Blood-based Biomarkers for Alzheimer’s Disease and Related Dementias

Plasma tau complements CSF tau and P-tau in the diagnosis of Alzheimer’s disease

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Abstract

\textbf{Introduction:} Plasma tau may be an accessible biomarker for Alzheimer’s disease (AD), but the correlation between plasma and cerebrospinal fluid (CSF) tau and the value of combining plasma tau with CSF tau and phospho-tau (P-tau) are still unclear.

\textbf{Methods:} Plasma-tau, CSF-tau, and P-tau were measured in 97 subjects, including elderly cognitively normal controls (n = 68) and patients with AD (n = 29) recruited at the NYU Center for Brain Health, with comprehensive neuropsychological and magnetic resonance imaging evaluations.

\textbf{Results:} Plasma tau was higher in patients with AD than cognitively normal controls (P < .001, area under the receiver operating characteristic curve = 0.79) similarly to CSF tau and CSF P-tau and was negatively correlated with cognition in AD. Plasma and CSF tau measures were poorly correlated. Adding plasma tau to CSF tau or CSF P-tau significantly increased the areas under the receiver operating characteristic curve from 0.80 and 0.82 to 0.87 and 0.88, respectively.

\textbf{Discussion:} Plasma tau is higher in AD independently from CSF-tau. Importantly, adding plasma tau to CSF tau or P-tau improves diagnostic accuracy, suggesting that plasma tau may represent a useful biomarker for AD, especially when added to CSF tau measures.

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\textbf{Keywords:} Plasma tau; CSF tau; CSF P-Tau; Cognition; Blood biomarkers; MRI
1. Introduction

Tau is a microtubule-associated protein that is highly expressed in the brain and functions as a structural element in the axonal cytoskeleton [1,2]. In patients with Alzheimer’s disease (AD), the neuronal and axonal degeneration results in increased release of tau from the microtubules. Furthermore, in pathological conditions such as AD, chronic traumatic encephalopathy, or other tauopathies, tau is truncated and/or phosphorylated [3,4]. Phosphorylated forms of tau (P-tau) aggregate in neurofibrillary tangles, contributing to cognitive impairment [5,6]. Elevated cerebrospinal fluid (CSF) tau and P-tau are established biomarkers for AD [7]. Plasma has been proposed as an ideal biofluid for biomarker analysis, as it allows collection of samples with minimal burden to the patients and facilitates longitudinal study designs [8]. However, until recently, AD biomarker measures were restricted to the CSF. Recently, novel technologies, such as single-molecule array (SIMOA), have enabled the detection of tau at very low concentrations (picomolar) in the blood [9]. Although plasma and CSF tau are not biomarkers specific for AD as CSF P-tau and blood tau has the potential to derive from other sources in addition to neuronal tau [10,11], work with ultrasensitive detection equipment suggests the potential for plasma tau to serve as a biomarker for neurodegeneration in AD as well as other neurological disorders associated with brain trauma and tauopathies [9,12–16]. Using the SIMOA technology, several studies showed higher plasma tau levels in patients with neurological disorders compared to cognitively normal (NL) controls [9,15,17,18]. These results were promising, although they typically showed a relatively high degree of overlap in plasma tau concentrations between AD and controls and weak correlations of plasma tau with CSF total tau and P-tau levels in AD [19]. Little information is currently available on the value of adding plasma tau to CSF tau and CSF P-tau in AD biomarker panels in AD clinical studies. Here, to explore the diagnostic value of plasma tau and its usefulness in comparison to or in combination with CSF tau and P-tau, we measured plasma and CSF tau in 97 subjects including patients with AD and nondemented controls recruited at the Center for Brain Health of NYU Langone Medical Center. Moreover, we validated the agreement of the different assays by comparing CSF samples run with SIMOA and gold-standard ELISA assays and we examined the relationships of plasma tau with cognitive and structural magnetic resonance imaging (MRI) measures.

