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RESEARCH ARTICLE

Associations of the A/T/N profiles in PET, CSF, and plasma biomarkers with Alzheimer's disease neuropathology at autopsy

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Abstract

INTRODUCTION: To examine the extent to which positron emission tomography (PET)-, cerebrospinal fluid (CSF)-, and plasma-related amyloid-β/tau/neurodegeneration (A/T/N) biomarkers are associated with Alzheimer's disease (AD) neuropathology at autopsy.

METHODS: A total of 100 participants who respectively underwent antemortem biomarker measurements and postmortem neuropathology were included in the Alzheimer's Disease Neuroimaging Initiative (ADNI). We examined the associations of PET-, CSF-, and plasma-related A/T/N biomarkers in combinations or alone with AD neuropathological changes (ADNC).

RESULTS: PET- and CSF-related A/T/N biomarkers in combination showed high concordance with the ADNC stage and alone showed high accuracy in discriminating autopsy-confirmed AD. However, the plasma-related A/T/N biomarkers alone showed better discriminative performance only when combined with *apolipoprotein E* (*APOE*) ε4 genotype.

DISCUSSION: This study supports that PET- and CSF-related A/T/N profiles can be used to predict accurately the stages of AD neuropathology. For diagnostic settings, PET-, CSF-, and plasma-related A/T/N biomarkers are all useful diagnostic tools to detect the presence of AD neuropathology.

KEYWORDS
A/T/N, Alzheimer's disease, autopsy, biomarker, cerebrospinal fluid, diagnose, neuropathology, PET, plasma

HIGHLIGHTS

- PET- and CSF-related A/T/N biomarkers in combination can accurately predict the specific stages of AD neuropathology.

Zhi-Bo Wang and Lan Tan contributed equally to this study.

- PET- and CSF-related A/T/N biomarkers alone may serve as a precise diagnostic tool for detecting AD neuropathology at autopsy.
- Plasma-related A/T/N biomarkers may need combined risk factors when used as a diagnostic tool.
- Aβ PET and CSF p-tau181/Aβ42 were most consistent with Aβ pathology, while tau PET and CSF p-tau181/Aβ42 were most consistent with tau pathology.

1 | BACKGROUND

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles containing hyperphosphorylated tau (p-tau). In 2018, the National Institute on Aging-Alzheimer's Association (NIA-AA) proposed the A/T/N profile for the definition and staging of AD using in vivo biomarkers like positron emission tomography (PET) and cerebrospinal fluid (CSF), which consisted of three classes of AD biomarkers: Aβ (A), tau (T), and neurodegeneration (N).[1] The primary objective of this profile is to define AD as a biological construct independently of clinical status, thereby improving the understanding of the sequence of AD events in a more precise approach.[1] Since then, this profile has been utilized in many studies for different research purposes in AD, including exploration of the concordance and discordance between the A/T/N profile and clinical diagnosis,[2–4] investigation of the association between the A/T/N profile and cognitive change,[3,5–7] the risk of mortality,[8] and the risk factor,[9,10] detection of the changes of AD-related markers over the A/T/N profiles,[6,11–14] and the use of the A/T/N biomarkers alone or in combination to determine optimal diagnostic markers.[15,16] With the development of high-performing assays for plasma biomarkers, increasing studies have investigated plasma-related A/T/N biomarkers against the pathological outcome based on PET or CSF biomarkers.[17–20] These studies have shown great promise for the potential of the A/T/N profile in predicting AD diagnosis and disease progression. However, few studies investigated the association between the A/T/N profile and the gold-standard neuropathology of AD. Before the A/T/N profile was used in clinical trials and clinical practice, it was crucial to determine the degree to which the A/T/N profile based on PET, CSF, or plasma biomarkers were associated with AD neuropathological changes (ADNC) at autopsy. Previous studies exploring the association between A/T/N biomarkers and AD neuropathology at autopsy typically assessed a single biomarker,[21–23] failed to investigate the correlation between the combination of A/T/N biomarkers and neuropathological changes, or generally focused on one modality among PET, CSF, and plasma without including all three modalities of biomarkers.[24–27]

Therefore, the primary aim of this study was to evaluate the concordance between the A/T/N profile in PET, CSF, and plasma and AD neuropathology at autopsy. To achieve this objective, we used PET-, CSF-, and plasma-related A/T/N biomarkers, alone and in combination, to assess their associations with ADNC in a large autopsy cohort. Furthermore, we assessed the diagnostic accuracy of these biomarkers in predicting the presence of AD neuropathology at autopsy. Finally, we explored the associations between these biomarkers and the odds of the risk of intermediate-high ADNC and their corresponding core AD neuropathology, such as Thal phase and Braak stage.

2 | METHODS

2.1 | Study population

All participants were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) at the central laboratory of the ADNI Neuropathology Core at the Knight Alzheimer's Disease Research Center at the Washington University School of Medicine in St Louis. The ADNI project, a public-private partnership, was initiated in 2003 to investigate the feasibility of combining clinical, imaging, genetic, and biochemical biomarkers for the early diagnosis and tracking of AD. These participants underwent each follow-up clinical assessment during life and donated their brains for neuropathological examination after death. Participants included in this study ranged from cognitively unimpaired (CN) to those with mild cognitive impairment (MCI) and dementia. Detailed information on clinical conditions and ADNI inclusion/exclusion criteria can be found at https://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf. This study selected participants who had both *ante mortem* biomarkers (one or more PET-, CSF-, and plasma-related A/T/N biomarkers) and neuropathological examination available and were restricted to the last follow-up of biomarkers if multiple assessments had been performed. The data sources of biomarkers and neuropathology in this study are presented in Table S1. All participants provided written informed consent according to the Declaration of Helsinki before study enrollment. The institutional review boards of all participating institutions in ADNI approved the data used for this study.

2.2 | PET and MRI biomarkers

The Aβ PET scans (AV45) in this study utilized the summary standardized uptake value ratio (SUVR). The SUVR was computed by measuring the frontal, anterior/posterior, cingulate, lateral parietal, and lateral temporal regions, which were then normalized

by the whole cerebellum reference region defined by FreeSurfer. The Tau PET (AV1451) was analyzed using a "MetaTemporal ROI" composed of Freesurfer-defined bilateral entorhinal, amygdala, fusiform, and inferior and middle temporal cortices. For the analysis of fluorodeoxyglucose (FDG) PET, the intensity-normalized mean value of the meta ROI (resulted from five regions: left angular gyrus, right angular gyrus, bilateral posterior cingular, left inferior temporal gyrus, and right inferior temporal gyrus) was divided by the mean of the top 50% of the pons/vermis reference region. A native-space MRI scan was used for each patient to construct a high-resolution cortical summary region for PET images. For further details, please refer to "UCBERKELEY_AV45_Methods_11.15.2021.pdf", "UCBERKELEY_AV1451_Methods_11.15.2021.pdf", and "ADNI_UC_Berkeley_FDG_Methods_20220323.pdf" on the ADNI website. In addition, MRI imaging was assessed on the FreeSurfer pipelines (Version 5.1)-derived 3 T structural MRI (MPRAGE). The procedures of the ADNI FreeSurfer-based criteria were available online (http://adni.loni.usc.edu/). In this study, we selected the volume of the hippocampus as the region of interest (ROI).

2.3 | CSF biomarkers

The CSF was collected antemortem via lumbar puncture. The ADNI Biomarker Core Team evaluated CSF levels of Aβ42, p-tau181, and t-tau using a fully-automated Roche Elecsys electrochemiluminescence immunoassay on a Cobas e601 instrument. Additionally, we incorporated Aβ42 values exceeding the maximum tested concentration based on calibration curve extrapolation. In this study, we also utilized the ratio of CSF p-tau181 and CSF Aβ42, as its values were deemed more precise than those expressed alone in prior research.[28] In sensitivity analyses, CSF biomarkers were measured by the research use only (RUO) INNOBIA AlzBio3 immunoassay (Fujirebio, Belgium).

