSF AD +) and absence (CSF AD -) of AD neuropathology, referencing CSF p-tau181/Aβ42 concentrations. Red dashed lines depict established cutpoints for plasma biomarkers (abnormal values: Aβ42/40 ≤ 0.0777 ["positive"], ≤ 0.0996 ["intermediate"]; p-tau217 ≥ 0.325 pg/mL ["positive"], ≥ 0.186 pg/mL ["intermediate"]; p-tau217/Aβ42 ≥ 0.0132 ["positive"], ≥ 0.0075 ["intermediate"]).[11] Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; p-tau, phosphorylated tau.

mean elevations in plasma p-tau217 of 0.350 compared to patients with normal creatinine clearance (95%CI: -0.015, 0.707, $p = 0.060$).

4 | DISCUSSION

Plasma p-tau217 concentrations reliably identified patients with symptomatic AD (95% sensitivity, 82% specificity) and closely paralleled results from established CSF biomarkers of AD neuropathology in patients assessed in a tertiary care memory disorder clinic. Strong correlations (rho = 0.74) and high diagnostic agreement were observed between plasma p-tau217 and CSF p-tau181/Aβ42 when applying biomarker cutpoints optimized to identify individuals with and without AD neuropathology (91% accuracy; $\kappa = 0.812$, $p < 0.001$). The diagnostic performance of plasma p-tau217 (clinical concensus diagnosis: AUC 0.91; 95% CI 0.88, 0.93; CSF AD biomarkers: AUC 0.94; 95% CI 0.91, 0.96) was superior to measures of Aβ42/40 alone (clinical concensus diagnosis: AUC 0.73; 95% CI 0.68, 0.77; CSF AD biomarkers: AUC 0.78; 95% CI 0.74, 0.83). Similar results were obtained when integrating plasma measures of Aβ42 (p-tau217/Aβ42, clinical concensus diagnosis: AUC 0.92; 95% CI 0.89, 0.94; CSF AD biomarkers: AUC 0.96; 95% CI 0.94, 0.98).

These findings add to a rapidly expanding literature affirming strong concordance between plasma p-tau217 measures and established markers of AD neuropathology, including amyloid PET[12, 16, 17, 19, 26, 45–47] and CSF Aβ42/40, p-tau181, p-tau217,[16, 18, 21, 22, 28] and *post mortem* measures of neuritic plaques and tau neuropathology.[48, 49] Our findings similarly attest to the superior performance of plasma p-tau217 versus Aβ42/40 biomarkers in identifying patients with conventional biomarkers of AD neuropathology (i.e., CSF biomarkers measured here and amyloid PET scans measured elsewhere).[12–14, 50] Biofluid measures of Aβ are influenced by several patient-specific factors (e.g., time-of-day of sampling,[51] fasting status[52]) and lab-based variables (e.g., collection tube,[53] freeze-thaw cycles,[54] storage time[55]), which may contribute to variability in plasma biomarker measures and lower diagnostic accuracy. By contrast, plasma p-tau217 measures are relatively impervious to preanalytic factors,[24] including centrifugation and thawing temperatures,[56] with similar performance reported in head-to-head studies utilizing various platforms (e.g., mass spectrometry, liquid chromatography, and commercially available assays [Fujirebio Lumipulse or Quanterix single-molecule assay {SIMOA}]).[57] The potential pre-analytical and analytical technical challenges and increased costs associated with Aβ measurements call into question the value added by integration of biomarkers of Aβ42/40 in clinical practice. In our clinic, the downsides and costs associated with consistent measurement of plasma Aβ appear to outweigh the modest (i.e., clinically negligible) improvements in diagnostic performance associated with integrated measures (i.e., p-tau217/Aβ42). This may change as assays and clinical algorithms evolve.

Prior studies evaluating plasma p-tau217 were limited to highly selected research populations with amyloid and tau status validated by CSF- or imaging-based assessments,[12–14, 16, 24, 45, 46] with few exceptions.[22, 23, 26, 48, 49] Our study expands upon these well-characterized cohorts by measuring plasma p-tau217 concentrations in patients presenting for evaluation of cognitive concerns to an established outpatient memory clinic. In this context, elevated plasma p-tau217 identified most patients with symptomatic AD (95%) and CSF-established AD pathology (92%)—similar to findings in a prior study including patients undergoing diagnostic evaluation of dementia in primary care clinics in Europe.[22] The specificity of p-tau217 for symptomatic AD diagnosis was somewhat reduced (82%), compared to previous studies (94%).[18] These differences may reflect differences in cohort characteristics, noting that our cohort included substantial proportions of older patients with AD-related dementias known to associate with AD co-pathology.[58–60] In support of this statement,

plasma p-tau217 specificity was lowest (< 65%) in patients with AD-related dementias associated with high rates of AD co-pathology (i.e., LATE, LBD, and vascular cognitive impairment),[61–64] and highest (> 85%) in patients with cognitive impairment attributed to FTLD and "other" causes of dementia.

