Received: 15 November 2022 | Revised: 18 January 2023 | Accepted: 19 January 2023

DOI: 10.1002/alz.12997

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Differences between *ante mortem* Alzheimer's disease biomarkers in predicting neuropathology at autopsy

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Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-ontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Funding information
Science and Technology Innovation 2030 Major Projects, Grant/Award Number: 2022ZD0211600; National Natural Science Foundation of China, Grant/Award Numbers: 82071201, 81971032; Shanghai Municipal Science and Technology Major Project, Grant/Award Number: 2018SHZDZX01; Huashan Hospital, Grant/Award Number: 2022QD002; Fudan University, Grant/Award Number: 3030277001

Abstract

Introduction: This study aimed to assess whether biomarkers related to amyloid, tau, and neurodegeneration can accurately predict Alzheimer's disease (AD) neuropathology at autopsy in early and late clinical stages.

Methods: We included 100 participants who had *ante mortem* biomarker measurements and underwent *post mortem* neuropathological examination. Based on *ante mortem* clinical diagnosis, participants were divided into non-dementia and dementia, as early or late clinical stages.

Results: Amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) amyloid beta (Aβ)42/phosphorylated tau (p-tau)181 showed excellent performance in differentiating autopsy-confirmed AD and predicting the risk of neuropathological changes in early and late clinical stages. However, CSF Aβ42 performed better in the early clinical stage, while CSF p-tau181, CSF t-tau, and plasma p-tau181 performed better in the late clinical stage.

Discussion: Our findings provide important clinical information that, if using PET, CSF, and plasma biomarkers to detect AD pathology, researchers must consider their differential performances at different clinical stages of AD.

KEYWORDS
Alzheimer's disease, autopsy, cerebrospinal fluid, plasma, positron emission tomography

Highlights

- Amyloid PET and CSF Aβ42/p-tau181 were the most promising candidate biomarkers for predicting AD pathology.

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

- CSF Aβ42 can serve as a candidate predictive biomarker in the early clinical stage of AD.
- CSF p-tau181, CSF t-tau, and plasma p-tau181 can serve as candidate predictive biomarkers in the late clinical stage of AD.
- Combining *APOE* ε4 genotypes can significantly improve the predictive accuracy of AD-related biomarkers for AD pathology.

1 | INTRODUCTION

The biological definition of Alzheimer's disease (AD) is the extracellular deposition of amyloid beta (Aβ) plaques and tau-related intraneuronal neurofibrillary tangles (NFTs).[1] In 2018, the National Institute on Aging–Alzheimer's Association (NIA-AA) research framework proposed that in vivo biomarkers, such as positron emission tomography (PET), cerebrospinal fluid (CSF), and plasma, could be used to track AD neuropathological changes.[2] Biomarker evidence consistent with AD in the previous study required at least one modality of an abnormal amyloid marker, but not tau measure,[3–5] or defined based on differentiating between clinical diagnosis of AD and controls.[6,7] However, the limitation of the former is that individuals with only abnormal amyloid pathology may not have AD because some individuals who had *ante mortem* abnormal amyloid markers but normal tau markers were not found to have AD at autopsy.[8] The limitation of the latter is that clinical diagnosis may not be consistent with the pathological diagnosis and may not accurately reflect the presence of AD neuropathology.[2] Ideally, the gold standard autopsy diagnosis should be used to define the diagnosis of AD, but only a few studies have done this.

In addition, AD biomarkers have been shown to change in different stages as disease progresses, and the entire disease course process can be > 20 years.[9] Fluid biomarkers of Aβ (in CSF and plasma) and fluid phosphorylated tau (p-tau) biomarkers appear to be abnormal in time or slightly before and after amyloid PET becomes abnormal, respectively.[10] It introduces uncertainty in diagnosing AD by using different clinical stages of biomarkers. A previous study demonstrated that preclinical AD biomarkers could accurately predict AD neuropathological change (ADNC) at autopsy.[11] However, another autopsy study reported that the correlation between CSF biomarkers of AD and ADNC decreased with disease progression in mid- and late-stage AD.[12] The association between plasma p-tau181 and ADNC was also more robust in demented than non-demented participants.[13] These studies suggest that the predictive accuracy of AD biomarkers for detecting ADNC may be significantly different across clinical stages, but relevant evidence from autopsy studies is sparse. Previous studies investigating the performance of biomarkers in predicting autopsy-confirmed AD have generally focused on one of early or late clinical stages and did not compare their performance in both stages,[11,12] or only investigated a single biomarker or one modality of PET, CSF, and plasma and did not combine all three modalities of biomarkers.[11,14–16]

In this study, we divided participants into non-demented and demented based on *ante mortem* clinical diagnosis, as early and late clinical stages of AD. We aimed to investigate whether PET, CSF, and plasma biomarkers can accurately predict AD neuropathology at autopsy in early or late clinical stages and to compare their performance in both stages.