2.4 | Plasma biomarkers

Blood samples were collected and processed following the ADNI protocol.[29] The single-molecule array (Simoa) method was used to assess the plasma concentrations of p-tau181 (University of Gothenburg), t-tau (Human total tau assay), and neurofilament light (NfL) (University of Gothenburg), as described previously.[30–32] The plasma Aβ42/40 ratio was calculated by dividing plasma Aβ42 by plasma Aβ40, which was assessed using Innogenetics research-use-only AlzBia reagents on a Luminex immunoassay platform (Luminex, Austin, TX).[33] Plasma Aβ42/40 was also measured in sensitivity analyses using liquid chromatography-tandem mass spectrometry (LC-MS/MS), blood extracellular vesicles (EV), and enzyme-linked immunosorbent assay (ELISA). In sensitivity analyses, plasma p-tau181 was measured using four assays, including Simoa pTau 181V2 Advantage, Roche Elecsys plasma Phospho-Tau(181P), Lumipulse G pTau 181 Plasma, and pTau181 Simoa running on the HD-1, Cobas e601, LUMIPULSE G1200 (FDA/CE), and Simoa HD-X platforms, respectively. For detailed information, visit www.adni-info.org.

RESEARCH IN CONTEXT

1. **Systematic Review**: Relevant literature was reviewed using PubMed and Google Scholar databases. Although previous studies have suggested using the amyloid-β/tau/neurodegeneration (A/T/N) profile based on in vivo biomarkers to define and stage Alzheimer's disease (AD), the association between A/T/N profiles in positron emission tomography (PET), cerebrospinal fluid (CSF), and plasma biomarkers and AD neuropathological changes (ADNC) at autopsy remains unclear.
2. **Interpretation**: We observed that A/T/N profiles in PET and CSF biomarkers were highly consistent with the neuropathological stages of AD at autopsy. Additionally, all A/T/N biomarkers related to PET, CSF, and plasma performed better in distinguishing between individuals with autopsy-confirmed AD and those without.
3. **Future Directions**: The findings suggest that PET and CSF-related A/T/N biomarkers have significant advantages in detecting AD neuropathology, both in diagnosing and predicting disease progression. Future research should focus on evaluating the association between the combination of plasma A/T/N biomarkers and AD neuropathology using different high-performing assays in larger autopsy cohorts.

2.5 | Neuropathological examination

The neuropathological examinations were conducted using established diagnostic criteria and were previously described in detail.[34] Following NIA-AA guidelines, three histopathological scoring systems were used to describe AD neuropathologic lesions. The Thal phase scoring system was used to indicate the distribution of Aβ plaques (scores 0–5), the Braak stage scoring system was used to indicate the distribution and density of neurofibrillary tangle tau pathology (scores 0–6), and the Consortium to Establish a Registry for AD (CERAD) scoring system was used to indicate the density of Aβ plaques (scores 0–3). The composite measure of ADNC was computed from these three aspects of AD neuropathologic lesions. It was then converted into a four-point scale, ranging from "none" (0) to "low" (1), "intermediate" (2), and "high" (3). An ADNC score of $\geq$2 indicates a diagnosis of autopsy-confirmed AD. Non-AD neuropathologies were also examined, including frontotemporal lobar degeneration (FTLD)-tau, Lewy body (LB), TAR DNA-binding protein (TDP)—43, Hippocampal sclerosis, and cerebrovascular conditions (cerebral amyloid angiopathy [CAA], arteriolosclerosis, atherosclerosis, old macroscopic infarcts, and old microinfarcts). The evaluation of these common non-AD neuropathologies resulted in dichotomized categories, with the presence or absence of these pathologies scored as 1 or 0, respectively. The specific measurements for LB, TDP-43, and CAA were previously reported.[35] The

presence of FTLD-tau pathology was assessed by having any subtypes. For a more detailed explanation of the implementation and operational definitions of the different neuropathology scoring scales, please refer to the Neuropathology Data Sheet Coding Guidelines of the National Alzheimer's Disease Coordinating Center.[36]

2.6 | Statistical analysis

The differences between none/low ADNC and intermediate/high ADNC were analyzed using one-way analysis of variance (ANOVA) for continuous variables, χ^2 tests for binary variables, and the Kruskal–Wallis test for ordinal variables. A log10 transformation was applied to variables that did not follow a normal distribution in statistical analysis. Outliers over four standard deviations were not included in the statistical analysis. Partial Spearman's correlation was used to determine the relationship between each biomarker (dependent variable) and both neuropathological lesions (independent variables), adjusting for age at death, sex, and years from last assessment to death. One-way analysis of covariance (ANCOVA) was used to determine if the levels of biomarkers differed between autopsy-confirmed AD and non-AD, controlling the similar covariates. To assess the diagnostic accuracy of each biomarker, we used receiver operating characteristic (ROC) curve analysis to predict the presence or absence of autopsy-confirmed AD. The concordance of the A/T/N profile based on biomarkers with ADNC stage has been visualized using Sankey diagrams (R package: "networkD3"), barplots, and scatter plots. The impact of each biomarker on the probability of intermediate/high ADNC was examined using the univariate binary logistic regression model. All statistical analyses were performed using R version 4.1.0 software. The significance level was set at a two-sided *P*-value of less than 0.05.

3 | RESULTS

3.1 | Sample characteristics

A total of 100 participants were included in this investigation and Table 1 summarizes their baseline characteristics, where these participants respectively underwent PET (Aβ PET: $N = 56$, 56%; tau PET: $N = 8$, 8%; FDG PET: $N = 80$, 80%), CSF (p-tau181/Aβ42: $N = 72$, 72%; Aβ42: $N = 73$, 73%; p-tau181: $N = 72$, 72%; t-tau: $N = 72$, 72%), and plasma (Aβ42/40: $N = 62$, 62%; p-tau: $N = 66$, 66%; t-tau: $N = 46$, 46%; NfL: $N = 93$, 93%). The participants were divided into autopsy-confirmed AD (intermediate/high ADNC: $N = 76$, 76%) or not (none/low ADNC: $N = 24$, 24%). Females, *apolipoprotein E (APOE)* ε4 carriers, and intermediate—high AD neuropathological scores (Thal phase, Braak stage, and CERAD) were more prevalent in participants with autopsy-confirmed AD than autopsy-confirmed non-AD (all $P < 0.01$). Excluding hippocampal sclerosis and FTLD-tau, all co-pathologies were more prevalent in individuals with autopsy-confirmed AD than autopsy-confirmed non-AD (all $P < 0.05$). No significant differences were observed for age at baseline, age at death, and educational years. The years from last assessment to death in each group were presented in Table S2. Moreover, mixed pathologies were common (Figure S1). In addition to the high prevalence of cerebrovascular conditions, and hippocampal sclerosis in this study, common non-AD pathologies seem to influence the levels of tau and neurodegeneration biomarkers but have a lesser impact on levels of Aβ-related biomarkers (Figures S2–S4).

3.2 | Associations of PET-related A/T/N biomarkers with ADNC

We first investigated the correlation between each PET biomarker and ADNC. We found that higher stages of ADNC were correlated with increased levels of Aβ PET and tau PET and decreased levels of FDG PET (Figure 1A). Participants with autopsy-confirmed AD showed higher levels of Aβ PET and lower levels of FDG PET, but not tau PET, than those with autopsy-confirmed non-AD (Figure 1B). Additionally, we evaluated the diagnostic accuracy of PET biomarkers in discriminating autopsy-confirmed AD from autopsy-confirmed non-AD(Figure 1C) and Table S3). The biomarker-only model (Model 1) demonstrated high area under the curve (AUC) for all biomarkers. When we added *APOE* ε4 status as a predictor (Model 2), the AUC value of tau PET and FDG PET slightly improved compared to Model 1, while the AUC value of Aβ PET was unchanged. When we further added age at death, sex, and years from last assessment to death as predictors (Model 3), the AUC value of all PET biomarkers did not improve compared to Model 2.