We used a two-cutpoint approach validated in research participants with and without "positive" amyloid PET scans.[11, 15, 32] This approach was selected to maximize sensitivity and specificity (> 90%; i.e., diagnostic accuracy), while minimizing the proportion of individuals with "intermediate" (or indeterminate) results.[24] Our findings attest to the merits of this approach. Definitive plasma p-tau217 results were obtained in 86% of patients in our series. Accordingly, plasma AD biomarker findings would have informed the clinical care of most patients with amnestic and non-amnestic concerns assessed in our outpatient memory clinic, with < 15% requiring additional testing to inform next steps in the clinical evaluation (e.g., conventional AD biomarkers, such as amyloid PET or CSF AD biomarkers). This approach can be further refined by integrating blood based biomarker results and knowledge of disease prevalence to inform the pretest probability of an AD diagnosis, with PPV > 95% in multicenter research cohorts comprised of individuals with AD dementia, and NPV > 90% in individuals with non-AD dementia syndromes.[65] These reports are particularly timely given the increasing demand for anti-amyloid treatments, and the increasingly pressing need for accessible, scalable, non-invasive, and reliable biomarkers to identify patients who may benefit from these emergent therapies.[25]

Impaired kidney function (eGFR < 60 mL/min/1.73 m^2) was associated with increased plasma p-tau217 concentrations in our study and others.[21, 26–29] Recent publications from our center further establish a non-linear relationship between plasma p-tau217 concentrations and kidney dysfunction, with plasma p-tau217 concentrations increasing to greater degree below an eGFR of 45 mL/min/1.73 m^2 than between an eGFR of 60 and 45 mL/min/1.73 m^2.[29] These findings emphasize the need to measure kidney function (i.e., creatinine or eGFR) contemporaneously with plasma AD biomarkers and integrate results when interpreting plasma biomarkers. Whereas low (i.e., "negative") biomarker concentrations remain informative, elevated plasma p-tau217 concentrations should be interpreted with caution. In patients with eGFR below 45 mL/min/1.73 m^2 (stage 3b chronic kidney disease) and elevated plasma p-tau217, CSF AD biomarkers or amyloid PET should be obtained, similar to patients with "intermediate" plasma p-tau217 results. Further studies are needed to establish reliable cutoffs for interpreting increased p-tau217 in individuals with impaired kidney function and to elucidate the mechanisms that underpin this relationship.

Our study has limitations. Our clinic-based cohort included patients across the adult lifespan, with balanced sex distribution, and a broad spectrum of amnestic and non-amnestic phenotypes that are commonly seen in clinical practice; yet most patients were non-Hispanic White individuals. Although early studies suggest that biomarker performance does not vary by race or ethnicity,[66] it is important to evaluate plasma biomarker measures in representative cohorts,[24] including greater proportions of Black / African American and Hispanic / Latino individuals who experience disproportionate burdens of dementia,[67] medical comorbidities that may influence biomarker performance (including kidney impairment),[68, 69] and diagnostic delays and misdiagnoses[68, 70–72] compared to non-Hispanic White Americans. Additionally, our setting as a large academic referral center with recognized expertise in NPH likely influenced referral patterns, contributing to overrepresentation of patients with NPH compared to that expected in community-based practices. Twelve patients (2.4%) in our cohort were < 50 years old. Additional research is needed to validate plasma AD biomarker cutpoints in younger patients, noting that this study applied biomarker cutpoints that were previously validated in individuals ≥ 50 years old.[11] Furthermore, in this study, kidney function was categorized using eGFR values obtained within 1 year of plasma p-tau217 measurement and not simultaneously. Kidney function may fluctuate over time, especially in older adults, emphasizing the importance of assessing plasma biomarkers and kidney function contemporaneously in the future. Finally, our study relied on clinical consensus diagnoses, integrating findings from established CSF AD biomarkers. Neuropathology remains the gold standard for definitive diagnosis. Further study in cohorts followed to autopsy will be necessary to definitively determine diagnostic outcomes in patients with "positive", "negative", and "intermediate" plasma AD biomarker results.

