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RESEARCH ARTICLE

Predicting amyloid PET positivity using plasma p-tau181 and other blood-based biomarkers

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Abstract

Introduction: This study aimed to determine the efficacy of combining plasma phosphorylated tau (p-tau)181, amyloid beta (Aβ)42/Aβ40, neurofilament light (NfL), and apolipoprotein E (*APOE*) genotypes for detecting positive amyloid positron emission tomography (PET), which is little known in the Asian population, in two independent cohorts.

Methods: Biomarkers were measured using a single-molecule array (Simoa) in a cohort study (Asan). All participants underwent amyloid PET. Significant changes in the area under the curve (AUC) and Akaike Information Criterion values were considered to determine the best model. The generalizability of this model was tested using another cohort (KBASE-V).

Results: In the Asan cohort, after adjusting for age and sex, p-tau181 (AUC = 0.854) or *APOE* ε4 status (AUC = 0.769) distinguished Aβ status with high accuracy. Combining them or adding NfL and Aβ42/40 improved model fitness. The best-fit model included the plasma p-tau181, *APOE* ε4, NfL and Aβ42/40. The models established from the Asan cohort were tested in the KBASE-V cohort. Additionally, in the KBASE-V cohort, these three biomarker models had similar AUC in cognitively unimpaired (AUC = 0.768) and mild cognitive impairment (MCI) (AUC = 0.997) participants.

Conclusions: Plasma p-tau181 showed a high performance in determining Aβ-PET positivity. Adding plasma NfL and APOE ε4 status improved the model fit without significant improvement in AUC.

Hyuk Sung Kwon, Eun-Hye Lee, and Hyung-Ji Kim contributed equally to this work and should be considered co-first authors.

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KEYWORDS
Alzheimer's disease, amyloid beta, amyloid positron emission tomography, APOE, neurofilament light, p-tau181

1 | BACKGROUND

The global burden of Alzheimer's disease (AD) is increasing.[1] Amyloid beta (Aβ) and tau pathology are important characteristics of AD.[2] Recently, anti-amyloid agents, including aducanumab, lecanemab, and donanemab, were shown to reduce visible amyloid plaques, as well as the progression of cognitive decline.[3–5] Additionally, recently the drugs aducanumab and lecanemab were approved by the US Food and Drug Administration. Detecting amyloid pathologies at an early stage has become increasingly important for the diagnosis and management of AD in clinical practice. Although Aβ positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) studies reflect the presence of amyloid pathologies, these methods are expensive and/or invasive.[6] To overcome these limitations, studies have focused on the use of blood-based biomarkers.

Plasma tau phosphorylated at threonine 181 (p-tau181) has shown high and robust accuracy in discriminating Aβ positivity detected by PET or CSF.[7,8] P-tau217 and p-tau231 was also associated with Aβ positivity using either Aβ-PET or CSF as the outcome; moreover, adding plasma Aβ42/40 evidenced a better performance.[9,10] However, the method for detecting plasma Aβ42/40 and its performance can vary.[11] Recently, a combined model with Aβ42/40 and p-tau231 showed high accuracy in determining Aβ positivity.[10] Adding neurofilament light (NfL) and apolipoprotein E (*APOE*) genotype improved the model fitness; however, it did not significantly improve the area under the curve (AUC) value. The determination of plasma NfL has been emphasized in AD.[12] NfL is related to axonal degeneration and it may reflect the burden of Aβ in AD.[6,12] However, NfL is not specific to AD and can be increased in other neurodegenerative diseases.[13]

To date, there have been few studies assessing the combination of p-tau181 and other blood-based biomarkers in predicting Aβ positivity. Moreover, information on the ethnic variation in blood-based biomarkers is lacking, especially in Asians. Here, we investigated the usefulness of detecting positive Aβ-PET using individual and different combinations of plasma biomarkers (p-tau181, NfL, and Aβ42/40) and *APOE* genotype in two independent cohorts in Korea. The derivation cohort was the Korean dementia cohort of the Asan Medical Center (Asan), and the validation cohort was the Korea Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE-V).

2 | METHODS

2.1 | Study participants of derivation cohort (Asan)

The participants of the derivation cohort were prospectively enrolled in the memory clinic of the Asan Medical Center, South Korea, from June 2018 to July 2020, as described previously.[14] The inclusion criteria were as follows: (1) age > 40 years and < 90 years; and (2) no evidence of parenchymal lesions that could influence the cognitive function based on brain MRI. This study was approved by the Institutional Review Board (IRB) of the Asan Medical Center (Approval #2018-0614). All the participants or their proxies provided written informed consent. A total of 100 participants (eight cognitively unimpaired [CU], 53 mild cognitive impairment [MCI], and 39 AD dementia [ADD]) were analyzed in this study. All the CU participants had an average education-adjusted performance on memory tests. The participants with MCI met the following criteria proposed by Petersen et al.[15]: (1) memory complaint, preferably corroborated by an informant; (2) impaired memory function for age and education; (3) preserved general cognitive function; (4) intact activities of daily living; (5) not demented. Participants with ADD met the following criteria: (1) diagnostic criteria for dementia, as per the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR), and (2) the criteria for probable ADD as per the NINCDS-ADRDA criteria.[16]