We next examined the concordance between the A/T/N profile and ADNC stage. Due to the limited number of tau PET scans in this study, we used the AN profile based on Aβ PET and FDG PET. We categorized each PET biomarker into dichotomous categories using cutoff values derived from Model 1 (Table S3). In the Sankey diagram, the A+N- and A+N+ categories, representing the AD continuum, corresponded more with the 2 and 3 stages of ADNC, while the A-N- and A-N+ categories, representing the non-AD continuum (healthy control and suspected non-AD pathology [SNAP]), generally corresponded with the 0 and 1 stages of ADNC (Figure 1D). A similar pattern was also observed in Figure 1E, with autopsy-confirmed AD participants consisting almost entirely of the AD continuum, while autopsy-confirmed non-AD participants primarily comprised the non-AD continuum. Scatter plots showed that all but two of the individuals with A+N- and A+N+ had autopsy-confirmed AD (Figure 1F).

As a sensitivity analysis, we replaced FDG PET with hippocampal volume as an N biomarker. While the performance of hippocampal volume alone in association with ADNC was inferior to FDG PET, the results of AN classification based on hippocampal volume were consistent with those based on FDG PET (Figure S5). Furthermore, we replicated our findings by utilizing the established cutoff value of PET biomarkers from the prior study[30] and achieved consistent outcomes (Figure S6).

TABLE 1 Sample characteristics.

	Total	None/low ADNC	Int./high ADNC	*p*-Value
N	100	24	76	–
Age at baseline, mean (SD)	76.6 (6.9)	77.9 (5.8)	76.2 (7.1)	0.26
Age at death, mean (SD)	82.6 (7.1)	84.2 (7.1)	82.1 (7.1)	0.23
Sex, *n* (%) female	24 (24.0)	5 (20.8)	19 (25.0)	0.004
Education at baseline, mean (SD)	16.3 (2.8)	16.7 (3.0)	16.2 (2.7)	0.48
APOE ε4 carriers, *n* (%)	60 (60.0)	3 (12.5)	57 (75.0)	<0.001
ADNC, *n* (%)				
None	5 (5.0)	5 (20.8)	0 (0.0)	<0.001
Low	19 (19.0)	19 (79.2)	0 (0.0)	
Intermediate	8 (8.0)	0 (0.0)	8 (10.5)	
High	68 (68.0)	0 (0.0)	68 (89.5)	
Thal phase, *n* (%)				
0	5 (5.0)	5 (20.8)	0 (0.0)	<0.001
1–2	7 (7.0)	7 (29.2)	0 (0.0)	
3	11 (11.0)	7 (29.2)	4 (5.3)	
4–5	77 (77.0)	5 (20.8)	72 (94.7)	
Braak stage, *n* (%)				
0	1 (1.0)	1 (4.2)	0 (0.0)	<0.001
I–II	21 (21.0)	21 (87.5)	0 (0.0)	
III–IV	8 (8.0)	1 (4.2)	7 (9.2)	
V–VI	70 (70.0)	1 (4.2)	69 (90.8)	
CERAD, *n* (%)				
None	21 (21.0)	18 (75.0)	3 (3.9)	<0.001
Low	10 (10.0)	6 (25.0)	4 (5.3)	
Intermediate	10 (10.0)	0 (0.0)	10 (13.2)	
High	59 (59.0)	0 (0.0)	59 (77.6)	
Hippocampal sclerosis, *n* (%)	9 (9.0)	4 (16.7)	5 (6.6)	0.74
FTLD-tau, *n* (%)	50 (50.0)	19 (79.2)	31 (40.8)	0.09
Lewy Body, *n* (%)	52 (52.0)	13 (54.2)	39 (51.3)	<0.001
TDP-43, *n* (%)	45 (50.6)	11 (52.4)	34 (50.0)	<0.001
CAA, *n* (%)	83 (83.0)	12 (50.0)	71 (93.4)	<0.001
Arteriolosclerosis, *n* (%)	95 (95.0)	23 (95.8)	72 (94.7)	<0.001
Atherosclerosis, *n* (%)	66 (82.5)	16 (84.2)	50 (82.0)	<0.001
Old macroscopic infarcts, *n* (%)	8 (8.1)	0 (0.0)	8 (10.7)	0.005
Old microinfarcts, *n* (%)	21 (21.0)	5 (20.8)	16 (21.1)	0.02

Notes: Baseline characteristics and *p*-values were compared between individuals with none/low ADNC and those with intermediate/high ADNC using one-way analysis of variance (ANOVA) for continuous variables and χ^2 test (for binary variables) and Kruskal–Wallis test (for ordinal variables) for categorical variables.

Abbreviations: ADNC, Alzheimer's disease neuropathological change; APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy; CERAD, Consortium to Establish a Registry for Alzheimer's disease; FTLD, frontotemporal lobar degeneration; TDP-43, TAR DNA-binding protein-43.

3.3 | Associations of CSF-related A/T/N biomarkers with ADNC

Next, we evaluated the correlation between CSF biomarkers and ADNC. The results showed that all CSF biomarkers were significantly correlated with ADNC. Specifically, CSF p-tau181/Aβ42, CSF p-tau181, and CSF t-tau exhibited a positive association, while CSF Aβ42 showed a negative association (Figure 2A). Consistent with the association results, CSF p-tau181/Aβ42, CSF p-tau181, and CSF t-tau were all higher, and CSF Aβ42 was lower in autopsy-confirmed

