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Original Research

Evaluation of plasma p-tau217 biomarkers in detecting amyloid pathology and predicting cognitive outcomes: Observations from Japanese Alzheimer's disease neuroimaging initiative cohort

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ABSTRACT

Background and Objectives: Plasma phosphorylated tau 217 (p-tau217) has shown strong potential as a blood-based biomarker for detecting amyloid pathology in Alzheimer's disease. This study evaluated the diagnostic and prognostic utility of plasma biomarkers, including p-tau217, in participants from the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) cohort.
Methods: We analyzed paired plasma and CSF samples from 172 J-ADNI participants. CSF and plasma biomarkers were quantified using the LUMIPULSE platform, and the same plasma samples were analyzed using the Simoa platform. The diagnostic accuracy for detecting amyloid pathology and the prognostic value of plasma p-tau217 biomarkers were assessed. Associations between plasma p-tau217 and polygenic risk scores (PRS), as well as potential confounding factors, were examined.
Results: Plasma p-tau217 levels measured using Lumipulse and Simoa assays were highly correlated ($p < 0.001$). All plasma p-tau217 assays showed high diagnostic accuracy for CSF Aβ42/Aβ40-defined amyloid pathology (AUC = 0.98). A single cutoff point based on the Youden index for p-tau217 and p-tau217/Aβ42 achieved >90% specificity and >90% sensitivity. The predefined FDA-approved two-cutoff model for p-tau217/Aβ42 was applicable to this cohort. PRS was significantly associated with plasma p-tau217 independently of *APOE* genotypes. Subjects with higher plasma p-tau217 levels showed a significantly increased risk of conversion to dementia and larger longitudinal cognitive declines. Plasma p-tau217 levels were significantly influenced by the body mass index, estimated glomerular filtration rate, and high-density lipoprotein cholesterol.
Conclusions: Plasma p-tau217 and p-tau217/Aβ42 are robust biomarkers for AD diagnosis and prognosis in the Japanese population.

1. Introduction

A definitive diagnosis of Alzheimer's disease (AD) currently requires detection of brain amyloid pathology through amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) biomarkers such as the Aβ42/Aβ40 and p-tau181/Aβ42 ratios [1]. Although these methods are highly valuable for diagnosing AD, they have several limitations. Amyloid PET is costly, available only at specialized centers, and

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involves radiation exposure. CSF testing requires lumbar puncture, which can impose psychological and physical burdens on patients. Moreover, both approaches are difficult to scale for population-level screening because they depend on specialized equipment and expertise [2].

To overcome these challenges, blood-based biomarkers have gained increasing attention as less invasive, more accessible, and cost-effective alternatives. Blood testing can be performed in outpatient settings with minimal burden and can be integrated into the existing medical infrastructure [2]. Recent technological advances have enabled the highly sensitive detection of trace plasma proteins, leading to extensive validation of several biomarkers, including plasma Aβ42/Aβ40 ratio, phosphorylated tau 181 (p-tau181), p-tau217, p-tau231, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) [3].

Among these candidates, plasma p-tau217 has demonstrated superior diagnostic performance in multiple large-scale studies [3,4]. It not only detects amyloid pathology with high sensitivity and specificity but also reflects tau pathology progression, making it useful for disease staging and predicting the onset of dementia [5–8]. Several analytical platforms have been developed to measure plasma p-tau217, including immunoprecipitation–mass spectrometry (IP-MS) [9]), single-molecule array (Simoa) [10], Meso Scale Discovery (MSD) [11], and LUMIPULSE using chemiluminescent enzyme immunoassay [12]. The diagnostic performances of these platforms are being validated in diverse populations, including Asian cohorts [13–28]. Recently, the U.S. Food and Drug Administration (FDA) approved the plasma p-tau217/Aβ42 assay on the LUMIPULSE platform as the first *in vitro* diagnostics (IVD) test for aiding in the diagnosis of AD.

Recent head-to-head comparison studies have characterized the diagnostic features of these platforms [29–37]. However, most of these studies have been conducted in Western populations, and no comparative analyses have been reported in Asian cohorts. Ethnic differences in genetic background, lifestyle, comorbidities, and other confounding factors may affect the biomarker concentrations and diagnostic accuracy. For instance, Japanese populations exhibit distinct features, including lower *APOE* ε4 allele frequencies [38,39], and a higher prevalence of cerebrovascular pathology [40].

In this study, we analyzed paired samples of plasma and CSF from the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI), a multicenter AD continuum research cohort [41,42]. The aims of this study were as follows: (1) to evaluate the diagnostic performance of blood biomarkers for detecting amyloid pathology; (2) to evaluate the prognostic utility of p-tau217 for mild cognitive impairment (MCI)--to-dementia conversion and longitudinal cognitive decline; (3) to validate the usefulness of the predefined FDA-approved two-cutoff thresholds in our cohort; and (4) to clarify potential confounding factors for plasma biomarkers.

2. Methods

2.1. Study population

The J-ADNI study was a multicenter research cohort in Japan designed to identify fluid and imaging biomarkers across the AD continuum, using a harmonized protocol with the ADNI [41,43]. The J-ADNI was aimed to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of late MCI and mild ADD (Alzheimer's disease dementia) in the Japanese population. A total of 715 volunteers aged 60–84 years were screened, and 537 participants were enrolled from 38 clinical sites in Japan.