2.2 | Positron emission tomography images

All participants underwent ^{18}F-florbetaben amyloid PET. All PET images were obtained using the Discovery 690, 710, and 690 Elite PET/CT scanners (GE Healthcare, Chicago, IL, USA). Amyloid PET images were collected for 20 min, which began 90 min after the injection of 300 $\pm$ 30 MBq ^{18}F-florbetaben. Two neurologists (H.J.K. and J.H.L.) and two nuclear medicine physicians reviewed the PET scans according to predefined regional cortical tracer uptake (RCTU) and brain amyloid plaque load (BAPL) scoring systems. In general, four regions of interest, including the frontal, temporal, and parietal cortices along with the posterior cingulate/precuneus, were interpreted in the visual assessment of the ^{18}F-florbetaben PET scans. The RCTU scores were then condensed into a single three-grade scoring system for each PET scan (BAPL score) as follows: 1, no Aβ load; 2, minor Aβ load; and 3, significant Aβ load. The final score was reached by consensus, with a BAPL score of 1 regarded as amyloid-negative (Aβ–) and BAPL scores of 2 and 3 as amyloid beta positive (Aβ+).[17] The participants were assigned to the Aβ+ and Aβ– groups according to the amyloid status on PET, irrespective of their cognitive status.

2.3 | Plasma sampling and analysis

Plasma samples were collected according to the procedure manual of Alzheimer's Disease Neuroimaging Initiative 2.[18] Blood samples were collected after overnight fasting of at least 6 h, and subsequently

centrifuged within an hour and stored at −80°C. Plasma p-tau181 and NfL levels were measured using the Simoa Human p-Tau181 Advantage V2 assay (Quanterix, Boston, MA, USA, PN/103714) and the NF-Light Advantage assay (Quanterix, Boston, MA, USA, PN/103186), respectively. Plasma Aβ40 and Aβ42 levels were measured using the Simoa Human Aβ40 Advantage assay (Quanterix, Boston, MA, USA, PN/101672) and Human Aβ42 Advantage assay (Quanterix, Boston, MA, USA, PN/101664), respectively. For a typically-run setup, each sample and control was transferred into 96-well Quanterix plates for duplicate tests with on-board 4× dilution by the instrument. The assay was performed using a Simoa HD-X instrument (Quanterix) in a two-step immunoassay.

The *APOE* genotype was identified after extracting genomic DNA from the venous blood. *APOE*-risk allele status was modeled as one variable coded for the presence of the ε4 allele (1 for ε4 carriers and 0 for noncarriers).

2.4 | Validation cohort (KBASE-V)

The KBASE-V subset was used as the independent validation cohort. Detailed methods including the inclusion and exclusion criteria of the KBASE-V have been described previously.[19] Briefly, the KBASE-V was approved by the IRB of each participating center (INHAUH 2015-03-021) and contained a nationwide cohort, including 167 CU, 72 MCI, and 56 ADD participants from nine hospitals. The criteria for CU and MCI in both the derivation and validation cohorts were the same, except for the limitations of the CDR score in the validation cohort (a score of 0 for CU and 0.5 for MCI). All participants in the KBASE-V were aged 55–90 years and underwent physical and neurological examinations, including the Mini-Mental State Examination,[20] Geriatric Depression Scale,[21] Blessed Dementia Scale-ADL,[22] clinical dementia rating scale,[23] and Consortium to Establish a Registry for Alzheimer's disease yearly.[24] All participants underwent 3.0 T brain MRI. The standard uptake value ratio (SUVR) was obtained using the ^{18}F-flutemetamol PET or ^{11}C-PiB PET. The Centiloid replication analysis was performed according to previous reports.[19,25] Elevated Aβ PET was defined as a cut-point of 10 Centiloid units.[26,27]

Based on our aim, this study analyzed participants who underwent amyloid PET and blood-based biomarker testing. A total of 134 participants (CU = 93 and MCI = 41) were analyzed. Serum NfL levels were estimated using the SIMOA NF-light Advantage kit produced by Quanterix. Plasma p-tau181 levels were measured using the same method as that used for the Asan cohort.

2.5 | Statistical analysis

Pearson's chi-square and Mann–Whitney *U* tests were used to compare baseline demographics, clinical data, and biomarker levels. The discrimination accuracies of plasma biomarkers for correctly identifying the amyloid status on PET were determined using logistic regression models and receiver operating characteristic (ROC) curve analysis. All the models were adjusted for age and sex. The AUC of different ROC curves was compared using the DeLong method. Improvements in model fit were estimated using the Akaike Information Criterion (AIC) with a decrease of two or more in the AIC indicating a better model fit.[10,28] The model with the lowest AIC was selected as the "best model fit." Models established using logistic regression analysis in patients with MCI in the Asan cohort were tested in patients with MCI in the KBASE-V cohort. Youden's Index was used to identify the optimal cutoff value for maximizing sensitivity and specificity.

RESEARCH IN CONTEXT

1. **Systematic Review**: A literature review was performed using PubMed and GoogleScholar for previous research related to "blood-based biomarkers", "Alzheimer's disease", "plasma phosphorylated tau (p-tau)181", "amyloid beta (Aβ)42/Aβ40", and "neurofilament light (NfL)". Relevant studies are cited and summarized. In current study, the authors investigated the efficacy of combining plasma p-tau181, Aβ42/Aβ40, NfL, and apolipoprotein E (APOE) genotypes in detecting positive amyloid positron emission tomography (PET) in a cohort (Asan cohort) and tested the prediction model using another cohort (KBASE-V cohort).
2. **Interpretation**: The plasma p-tau181 alone or combined with other blood-based biomarkers showed a high discriminative value in determining Aβ-PET positivity. The best-fit model included the plasma p-tau181, *APOE* ε4, NfL, and Aβ42/40 by Asan cohort. Models using these blood-based biomarkers established in patients with MCI in the Asan cohort were cross-validated in patients with MCI in the KBASE-V cohort.
3. **Future Directions**: High performance of blood-based biomarkers in discriminating Aβ-PET positivity might help early AD diagnosis and recruiting subjects for anti-amyloid agents. This study demonstrated that plasma p-tau181 shows a high discriminative value in detecting Aβ-PET positivity. Further validation studies are required in diverse ethnic and primary care populations.