Plasma p-tau217 and p-tau217/Aβ42 concentrations demonstrated robust diagnostic performance in a heterogeneous clinical cohort, with high sensitivity and specificity, similar performance in patients older and younger than 65-years, and excellent correlation with CSF-based biomarkers of AD neuropathology. Our findings suggest that plasma p-tau217 concentrations may serve as a standalone biomarker to improve diagnostic accuracy in appropriate patients, with additional testing (CSF analysis or amyloid PET) prioritized in the < 15% of cases with indeterminate results or in patients with impaired kidney function and abnormal plasma biomarkers.

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CONFLICT OF INTEREST STATEMENT

Y.D. Piura reports no conflicts of interest. D.J. Figdore reports no conflicts of interest. C. Lachner reports no conflicts of interest. His research is supported by the NIH (UH2-AG083186, ARDC AG062677 Clinical Core, AG075802, NS125417). J. Bornhorst has participated on an advisory board for Sunbird Bio and received an honorarium from Roche Diagnostics. A. Algeciras-Schimnich has participated on advisory boards for Roche Diagnostics and Fujirebio Diagnostis, and has received a honorarium from Roche Diagnostics. N.R. Graff-Radford reports no conflicts of interest. His research is supported by NIH. He has participated in multicenter therapy studies sponsored by Biogen, Eisai and Lilly. G.S. Day reports no conflicts of interest.

His research is supported by NIH (R01AG089380, U01AG057195, U01NS120901, U19AG032438). He serves as a consultant for Arialys Therapeutics and Parabon Nanolabs Inc, and as a Topic Editor (Dementia) for DynaMed (EBSCO). He is a co-Project PI for a clinical trial in anti-NMDAR encephalitis, which receives support from NINDS (U01NS120901) and Amgen Pharmaceuticals. He has developed educational materials for Continuing Education Inc and Ionis Pharmaceuticals. He owns stock in ANI pharmaceuticals. Dr. Day's institution has received in-kind contributions for radiotracer precursors for tau-PET neuroimaging in studies of memory and aging (via Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly). Author disclosures are available in the supporting information.

CONSENT STATEMENT

Participants or their legal representatives provided written informed consent for research participation, including blood and CSF collection and banking.