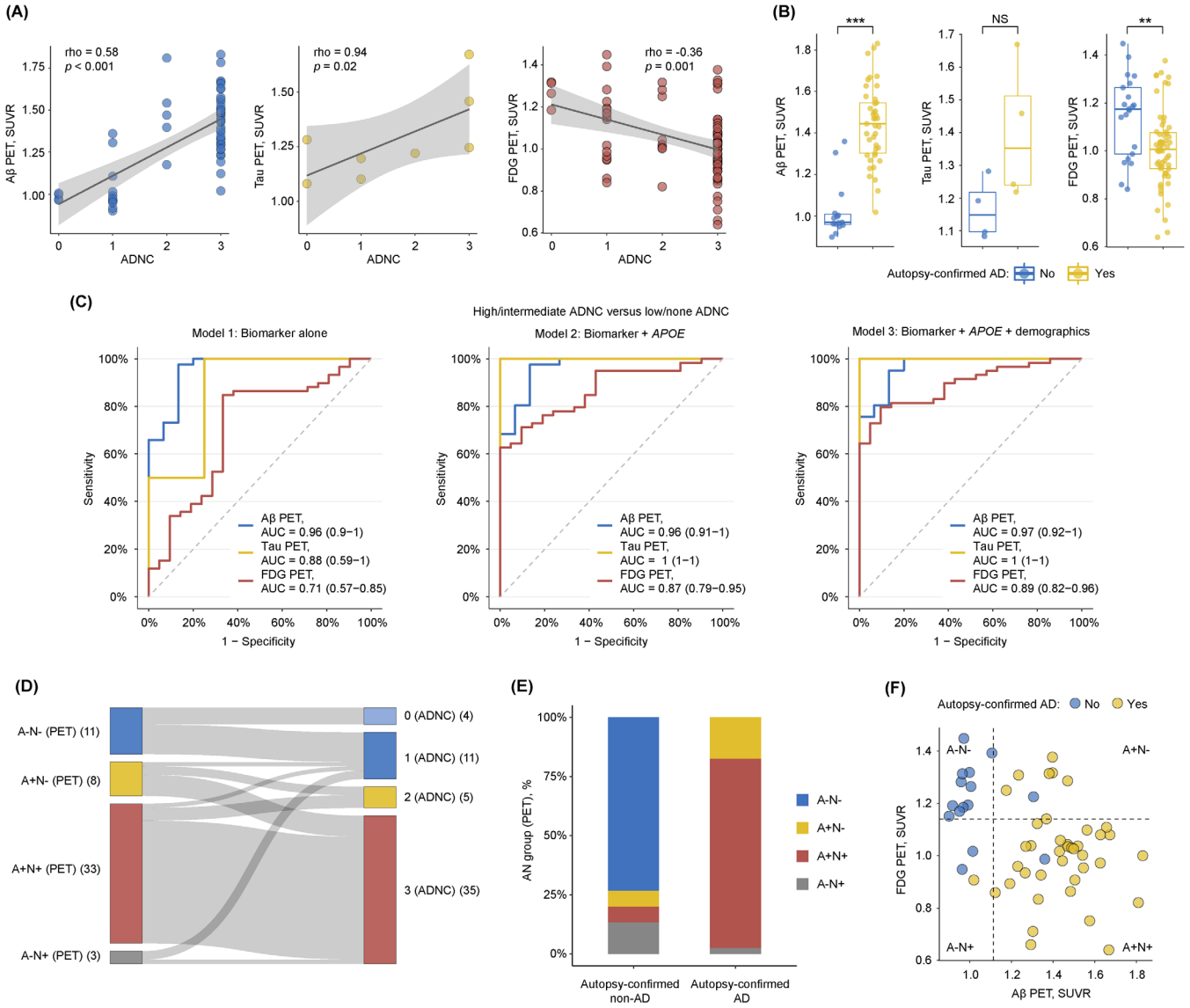

FIGURE 1 Associations between PET-related amyloid-β/tau/neurodegeneration (A/T/N) biomarkers and ADNC. (A) Scatter plots showed the correlation of ADNC with Aβ PET, tau PET, and FDG PET. The standardized Spearman's coefficients (rho) and *p*-values were derived from partial Spearman's correlation, adjusting for age at death, sex, and years from the last assessment to death. Raw data are represented by dots, while the shadowed area represents the 95% CI. (B) The box plot displayed group differences of Aβ PET, tau PET, and FDG PET between participants with autopsy-confirmed AD and those without. Median (horizontal bar), IQR (hinges), and 1.5 × IQR (whiskers) were depicted in the box plots. The *p*-values were derived from ANCOVA, controlling for age at death, sex, and years from the last assessment to death. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. (C) The predictive accuracy of PET biomarkers for autopsy-confirmed AD versus autopsy confirmed non-AD was assessed using ROC curves. Three models were used, including model 1, based on biomarkers alone, model 2, using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status (0 = non-carriers, 1 = ε4 carriers), and model 3, using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status and demographics (age at death, sex, and years from the last assessment to death). (D) The Sankey diagram was used to demonstrate the correspondence between the PET-based AN classification (A: Aβ PET; N: FDG PET) and ADNC stage. (E) The proportion of PET-based AN classification is shown in individuals with autopsy-confirmed AD and those without was demonstrated. (F) The dotted vertical lines correspond to the Aβ PET cutoffs of >1.114 SUVR, and the dotted horizontal lines correspond to the FDG PET cutoffs of <1.14 SUVR. Aβ, amyloid-β; AD, Alzheimer's disease; ADNC, AD neuropathological changes; *APOE*, apolipoprotein E; ANCOVA, one-way analysis of covariance; AUC, area under the curve; CI, confidence interval; FDG, fluorodeoxyglucose; IQR, interquartile range; PET, positron emission tomography; ROC, receiver operating characteristic.

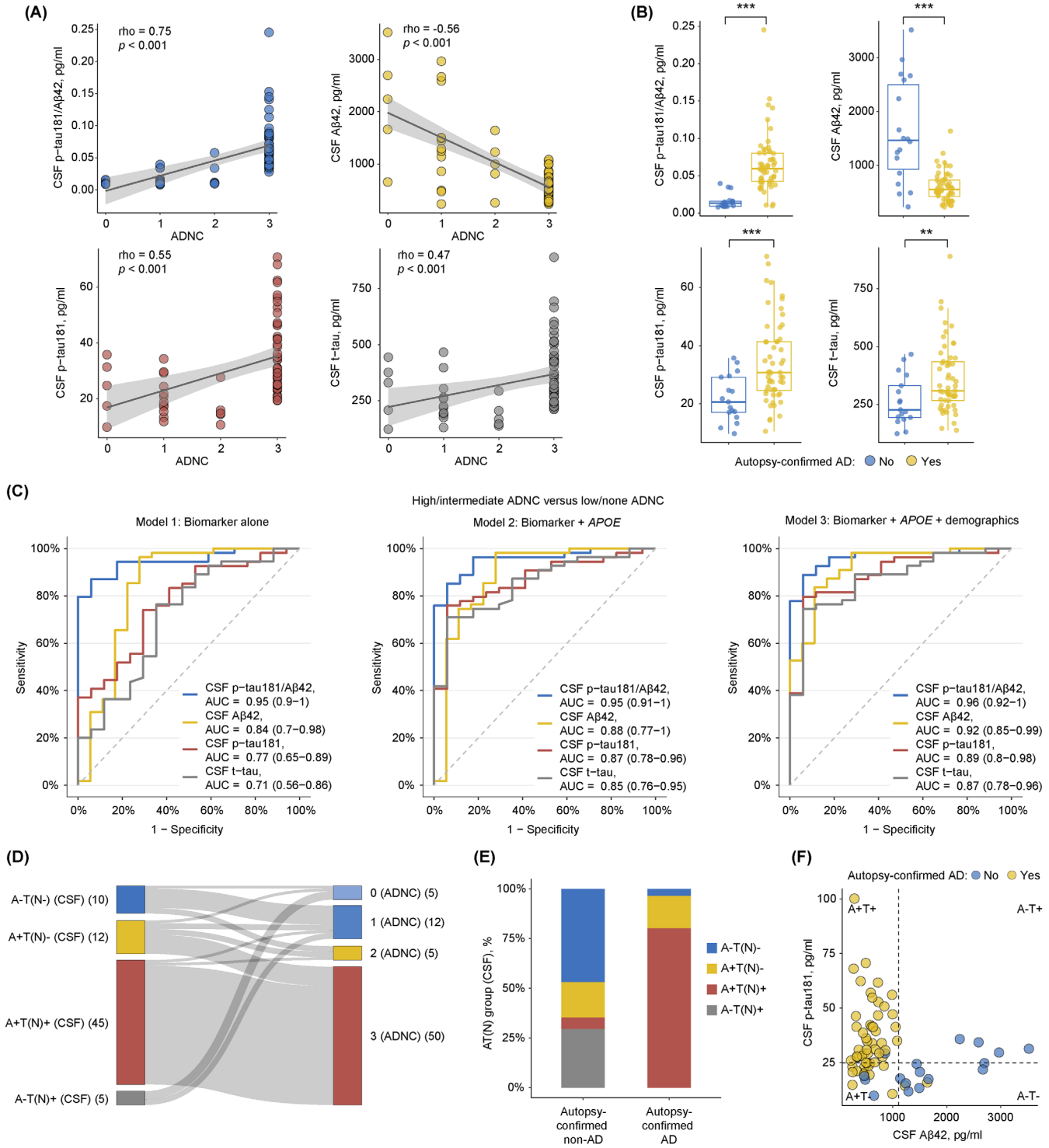

FIGURE 2 Associations between CSF-related A/T/N biomarkers and ADNC. (A) Scatter plots showed the correlation of ADNC with CSF biomarkers of p-tau181/Aβ42, Aβ42, p-tau181, and t-tau. The standardized Spearman's coefficients (rho) and *p*-values were derived from partial Spearman's correlation, adjusting for age at death, sex, and years from the last assessment to death. Raw data are represented by dots, while the shadowed area represents the 95% CI. (B) The box plot displayed group differences in CSF biomarkers of p-tau181/Aβ42, Aβ42, p-tau181, and t-tau between participants with autopsy-confirmed AD and those without. Median (horizontal bar), IQR (hinges), and 1.5 × IQR (whiskers) were depicted in the box plots. The *p*-values were derived from ANCOVA, controlling for age at death, sex, and years from the last assessment to death. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. (C) The predictive accuracy of CSF biomarkers for autopsy-confirmed AD versus autopsy confirmed non-AD was assessed using ROC curves. Three models were used, including Model 1, based on biomarkers alone, Model 2, using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status (0 = non-carriers, 1 = ε4 carriers), and Model 3, using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status and demographics (age at death, sex, and years from the last assessment to death). (D) Sankey diagrams were used to demonstrate the correspondence between the CSF-based AT(N) classification (A: CSF

AD compared to autopsy-confirmed non-AD (Figure 2B). In addition, all CSF biomarkers in Model 1 showed high AUCs for distinguishing autopsy-confirmed AD from non-AD cases. In Model 2, AUC values improved for all CSF biomarkers except CSF p-tau181/Aβ42 and CSF Aβ42, whereas in Model 3, AUC values did not improve further for all CSF biomarkers (Figure 2C and Table S4).