We measured Aβ40, Aβ42, p-tau181, total tau (t-tau), and NfL in CSF and Aβ40, Aβ42, p-tau217, and GFAP in plasma in 172 participants using the LUMIPULSE platform (Supplementary Fig. 1). Plasma samples for Simoa p-tau217 measurement were not available for 29 of these participants, who exhibited milder clinical severity and biomarker profiles than the remaining 143 participants (data not shown). Therefore, we conducted a head-to-head comparison of the Lumipulse and Simoa assays for p-tau217 in 143 individuals using matched plasma samples. The subjects were further analyzed for the association between plasma biomarkers and polygenic risk score (PRS), as well as confounding factors. Predictive analyses of clinical conversion were conducted in 98 individuals with baseline Clinical Dementia Rating (CDR) scores of 0 or 0.5 and available longitudinal follow-up data.

This study was conducted in accordance with the Declaration of Helsinki and approved by ethics committee of Niigata University (2023-0120). The J-ADNI study protocol (UMIN000001374) was approved by the institutional review boards of all participating sites. Written informed consent was obtained from all participants prior to their enrollment in the study.

2.2. CSF and plasma collection and analyses

CSF samples were obtained via lumbar puncture at each participating site as previously described [41]. After collection, the samples were transferred into polypropylene tubes, frozen, and shipped to the J-ADNI biomarker core laboratory at Niigata University. CSF was aliquoted into 0.5 mL portions and stored at −80 °C until biomarker analysis. Blood samples were collected in EDTA tubes. For plasma separation, the samples were centrifuged at 2000 × *g* for 10 min at room temperature. After separation, plasma was aliquoted into 500 μL portions in 0.5 mL polypropylene tubes and immediately stored at −80 °C until analysis. Prior to analysis, the plasma samples were thawed and centrifuged at 2000 × *g* for 5 min at room temperature.

CSF biomarkers were measured using Lumipulse *G* kits (β-Amyloid1-40, β-Amyloid1-42, p-tau181, Total Tau, and NfL CSF) on the LUMIPULSE *G*1200 (FUJIREBIO INC., Tokyo, Japan). Plasma p-tau217 was measured using both Lumipulse *G* pTau217 Plasma kit on the LUMIPULSE G1200 and Simoa ALZpath kit on HD-X platform (Quanterix, Billerica, MA, USA). Plasma Aβ40, Aβ42, and GFAP levels were measured using Lumipulse G Plasma kits (Aβ1-40, Aβ1-42, and GFAP) on the LUMIPULSE G1200. All analyses were performed by experienced personnel blinded to clinical diagnosis, following the manufacturer's instructions. The intra- and inter-assay coefficients of variation were below 20% for all measurements. CSF cutoff values were calculated using Gaussian Mixture Modeling (GMM) from 174 J-ADNI participants for whom both CSF Aβ42/Aβ40 ratio and p-tau181 measurements were available. An Aβ42/Aβ40 ratio < 0.071 was defined as positive A status.

2.3. Acquisition of clinical, PET imaging, and APOE genotypes information and laboratory data

Clinical, PET imaging, laboratory data and *APOE* genotypes of the participants in the J-ADNI were obtained from the J-ADNI database deposited at the National Bioscience Database Center (Tokyo, Japan, https://humandbs.dbcls.jp/en/hum0043-v1manDatabase). Positive amyloid pathology was defined by positive or equivocal amyloid deposition on ^{11}C-PiB or ^{11}C-BF–227 PET by visual reading. Perfect agreement was observed between the *APOE* genotypes and Lumipulse-based proteotypes, which were determined using the ApoE4/PanApoE ratio to discriminate between *APOE* ε4 non-carriers, heterozygotes, and homozygotes. Routine laboratory data were obtained from the ISO-certified SRL central laboratory (Tokyo, Japan). The estimated glomerular filtration rate (eGFR [mL/min/1.73m^2]) was calculated based on creatinine, age and sex.

2.4. Polygenic risk score (PRS)

We determined the PRSs of 170 participants as previously described [44]. We calculated two types of PRSs: PRS (total) covering the total risk for AD, including the *APOE* region, and PRSnoAPOE, composed of

genetic risk for AD beyond *APOE*. PRS (total) was constructed using 173 single nucleotide polymorphisms (SNPs) and PRSnoAPOE using 131 SNPs. To evaluate the diagnostic performance of plasma biomarker combined with PRS, plasma biomarker levels and PRS were integrated in a logistic regression model to estimate the probability of disease.

2.5. Statistical analyses

Statistical analyses were conducted using GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA) and R (version 4.4.2). For continuous variables, comparisons were performed using the Mann–Whitney U test for two groups. Categorical variables were analyzed using the chi-square or Fisher's exact test, as appropriate. The correlations between continuous variables were assessed using Spearman's rank correlation coefficient.

The diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. The areas under the curve (AUCs) were calculated and compared using DeLong's test. Biomarker cutoff values were determined using both the maximum Youden index and GMM.

The associations between sample characteristics and p-tau217 or the p-tau217/Aβ42 ratio were analyzed using linear regression models. The covariates included in the analyses were age, sex, years of education, *APOE* ε4 allele count, body mass index (BMI), and laboratory parameters. Each covariate was evaluated in both an unadjusted base model and a model further adjusted for age, sex, education, *APOE* ε4 status, and CSF-based Aβ status.