2 | MATERIALS AND METHODS

2.1 | Study population

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). As a public–private partnership, the ADNI project was launched in 2003 to determine whether clinical, imaging, genetic, and biochemical biomarkers can be combined to develop and validate the early diagnosis of AD. Data collection and sharing were approved by all participating institutions in ADNI.

In this study, we included a total of 100 participants from ADNI, including the previous version of the population (81 participants, data released on May 17, 2022) and the new version of the population (19 participants, data released on November 14, 2022). We used the previous version of the population as the primary analysis. Participants with the new version and participants after the new and old versions were combined for the replication and sensitivity analyses. These participants donated their brains for neuropathological examination 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. These participants underwent follow-up clinical assessment, including Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE). Assigned CDR and MMSE scores describe clinical diagnosis as cognitively normal (CN, MMSE > 24, CDR = 0), mild cognitively impaired (MCI, MMSE > 24, CDR = 0.5), or dementia based on pre-established criteria.[17] Participants were included in this study if they had available *ante mortem* measurements of amyloid PET imaging (18F-AV-45 [AV45]), CSF, and plasma biomarkers, respectively. If multiple biomarker assessments have been performed, the most recent was used in this study, and clinical diagnosis was based on *ante mortem* diagnosis at last follow-up of biomarkers. We included CN and MCI participants as non-dementia then divided participants into non-dementia and dementia groups.

RESEARCH IN CONTEXT

1. **Systematic review**: Biomarkers related to amyloid, tau, and neurodegeneration, are widely accepted as surrogate markers for detecting Alzheimer's disease (AD) pathophysiology in vivo. Although these biomarkers have been shown to change as the disease progresses, few studies have evaluated the association between these biomarkers sampling in different clinical stages and autopsy AD neuropathology.
2. **Interpretation**: For predicting autopsy AD neuropathology, amyloid PET and CSF Aβ42/p-tau181 demonstrated perfect performance in early and late clinical stages. However, CSF Aβ42 performed better in early clinical stage, while CSF p-tau181, CSF t-tau, and plasma p-tau181 performed better in late clinical stage. Note that combining *APOE* ε4 genotypes can significantly improve their predictive accuracy.
3. **Future directions**: This study provides neuropathological validation for using these biomarkers to track AD pathology and reveals their differential predictive performances in early and late clinical stages. It needs to be considered in future clinical settings, clinical trial enrollment, and research design.

2.2 | Amyloid PET imaging and MRI assessment

Amyloid PET scans in this study were quantified during 4 × 5 minute time frames measured 50 to 70 minutes post-injection of 18F-florbetapir (AV45). All PET images used a native-space magnetic resonance imaging (MRI) scan for each subject to use FreeSurfer to define a high-resolution cortical summary region. For the analysis of amyloid PET images, the summary florbetapir standardized uptake value ratios (SUVRs) were calculated by frontal, anterior/posterior, cingulate, lateral parietal, and lateral temporal regions, and they were normalized by the FreeSurfer-defined whole cerebellum.[18] Details of MRI assessments can be found in Supplementary Methods in supporting information.

2.3 | CSF biomarkers

Ante mortem CSF was obtained by lumbar puncture. CSF concentrations of Aβ42, total tau (t-tau) and p-tau181 were measured using fully automated Roche Elecsys electrochemiluminescence immunoassays on a cobas 601 instrument. In the present study, the detectable concentration of Aβ42 ranged from 200 to 1700 pg/mL, and Aβ42 values beyond the maximum detection concentration were also included, which was provided based on the extrapolation of a calibration curve.

2.4 | Plasma biomarkers

The collection and processing of blood samples followed the ADNI protocol.[19] *Ante mortem* plasma p-tau181, t-tau, and neurofilament light chain (NfL) levels were measured using the ultrasensitive single-molecule array technique described previously.[20] Plasma Aβ42 and Aβ40 levels were quantified using Innogenetics research use-only reagents on a Luminex immunoassay platform.[21] Detailed information can be found at www.adni-info.org.