2. Methods

2.1. Subjects

All subjects were recruited at the Center for Brain Health of NYU School of Medicine (NYUSOM) and provided written, informed consent to protocols approved by the NYUSOM Institutional Review Board (IRB) to participate in our National Institute of Health (NIH)–supported biofluids and imaging studies of aging and AD. The patients with mild AD enrolled were judged capable of understanding the consent forms as determined by an independent clinician. The standardized examinations were consistent with the NIH-National Alzheimer Coordinating Center (NACC) guidelines. The examinations included history, physical and neurological assessments, psychiatric screens, clinical laboratories, MRI, genetic testing, and neuropsychological evaluations, which included Mini–Mental Status Examination [20] and Clinical Dementia Rating Scale [21] as well as other elements of the Alzheimer’s Disease Center Uniform Data Set Neuropsychological Test Battery [22]. Diagnosis of normal or AD was made in accord with standard criteria [23,24] by an experienced clinician based on progressive memory and cognitive complaints corroborated by an informant, clinically observed cognitive impairment as previously described [25], and MRI to rule out other causes of impairment. The patients with AD had Global Deterioration Scale scores of 4 or 5 and met DSM-IV [26] and NINCDS-ADRDA [27] criteria for dementia. NL was defined on the basis of consensus review of the aforementioned materials and achieved Global Deterioration Scale scores of 0 or 2 [28], a Clinical Dementia Rating score of 0, with Mini-Mental State Examination scores of 28 or higher [20]. The norm-based neuropsychological battery of tests was constructed as previously described [29]. Four cognitive domains were assessed from the following tests: memory (immediate and delayed recall of a paragraph [PAR PARD] and immediate and delayed recall of paired associates [PRDI and PRDD]), executive function (Wechsler Adult Intelligence Scale Digit Symbol Substitution), language (Object Naming Test and Wechsler Adult Intelligence Scale vocabulary), and visuospatial performance (Block Design Test). The apolipoprotein E (APOE) genotypes were determined using published methods.

2.2. Biofluid samples

CSF samples were processed as described previously [25]. Briefly, after an overnight fast and a light breakfast before 9 am, the lumbar puncture procedure began at 12 pm using a 25-G Sprotte needle guided by fluoroscopy. 15 mL of CSF was collected in three polypropylene tubes. Samples were kept on ice for up to 1 h until centrifuged for 10 min at 2000 g at 4°C. 250 μL of samples was aliquoted into 1-mL polypropylene tubes and stored at −80°C until thawed for the assays.

Blood samples were collected at the time of the lumbar puncture and processed within 2 h from collection, following consensus recommendations [30]. To obtain plasma, 10 mL of blood was collected into EDTA tubes, inverted 5 times immediately after collection, and then centrifuged (10 minutes, 2,000g, 4°C). All samples were aliquoted (0.250 μL) into 1-mL polypropylene tubes and stored at −80°C. To avoid batch effects, experiments
were predesigned including a similar number of individuals from all study groups once sufficient samples were collected. Investigators running the experiments were blind to study groups.

2.3. Plasma total tau quantification

The plasma total tau assays were conducted at NYUSOM in Dr. Fossati’s laboratory. Plasma total tau was measured using SIMOA technology (Quanterix Corporation, MA), as directed by the manufacturer. Briefly, the SIMOA enzyme-linked immunosassay method uses a combination of a capture antibody which recognizes amino acid 16-24 and a detector antibody recognizing amino acid 218-222, with a digital array technology that allows the measurement of total tau in plasma or serum with a limit of detection of 0.019 pg/mL. All assays were run in duplicate. Samples showing coefficients of variation higher than 20% were excluded and reexamined.

2.4. CSF tau and P-tau quantification

The CSF total tau and P-tau 181 assays were conducted at the Sahlgrensa University Hospital in Sweden, as previously described [25]. Briefly, P-tau 181 was measured by a gold-standard sandwich ELISA (INNOTEEST, Fujirebio) using antibodies HT7 for capture and AT270 for detection and a synthetic custom phosphopeptide phosphorylated threonine 181 (P-tau181) as the standard calibrator [31]. Limit of detection of this setting is 15.6 pg/mL. Intra-assay and inter-assay coefficient variations are below 10%. The lower limit of quantification was determined to be 25 pg/mL. CSF total tau was measured using a similar gold-standard ELISA protocol (INNOTEEST, Fujirebio), based on using the monoclonal mid-domain antibodies AT120 for capture and HT7 and BT2 for detection [32]. Samples showing coefficients of variation higher than 20% were remeasured. CSF tau was also measured by Quanterix SIMOA at NYUSOM, as described previously, in a subset of the normal subjects to compare the 2 assays.