We used the same method as for PET biomarkers to dichotomize each CSF biomarker (Table S4), which was done to examine the concordance between the A/T/N profile (A: CSF Aβ42; T: CSF p-tau181; N: CSF t-tau) and the ADNC stage. We merged T and N groups due to the limitation of the number of participants, resulting in four categories: A-T(N)-, A+T(N)-, A+T(N)+, and A-T(N)+. T(N)- was defined as having both T- and N-, whereas T(N)+ was defined as T+ or N+. The Sankey diagram shows that the non-AD continuum, that is, A-T(N)- and A-T(N)+, is primarily corresponded with stages 0 and 1 of ADNC, whereas the AD continuum, that is, A+T(N)- and A+T(N)+, is corresponded with stages 2 and 3 of ADNC (Figure 2D). The barplot also showed a higher proportion of AD continuum in autopsy-confirmed AD participants, whereas autopsy-confirmed non-AD participants mainly comprised the non-AD continuum (Figure 2E). Scatterplots indicated that almost all individuals with an A+T+ category had autopsy-confirmed AD (Figure 2F). A similar pattern was observed using N instead of T (Figure S7).

We performed a sensitivity analysis using the cutoff values reported in the previous study to define biomarker status.[37] The results based on the previous cutoff values showed that the A-T(N)+ category corresponded more with intermediate-high ADNC (Figure S8) than the above findings using the main cutoff values. Moreover, we used the INNOBIA AlzBio3 immunoassay from Fujirebio to replicate the results of the Simoa assay. The results were similar to the results of the Simoa assay, except that the AUC value of CSF p-tau181 in the AlzBio3 immunoassay improved compared to the Simoa assay (Figure S9).

3.4 | Associations of plasma-related A/T/N biomarkers with ADNC

When evaluating the correlation between plasma biomarkers and ADNC, we observed that only plasma p-tau and t-tau were positively associated with ADNC (Figure 3A). Significant differences between autopsy-confirmed AD and non-AD cases were also found only with plasma p-tau and t-tau (see Figure 3B). As for the diagnostic accuracy of plasma biomarkers, Model 1 performed poorly or adequately in distinguishing between participants with and without autopsy-confirmed AD (Figure 3C and Table S5). Interestingly, the AUC value of every plasma biomarker improved substantially in Model 2. However, the AUC values of all plasma biomarkers were not substantially higher in Model 3 than in Model 2 (Figure 3C).

To investigate the correlation between the A/T/N profile (A: plasma Aβ42/40; T: plasma p-tau181; N: plasma t-tau) and ADNC stage, each plasma biomarker was dichotomized using the same approach as for PET biomarkers (Table S5) and followed the same A/T/N categorization approach as for CSF biomarkers. The Sankey diagram indicates that, for the AD continuum, the majority of the A+T(N)+ category correspond to stages 2 and 3 of ADNC, while a small proportion of A+T(N)+ and all A+T(N)- categories correspond to stage 1 of ADNC. Regarding the non-AD continuum, the A-T(N)- category was consistent with ADNC stages 0 and 1, but all A-T(N)+ category corresponded to ADNC stages 2 and 3 (Figure 3D). These inconsistencies between the A/T/N profile and ADNC stage were also observed in the barplot (Figure 3E). Furthermore, similar discrepancies were observed when assessing the distribution of plasma Aβ42/40 and plasma p-tau181 with autopsy-confirmed AD (Figure 3F), and when evaluating the distribution of plasma Aβ42/40 and plasma t-tau or plasma NfL with autopsy-confirmed AD (Figure S10).

In sensitivity analyses, we utilized various assays of plasma Aβ42/40 and plasma p-tau181 to replicate the above results. We discovered a correlation between lower plasma Aβ42/40 and higher ADNC, particularly for the LS-MS/MS assay; however, it was not statistically significant (Figure S11). Notably, when distinguishing participants who were autopsy-confirmed AD from those who were not, the LS-MS/MS assay exhibited excellent discrimination (AUC = 0.78; 95% confidence interval [CI], 0.51–1), followed by the ELISA assay (AUC = 0.69; 95% CI, 0.4–0.97) and the EV assay (AUC = 0.55; 95% CI, 0.33–0.78) (Figure S11). Regarding plasma p-tau181, only the Simoa HD-X assay demonstrated a significant correlation with ADNC stage ($P = 0.04$), while a positive correlation trend was observed for other assays, although it was not significant (Figure S12). We observed a similar pattern with the diagnostic accuracy, with the Simoa HD-X assay exhibiting the highest AUC among four assays (AUC = 1; 95% CI, 1–1), although the other three assays also showed better discrimination (Lumipulse, AUC = 1; 95% CI, 1–1; Cobas e601, AUC = 0.83; 95% CI, 0.46–1; HD-1, AUC = 0.75; 95% CI, 0.23–1) (Figure S12).

3.5 | Associations of A/T/N biomarkers with odds of intermediate-high ADNC

In this analysis, we investigated the effect of A/T/N biomarkers on the probability of intermediate-high ADNC (Table S6). Our observations of PET-related A/T/N biomarkers showed that except for tau PET, elevated Aβ PET and FDG PET levels were significantly correlated to

Aβ42; T: CSF p-tau181; N: CSF t-tau) and ADNC stage. (E) The proportion of CSF-based AT(N) classification is shown in individuals with autopsy-confirmed AD and those without was demonstrated. (F) The dotted vertical lines correspond to the CSF Aβ42 cutoffs of <1110.5 pg/mL, and the dotted horizontal lines correspond to the CSF p-tau181 cutoffs of >24.755 pg/mL. Aβ, amyloid-β; AD, Alzheimer's disease; ADNC, AD neuropathological changes; *APOE*, apolipoprotein E; ANCOVA, one-way analysis of covariance; AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; IQR, interquartile range; p-tau, phosphorylated tau; ROC, receiver operating characteristic; t-tau, total tau.