3 | RESULTS

3.1 | Participant characteristics of derivation cohort (Asan)

The baseline and clinical characteristics of the participants are presented in Table 1 and supplementary Table 1. Aβ+ was observed in 52 (52%) participants. Compared with Aβ− participants, Aβ+ participants were younger and had lower mini-mental status examination scores,

TABLE 1 Baseline characteristics and blood biomarkers of patients according to amyloid positivity on PET in the derivation cohort (Asan) and validation cohort (KBASE-V)

	Derivation cohort (Asan)			Validation cohort (KBASE-V)		
	Aβ-negative (*n* = 48)	Aβ-positive (*n* = 52)	*P* Value	Aβ-negative (*n* = 103)	Aβ-positive (*n* = 31)	*P* value
Demographics						
Age, years	71.5 ± 8.5	66.7 ± 10.4	0.013	67.1 ± 7.6	73.2 ± 7.6	<0.001
Sex, female (%)	22 (45.8)	32 (61.5)	0.145†	56 (54.4)	17 (54.8)	0.963†
Education, years	11.6 ± 4.7	11.4 ± 4.8	0.789	10.5 ± 4.8	10.5 ± 4.4	0.977
Cognitive stage			0.444†			0.014†
CU (%)	5 (10.4)	3 (5.8)		77 (74.8)	16 (51.6)	
MCI (%)	27 (56.3)	26 (50.0)		26 (25.2)	15 (48.4)	
Dementia (%)	16 (33.3)	23 (44.2)		.		
Medical history						
Hypertension	22 (45.8)	25 (48.1)	0.822†	44/101 (43.6)	14 (45.2)	0.875
Diabetes mellitus	22 (45.8)	10 (19.2)	0.004†	18 (17.5)	5 (16.1)	0.862†
Dyslipidemia	19 (33.6)	26 (50.0)	0.296†	43/100 (43.0)	13 (41.9)	0.917†
Coronary artery disease	7 (14.6)	7 (13.5)	0.872†	5 (4.9)	2 (6.5)	0.726†
MMSE score, median (IQR)	25.0 (22.0, 28.0)	23.0 (20.0, 25.75)	0.035‡	26.0 (23.0, 29.0)	26.0 (21.0, 28.0)	0.166‡
CDR score, median (IQR)	0.0 (0.0, 0.5)	0.5 (0.5, 1.0)	0.466‡	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.025‡
CDR-SOB score, median (IQR)	2.0 (0.5, 5.0)	3.0 (1.5, 5.0)	0.249‡	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.009‡
APOE ε4 carrier	9 (18.8)	31 (59.6)	<0.001†	14 (13.6)	15 (48.4)	<0.001
Plasma p-tau181 (pg/mL)	2.30 ± 1.16	4.43 ± 1.82	<0.001	2.01 ± 1.58	3.63 ± 2.11	<0.001
Plasma/Serum NfL (pg/mL)[a]	38.12 ± 31.11	28.54 ± 17.46	0.065	22.59 ± 14.12	24.20 ± 9.69	0.553
Plasma Aβ42 (pg/mL)	7.71 ± 2.51	7.56 ± 2.13	0.756	.	.	
Plasma Aβ40 (pg/mL)	218.2 ± 103.7	210.7 ± 81.2	0.691	.	.	
Plasma Aβ42/40 ratio	0.040 ± 0.015	0.038 ± 0.010	0.395	.	.	
MCI						
Number	27	26		26	15	
Plasma p-tau181 (pg/mL)	2.53 ± 1.26	4.11 ± 1.87	0.001	1.81 ± 0.78	4.04 ± 1.81	<0.001
APOE ε4 carrier	7 (25.9)	16 (61.5)	0.009†	1 (3.8)	8 (53.3)	<0.001†
Plasma/Serum NfL (pg/mL)[a]	40.44 ± 37.10	26.94 ± 11.14	0.080	22.80 ± 17.65	27.02 ± 10.10	0.402

Note: Data are presented as mean ± SD or number (%) unless otherwise indicated.

Abbreviations: APOE, apolipoprotein E; CDR-SOB, Clinical Rating Scale sum of boxes; CU, cognitive unimpaired; IQR, interquartile range; KBASE-V, Korea Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NfL, neurofilament light; PET, positron emission tomography.

Student's *t*- test.

†Pearson's chi-square test.

‡Mann–Whitney *U* test were used.

[a]Plasma NfL was measured in the derivation cohort and serum NfL was measured in the validation cohort.

memory function, and visuospatial function. DM was more frequent in the Aβ− participants. Other demographics, cognitive stages, and the proportion of risk factors did not differ between the Aβ− and Aβ+ groups.

In total, participants with MCI or dementia had a significantly increased prevalence of *APOE* ε4 carriers. Moreover, higher plasma p-tau181 levels were noted in the Aβ+ group. The plasma NfL levels and Aβ42/40 ratio were slightly lower in the Aβ+ group without any statistical significance.