2.5. Magnetic resonance imaging and processing

All MRI was performed on the 3T system (Siemens, Erlangen, Germany). The imaging protocol consisted of sagittal T1-weighted magnetization prepared rapid acquisition gradient echo. Intracranial volumes were estimated using Statistical Parametric Mapping segmentation procedure (SPM, ver.12, with new-segment extension). Cortical thickness and hippocampal, CSF, and ventricular volumes were obtained using the FreeSurfer (ver.6.0, MHG/HST Martins Center for Biomedical Imaging, USA). Hippocampal volume was measured as Left Hippocampus + Right Hippocampus/IntracranialVol*100. Cortical thickness was averaged with surface regions of interest, which were defined by the Desikan-Killiany atlas [33].

2.6. Statistical analyses

Demographic differences between diagnostic groups were assessed using t-tests for continuous variables and \( \chi^2 \) tests for nominal variables. The mean difference in plasma tau between NL controls and patients with AD was tested with a t-test and confirmed with a Mann-Whitney U test.

Binary logistic regression models were used to determine the accuracy of plasma tau alone, as well as added to CSF P-tau and total Tau, in categorizing patients with AD versus NL controls after adjusting the models for age, APOE genotype, and sex as confounds. In the accompanying receiver operating characteristic curve analyses, the sensitivity level was set to 80% and differences in specificity levels between the combined plasma and CSF tau and the individual measures were compared using the McNemar test for the comparison of paired binomial proportions. We used bootstrap resampling with 2000 independent replications to obtain the areas under the receiver operating characteristic curve (AUCs) with a 95% CI, as well as the difference in AUCs between models (\( \Delta \text{AUC} \)).

Spearman correlations were used within the NL and AD groups separately to test for associations between plasma tau and a cognitive test of delayed memory (delayed paragraph recall) as well as the hippocampal volume and cortical thickness measurements. All analyses were checked for violations of the model assumptions and any conflicts are reported. The Box-Cox transformation procedure was used to determine the most appropriate power transformation to reconfigure values to a normal distribution. Differences in variances were tested using Levene’s Test for Equality of Variances, and the tests where equal variance was not assumed were used when Levene’s Test was significant. For all results, statistical significance was defined as a two-sided \( p \) value of less than 5%. Statistical analyses were performed using IBM SPSS (version 23.0).

3. Results

3.1. Demographic and clinical characteristics

The demographic characteristics of the participants are shown in Table 1. The AD group did not differ from the NL group for gender, education, or race. The AD group was on average 5 years older (\( P = .011 \)) than the NL group. As expected, the AD group had significantly higher prevalence of \( \text{APOE} \varepsilon 4 \) carriers than the NL group (\( P < .018 \)).

3.2. Elevated plasma tau levels in AD

Significantly higher concentrations of plasma tau were found in the AD group (\( n = 29 \)) compared with age-matched NL controls (\( n = 68 \)) (mean [SD], 3.67 [1.06] vs. 2.74 [0.76] pg/mL, respectively; Effect size = 1.1; \( P < .001 \); Fig. 1A). This difference persisted after corrections for plasma albumin concentrations (a
control procedure for possible group blood volume effects. Plasma tau did not correlate with age, whereas CSF tau and CSF P-tau were weakly correlated with age (Spearman $r = 0.26; P = .0045$ for CSF tau and $r = 0.21; P = .02$ for CSF P-tau). Receiver operating characteristic analyses for the classification of the AD group and NL group showed similar AUCs for plasma tau (AUC = 0.79), CSF tau (AUC = 0.80), and CSF P-tau (AUC = 0.82) (Fig. 1B).