2.5 | Neuropathological examination

Neuropathological processing and evaluation were performed according to the NIA-AA guidelines and following previously described procedures.[22] Three rating scales are used to describe core hallmarks of AD neuropathology, including Thal phase for the location of Aβ plaques (ranging from 0 to 5), Braak stages for the location of tau NFT pathology (ranging from 0 to 6), and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores for density of neuritic plaques (ranging from 0 to 3). Following the NIA-AA guidelines, the rating of Thal phases and Braak stages was translated into a 4-point scale named A and B scores. Then, each 4-point scale represented the degree of neuropathological change, ranging from none (0) to low (1), intermediate (2), and high (3). The combination of the A, B, and C (CERAD) scores represented ADNC levels and then translated into a 4-point score likelihood, with scores ≥2 and <2, respectively, considered an autopsy diagnosis of AD and non-AD. Co-morbid pathology, including cerebral amyloid angiopathy (CAA), Lewy body (LB), and TAR DNA-binding protein (TDP)-43, were also assessed in the ADNI center, whose neuropathological assessment scale translated to absent or present each co-pathology, as previously described.[23] More details on the implementation and operational definitions of the different neuropathology scoring scales are provided in the National Alzheimer's Coordinating Center's Coding Guidebook for the Neuropathology Form.[24]

2.6 | Statistical analysis

All analyses were conducted using R version 4.1.0 software, with significance levels defined as a two-side $P < 0.05$. The distribution normality of each biomarker was tested using the Kolmogorov–Smirnov test. If the variable did not follow a normal distribution, it would be log10 transformed in the statistical analysis. Outliers (outside four standard deviations) were excluded from statistical analysis. Differences between groups using one-way analysis of covariance for continuous variables and χ^2 tests and Kruskal–Wallis test for categorical variables were calculated for all participants and the subgroups defined by clinical and autopsy diagnosis. The discriminative accuracy of biomarkers in predicting with and without autopsy confirmed AD using the area under the receiver operating curve (ROC) statistic. Three ROC models were performed (1) based on biomarker alone and (2) using predicted probabilities from the multivariable binary logistic

TABLE 1 Sample characteristics.

	Total	Non-dementia	Dementia	*P*-value
N	81	18	63	–
Age at baseline, mean (SD)	77.1 (7.1)	79.7 (5.6)	76.4 (7.4)	0.08
Age at death, mean (SD)	82.4 (7.6)	85.3 (6.4)	81.6 (7.7)	0.07
Sex, *n* (%) female	22 (27.2)	6 (33.3)	16 (25.4)	0.03
Education at baseline, mean (SD)	16.5 (2.5)	16.1 (2.9)	16.6 (2.4)	0.51
APOE ε4 carriers, *n* (%)	46 (56.8)	7 (38.9)	39 (61.9)	<0.001
ADNC, *n* (%)				
None	4 (4.9)	2 (11.1)	2 (3.2)	
Low	16 (19.8)	7 (38.9)	9 (14.3)	<0.001
Intermediate	5 (6.2)	3 (16.7)	2 (3.2)	
High	56 (69.1)	6 (33.3)	50 (79.4)	
Thal, *n* (%)				
None	4 (4.9)	2 (11.1)	2 (3.2)	
Low	6 (7.4)	3 (16.7)	3 (4.8)	<0.001
Intermediate	8 (9.9)	5 (27.8)	3 (4.8)	
High	63 (77.8)	8 (44.4)	55 (87.3)	
Braak, *n* (%)				
None	1 (1.2)	1 (5.6)	0 (0.0)	
Low	18 (22.2)	8 (44.4)	10 (15.9)	<0.001
Intermediate	5 (6.2)	3 (16.7)	2 (3.2)	
High	57 (70.4)	6 (33.3)	51 (81.0)	
CERAD, *n* (%)				
None	17 (21.0)	10 (55.6)	7 (11.1)	
Low	8 (9.9)	2 (11.1)	6 (9.5)	<0.001
Intermediate	5 (6.2)	1 (5.6)	4 (6.3)	
High	51 (63.0)	5 (27.8)	46 (73.0)	
CAA, *n* (%)	14 (17.3)	1 (5.6)	13 (20.6)	0.001
LB, *n* (%)	40 (49.4)	4 (22.2)	36 (57.1)	<0.001
TDP-43, *n* (%)	33 (44.6)	6 (40.0)	27 (45.8)	<0.001