We performed survival analyses to evaluate the prognostic utility of plasma biomarkers for conversion from MCI to dementia. Participants were stratified into High and Low groups based on the cutoff values of plasma biomarkers (Simoa p-tau217, Lumipulse p-tau217, and p-tau217/Aβ42) determined by the maximum Youden index. Kaplan–Meier curves were generated to visualize the cumulative probability of conversion to dementia (CDR $\geq$ 1) over time, and differences between the groups were assessed using log-rank tests. Cox proportional hazards models were employed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for conversion risk, adjusted for potential confounders including age, sex, education, *APOE* ε4 status, and baseline MMSE scores.

A linear mixed-effects model was fitted using the lmerTest package in R, with the cognitive score as the outcome. The fixed effects included plasma biomarker groups (High and Low), time from baseline (months), their interaction, age, sex, and years of education. Random intercepts and slopes for time were specified for each participant to account for the individual-level variation. The interaction term between plasma biomarker groups and time was used to test differences in the rate of cognitive decline between groups. For all analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study participants

We first measured the IVD-approved CSF Aβ42/Aβ40 in 172

Table 1
Baseline characteristics of J-ADNI cohort with negative and positive amyloid pathology.

	Total (n = 172)		A- (n = 55)		A+ (n = 117)		A- vs A+ *p*-value
Age, years	72	(11)	67	(9)	73	(8)	0.002
Female, n (%)	85	(49.4)	25	(45.5)	60	(51.3)	0.516
Education, years	13	(4)	14	(4)	13	(4)	0.253
MMSE score	26	(5)	29	(2)	25	(4)	< 0.001
ADAS	20.0	(15.1)	8.3	(9.5)	23.0	(8.7)	< 0.001
Global CDR score							< 0.001
0	42	(24.4)	34	(61.8)	8	(6.8)	
0.5	116	(67.4)	21	(38.2)	95	(81.2)	
1	14	(8.1)	0	(0)	14	(12.0)	
CDR sum of boxes	1.5	(2.5)	0	(0.8)	2	(2.5)	< 0.001
FAQ	3	(7)	0	(1)	5	(7)	< 0.001
Clinical status, n (%)							< 0.001
CU	42	(24.4)	34	(61.8)	8	(6.8)	
MCI	82	(47.7)	20	(36.4)	62	(53.0)	
ADD	48	(27.9)	1	(1.8)	47	(40.2)	
APOE ε4 allele, n (%)							< 0.001
0	90	(52.3)	51	(92.7)	39	(33.3)	
1	63	(36.6)	4	(7.3)	59	(50.4)	
2	19	(11.0)	0	(0)	19	(16.2)	
Amyloid PET, n (%)							< 0.001
Negative	40	(47.1)	35	(100)	5	(10.0)	
Positive	45	(52.9)	0	(0)	45	(90.0)	
CSF Aβ40, pg/mL	9405.0	(3656.5)	9410.0	(3351.0)	9400.0	(3676.0)	0.876
CSF Aβ42, pg/mL	470.5	(318.5)	871.0	(327.5)	396.0	(145.0)	< 0.001
CSF Aβ42/Aβ40	0.048	(0.045)	0.091	(0.010)	0.043	(0.011)	< 0.001
CSF p-tau181, pg/mL	56.8	(56.2)	31.2	(14.8)	77.2	(45.8)	< 0.001
CSF t-tau, pg/mL	453.5	(390.8)	251.0	(163.5)	593.0	(325.0)	< 0.001
CSF NfL, pg/mL	733.0	(366.5)	600.0	(309.0)	789.0	(373.0)	< 0.001
Plasma Aβ40, pg/mL	293.7	(64.5)	290.9	(57.5)	293.7	(65.9)	0.976
Plasma Aβ42, pg/mL	19.9	(5.5)	23.3	(5.5)	18.8	(4.6)	< 0.001
Plasma Aβ42/Aβ40	0.067	(0.013)	0.078	(0.012)	0.063	(0.008)	< 0.001
Plasma p-tau217, pg/mL	0.296	(0.466)	0.068	(0.054)	0.463	(0.372)	< 0.001
Plasma p-tau217/Aβ42*10^3	16.2	(25.6)	3.0	(2.1)	23.6	(21.4)	< 0.001
Plasma GFAP, pg/mL	68.6	(55.3)	43.2	(19.9)	90.1	(45.7)	< 0.001

Data are median (IQR). Differences in baseline characteristics of participants were assessed using Mann-Whitney U-test for continuous variables, or Fisher's exact test for categorical variables.

ADAS, Alzheimer's Disease Assessment Scale; ADD, Alzheimer's disease dementia; CDR, Clinical Dementia Rating; CU, cognitively unimpaired; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain; PET, Positron emission tomography; p-tau, phosphorylated tau; t-tau, total tau

participants of J-ADNI on Lumipulse platform (Supplementary Fig. 1). The participants were divided into A+ (n = 104) and A– (n = 39) groups according to amyloid pathology status defined by CSF Aβ42/Aβ40 with a cutoff value of <0.071. Table 1 shows the baseline demographics of the J-ADNI participants (median age 72 years, 51.0% female). Compared with the A– group, the A+ group was older, showed greater clinical cognitive impairment, and demonstrated more abnormal AD-related CSF biomarkers. These participants were further categorized as cognitively unimpaired (CU, n = 31) and cognitively impaired (CI, n = 112), the latter comprising individuals with MCI or AD dementia. Detailed comparisons of baseline demographics and biomarker profiles between A− and A+ participants within the CU and CI groups were shown in Supplementary Table 1.

Of the 172 participants, 143 had matched plasma p-tau217 measurements on both the LUMIPULSE and Simoa platforms (Supplementary Fig. 1). The correlation between p-tau217 levels measured using Simoa and Lumipulse was strong (r = 0.949 [95% CI: 0.929-0.963], p <0.001) (Supplementary Fig. 2).