### 3.3. Relationship between CSF and plasma total tau levels

We explored the correlation between tau levels detected in CSF and plasma in the same subjects. Results showed weak correlations in the full cohort for plasma tau with CSF tau (Spearman $r = 0.26; P = .009$) and plasma tau with CSF P-tau (Spearman $r = 0.29; P = .003$). The significance of the association between plasma tau and both CSF tau and P-tau was lost after correcting for diagnostic group in linear regression models or in partial correlations ($r = 0.12; \text{Sig 2-tailed} = 0.25$). When splitting the samples into the two study groups (AD or NL), there was also no significant correlation (in NL, CSF t-tau vs. plasma tau: Pearson $r = 0.07$, Sig 2-tailed = 0.55; Spearman $\rho = 0.05$, Sig 2-tailed = 0.70; in NL, CSF P-tau vs. plasma tau: Pearson $r = 0.13$, Sig 2-tailed = 0.29; Spearman $\rho = 0.13$, Sig 2-tailed = 0.28; in AD, CSF t-tau vs. plasma tau: Pearson $r = 0.20$, Sig 2-tailed = 0.33; Spearman $\rho = 0.25$, Sig 2-tailed = 0.22; in AD, CSF P-tau vs. plasma tau: Pearson $r = 0.15$, Sig 2-tailed = 0.47; Spearman $\rho = 0.14$, Sig 2-tailed = 0.48) (Fig. 2A). Because CSF tau and CSF P-tau were measured using ELISA (Fujirebio), whereas plasma tau was measured with SIMOA (ELISA assays are not sensitive enough to obtain plasma tau measurements), we...
compared ELISA and SIMOA results in the same CSF samples, to explore the consistency between the two different assays. ELISA and SIMOA tau signals obtained in the same CSF samples showed a very strong correlation ($r = 0.9517; P < .0001$; Fig. 2B), suggesting that the two different assays perform very similarly when used in the same medium.

### 3.4. Correlations with MRI and cognitive measures

Plasma tau was negatively correlated with delayed paragraph recall (PARD) (Spearman’s $r = −0.538; P = .012$), a measure of cognitive performance of Wechsler Memory Scale-Revised test [29], in the AD group (Fig. 3). When analyzing correlations of plasma tau with MRI measures, we found that the correlation of plasma tau with hippocampal volume or cortical thickness did not reach significance in the AD group ($P > .12$ and $P > .26$, respectively). There was also no significant correlation of plasma tau, CSF tau, or CSF P-tau with CSF volumes or ventricular volumes.

#### 3.5. Increased specificity for the combination of plasma tau with either CSF tau or CSF P-tau

We also aimed to explore if the addition of plasma tau to CSF tau or P-tau could improve the differentiation between study groups. When adding plasma tau (AUC 0.79) to CSF tau (AUC 0.80) or plasma tau to CSF P-tau (AUC 0.82), we achieved significant increments, reaching AUCs of 0.87 and 0.88, respectively, for the combinations (Fig. 4), indicating that the addition of plasma tau to both CSF tau measures increased diagnostic accuracy for the

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**Fig. 2.** Correlation between plasma and CSF tau and correlation of SIMOA versus ELISA for CSF tau. (A) The significance of the association between plasma tau and both CSF P-tau and tau is lost after correcting for diagnostic group in linear regression models or partial correlations ($P > .05$). The black line represents the full group, the blue line represents NL, and the red line represents AD. (B) CSF tau measured by Simoa and ELISA in the same samples shows a strong correlation ($r = 0.9517; P < .0001$). Abbreviations: AD, Alzheimer’s disease; CSF, cerebrospinal fluid; NL, cognitively normal; P-tau, phospho-tau.

**Fig. 3.** Correlation between plasma tau and cognitive function (PARD) (A) and hippocampal volume (B): (A) A significant negative correlation between plasma tau and PARD was found in the AD group (Spearman’s $r = −0.54; P = .01$), indicating worse cognitive performance in patients with AD with higher plasma tau. (B) The correlation between plasma tau and hippocampal volume did not reach significance ($P = .12$), although empirically showing a downward slope in the AD group, suggesting smaller hippocampal volumes in subjects with higher plasma tau. Abbreviations: AD, Alzheimer’s disease; CSF, cerebrospinal fluid; NL, cognitively normal; ROC, receiver operating characteristic; P-tau, phospho-tau; PARD, delayed paragraph recall.
differentiation of study groups. Using bootstrap resampling with 2000 independent replications to obtain the AUCs with a 95% CI, as well as the difference in AUCs between models (ΔAUC), the combined CSF and plasma models had a positive difference (i.e. higher predictive accuracy) in 99% of the replications, and the 95% CI of the ΔAUC was greater than 0 for both combined models compared with plasma tau and their respective CSF tau measures. We are therefore 95% confident that the model including both CSF and plasma tau yields a greater AUC than the AUC of either biomarker alone (Fig. 4C, D).