Note: Baseline characteristics and *P*-value using one-way analysis of covariance for continuous variables and χ^2 test (binary variable) and Kruskal–Wallis test (ordinal variable) for categorical variables were compared in individuals with clinical diagnosis of non-dementia and dementia.
Abbreviations: ADNC, Alzheimer's disease neuropathological change; *APOE*, apolipoprotein E; CAA, cerebral amyloid angiopathy; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; LB, Lewy body; SD, standard deviation; TDP-43, TAR DNA-binding protein-43.

regression that included apolipoprotein E (*APOE*) ε4 status (0 = non-carriers, 1 = ε4 carriers) as well as (3) using predicted probabilities from the multivariable binary logistic regression that included *APOE* ε4 status, age at death, sex, and years from last assessment to death. The univariate ordinal logistic regression model was used to examine the effect of each biomarker on the odds of each degree of distinct aspects of neuropathological scores (Thal, Braak, and CERAD). The multivariable ordinal logistic regression models were also performed by controlling the above covariates of ROC models. The specificity, sensitivity, and area under the curve (AUC) and 95% confidence intervals (CI) were reported for each ROC statistical analysis. The logistical regression models reported the odds ratio (OR) and their 95% CI with *P*-values. The DeLong test was used to compare the AUC of two ROCs.

3 | RESULTS

3.1 | Sample characteristics

Demographic, clinical, and neuropathologic characteristics of the present study are summarized and presented in Table 1 and supporting information. In the primary analysis, a total of 81 participants underwent amyloid PET (n = 40, 49%), CSF (p-tau181/Aβ42: n = 57, 70%; Aβ42: n = 58, 72%; p-tau181: n = 57, 70%; t-tau: n = 57, 70%), and plasma (Aβ42/40: n = 52, 64%; p-tau: n = 50, 62%; t-tau: n = 39, 48%; NfL: n = 74, 91%) collection. Clinical diagnostics, that is, non-dementia and dementia, were defined at the time of last clinical assessment of biomarkers. In total samples of the primary analysis, the mean age at

TABLE 2 The differences in biomarker levels among groups defined by clinical and autopsy diagnoses.

	Non-dementia					Dementia					
	Non–autopsy-confirmed AD		Autopsy-confirmed AD			Non–autopsy-confirmed AD		Autopsy-confirmed AD			
	N	Mean (SD)	*N*	Mean (SD)	*P*-value*	*N*	Mean (SD)	*N*	Mean (SD)	*P*-value**	*P*-value***
Amyloid PET SUVR	7	1.0 (0.1)	4	1.4 (0.1)	<0.001	4	1.1 (0.2)	25	1.4 (0.2)	<0.001	<0.001
CSF p-tau181/Aβ42, pg/mL	9	0.01 (0.003)	11	0.06 (0.02)	<0.001	5	0.02 (0.01)	31	0.07 (0.03)	<0.001	<0.001
CSF Aβ42, pg/mL	9	2098 (843.6)	11	717.4 (391.9)	<0.001	6	746.8 (474.0)	32	533.6 (198.3)	0.18	<0.001
CSF p-tau181, pg/mL	9	23.0 (7.6)	11	34.2 (11.6)	0.02	5	15.5 (3.7)	31	33.9 (13.7)	<0.001	<0.001
CSF t-tau, pg/mL	9	285.9 (121.2)	11	342.0 (96.2)	0.11	5	183.0 (35.8)	32	366.1 (156.8)	0.005	0.007
Plasma p-tau181, pg/mL	8	27.4 (17.1)	5	20.1 (13.3)	0.60	6	20.6 (9.4)	31	28.5 (10.2)	0.03	0.04
Plasma Aβ42/40, pg/mL	8	0.03 (0.1)	12	0.03 (0.06)	0.98	5	0.23 (0.1)	26	0.2 (0.1)	0.77	0.21
Plasma t-tau, pg/mL	9	2.2 (1.2)	16	3.1 (1.7)	0.12	1	2.54 (NA)	13	3.5 (1.7)	0.84	0.15
Plasma NfL, pg/mL	12	76.6 (52.3)	11	65.3 (30.0)	0.78	7	58.2 (18.5)	43	60.3 (24.4)	0.86	1

Notes: Non-dementia and dementia were assessed by clinical diagnosis at the last follow-up. The diagnosis of autopsy-confirmed AD and non–autopsy-confirmed AD was accorded with National Institute on Aging-Reagan Institute criteria. The *P*-value was derived from the analysis of covariance models adjusting for age and sex. The number of participants in each category was reported.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADNC, Alzheimer's disease neuropathological change; CSF, cerebrospinal fluid; NfL, neurofilament light; PET, positron emission tomography; p-tau181, tau phosphorylated at threonine 181; SD, standard deviation; SUVR, standardized uptake value ratio; t-tau, total tau.