3.2. Predictive value of plasma biomarkers for amyloid status

We evaluated the predictive performance of plasma biomarkers measured using Lumipulse—including p-tau217, Aβ42/Aβ40 ratio, GFAP, and p-tau217/Aβ42 ratio for identifying amyloid pathology (Supplementary Fig. 3). Both plasma p-tau217 and the p-tau217/Aβ42 ratio showed significantly higher AUCs than the Aβ42/Aβ40 ratio and GFAP levels (DeLong's test, p < 0.05).

The diagnostic accuracy for predicting amyloid pathology was AUC 0.978 (95% CI: 0.959-0.998) for Simoa p-tau217, AUC 0.981 (95% CI: 0.961-1.000) for Lumipulse p-tau217, and AUC 0.983 (95% CI: 0.965-1.000) for Lumipulse p-tau217/Aβ42, with no significant differences between biomarkers by DeLong's test (Fig. 1).

Next, we conducted subgroup analyses by dividing the participants into CU and CI groups (Supplementary Fig. 4, 5). In the CU group, all three plasma p-tau217 biomarkers showed moderately high diagnostic accuracy (AUCs: 0.881–0.893), with no significant differences among them (Supplementary Fig. 5). In the CI group, the diagnostic accuracy for predicting amyloid pathology was remarkably high (AUCs:

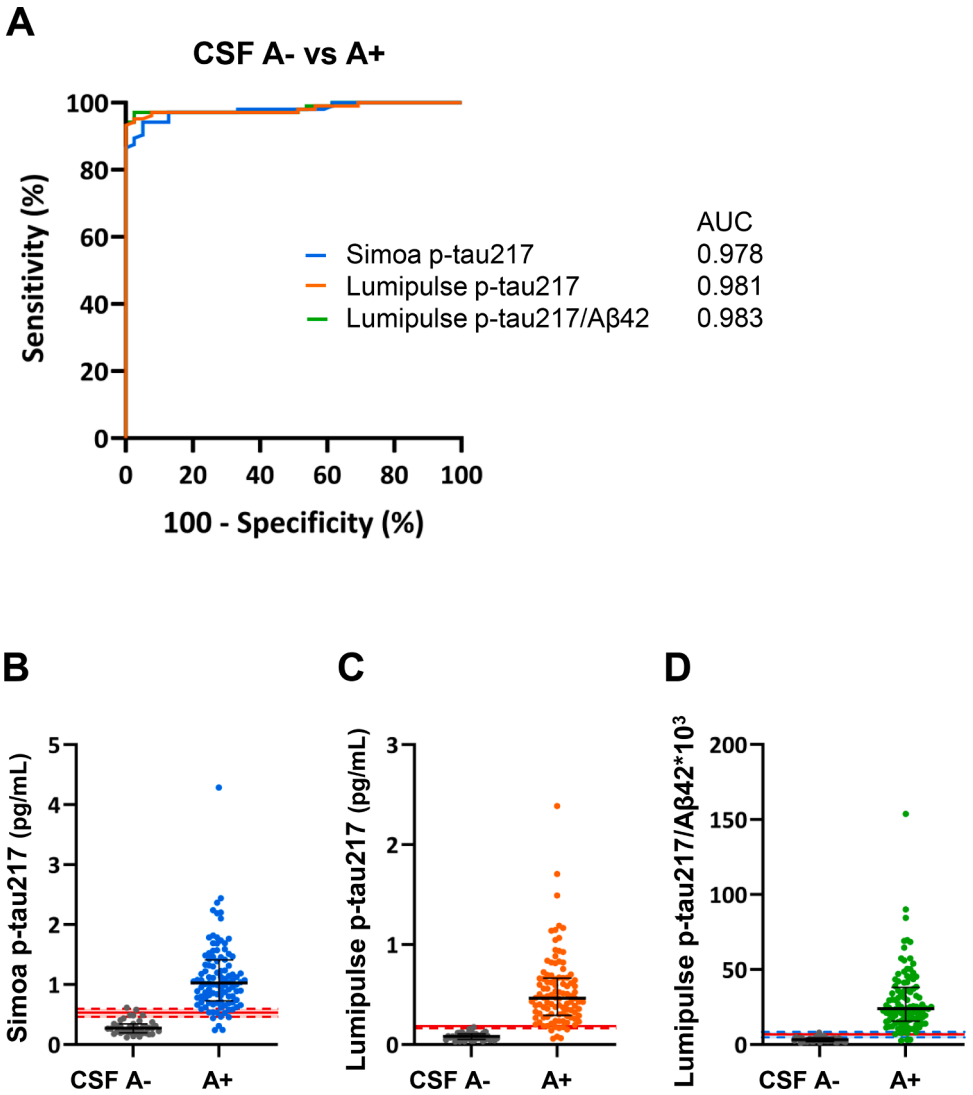

Fig. 1. Diagnostic performance and cutoff points of plasma p-tau217 biomarkers for detecting amyloid pathology (**A**) ROC curves showing the AUCs of each plasma biomarker in discriminating amyloid pathology, as defined by the CSF Aβ42/Aβ40 ratio. (**B**) Simoa p-tau217, (**C**) Lumipulse p-tau217, and (**D**) Lumipulse p-tau217/Aβ42 × 10^3 plots are shown. The red solid lines indicate the single-point cutoffs determined by the maximum Youden index. The red dashed lines represent the two-point cutoffs achieving >95% sensitivity and >95% specificity, with the intermediate zones shaded in red. For Lumipulse p-tau217, only one cutoff is shown as it meets both criteria using a single threshold. For Lumipulse p-tau217/Aβ42, the single-point and two-point cutoffs were identical, and thus only the red solid line is displayed. FDA-approved two-point cutoffs are indicated by blue dashed lines, with the intermediate zones shaded in blue.