3.2 | Detecting amyloid positivity confirmed by PET in the derivation cohort (Asan)

3.2.1 | Total participants

In all participants (Table 2, Figure 1A, Figure 1D), univariate analysis revealed a significant association with Aβ positivity in plasma p-tau181 (AUC = 0.884, confidence interval [CI] = 0.777–0.931), odds ratio [OR] = 2.504, $P < 0.001$) and *APOE* ε4 carriers (AUC = 0.769,

TABLE 2 Associations with Aβ-PET status and plasma biomarkers (total participants) in the derivation cohort (Asan)

	Odds ratio (*P* value)						
Model	p-tau181	APOE	NfL	Aβ42/40	AUC (95% CI)	*P value vs. p-tau181	AIC (ΔAIC) vs. p-tau181
P-tau181, APOE, NFL, Aβ42/40	2.961 (<0.001)	5.902 (0.004)	0.972 (0.047)	1.163 (0.578)	0.906 (0.846–0.965)	0.145	88.2 (−15.1)
P-tau181, APOE, NFL	2.514 (<0.001)	4.950 (0.006)	0.976 (0.075)	…	0.889 (0.822–0.956)	0.139	93.6 (−9.7)
P-tau181, APOE	2.248 (<0.001)	5.587 (0.002)	…	…	0.873 (0.802–0.945)	0.285	95.2 (−8.1)
P-tau181, per 1 pg/mL increase	2.504 (<0.001)	…	…	…	0.854 (0.777–0.931)	ref	103.3 (ref)
APOE, positive	…	7.720 (<0.001)	…	…	0.769 (0.674–0.864)	0.116	107.7 (4.4)
NfL, per 1 pg/mL increase	…	…	0.987 (0.178)	…	0.687 (0.582–0.791)	0.005	135.1 (31.8)
Aβ42/40, per 0.01 increase	…	…	…	0.844 (0.349)	0.666 (0.558–0.773)	<0.001	134.2 (30.9)

Note: Results from logistic regression models with binarized Aβ positivity confirmed using PET as an outcome after adjusting for age and sex. For blood biomarkers, odds ratios represent an increased risk of Aβ-positivity.
Abbreviations: Aβ, amyloid beta; AIC, Akaike Information Criterion; APOE, apolipoprotein E; AUC, area under the curve; CI, confidence interval; NfL, neurofilament light; p-tau, phosphorylated tau; ref, reference.
**P* values are for comparisons of AUCs (using the DeLong test) between the p-tau181 alone and other models.

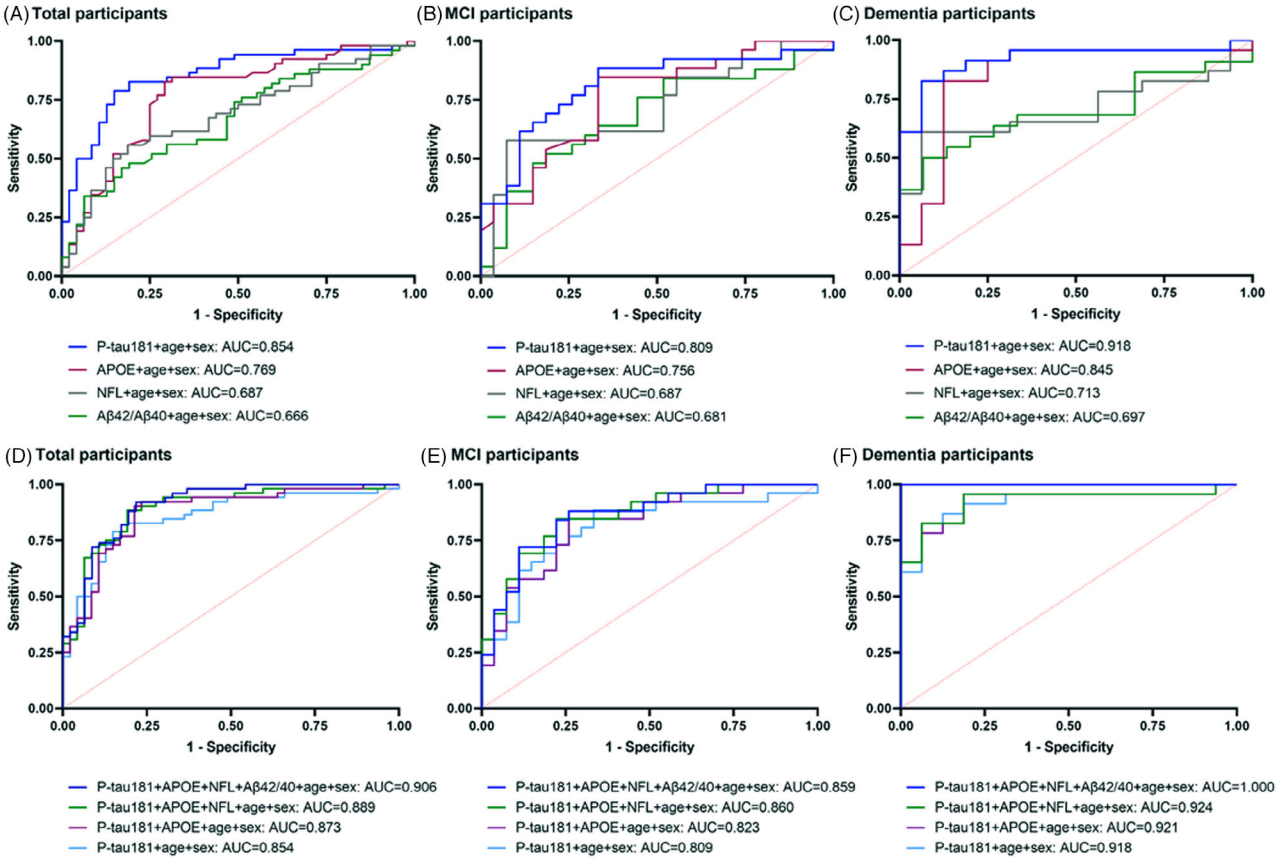

FIGURE 1 ROC curve using blood biomarkers in Asan cohort. ROC curve analysis of each (A–C) and combined (D–F) biomarkers for predicting Aβ status using PET in the derivation cohort (Asan). ROC curves are shown for plasma p-tau181, *APOE* status, plasma NfL, plasma Aβ42/40, a combination of plasma p-tau181 and APOE status, a combination of plasma p-tau181, *APOE* status, and plasma NfL, and the model including all four biomarkers. Aβ, amyloid beta; *APOE*, apolipoprotein E; NfL, neurofilament light; PET, positron emission tomography; ROC, receiver operating characteristic