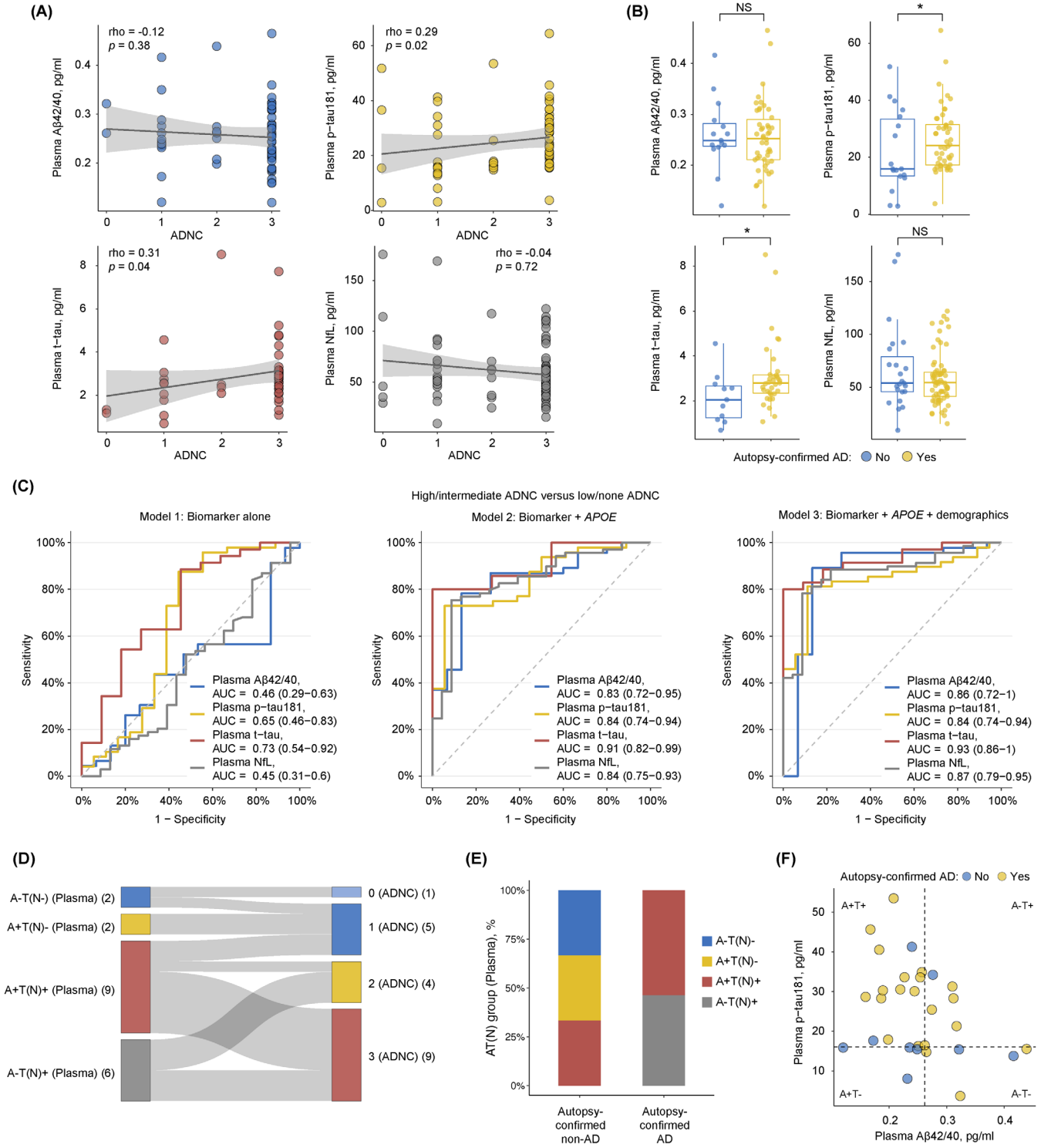

FIGURE 3 Associations between plasma-related A/T/N biomarkers and ADNC. (A) Scatter plots showed the correlation of ADNC with plasma biomarkers of Aβ42/40, p-tau181, t-tau, and NfL. The standardized Spearman's coefficients (rho) and *p*-values were derived from partial Spearman's correlation, adjusting for age at death, sex, and years from the last assessment to death. Raw data are represented by dots, while the shadowed area represents the 95% CI. (B) The box plot displayed group differences in plasma biomarkers of Aβ42/40, p-tau181, t-tau, and NfL between participants with autopsy-confirmed AD and those without. Median (horizontal bar), IQR (hinges), and 1.5 × IQR (whiskers) were depicted in the box plots. The *p*-values were derived from ANCOVA, controlling for age at death, sex, and years from the last assessment to death. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. (C) The predictive accuracy of plasma biomarkers for autopsy-confirmed AD versus autopsy confirmed non-AD was assessed using ROC curves. Three models were used, including Model 1, based on biomarkers alone, Model 2, using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status (0 = non-carriers, 1 = ε4 carriers), and Model 3, using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status and demographics (age at death, sex, and years from the last assessment to death). (D) Sankey diagrams were used to demonstrate the correspondence between the plasma-based AT(N)

increased and decreased odds of intermediate-high ADNC (Figure 4A). For CSF-related A/T/N biomarkers, increased CSF Aβ42 were significantly associated with a decreased risk of intermediate-high ADNC, whereas increased levels of CSF p-tau181/Aβ42, CSF p-tau181, and CSF t-tau were associated with an increased risk of intermediate-high ADNC (Figure 4B). However, except for higher plasma t-tau levels, which were related to higher odds of intermediate-high ADNC, no other plasma-related A/T/N biomarkers demonstrated a significant association (Figure 4C).

3.6 | Associations of A/T/N biomarkers with corresponding neuropathology

We found significant associations between Aβ-related biomarkers and Thal phase. Specifically, Aβ PET, CSF p-tau181/Aβ42, and CSF Aβ42 showed strong correlations, whereas plasma Aβ42/40 did not. Additionally, a positive Thal phase status (3–5) strongly corresponded with the positive status of Aβ PET, CSF p-tau181/Aβ42, and CSF Aβ42, but not plasma Aβ42/40 (Figure 5A and Table S7). These results were consistent when using CERAD stages as the outcome of Aβ neuropathology, except that the consistency between positive CERAD stages (2–3) and positive status of Aβ PET and CSF Aβ42 was somewhat lower than that of Thal phase (Figure S13). We also observed significant associations between all tau-related biomarkers and Braak stage. Positive Braak stage status (III–VI) strongly corresponded with the positive status of tau PET and CSF p-tau181/Aβ42, followed by CSF p-tau181 and plasma p-tau181 (Figure 5B and Table S7).

4 | DISCUSSION

In this study, we investigated the association between PET-, CSF-, and plasma-related A/T/N biomarkers and AD neuropathology at autopsy. All PET and CSF biomarkers significantly correlated with ADNC stages, while only p-tau181 and t-tau showed such a correlation in plasma biomarkers. Moreover, PET and CSF biomarkers, except for tau PET, were strongly associated with higher odds of intermediate-high ADNC, but plasma biomarkers did not. Furthermore, PET and CSF biomarkers showed a discrimination level ranging from acceptable to excellent in detecting autopsy-confirmed AD. The diagnostic accuracy of plasma biomarkers was worse than that of PET and CSF biomarkers. However, we found that plasma biomarkers combined with *APOE* ε4 genotype showed similar diagnostic accuracy as PET and CSF biomarkers. In addition, we report that the greater concordance between the A/T/N profile and ADNC stage was based on PET and CSF measures but not plasma measures. Among AD specific pathology (Aβ plaques and tau tangles), Aβ PET and CSF p-tau181/Aβ42 were most consistent with Aβ pathology, while tau PET and CSF p-tau181/Aβ42 were most consistent with tau pathology. In summary, our results indicated that PET- and CSF-related A/T/N biomarkers are superior biomarkers of AD neuropathology, while plasma-related A/T/N biomarkers only showed better diagnostic utility.

Previous studies found moderate concordance between the A/T/N profiles in PET and CSF biomarkers and clinical diagnosis groups (CN, MCI, and AD).[2,3] Our results demonstrated that PET- and CSF-related A/T/N profiles were moderately consistent with ADNC stage, with the AD continuum corresponding to intermediate-high ADNC and the non-AD continuum corresponding to none-low ADNC, implying that PET- and CSF-related A/T/N profiles could be used for monitoring the pathological progression. Furthermore, our results showed that almost all cases of the A+T(N)+ category based on PET and CSF biomarkers had a diagnosis of autopsy-confirmed AD. This finding is in line with a recent study that found in three independent autopsy cohorts that individuals with CSF A+T+ all had autopsy-confirmed AD, while only 73% of A+T- participants had autopsy-confirmed AD,[25] suggesting that A+T+ compared to A+T- may be a more accurate biological marker for the diagnosis of AD. The ability to identify A+T+ individuals using PET or CSF biomarkers can be used in clinical trials and clinical practice to screen high-risk populations that may progress to a neuropathological diagnosis of AD in the future. Supporting this notion, the recent study used PET biomarkers and found that participants with A+T+ had a significantly higher risk for clinical progression than participants with A+T- or A-T-[5]. However, in our study, one case of PET-related A+N+ and one case of CSF-related A+T(N)+ did not meet the diagnosis of autopsy-confirmed AD, both of which exhibited relatively severe Aβ burden but no modest tau pathology at autopsy. It is possible that all discordant cases had biomarker levels near the cutoff threshold, and there was a lack of a range close to the cutoff value to include this group of participants. Therefore, cutoffs allowing for a "gray zone" may have added value for diagnosing AD.[38] Furthermore, our study suggests that the use of plasma-related A/T/N profiles is not appropriate for monitoring AD neuropathological progression. Because their association with ADNC is inconsistent, possibly due to the use of different assays and the susceptibility of plasma to multiple factors (as discussed below).