0.977–0.989), and there were no significant differences among the biomarkers.

We assessed the predictive accuracy in a subsample of 60 participants who underwent amyloid PET imaging, of whom 35 were visually rated as positive. Plasma biomarkers demonstrated high diagnostic performance for predicting PET positivity: Simoa p-tau217 (AUC = 0.915, 95% CI: 0.836–0.995), Lumipulse p-tau217 (AUC = 0.929, 95% CI: 0.855–1.000), and Lumipulse p-tau217/Aβ42 (AUC = 0.936, 95% CI: 0.866–1.000) (Supplementary Fig. 6). No significant differences were observed between the biomarkers.

3.3. Cutoff determination

The single cutoff values for plasma p-tau217 and p-tau217/Aβ42 were determined using the Youden index (Table 2). Sensitivity and specificity, along with the overall percent agreement (OPA), positive predictive value (PPV), and negative predictive value (NPV) were calculated. Notably, p-tau217 and p-tau217/Aβ42 by the single cutoff achieved both sensitivity and specificity greater than 90%.

Next, we applied a two-cutoff approach to achieve both 95% sensitivity and 95% specificity (Table 2). Using the two cutoff points, p-tau217 and p-tau217/Aβ42 showed notably high PPV (98.9–99%) and relatively high NPV (87.2–92.7%) with a small intermediate range (0–7%). Using the FDA-approved two-point cutoffs (high: 7.38 and low: 3.7), the diagnostic performance of p-tau217/Aβ42 showed a sensitivity of 97.1%, specificity of 95.5%, OPA of 87.4%, PPV of 99.0%, and NPV of 87.5% with a 12.6% intermediate range.

Cutoff values were also analyzed for the CU and CI groups (Supplementary Table 2, 3). The CU group with a lower amyloid pathology frequency (22.6%) showed high NPVs (94.3%) for plasma p-tau217 and p-tau217/Aβ42 with a single cutoff. In contrast, the CI group, which had a higher amyloid pathology frequency (86.6%), showed notably high PPVs (100%).

3.4. Association between plasma biomarkers and PRS

Given our previous finding that PRS was significantly associated with the risk of AD in a Japanese population [44], we hypothesized that PRS may also be associated with plasma p-tau217 levels. We constructed two PRS models: PRS (total) covering total risk for AD, including the *APOE* region and PRSnoAPOE reflecting genetic risk for AD excluding the *APOE* region. PRS (total) and PRSnoAPOE were significantly associated with p-tau217 and p-tau217/Aβ42 levels (Supplementary Fig. 7). Next, we performed a regression analysis of PRSs with plasma biomarkers. PRS (total) was significantly associated with both plasma p-tau217 measured using two assays (FDR $p < 0.016$), but not with the CSF-adjusted p-tau217/Aβ42 after adjustment for covariates (Table 3). PRS excluding *APOE* region (PRSnoAPOE) was significantly associated with p-tau217 measured using two assays (FDR $p < 0.05$), but not with p-tau217/Aβ42 after adjustment for covariates. Neither PRS (total) nor PRSnoAPOE was associated with other plasma biomarkers, including Aβ42/40 or GFAP (data not shown).

3.5. Associations of plasma p-tau217 with various covariates

Although previous studies have reported that plasma p-tau217 levels are affected by physiological and clinical factors, including BMI, renal function (as indicated by the eGFR), and various comorbidities [45–49], it has been unknown whether such confounding factors significantly contribute to the Japanese population.

Consistent with previous reports [45–49], we confirmed that BMI and eGFR significantly affected p-tau217 levels even after adjusting for amyloid status (Supplementary Fig. 8). After full adjustment, p-tau217 levels measured using the Simoa and Lumipulse assays were affected by hemoglobin and vitamin B12 levels, and Simoa p-tau217 also showed an association with triiodothyronine (T_3) levels. However, none of these associations remained statistically significant after the FDR correction. Interestingly, a significant association between p-tau217 and p-tau217/Aβ42 by the Lumipulse assay with high-density lipoprotein cholesterol (HDL-C) was found even after FDR correction. This finding

Table 2
Diagnostic accuracy of plasma p-tau217.

Analyte	AUC (age-adjusted)	Cutoff values	Sensitivity (%)	Specificity (%)	Plasma biomarker	CSF Aβ42/Aβ40 ratio		OPA (%)	PPV (%)	NPV (%)	Int. (%)
						Negative (n)	Positive (n)				
Single point											
Simoa p-tau217	0.978 (0.962)	Youden: 0.530	93.3	94.9	Negative Positive	37 2	7 97	93.7	98.0	84.1	NA
Lumipulse p-tau217	0.981 (0.975)	Youden: 0.176	93.3	100	Negative Positive	39 0	7 97	95.1	100	84.8	NA
Lumipulse p-tau217/ Aβ42*10^3	0.983 (0.980)	Youden: 6.32	97.1	97.4	Negative Positive	38 1	3 101	97.2	99.0	92.7	NA
Double points											
Simoa p-tau217	NA	95% Sen: 0.460 95% Spe: 0.584	NA	NA	Negative Int Positive	34 4 1	5 6 93	95.5	98.9	87.2	7.0
Lumipulse p-tau217	NA	95% Sen: 0.160 95% Spe: 0.160	NA	NA	Negative Int Positive	38 0 1	5 0 99	95.8	99.0	88.4	0
Lumipulse p-tau217/ Aβ42*10^3	NA	95% Sen: 6.32 95% Spe: 6.32	NA	NA	Negative Int Positive	38 0 1	3 0 101	97.2	99.0	92.7	0
FDA pre-defined											
Lumipulse p-tau217/ Aβ42*10^3	NA	Lower: 3.70 Higher: 7.38	97.1	95.5	Negative Int Positive	21 17 1	3 1 100	87.4	99.0	87.5	12.6