4. Discussion

Plasma tau has the potential to be among the first blood biomarkers for neurological disorders to be implemented in the clinical setting. The addition of plasma biomarkers such as tau or neurofilament light to current CSF assays for AD clinical trials [16,34,35] is currently under consideration. In this study, we first replicated previous findings showing that plasma tau levels are higher in patients with AD compared with noncognitively impaired controls [9,15–17]. We found that plasma tau was able to discriminate NL controls and patients with AD in our cohort with a large effect size of 1.1. This significant difference remained after we corrected for plasma albumin, to rule out the possibility that patients with AD may have lower blood volumes. Plasma tau alone classified NL controls and patients with AD with a similar accuracy when compared with the current gold-standard CSF total tau or CSF P-tau assays. Second, we corroborate that plasma tau seems independent of CSF tau measures, as no significant correlations were detected between plasma tau and CSF tau or P-tau [9,17]. Third, we report the novel finding that adding plasma tau to CSF tau or CSF P-tau measures increases the accuracy or the differentiation of patients with AD versus NL controls in our cohort.

A recent prospective study by Mattsson et al. using the ADNI cohort showed that plasma tau differentiated AD from controls, although there was a significant overlap between study groups [17]. Our results are in line with this work. Our study also confirmed a correlation between plasma tau and cognitive dysfunction, which...
was previously reported [15,17]. In addition, we found a weak correlation of plasma tau with CSF tau and P-tau, which was lost when correcting for study groups. The loss of correlation between plasma and CSF tau values when correcting or separating by the study groups is also in line with previous findings [9,17], suggesting that the higher mean value of CSF tau and plasma tau in patients with AD compared with NL controls drives the correlation when both groups are included without correcting for diagnostic group. The lack of correlation in the split groups could be also due to fact that the smaller sample size lacks power to reach statistical significance. The weak correlation between plasma and CSF may also suggest potential differences in tau fragments in the CSF and plasma compartments and/or that these fragments would be differently recognized by the SIMOA (plasma) and INNOTEST (CSF) antibody combinations. However, in one of the first studies on plasma tau in AD, an INNOTEST-like antibody combination (Tau5 for capture [similar to AT120 in INNOTEST] and HT7 and BT2 [identical to INNOTEST]) was used on SIMOA [9], suggesting that potential tau proteolysis or other forms of clearance in plasma, as well as non-central nervous system sources of tau, would affect the two assay formats in a similar manner, which should be explored in more detail.

In this work, we show that the SIMOA and ELISA assays used perform with very high correlation in the same CSF samples, suggesting that the lack of correlation between plasma and CSF is driven mostly by the biological compartment. A higher metabolism of tau by plasma proteases could be one of the reasons of these differences. Owing to different catabolic cleavage, the tau fragments present in CSF and plasma will likely differ and smaller or different fragments in plasma may remain undetected by the same immunoassay that detects CSF fragments. The presence in blood of tau derived from other sources different from brain cells could also explain the lack of correlation with CSF [10,11]. The expression of tau has been shown in platelets [10], as well as in muscle, kidney, and other tissues (https://www.proteinatlas.org/ENSG00000186868-MAPT/tissue), expanding the pool of plasma tau to additional sources compared with those for CSF tau. Moreover, differential clearance pathways for interstitial fluid tau to the CSF or plasma could contribute to the lack of correlation [36–38]. For example, interstitial fluid tau may be internalized by glial cells or further catabolized before or after being released to plasma [39]. Also, smaller fragments of tau that are able to pass a dysfunctional blood brain barrier in AD may not remain in the CSF for a sufficient time to be detected, resulting in an increase in plasma tau fragments in patients with AD with a more damaged blood brain barrier. Different antibody specificity and assay performance in plasma versus CSF could also contribute to the weak correlation between the tau levels in the two compartments. Although this study cannot determine the causes of the weak correlation, these differences in assay results between CSF and plasma could contribute to the better discrimination of patients with AD and NL controls that we achieve adding plasma tau to CSF tau measures.