When testing the A/T/N biomarkers alone, all PET and CSF biomarkers showed a significant correlation with ADNC stage and a significant difference between autopsy-confirmed AD and non-AD. The associations remained robust for CSF biomarkers even when using the other high-performing assay (INNOBIA AlzBio3 immunoassay). These findings are consistent with previous studies investigating pathology-specific associations of PET and CSF biomarkers.[23,35,39] These results

classification (A: plasma Aβ42/40; T: plasma p-tau181; N: plasma t-tau) and ADNC stage. (E) The proportion of plasma-based AT(N) classification is shown in individuals with autopsy-confirmed AD and those without was demonstrated. (F) The dotted vertical lines correspond to the plasma Aβ42/40 cutoffs of <0.262 pg/mL, and the dotted horizontal lines correspond to the plasma p-tau181 cutoffs of >16.024 pg/mL. Aβ, amyloid-β; AD, Alzheimer's disease; ADNC, AD neuropathological changes; *APOE*, apolipoprotein E; ANCOVA, one-way analysis of covariance; AUC, area under the curve; CI, confidence interval; IQR, interquartile range; NfL, neurofilament light; p-tau, phosphorylated tau; ROC, receiver operating characteristic; t-tau, total tau.

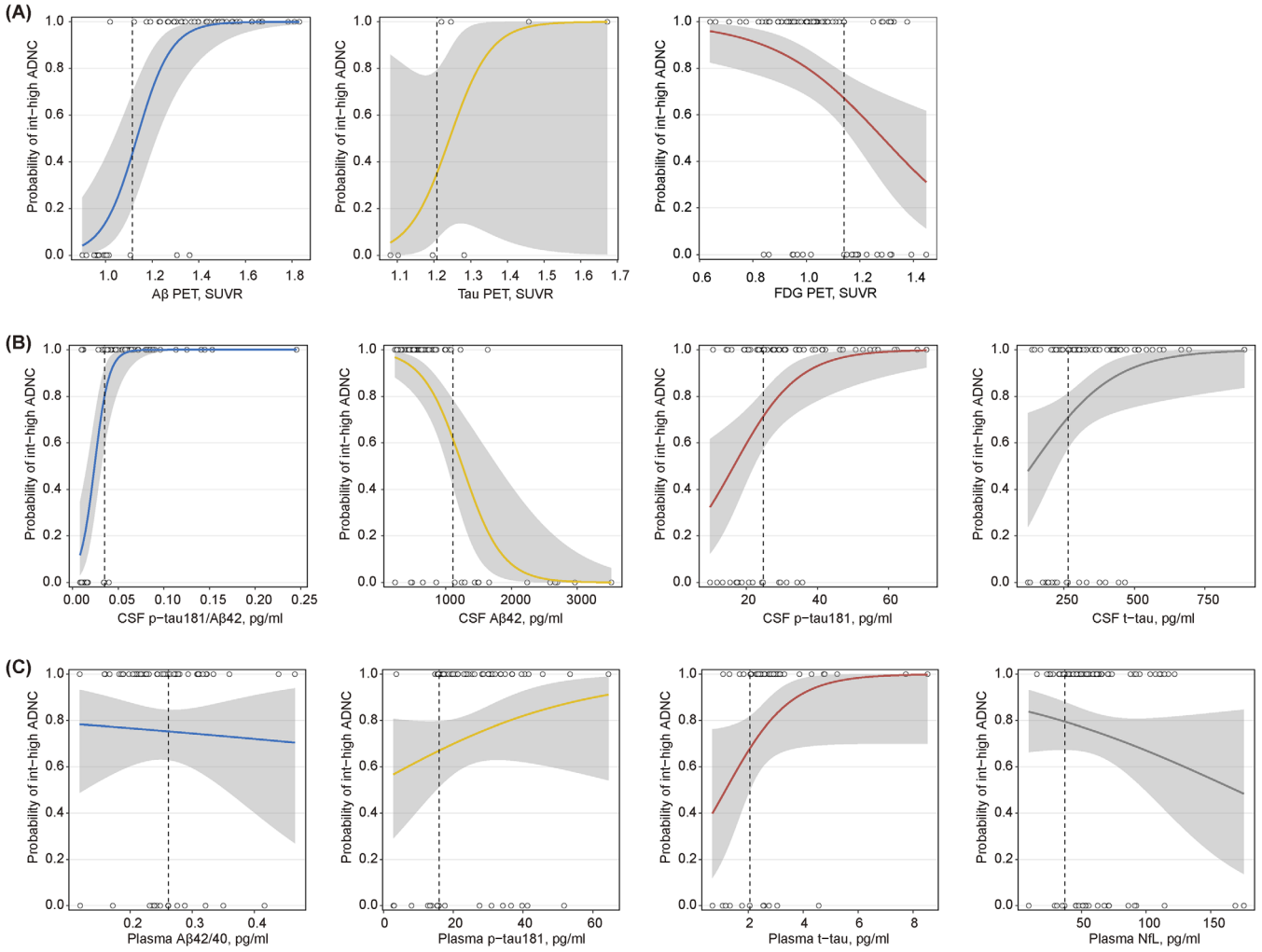

FIGURE 4 Probability curves of ADNC pathology as a function of baseline single biomarker values. Probability curves (with shaded 95% confidence intervals) of intermediate-high ADNC at autopsy as a function of baseline levels of PET- (A), CSF- (B), and plasma-related (C) A/T/N biomarkers. Probability curves are generated from univariate logistic regression models with biomarker level as the independent variable and probability of intermediate-high ADNC as the dependent variable. AD, Alzheimer's disease; ADNC, AD neuropathological changes; A/T/N, amyloid-β/tau/neurodegeneration; CSF, cerebrospinal fluid; PET, positron emission tomography.

suggest that PET- and CSF-related A/T/N biomarkers in isolation can be used as accurate diagnostic markers in clinical settings and research design. However, their differential performances in different clinical stages should be noted.[28] In addition, our results are in line with a recent neuropathologic study that found that PET- and CSF-related A/T/N biomarkers alone were all significantly associated with the probability of harboring intermediate-high ADNC.[26] For plasma biomarkers, both our study and recent studies found only a weak or nonsignificant association with ADNC stage.[24,40] However, although not statistically significant, we observed a trend for plasma Aβ42/40 (LS-MS/MS) and plasma p-tau181 (all four assays) using other assays, implying that high-performing assays are required for plasma biomarkers in future AD research. Moreover, we found that plasma-related A/T/N biomarkers alone showed lower discrimination for autopsy-confirmed AD compared to PET and CSF biomarkers. However, plasma biomarkers combined with *APOE* ε4 genotype had similar diagnostic accuracy as PET and CSF biomarkers, and this is consistent with recent studies using plasma biomarkers to predict Aβ and tau PET stages, which showed that plasma biomarkers better distinguish Aβ and tau PET stages only when combined with risk factors (age, sex, and *APOE* ε4 genotype).[18] Therefore, using plasma biomarkers in clinical practice to predict the presence of AD pathology may depend on risk factors, such as *APOE* ε4 genotype. Furthermore, we observed that the AUC of plasma p-tau181 measured by the Simoa assay from the University of Gothenburg was lower than a previous study using the pTau-181 V2 Advantage Kit,[24] implying that the use of assays may be a strong confounding factor for plasma biomarker performance. In fact, we used different new assays of plasma p-tau181 and plasma Aβ42/40 that found excellent diagnostic performance, although only in a subsample of 10 participants. These results further emphasize the importance of standardizing assays and procedures for plasma biomarkers in future research and clinical