AUC, area under the curve; CSF, cerebrospinal fluid; Int, intermediate; CI, cognitively impaired; CU, cognitively unimpaired; NA, not applicable; NPV, negative predictive value; OPA, Overall Percent Agreement; PPV, positive predictive value; Int, intermediate range; Se, sensitivity; Sp, specificity; NA, not applicable

Table 3
Association of PRSs with plasma p-tau217 biomarkers.

	PRS (total)				PRSnoAPOE			
	Estimate	95% CI	P value	FDR	Estimate	95% CI	P value	FDR
Simoa plasma p-tau217								
unadjusted	0.298	0.136–0.460	**4.30.E-04**	**6.45.E-04**	0.228	0.069–0.388	**5.80.E-03**	**0.012**
age-sex-edu-adjusted	0.312	0.151–0.473	**2.12.E-04**	**6.36.E-04**	0.233	0.074–0.391	**4.61.E-03**	**0.012**
age-sex-edu-*APOE* ε4-adjusted	NA	NA	NA	NA	0.204	0.049–0.358	**0.011**	**0.014**
age-sex-edu-(*APOE* ε4)-CSF-adjusted	0.185	0.036–0.333	**0.016**	**0.016**	0.185	0.036–0.333	**0.016**	**0.016**
Lumipulse plasma pTau217								
unadjusted	0.262	0.116–0.408	**5.65.E-04**	**8.48.E-04**	0.206	0.058–0.354	**7.14.E-03**	**0.014**
age-sex-edu-adjusted	0.269	0.124–0.415	**3.87.E-04**	**8.48.E-04**	0.209	0.061–0.356	**6.24.E-03**	**0.014**
age-sex-edu-*APOE* ε4-adjusted	NA	NA	NA	NA	0.181	0.036–0.326	**0.015**	**0.021**
age-sex-edu-(*APOE* ε4)-CSF-adjusted	0.135	-0.002–0.272	0.055	0.055	0.145	0.013–0.277	**0.032**	**0.032**
Lumipulse plasma pTau217/Aβ42 (x1,000)								
unadjusted	0.215	0.068–0.363	**4.83.E-03**	**7.24.E-03**	0.180	0.031–0.329	**0.019**	**0.038**
age-sex-edu-adjusted	0.224	0.076–0.371	**3.37.E-03**	**7.24.E-03**	0.185	0.037–0.333	**0.016**	**0.038**
age-sex-edu-*APOE* ε4-adjusted	NA	NA	NA	NA	0.159	0.013–0.305	**0.035**	**0.046**
age-sex-edu-(*APOE* ε4)-CSF-adjusted	0.093	-0.047–0.232	0.196	0.196	0.124	-0.010–0.259	0.071	0.071

P values in **bold** are statistically significant. Edu, years of education; NA: not applicable

suggests that elevated HDL-C levels may lead to false-positive p-tau217 results in the Lumipulse assay.

3.6. Predictive value for clinical and cognitive prognosis

We next evaluated the prognostic performance of plasma p-tau217 and p-tau217/Aβ42 for longitudinal cognitive decline. Participants were stratified into High (above the cutoff) and Low (below the cutoff) groups for each biomarker. Longitudinal changes in cognitive and clinical scales (MMSE, ADAS, CDR-SB, and FAQ) over 36 months were compared after adjusting for age, sex, and years of education as covariates. Irrespective of the biomarker employed, the High-biomarker group demonstrated poorer baseline clinical scores relative to the Low-biomarker group and a more rapid longitudinal decline (Supplementary Table 4, Supplementary Fig. 9).

Next, we examined the relationship between biomarker status and progression to dementia. Our analysis included 98 subjects with baseline CDR global score of 0.5. During the median 24-month (range, 6–36 months) follow-up period, 47 participants (48.0%) progressed to a CDR global score of ≥1. Using the cutoff values for CI determined by the Youden index (Supplementary Table 3), we stratified the subjects into High (above cutoff) and Low (below cutoff) groups and analyzed their risk of conversion to CDR ≥1. At 36 months, conversion rates were markedly higher in the High-biomarker group than in the Low-biomarker group, showing a 2.9-fold increase for Simoa p-tau217, a 10.3-fold increase for Lumipulse p-tau217, and a 9.6-fold increase for the Lumipulse p-tau217/Aβ42 ratio. Kaplan–Meier analysis revealed that participants in the High-biomarker group exhibited significantly higher rates of conversion to dementia than those in the Low-biomarker group (Fig. 2). This effect was stronger for Lumipulse p-tau217 (log-rank test, $p < 0.001$) and p-tau217/Aβ42 ratio ($p < 0.001$) than for Simoa p-tau217.