**P*-values derived from tests comparing mean values between non–autopsy-confirmed AD and autopsy-confirmed AD subgroups in non-dementia participants.

***P*-values derived from tests comparing mean values between non–autopsy-confirmed AD and autopsy-confirmed AD subgroups in dementia participants.

****P*-values derived from tests comparing mean values between non–autopsy-confirmed AD and autopsy-confirmed AD subgroups in non-dementia and dementia participants, respectively.

baseline and death was 77.1 (± 7.1) and 82.4 (± 7.6) years, respectively. Participants in this study were slightly more likely to be *APOE* ε4 carriers (56%) and were more frequently male (73%), with a dementia diagnosis (78%), and have intermediate–high AD neuropathological scores (ADNC: 75%; Thal: 88%; Braak: 77%; CERAD: 69%).

Participants diagnosed with dementia tended to be more female ($P = 0.03$), were more likely *APOE* ε4 carriers ($P < 0.001$), and were more likely to have intermediate–high AD neuropathological scores (ADNC, Thal, Braak, CERAD, all $P < 0.001$), compared to participants diagnosed with non-dementia. For non-AD neuropathologies, a greater proportion of CAA ($P = 0.001$), LB ($P < 0.001$), and TDP-43 ($P < 0.001$) was also observed in dementia compared to the non-dementia group. The mean age at baseline and death was younger in dementia relative to the non-dementia group, despite no differences between groups. The years from last assessment to death were mostly longer in the non-dementia than dementia group (see Table S1 in supporting information).

3.2 | Comparisons of biomarker levels among groups defined by clinical and autopsy diagnosis

We assessed *ante mortem* biomarker levels between groups defined based on clinical and autopsy diagnoses (Table 2). Among the non-dementia group, individuals diagnosed with autopsy-confirmed AD had higher levels of amyloid PET, CSF p-tau181/Aβ42, and CSF p-tau181 and lower levels of CSF Aβ42 compared to those diagnosed as non–autopsy-confirmed AD. However, no difference was observed for CSF t-tau and plasma biomarkers. Among the dementia group, amyloid PET, CSF p-tau181, CSF p-tau181/Aβ42, CSF t-tau, and plasma p-tau181 levels were significantly higher in individuals with autopsy-confirmed AD compared to non–autopsy-confirmed AD. However, no difference was found for CSF Aβ42 and other plasma biomarkers.

To determine disease stage, we stratified participants into control (non-dementia and non–autopsy-confirmed AD), early stages of AD (non-dementia and autopsy-confirmed AD), late stages of AD (dementia and autopsy-confirmed AD), and non-AD dementia (dementia and non–autopsy-confirmed AD). Biomarker levels in these groups are shown in Figure 1. We only found that the levels of amyloid PET, CSF biomarkers, and plasma p-tau181 were significantly different between four groups (Table 2). On a trend level, these biomarkers were changed in the AD category (control, early AD, and late AD) and reached the peak level of biomarkers in individuals with late stages of AD. However, there are no differences in MRI markers between groups (see Supplementary Results and Figure S3 in supporting information).