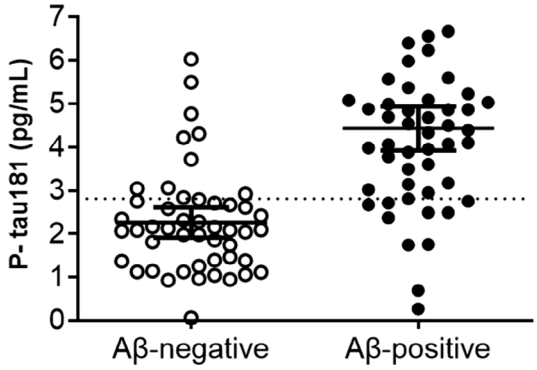

FIGURE 2 Comparison of p-tau181 level in Aβ status. Dot plots comparing plasma p-tau181 level between participants with amyloid PET negative and positive in the Asan cohort. The solid line represents the mean with 95% confidence interval. The dotted line at 2.81 pg/mL of p-tau181 level represents the suggested threshold for Aβ-positivity. Aβ, amyloid beta; p-tau181, phosphorylated tau-181; PET, positron emission tomography

CI = 0.674–0.864, OR = 7.720, $P < 0.001$). A two-biomarker model that combined plasma p-tau181 and *APOE*, demonstrated high discriminative accuracy (AUC = 0.873, CI = 0.802–0.945). This model showed better performance than p-tau181 alone, however, it did not significantly improve the AUC compared to p-tau181 alone (Table 2, $P = 0.285$). The three-biomarker model (p-tau181, *APOE*, and NfL) demonstrated a high discriminative value (AUC = 0.889) but did not significantly improve the AUC compared to p-tau181 model ($P = 0.139$) or the two-biomarker model ($P = 0.221$). The full plasma model, including p-tau181, *APOE*, NfL, and Aβ42/40 showed a high discriminative value (AUC = 0.906) with the lowest AIC (best model fit). In conclusion, p-tau181 distinguished Aβ+ patients from Aβ− patients with a high accuracy. Adding *APOE* ε4 status, plasma NfL, or Aβ42/40 improved model fitness in terms of AIC but did not significantly improve the AUCs. If we consider p-tau181 only, the suggested threshold was 2.81 pg/mL (Figure 2, Table S1)

3.2.2 | MCI participants

In MCI participants (Table 3, Figure 1B, Figure 1E), univariate analysis revealed a statistically significant association with Aβ+ status in plasma p-tau181 (AUC = 0.809, CI = 0.688–0.931, OR = 1.951, $P = 0.007$) and *APOE* ε4 carriers (AUC = 0.756, CI = 0.625–0.886, OR = 63278, $P = 0.005$). The model combining plasma p-tau181 and *APOE* showed slightly higher discriminative accuracy (AUC = 0.823, CI: 0.711–0.936). The three-biomarker model (p-tau181, *APOE*, and NfL) showed high discriminative accuracy (AUC = 0.849, CI = 0.742–0.956) and the lowest AIC (best model fit). This model showed no statistically significant difference from the full plasma model ($P = 0.838$) or the p-tau181-only model ($P = 0.217$).

3.2.3 | Participants with dementia

In participants with dementia (Table 3, Figure 1C, Figure 1F), univariate analysis revealed a significant association with Aβ+ status in plasma p-tau181 (AUC = 0.918 [CI: 0.825–1.000], OR = 3.219, $P = 0.001$) and *APOE* ε4 carriers (AUC = 0.845, CI = 0.698–0.993, OR = 9.767, $P = 0.015$). In terms of AIC, combining other plasma biomarkers with p-tau181 did not improve the model's fitness. The two-biomarker model slightly improved the discriminative accuracy (AUC = 0.921, CI = 0.829–1.000), without a statistically significant difference compared to p-tau181 alone ($P = 0.890$). All four-biomarker models showed high discriminative accuracy with an AUC of 1.000. However, no statistically significant difference was noted compared to the p-tau181 alone ($P = 0.139$).

3.3 | Validation cohort (KBASE-V)