Owing to the overlap between study groups (AD vs. NL) and to the lack of a strong correlation with CSF tau discussed previously, the validity of plasma tau alone as a biomarker for AD has been debated [17,19]. However, recent studies found that, in regression models adjusted for age, gender, education, and APOE, higher plasma tau was associated with worse memory performance and abnormal cortical thickness in an AD signature region, highlighting the potential of plasma tau as a valid neurodegeneration biomarker in AD [15]. Moreover, higher levels of plasma tau, examined as a continuous variable, were associated with significant declines in global cognition, memory, attention, and visuospatial ability over a median follow-up of 3.0 years and with greater decline in both visuospatial ability and global cognition at 15 months in mild cognitive impairment patients [16]. Plasma tau was also negatively correlated with gray matter density in the medial temporal lobe, precuneus, thalamus, and striatum [14]. We are aware that elevated tau alone, both in plasma and CSF, cannot be considered a specific biomarker for AD. Elevated tau levels have also been related to traumatic brain injury and postconcussive cognitive symptoms in both acute [19,40] and chronic traumatic brain injury [41] and to the effect of anesthesia and surgery [42]. This body of work highlights the potential validity of plasma tau as a measure of neurodegeneration, in agreement with our current data, which demonstrate a negative correlation between plasma tau and cognitive function (PARD).

Our study reports the interesting and novel finding that, when combining plasma tau with CSF total tau or CSF P-tau, the accuracy for the differentiation of AD versus NL increases, suggesting that plasma tau may be a useful biomarker to add to CSF tau, and to the AD-specific CSF P-tau, in AD panels to increase diagnostic power and determinations of therapeutic efficacy. Plasma tau may also be useful in addition to other blood biomarkers of neurodegeneration such as neurofilament light [35,43], to better determine cognitive improvements in clinical trials. The possibility of adding measures of plasma or serum P-tau would also also be an important future development for the field. Multiple assays are under development with Simoa, MSD [18], and other platforms [44] to achieve this scope, although not yet commercially available.

Future clinical studies should focus on confirming if combining plasma and CSF tau determinations is feasible and beneficial in terms of costs versus gain.

Overall, this study adds to the current literature in suggesting that plasma tau could represent a valuable biomarker to include in panels for AD clinical studies in addition to CSF biomarkers. More research is needed to better understand the molecular pathways responsible for the
We report that plasma tau discriminates NL controls from patients with AD with similar AUCs compared with CSF tau and P-tau and is associated with cognitive measures. We observe a lack of correlation of plasma tau with CSF tau, possibly due to the differential influence of tau clearance and metabolism, as well as other possible sources of tau contributing to the plasma pool. Importantly, we detect an increase in the ability to discriminate patients with AD and NL controls when adding plasma tau to either CSF tau or CSF P-tau measures, suggesting that including plasma tau determinations in addition to CSF tau in AD studies could improve accuracy of diagnosis and detection of therapeutic effects in clinical trials.

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**RESEARCH IN CONTEXT**

1. Systematic review: Novel technologies over the last few years have enabled the detection of tau in the blood. Articles related to the development of plasma tau assays and their relationship with CSF tau measures were searched on PubMed, and contributed to the development of our study.

2. Interpretation: This study contributes to the field showing that plasma tau classifies cognitively normal controls and patients with Alzheimer’s disease with similar accuracy when compared with the current gold-standard cerebrospinal fluid (CSF) tau or CSF P-tau. Our data corroborates a lack of correlation between plasma and CSF tau, suggesting that plasma tau is independent and likely complementary to CSF tau measures. Importantly, this study reports the novel finding that adding plasma tau to CSF tau or CSF P-tau measures increases the accuracy of the differentiation of patients with AD versus cognitively normal controls.

3. Future directions: Future studies are encouraged to replicate the results from this report using larger sample sizes, as well as longitudinal studies, to confirm that including plasma tau in addition to CSF tau in AD studies will improve accuracy of diagnosis and detection of therapeutic effects.

**References**