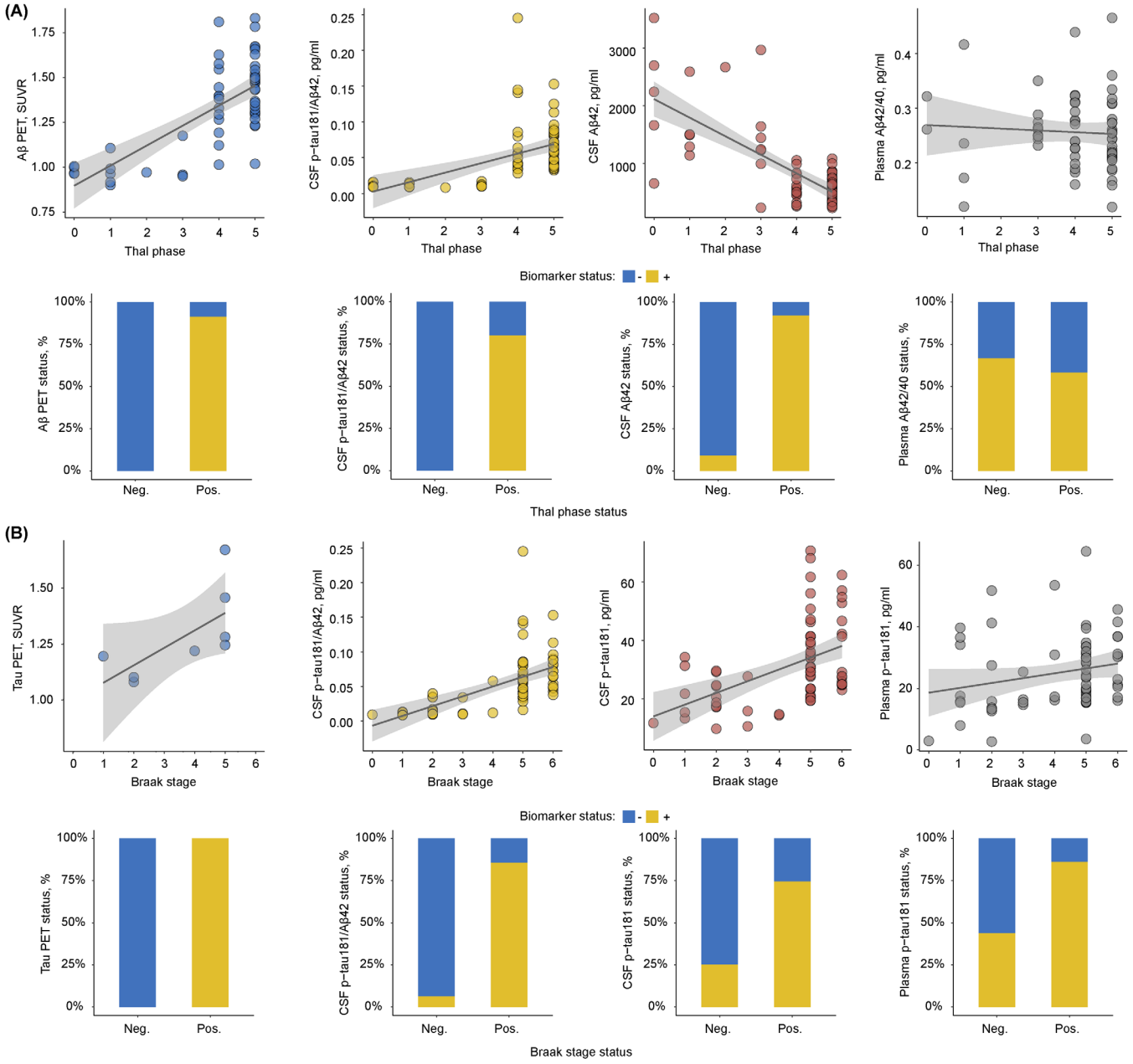

FIGURE 5 Associations between A/T biomarkers and their corresponding pathology. Scatter plots show the correlation between Thal phase and Aβ-related biomarkers (A) and the correlation between Braak stage and tau-related biomarkers (B). Partial Spearman correlation fits are indicated with 95% confidence intervals. These models adjusted for age at death, sex, and years from last assessment to death. Raw data are represented by dots, while shadowed areas represent the 95% CI. The proportion of biomarker negative (Neg.) and positive (Pos.) status is also shown in individuals with Thal phase positive (3–5) and negative (0–2) (A) and in individuals with Braak stage positive (III–VI) and negative (0–II) (B). Aβ amyloid-β; CI, confidence interval.

settings. Moreover, plasma biomarker levels and their diagnostic accuracy appear to be affected by multiple comorbidities[41,42] and peripherally derived plasma biomarkers.[43,44] Therefore, comprehending the impact of these comorbidities on plasma levels is also crucial for their prospective interpretation in the context of clinical screening, diagnosis, or prognosis at the population level.

Another novelty of our study was investigating the relationship between each biomarker and its respective target pathology at autopsy. Specifically, we compared Aβ-related biomarkers with Thal phase and CERAD stage and tau-related biomarkers with Braak stage. Our results showed that Aβ PET and CSF p-tau181/Aβ42 were the most effective biomarkers associated with Aβ plaques. Their abnormality was closely related to the abnormality of Aβ plaques. For tau tangles, tau PET demonstrated the highest consistency with Braak stage, followed by CSF p-tau181/Aβ42. However, we only observed a weaker agreement between plasma p-tau181 and Braak stage, in contrast

to a previous study.[40] One possible explanation for this discrepancy may be the use of assays in our study, which may have mitigated the performance of plasma p-tau181, as discussed in the previous paragraph. Further research is necessary to compare the performance of plasma biomarkers using different assays in a large autopsy cohort.

The primary advantage of this study is the availability of PET, CSF, and plasma biomarkers, including amyloid/tau/neurodegeneration biomarkers and different assays for CSF and plasma biomarkers, in a relatively large neuropathology cohort. Moreover, the use of in vivo biomarkers and autopsy neuropathology allowed for a direct comparison of the concordance and discordance between the A/T/N profiles and the gold-standard neuropathological changes of AD. However, we must acknowledge some limitations. First, due to the limited sample size, especially for tau PET (only 8% available), we could not compare the association between these biomarkers and ADNC in completely identical populations. Second, co-morbidities are prevalent in AD patients,[45] and they may impact the performance of AD-related biomarkers. However, due to the limited sample size and the high rate of comorbidities, we could not exclude participants with these co-morbidities in this study. Third, some promising plasma biomarkers, including GFAP, p-tau 231, and p-tau 217, were not available in our study. Fourth, a head-to-head comparison of different biomarker assays against neuropathological outcomes is required, but this need could not be realized in this study. Finally, we recognize the need for replication in large and independent cohorts of different races and for using high-performing assays to establish the robustness of our findings.

In conclusion, this study supports that PET- and CSF-related A/T/N biomarkers alone may be sufficient as precise diagnostic tools to detect AD pathology and as predictive tools to assess the staging and severity of AD pathology and that the combination of PET- and CSF-related A/T/N profiles can provide valuable predictive information about the neuropathological progression. Furthermore, we believe incorporating risk factor variables, such as *APOE* ε4 genotype, is appropriate when using plasma-related A/T/N biomarkers as diagnostic tools in clinical trials and future clinical practice. Overall, PET and CSF scans will remain necessary for clinical trials focused on interventions targeted to more specific stages of AD, and plasma measures are unlikely to completely replace the more established AD diagnostic biomarkers (PET and CSF) in the near future.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

ADNI was approved by the Institutional Review Boards of all participating institutions. All participants provided written informed consent in accordance with the Declaration of Helsinki prior to study enrollment.

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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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