In the MCI participants of Asan cohort, the three-biomarker (p-tau181, *APOE*, and NfL) and two-biomarker model demonstrated high discriminative value in predicting amyloid positivity. The generalizability of this model was tested using an independent subset of the KBASE-V cohort. Clinical characteristics and blood-based biomarkers are described in Table 1, Table S2, and Table S3. When testing this three-biomarker model in KBASE-V, the accuracy (AUC = 0.843, CI = 0.763–0.924) was similar to that of the Asan cohort (AUC = 0.889) (Figure 3A). In CU participants, the AUC (CI) of this three-biomarker model was 0.768 (0.646–0.889) (Figure 3B). In MCI participants, the accuracy of this three-biomarker model (AUC = 0.997, CI = 0.990–1.000 in KBASE-V) in discriminating amyloid PET positivity was higher than that in the Asan cohort (AUC = 0.860, CI = 0.762–0.959) (Figure 3C). The established logistic regression models in patients with MCI in the Asan cohort were cross-validated in patients with MCI in the KBASE-V cohort (Figure 3D). When the estimated three-biomarkers model (including p-tau181, APOE, and NfL) from Asan cohort were validated in KBASE-V, the AUC was 0.892 (CI = 0.794–0.990). Using threshold of prediction probability of 95.404% by three-biomarker model provided sensitivity of 100.0%, specificity of 65.4%, positive predictive value (PPV) of 40.0%, and negative predictive value (NPV) of 100.0% (Table S4). When the estimated two-biomarker model (including p-tau181 and APOE) from the Asan cohort was validated in KBASE-V, the AUC was 0.977 (CI = 0.943–1.000). Using the threshold of prediction probability of 90.184% in the two-biomarker model provided a sensitivity of 93.3%, specificity of 84.6%, PPV of 73.3%, and NPV of 96.2% (Table S5).

4 | DISCUSSION

This study demonstrates the utility of blood-based biomarkers, including p-tau181, *APOE* genotype, NfL, and Aβ42/40 in discriminating amyloid PET positivity. In the Asan cohort, we found that plasma p-tau181 (AUC = 0.854) and *APOE* status (AUC = 0.769) discriminated

TABLE 3 Associations with Aβ-PET status and plasma biomarkers in MCI and dementia patients

Model	Odds ratio (*P* value)				AUC (95% CI)	*P* value vs. p-tau181	AIC (ΔAIC) vs. p-tau181
	p-tau181	APOE	NfL	Aβ42/40			
MCI							
P-tau181, APOE, NfL, Aβ42/40	2.364 (0.014)	3.331 (0.106)	0.958 (0.092)	1.198 (0.633)	0.859 (0.758–0.960)	0.276	62.4 (−4.5)
P-tau181, APOE, NfL	2.219 (0.012)	3.385 (0.095)	0.961 (0.095)	…	0.860 (0.762–0.959)	0.217	61.1 (−5.8)
P-tau181, APOE	1.760 (0.023)	4.812 (0.025)	…	…	0.823 (0.711–0.936)	0.687	63.4 (−3.5)
P-tau181, per 1 pg/mL increase	1.951 (0.007)	…	…	…	0.809 (0.688–0.931)	ref	66.9 (ref)
APOE, positive	…	6.278 (0.005)	…	…	0.756 (0.625–0.886)	0.474	64.6 (−2.3)
NfL, per 1 pg/mL increase	…	…	0.979 (0.129)	…	0.687 (0.582–0.792)	0.140	73.5 (6.6)
Aβ42/40 ratio, per 0.01 increase	…	…	…	0.833 (0.494)	0.682 (0.531–0.832)	0.107	75.5 (8.6)
Dementia							
P-tau181, APOE, NfL, Aβ42/40	NA	NA	NA	NA	[a]1.000 (1.000-1.000)	0.139	NA
P-tau181, APOE, NfL	2.881 (0.004)	5.285 (0.114)	1.002 (0.931)	…	0.924 (0.832–1.000)	0.801	37.9 (1.2)
P-tau181, APOE	2.880 (0.004)	5.325 (0.111)	…	…	0.921 (0.829–1.000)	0.890	36.0 (−0.7)
P-tau181, per 1 pg/mL increase	3.219 (0.001)	…	…	…	0.918 (0.825–1.000)	ref	36.7 (ref)
APOE, positive	…	9.767 (0.015)	…	…	0.845 (0.698–0.993)	0.391	48.1 (11.4)
NfL, per 1 pg/mL increase	…	…	1.000 (0.989)	…	0.713 (0.570–0.857)	0.021	53.7 (17.0)
Aβ42/40 ratio, per 0.01 increase	…	…	…	0.918 (0.751)	0.697 (0.525–0.869)	0.003	51.7 (15.0)

Note: Results from logistic regression models with binarized Aβ positivity confirmed using PET as an outcome after adjusting for age and sex. For blood biomarkers, odds ratios represent an increased risk of Aβ-positivity.

Abbreviations: Aβ, amyloid beta; AIC, Akaike Information Criterion; APOE, apolipoprotein E; AUC, area under the curve; CI, confidence interval; MCI, mild cognitive impairment; NfL, neurofilament light; p-tau, phosphorylated tau; ref, reference.

[a]As AUC = 1, odd ratios and AIC were not calculated.

**P* values are for comparisons of AUCs (using the DeLong test) between the p-tau181 alone and other models.

amyloid positivity better than plasma NfL (AUC = 0.687) and Aβ42/40 (AUC = 0.666). The best-performing model included plasma p-tau181, *APOE* ε4, NfL, and Aβ42/40 (four-biomarker model). But this model did not significantly improve the AUC compared to p-tau181 alone. In each MCI or dementia subgroup, p-tau181 discriminated Aβ status with high accuracy (AUC = 0.809 in MCI, AUC = 0.918 in dementia). In MCI participants, the best model included the plasma p-tau181, *APOE* ε4, and NfL. In dementia participants, addition of other biomarkers to p-tau181 did not improve the performance of the model in terms of AUC or AIC. The generalizability of these biomarkers was tested using a subset of the KBASE-V cohort. P-tau181 alone, two-biomarker model (p-tau181 and *APOE* ε4), and three-biomarker model showed high AUC value, especially in MCI participants. The model established in MCI patients of Asan cohort was tested in KBASE-V cohort and showed high efficacy (AUC of the three-biomarker model = 0.892; AUC of the two-biomarker model = 0.933).