In the multivariable Cox proportional hazards model adjusted for age, sex, education, *APOE* ε4 status, and baseline MMSE score, all plasma biomarkers remained significantly associated with conversion to dementia (Supplementary Table 5). Lumipulse p-tau217 showed the strongest association with conversion, with an adjusted hazard ratio (HR) of 4.717 (95% CI: 2.371–8.856, $p < 0.001$), indicating that individuals in the High group had an approximately five-fold increased risk of conversion to dementia throughout the observation period. In comparison, Simoa p-tau217 showed a moderate but still statistically significant association, with an adjusted HR of 2.557 (95% CI: 1.668–3.746, $p < 0.001$).

We next examined whether the PRS provided additional predictive

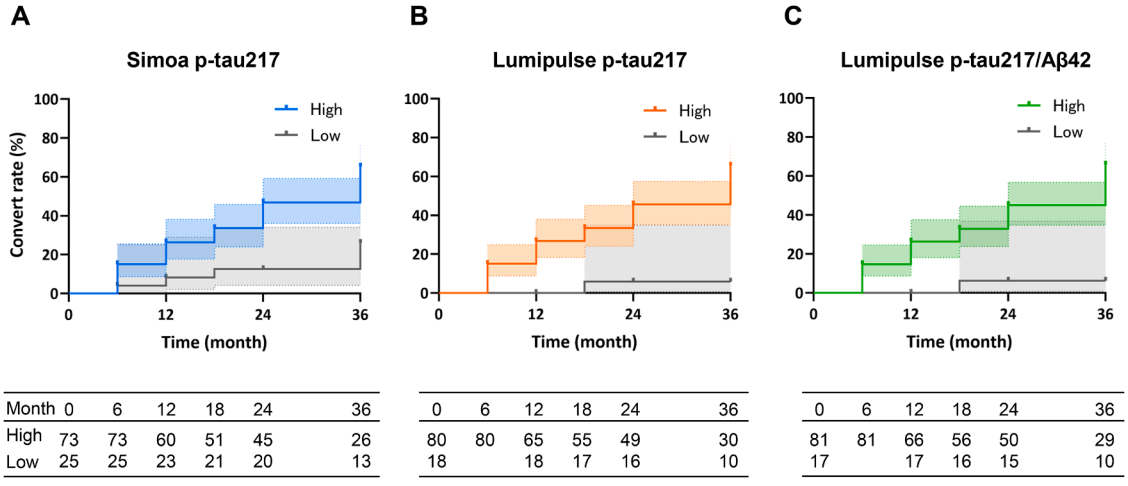

Fig. 2. Kaplan–Meier curves showing risk of conversion to AD dementia based on plasma p-tau217 **biomarkers** Participants were stratified into high (above cutoff) and low (below cutoff) groups using cutoff values determined by the maximum Youden index. (**A**) Simoa p-tau217, (**B**) Lumipulse p-tau217, and (**C**) Lumipulse p-tau217/Aβ42 ratio. Participants in the high-biomarker group exhibited significantly higher rates of conversion to AD dementia during follow-up. Log-rank test p-values were as follows: Simoa p-tau217 ($p = 0.002$), Lumipulse p-tau217 ($p < 0.001$), and Lumipulse p-tau217/Aβ42 ($p < 0.001$). Numbers at risk are shown in the bottom.

value for conversion to dementia beyond plasma p-tau217 biomarkers. There was no significant difference in predictive performance between the model including p-tau217 alone (AUC = 0.981) and the model combining PRS with p-tau217 (AUC = 0.975), as assessed by DeLong's test (p = 0.466). These findings suggest that plasma p-tau217 levels largely capture the information conveyed by the AD-related PRS.

4. Discussion

In this study, we evaluated the diagnostic and prognostic performance of several plasma biomarkers including p-tau217, using samples from the Japanese ADNI cohort. Our major observations were as follows: (1) plasma p-tau217 and p-tau217/Aβ42 exhibited high accuracy (AUC 0.97–0.98) for detecting amyloid pathology; (2) Lumipulse assays demonstrated diagnostic accuracy comparable to that of the Simoa platform; (3) the FDA-approved cutoff points for p-tau217/Aβ42 were applicable to our Japanese cohort; (4) plasma p-tau217 levels were significantly correlated with PRS; (5) higher plasma p-tau217 levels were significantly associated with conversion to AD dementia and longitudinal cognitive decline; and (6) in addition to eGFR and BMI, HDL-C significantly influenced plasma p-tau217 levels.

We showed notably high diagnostic accuracy exceeding 90% sensitivity and 90% specificity for the detection of amyloid pathology defined by the CSF Aβ42/40 ratio of plasma p-tau217 (AUC = 0.978 by Simoa and 0.981 by Lumipulse) and p-tau217/Aβ42 (AUC = 0.983 by Lumipulse) in our cohort. Similar high performance was observed when amyloid PET status served as a reference for plasma p-tau217 (AUC = 0.915 by Simoa and 0.929 by Lumipulse) and p-tau217/Aβ42 (AUC = 0.936 by Lumipulse). Our previous report showed that CSF Aβ42/40 had an AUC of 0.94 using amyloid PET status as a reference in the J-ADNI study [50]. This indicates that the diagnostic performance of plasma p-tau217 and p-tau217/Aβ42 for detecting amyloid pathology was comparable to that of CSF Aβ42/40 when amyloid PET status was used as a reference. Reflecting their highly accurate performance, a single cutoff determined by the Youden index achieved both >90% sensitivity and >90% specificity for detecting amyloid pathology. The Lumipulse p-tau217/Aβ42 assay was recently approved by the FDA as a blood test to aid in AD diagnosis using two cutoff points [51]. The predefined two cutoff points for p-tau217/Aβ42 were applicable to the J-ADNI cohort.