REFERNCES

1. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *The Lancet Neurology*. 2016;15(7):673-684.
2. Chouliaras L, O'Brien JT. The use of neuroimaging techniques in the early and differential diagnosis of dementia. *Mol Psychiatry*. 2023;28(10):4084-4097.
3. Bouwman FH, Frisoni GB, Johnson SC, et al. Clinical application of CSF biomarkers for Alzheimer's disease: from rationale to ratios. *Alzheimers Dement (Amst)*. 2022;14(1):e12314.
4. Wu L, Rosa-Neto P, Gauthier S. Use of biomarkers in clinical trials of Alzheimer disease: from concept to application. *Molecular Diagnosis & Therapy*. 2011;15:313-325.
5. Ossenkoppele R, Prins ND, van Berckel BNM. Amyloid imaging in clinical trials. *Alzheimer's Research & Therapy*. 2013;5(4):36.
6. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement*. 2013;9(1):e1-16.
7. Day GS, Rappai T, Sathyan S, Morris JC. Deciphering the factors that influence participation in studies requiring serial lumbar punctures. *Alzheimers Dement (Amst)*. 2020;12(1):e12003.
8. Omar SH, Preddy J. Advantages and Pitfalls in Fluid Biomarkers for Diagnosis of Alzheimer's Disease. *J Pers Med*. 2020;10(3).
9. Contador J, Vargas-Martínez AM, Sánchez-Valle R, Trapero-Bertran M, Lladó A. Cost-effectiveness of Alzheimer's disease CSF biomarkers and amyloid-PET in early-onset cognitive impairment diagnosis. *Eur Arch Psychiatry Clin Neurosci*. 2023;273(1):243-252.
10. Karikari TK, Ashton NJ, Brinkmalm G, et al. Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility. *Nat Rev Neurol*. 2022;18(7):400-418.
11. Figdore DJ, Griswold M, Bornhorst JA, et al. Optimizing cutpoints for clinical interpretation of brain amyloid status using plasma p-tau217 immunoassays. *Alzheimers Dement*. 2024;20(9):6506-6516.
12. Rissman RA, Langford O, Raman R, et al. Plasma Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's disease. *Alzheimers Dement*. 2024;20(2):1214-1224.
13. Devanarayan V, Doherty T, Charil A, et al. Plasma pTau217 predicts continuous brain amyloid levels in preclinical and early Alzheimer's disease. *Alzheimer's & Dementia*. 2024;20(8):5617-5628.
14. Ashton NJ, Janelidze S, Mattsson-Carlgren N, et al. Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. *Nat Med*. 2022;28(12):2555-2562.
15. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *JAMA Neurol*. 2024;81(3):255-263.
16. 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(2):1239-1249.
17. Therriault J, Ashton NJ, Pola I, et al. Comparison of two plasma p-tau217 assays to detect and monitor Alzheimer's pathology. *EBioMedicine*. 2024;102:105046.
18. Kivisäkk P, Fatima HA, Cahoon DS, et al. Clinical evaluation of a novel plasma pTau217 electrochemiluminescence immunoassay in Alzheimer's disease. *Sci Rep*. 2024;14(1):629.
19. Jonaitis EM, Janelidze S, Cody KA, et al. Plasma phosphorylated tau 217 in preclinical Alzheimer's disease. *Brain Commun*. 2023;5(2).
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. *Alzheimer's research & therapy*. 2022;14(1):67.
21. Arranz J, Zhu N, Rubio-Guerra S, et al. Diagnostic performance of plasma pTau217, pTau181, Aβ1-42 and Aβ1-40 in the LUMIPULSE automated platform for the detection of Alzheimer disease. *Alzheimer's Research & Therapy*. 2024;16(1):139.
22. Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA*. 2024;332(15):1245-1257.
23. Eratne D, Li Q-X, Lewis C, et al. Strong diagnostic performance of plasma ptau217 for CSF biomarker-defined young-onset Alzheimer disease in a diagnostically heterogeneous clinical cohort. *J Neurol*. 2024;272(1):25.
24. Schöll M, Vrillon A, Ikeuchi T, et al. Cutting through the noise: a narrative review of Alzheimer's disease plasma biomarkers for routine clinical use. *J Prev Alzheimers Dis*. 2025:100056.
25. VandeVrede L, Schindler SE. Clinical use of biomarkers in the era of Alzheimer's disease treatments. *Alzheimers Dement*. 2024.
26. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405.
27. Janelidze S, Barthélemy NR, He Y, Bateman RJ, Hansson O. Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios. *JAMA Neurol*. 2023;80(5):516-522.
28. Cecchetti G, Agosta F, Rugarli G, et al. Diagnostic accuracy of automated Lumipulse plasma pTau-217 in Alzheimer's disease: a real-world study. *J Neurol*. 2024;271(10):6739-6749.
29. Bornhorst JA, Lundgreen CS, Weigand SD, et al. Quantitative Assessment of the Effect of Chronic Kidney Disease on Plasma P-Tau217 Concentrations. *Neurology*. 2025;104(3):e210287.
30. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21.
31. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: the TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527.
32. Brum WS, Cullen NC, Janelidze S, et al. A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases. *Nat Aging*. 2023;3(9):1079-1090.
33. Li W, Petersen RC, Algeciras-Schimnich A, et al. Alzheimer Disease Cerebrospinal Fluid Biomarkers in a Tertiary Neurology Practice. *Mayo Clin Proc*. 2024;99(8):1284-1296.
34. 16th Clinical Trials on Alzheimer's Disease (CTAD) Boston, MA (USA) October 24-27, 2023: posters. *The Journal of Prevention of Alzheimer's Disease*. 2023;10(1):56-240.
35. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.

36. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269.
37. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100.
38. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. Pt.
39. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014.
40. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013;80(5):496-503.
41. Skrobot OA, O'Brien J, Black S, et al. The Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers Dement*. 2017;13(6):624-633.
42. Nakajima M, Yamada S, Miyajima M, et al. Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (Third Edition): endorsed by the Japanese Society of Normal Pressure Hydrocephalus. *Neurol Med Chir (Tokyo)*. 2021;61(2):63-97.
43. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;142(6):1503-1527.
44. Wolk DA, Nelson PT, Apostolova L, et al. Clinical criteria for limbic-predominant age-related TDP-43 encephalopathy. *Alzheimer's & Dementia*. 2025;21(1). doi:10.1002/alz.14202
45. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *JAMA Neurol*. 2024;81(3):255-263.
46. 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;30(4):1085-1095.
47. Warmenhoven N, Salvadó G, Janelidze S, et al. A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests. *Brain*. 2024.
48. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA*. 2020;324(8):772-781.
49. 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(8):1353-1364.
50. Janelidze S, Barthélemy NR, Salvadó G, et al. Plasma Phosphorylated Tau 217 and Aβ42/40 to Predict Early Brain Aβ Accumulation in People Without Cognitive Impairment. *JAMA Neurol*. 2024;81(9):947-957.
51. Lucey BP, Fagan AM, Holtzman DM, Morris JC, Bateman RJ. Diurnal oscillation of CSF Aβ and other AD biomarkers. *Mol Neurodegener*. 2017;12(1):36.
52. Vasquez EL, Kautz TF, Kivisäkk P, et al. The effect of fasting status on Alzheimer's disease plasma biomarkers AB40, AB42, GFAP, NfL, CD-14, and YKL-40. *Alzheimer's & Dementia*. 2023;19:e077508.
53. Pica-Mendez AM, Tanen M, Dallob A, Tanaka W, Laterza OF. Nonspecific binding of Aβ42 to polypropylene tubes and the effect of Tween-20. *Clin Chim Acta*. 2010;411(21-22):1833.
54. Ashton NJ, Suárez-Calvet M, Karikari TK, et al. Effects of pre-analytical procedures on blood biomarkers for Alzheimer's pathophysiology, glial activation, and neurodegeneration. *Alzheimers Dement (Amst)*. 2021;13(1):e12168.
55. Okereke OI, Xia W, Irizarry MC, et al. Performance characteristics of plasma amyloid-beta 40 and 42 assays. *J Alzheimers Dis*. 2009;16(2):277-285.
56. Bali D, Hansson O, Janelidze S. Effects of certain pre-analytical factors on the performance of plasma phospho-tau217. *Alzheimer's Research & Therapy*. 2024;16(1):31.
57. Schindler SE, Petersen KK, Saef B, et al. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. *medRxiv*. 2024.
58. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-2686.
59. Robinson JL, Richardson H, Xie SX, et al. The development and convergence of co-pathologies in Alzheimer's disease. *Brain*. 2021;144(3):953-962.
60. King A, Bodi I, Troakes C. The Neuropathological Diagnosis of Alzheimer's Disease-The Challenges of Pathological Mimics and Concomitant Pathology. *Brain Sci*. 2020;10(8).
61. Toledo JB, Abdelnour C, Weil RS, et al. Dementia with Lewy bodies: impact of co-pathologies and implications for clinical trial design. *Alzheimer's & Dementia*. 2023;19(1):318-332.
62. Hall S, Janelidze S, Londos E, et al. Plasma Phospho-Tau Identifies Alzheimer's Co-Pathology in Patients with Lewy Body Disease. *Mov Disord*. 2021;36(3):767-771.
63. Eisenmenger LB, Peret A, Famakin BM, et al. Vascular contributions to Alzheimer's disease. *Translational Research*. 2023;254:41-53.
64. Inoue Y, Shue F, Bu G, Kanekiyo T. Pathophysiology and probable etiology of cerebral small vessel disease in vascular dementia and Alzheimer's disease. *Molecular neurodegeneration*. 2023;18(1):46.
65. Therriault J, Janelidze S, Benedet AL, et al. Diagnosis of Alzheimer's disease using plasma biomarkers adjusted to clinical probability. *Nat Aging*. 2024;4(11):1529-1537.
66. Ramanan VK, Graff-Radford J, Syrjanen J, et al. Association of Plasma Biomarkers of Alzheimer Disease With Cognition and Medical Comorbidities in a Biracial Cohort. *Neurology*. 2023;101(14):e1402-e1411.
67. Novak P, Chu J, Ali MM, Chen J. Racial and Ethnic Disparities in Serious Psychological Distress Among Those With Alzheimer's Disease and Related Dementias. *Am J Geriatr Psychiatry*. 2020;28(4):478-490.
68. Lachner C, Craver EC, Babulal GM, et al. Disparate Dementia Risk Factors Are Associated with Cognitive Impairment and Rates of Decline in African Americans. *Ann Neurol*. 2024;95(3):518-529.
69. Chu CD, Powe NR, McCulloch CE, et al. Trends in Chronic Kidney Disease Care in the US by Race and Ethnicity, 2012-2019. *JAMA Netw Open*. 2021;4(9):e2127014-e.
70. Gianattasio KZ, Prather C, Glymour MM, Ciarleglio A, Power MC. Racial disparities and temporal trends in dementia misdiagnosis risk in the United States. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2019;5:891-898.
71. Lin P-J, Daly AT, Olchanski N, et al. Dementia Diagnosis Disparities by Race and Ethnicity. *Med Care*. 2021;59(8).
72. Chin AL, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2011;25(3):187-195.

SUPPORTING INFORMATION

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

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