Plasma p-tau181 has received much attention because it has been shown to increase along the AD continuum, predict the progression of AD, and discriminate Aβ status.[8,29] In the current study, we validated the usefulness of p-tau181 in determining Aβ PET positivity in two independent Korean prospective cohorts. Models combining *APOE* ε4 status and NfL with p-tau181 improved model fitness, but the improvement in AUC was not statistically significant. Carrying *APOE* ε4 allele increases the risk of AD but it does not reflect the Aβ status.[10] In addition, NfL might be closely related to neuronal degeneration and the progression of AD but not to AD-specific pathology.[6]

The level of plasma p-tau181 varied among previous studies.[30,31] In the Asan cohort, mean ± SD of plasma p-tau181 was 3.30 ± 1.77 pg/mL in participants with MCI and 4.84 ± 1.81 in Aβ+ participants with dementia. This level was similar in the validation cohort (KBASE-V cohort) and in one of the previous reports.[30] However, other studies that analyzed participants in TRIAD or the BioFINDER-2 cohort showed higher plasma p-tau181 level (mean of 9.4 to 10.0 pg/mL [CU] and 12.5 to 14.8 pg/mL [MCI]).[8] Another study, which demonstrated the efficacy of p-tau as a predictor of AD diagnosis in a multi-ethnic study, showed a lower p-tau181 level than our study (mean ± SD: 0.86 ± 0.73 pg/mL in control and 1.24 ± 1.09 pg/mL in clinical AD).[31] The reasons for these differences are unclear. The type or version of the detection method, diurnal variation, ethnicity, fasting status, and comorbidities may have affected the results. Refinement of the preanalytical and analytical factors for p-tau levels is required.[32]

Plasma Aβ42/40 levels showed a relatively low discriminative value for amyloid PET positivity. In previous studies, plasma Aβ42/40 was considered a useful screening tool for identifying the Aβ status.[33]

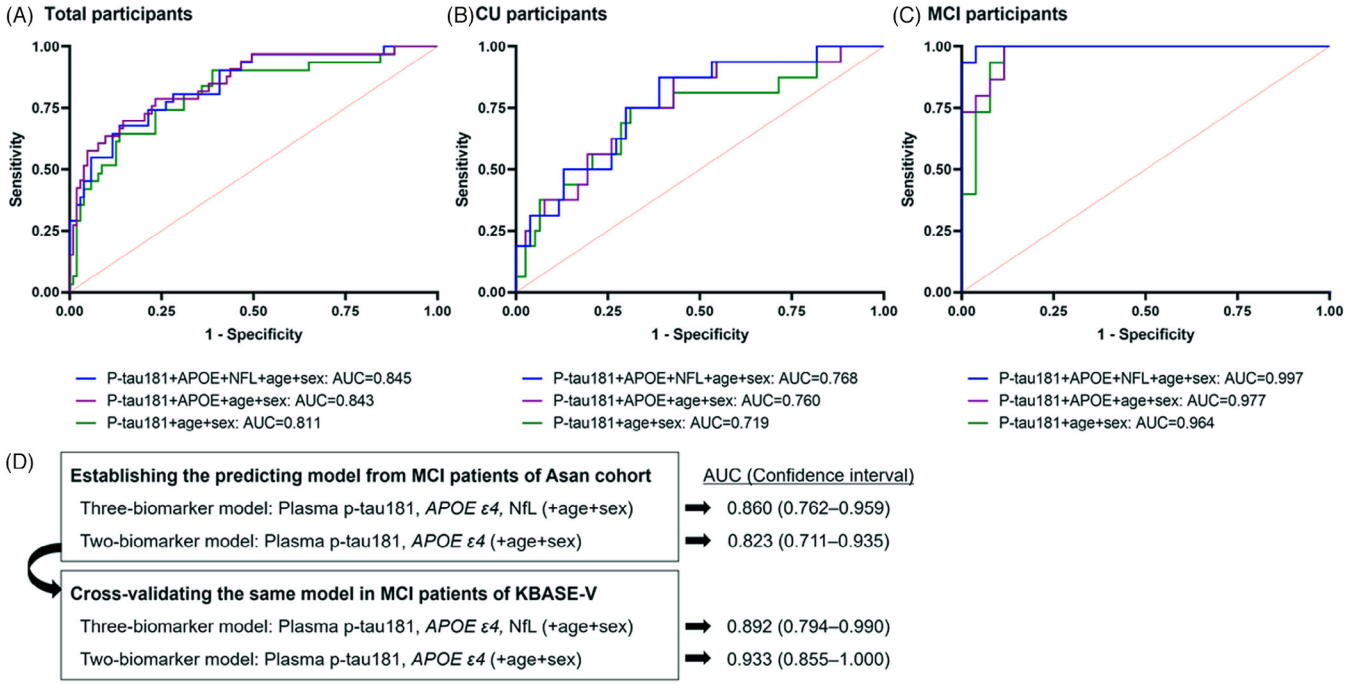

FIGURE 3 ROC curve using blood biomarkers in KBASE-V cohort. ROC curve analysis of biomarkers for predicting Aβ status using PET in the validation cohort (KBASE-V). ROC curves are shown for plasma p-tau181, a combination of plasma p-tau181 and *APOE* status, and a combination of plasma p-tau181, *APOE* status, and serum NfL in total (A), CU (B), and MCI (C) participants. Logistic regression models established in MCI patients of Asan cohort were tested in KBASE-V cohort (D). Continuous plasma p-tau181 and NfL (pg/mL) were used in Asan cohort, and continuous plasma p-tau181 and serum NfL (pg/mL) in validation cohort (KBASE-V). Aβ, amyloid beta; *APOE*, apolipoprotein E; CU, cognitively unimpaired; KBASE-V, Korea Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease; MCI, mild cognitive impairment; NfL, neurofilament light; PET, positron emission tomography; ROC, receiver operating characteristic