This study represents the first head-to-head comparison of plasma p-tau217 measurements using Lumipulse and Simoa assays in an Asian population. The p-tau217 levels measured by both assays were highly correlated, although the cutoff value for Lumipulse to discriminate amyloid pathology was lower than that of Simoa. The AUCs for detecting amyloid pathology did not differ significantly between the two methods. Previous studies have reported comparable or superior performance of the Lumipulse assay relative to Simoa [30,32]. Further validation of the performance of p-tau217 measured using different methods is warranted to confirm these findings in an independent Japanese cohort.

PRS estimates genetic susceptibility by aggregating small genetic effects across multiple loci implicated in disease pathways. In this study, we demonstrated that both the total PRS and the PRS excluding the *APOE* region (PRSnoAPOE) were significantly associated with plasma p-tau217 levels. This association remained significant after adjusting for *APOE* genotypes and amyloid status, suggesting that the effect of PRSs may operate through mechanisms independent of *APOE* or amyloid pathology. Although PRS for AD has been linked to various endophenotypes, including CSF biomarkers, amyloid PET, and brain volume, studies examining their relationship with plasma biomarkers remain limited. Zettergren et al. reported that plasma p-tau181 levels were associated with PRS for AD using data obtained from the ADNI study [52]. They found that PRS, including *APOE* genotypes, was associated with plasma p-tau181 across all diagnostic groups including CU, MCI, and AD, whereas PRS excluding the *APOE* region was associated with plasma p-tau181 only in the MCI group. Our previous study using the J-ADNI cohort showed that total tau/Aβ42 and p-tau181/Aβ42 ratios in CSF were significantly associated with PRS excluding the *APOE* region in the MCI group [44]. These results suggest that integrating genetic risk information from PRS with plasma biomarkers may provide new insights into the complex mechanisms underlying AD progression.

We further demonstrated that plasma p-tau217 levels were associated with an increased risk of conversion to AD dementia and greater longitudinal cognitive decline over three years. These findings are consistent with those of previous studies [53,54]. Notably, only a small proportion of MCI patients with plasma p-tau217 and p-tau217/Aβ42 levels below the cutoff values, converted to AD dementia within 3 years. We also showed that changes in clinical and cognitive scores were minimal in participants with plasma biomarker levels below the cutoff values. This suggests that these plasma biomarkers function not only as indicators of amyloid pathology but also as prognostic markers. Given that anti-Aβ antibody therapies have been clinically implemented for AD patients at the MCI stage in several countries, plasma p-tau217 could serve as an efficient tool to guide therapeutic decision-making by selecting MCI patients at high risk of progression who are most likely to benefit from the intervention.

In this study, a higher BMI was associated with lower p-tau217 levels, whereas reduced kidney function as indicated by eGFR was linked to elevated p-tau217 levels, consistent with previous reports [47–49,55,56]. Notably, we first found that HDL-C levels were positively associated with plasma p-tau217 measured by Lumipulse, even after adjusting for amyloid pathology. Such an association was not observed between HDL-C and p-tau217 levels measured using Simoa. This association between HDL-C and plasma p-tau217 levels was absent in the Korean cohort [47]. Further validation in independent cohorts is required. These findings emphasize the need for caution when interpreting plasma p-tau217 levels obtained using the Lumipulse platform, considering BMI, renal function, and HDL-C levels.

4.1. Strengths and limitations

A key strength of this study lies in the use of plasma samples collected under a uniform protocol across multiple J-ADNI sites, which enhances the generalizability and reliability of our findings in the Japanese population. However, several notable limitations warrant consideration. The overall sample size was modest, particularly in the CU subgroup, which limited the statistical power and precision of the cutoff determination. Validation in larger, real-world cohorts, especially those including individuals with diverse comorbidities, is necessary to start applying plasma biomarkers for routine clinical practice. Furthermore, a cross-ethnic comparison of the cutoff values of plasma p-tau217 will be important to determine whether the optimal cutoff values differ across populations.

4.2. Conclusion

In summary, our findings reinforce the clinical utility of plasma p-tau217 biomarkers as reliable and scalable markers for AD. The Lumipulse p-tau217 and p-tau217/Aβ42 assays demonstrated diagnostic and prognostic performances comparable to those of the Simoa platform. Potential confounding factors such as BMI, renal dysfunction, and HDL-C levels, should be considered when interpreting plasma p-tau217 levels in clinical settings. Overall, these results highlight the value of plasma p-tau217 biomarkers as diagnostic and prognostic markers in symptomatic patients with AD spectrum, covering MCI to dementia stages.

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Data sharing statement

The data described in the manuscript will be made available upon request pending approval by the corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

Generative AI and AI-assisted technologies were not used during the preparation of this manuscript.

CRediT authorship contribution statement

Kensaku Kasuga: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Masataka Kikuchi:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Emiko Kikkawa-Saito:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tamao Tsukie:** Methodology, Formal analysis, Data curation. **Takanobu Ishiguro:** Writing – review & editing, Methodology, Data curation. **Akinori Miyashita:** Writing – review & editing, Investigation, Formal analysis. **Takeshi Iwatsubo:** Writing – review & editing, Supervision, Funding acquisition. **Takeshi Ikeuchi:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

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Supplementary materials

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