Nevertheless, methods to determine plasma Aβ42/40, including electrophoresis immunoassays, immunoprecipitation mass spectrometry (IP-MS), and single molecule array (Simoa), are different in various studies. The results are quite variable depending on the detection method.[11] The performance of plasma Aβ42/40 detected by the IP-MS method might be superior to that of the Simoa method in discriminating Aβ status.[11] As changes in plasma Aβ42/40 of individuals with amyloid pathology are only about 10%, variability of results by detection methods may significantly affect the performance of plasma Aβ42/40.[34]

NfL levels were lower in Aβ− participants. As plasma NfL levels are associated with aging and diabetes mellitus (DM),[35] older age and higher prevalence of DM in our Aβ− participants may have led to these results. In the current study, NfL levels were higher in patients with DM, but p-tau181, Aβ42, and Aβ40 were not (Table S6). After adjusting age and sex, NfL evidenced a moderate value in discriminating Aβ status (AUC = 0.687). Some previous reports have shown the possibility of using plasma NfL to discriminate Aβ status.[36] The NfL levels may potentially improve the performance of other plasma biomarkers that are specific to AD; however, it is important to note that NfL is not an AD-specific biomarker.

This study had some limitations. First, it included the enrolment of participants of a single ethnicity. In previous studies, including a study that analyzed the effect of p-tau181 in a multi-ethnic population, information on Asians was lacking.[37] Recently, the efficacy of blood-based biomarkers in predicting amyloid positivity, hippocampal atrophy and future cognitive stage transition in the Asian population has been reported.[29,38,39] However, it is still unclear how p-tau181 differs between ethnicities and validating the discriminative value of p-tau181 in a single ethnicity is also important. Second, a limited number of amyloid PET participants (41 in the MCI group and 23 in the dementia group) were analyzed in the current study. It is necessary to replicate the results of the current study with a larger population. In the Asan cohort, only eight participants with CIm were enrolled, among which three obtained a positive result in the amyloid PET. Nonetheless, among CU participants, plasma p-tau181 levels was significantly higher (4.02 ± 1.20 vs. 1.49 ± 0.57 pg/mL, $P = 0.006$) in Aβ+ individuals ($n = 3$) than Aβ− individuals ($n = 5$). The AUC of both the two-biomarker model (p-tau181 and *APOE* ε4) and the three-biomarker model (p-tau181, *APOE* ε4, and NfL) were 1.000 in eight CU participants. The efficacy of the three blood-based biomarkers (including p-tau181, *APOE* ε4, and NfL) was also evaluated in the CU participants ($n = 93$) of the KBASE-V cohort and showed relatively high discriminative value (AUC = 0.768). In addition, it is important to confirm that plasma p-tau181, which increases from the early stage of AD, maintains a high discriminative value for Aβ pathology until the late stage. Third, NfL was measured in plasma in Asan cohort and serum in KBASE-V cohort. However, previous reports showed strong correlation between plasma and serum NfL level.[40] Fourth, Aβ40 and Aβ42 levels were measured only in the derivation cohort. As the discriminative value of the plasma Aβ42/40

ratio measured using the Simoa assay in predicting Aβ-PET positivity was lower than expected (AUC = 0.469 before adjusting age and sex; AUC = 0.666 after adjusting age and sex), we decided not to analyze Aβ42/40 in the validation cohort. Fifth, the criteria for determining amyloid PET positivity differed between the two cohorts. The BAPL score was used in the derivation cohort, and the Centiloid scale was used in the validation cohort. To find out the early accumulation of Aβ, cutoff point values of 10 were used for Centiloid.[26] However, it is meaningful that blood biomarkers, including p-tau181, showed high discriminative value even though different standards of amyloid PET positivity were considered as the outcomes.

Despite these limitations, the results of the current study provide evidence for the discriminative value of plasma p-tau181 in detecting Aβ pathology. Regardless of disease severity, plasma biomarkers could serve as reliable, cost-saving, and noninvasive methods for the discernment of individuals.

In conclusion, we demonstrated the robust discriminative value of plasma p-tau181 for detecting positive Aβ-PET in two independent Korean cohorts. Adding the APOE genotype and plasma NfL level increased the model fit without a significant increase in AUC. Establishing a common detection method with a universal cutoff value will be important in future studies.

AUTHOR CONTRIBUTIONS

Hyuk Sung Kwon, Eun-Hye Lee, Hyung-Ji Kim, Seong-Ho Koh, Seong Hye Choi, and Jae-Hong Lee designed the study; Hyuk Sung Kwon, Eun-Hye Lee, and Hyung-Ji Kim interpreted the data and drafted the manuscript; Seong-Ho Koh, Seong Hye Choi, and Eun-Hye Lee supervised and revised the manuscript; Hyung-Ji Kim, Hyun-Hee Park, and Jae-Hong Lee collected data and supervised the study; Hyuk Sung Kwon performed the data analysis; Eun-Hye Lee and Hyun-Hee Park interpreted the data and performed the experiments. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

All data supporting this study will be shared by qualified academic researchers after obtaining the consent of researchers.

CONSENT STATEMENT

This study was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki and approved by the Institutional Review Board of Asan Medical Center, Republic of Korea (Approval #2018-0614) and each participating centers (INHAUH 2015-03-021). All the participants or their proxies provided written informed consent.

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SUPPORTING INFORMATION

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

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