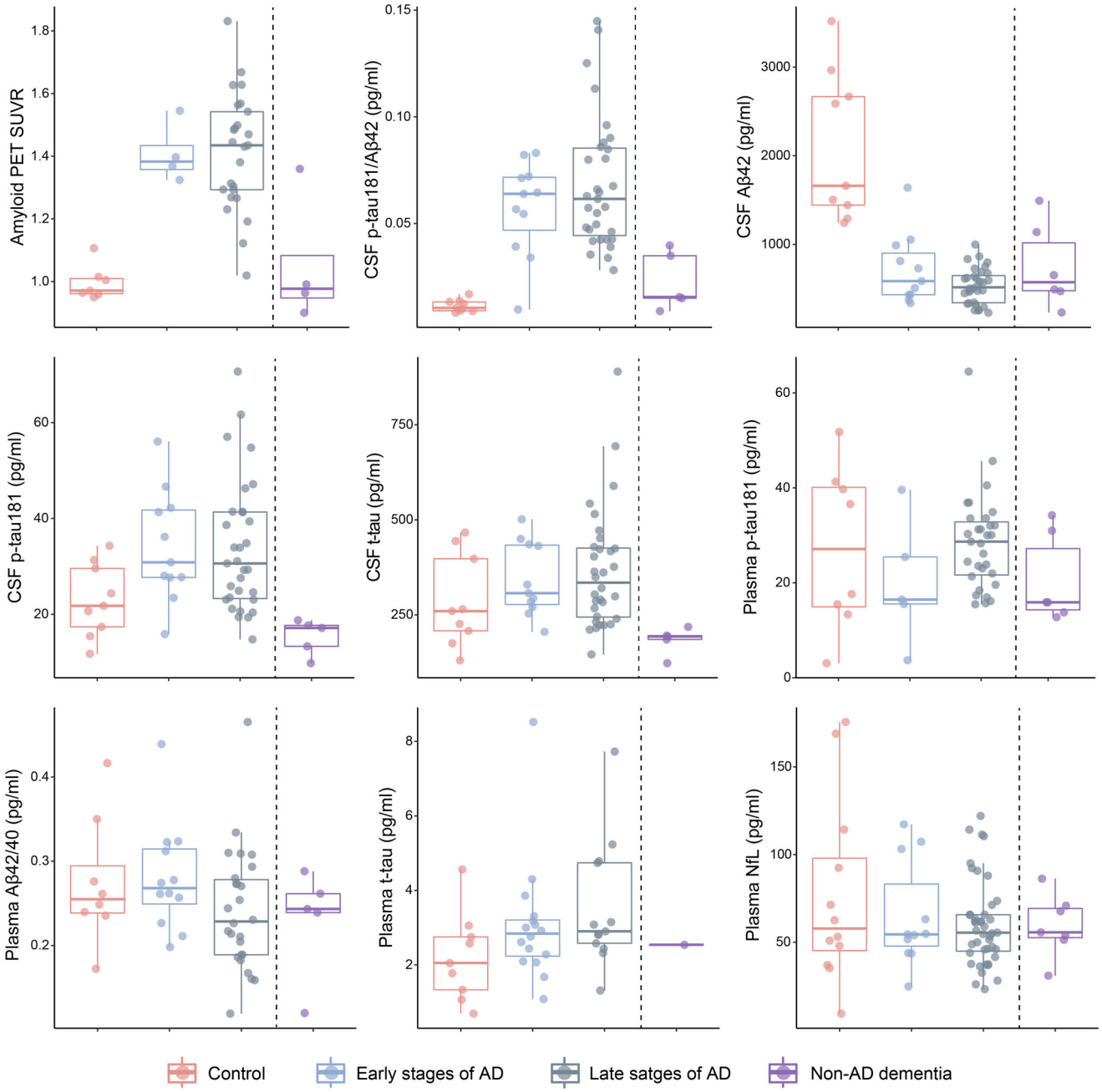

FIGURE 1 Biomarker levels in participants stratified by clinical and autopsy diagnoses. To determine disease stage, we stratified participants into control (non-dementia and non–autopsy-confirmed AD), early stages of AD (non-dementia and autopsy-confirmed AD), late stages of AD (dementia and autopsy-confirmed AD), and non-AD dementia (dementia and non–autopsy-confirmed AD). The figure shows boxplots of each biomarker level in the groups, each showing the median (bar) and interquartile range (whiskers) and the individual data points. Clinical diagnosis of non-dementia and dementia was based on *ante mortem* diagnosis at the last follow-up of biomarkers. The ADNC scores ≥2 and <2 are respectively considered an autopsy diagnosis of AD and non-AD. A*β*, amyloid beta; AD, Alzheimer's disease; ADNC, Alzheimer's disease neuropathological change; CSF, cerebrospinal fluid; NfL, neurofilament light; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; t-tau, total tau.

3.3 | Accuracy of biomarkers in predicting autopsy-confirmed AD among clinical diagnosis groups

We next tested the accuracy of each biomarker in differentiating autopsy-confirmed AD versus non–autopsy-confirmed AD among clinical diagnosis groups. The optimal cutoff value of each biomarker and their specificity, sensitivity, and AUC are summarized in Table 3 and presented in Figure 2A. Both in the non-demented group and dementia group, amyloid PET and CSF p-tau/A*β*42 were observed to predict autopsy-confirmed AD with high accuracy in both specificity and sensitivity. CSF A*β*42 performed better in the non-dementia group

TABLE 3 Accuracy of biomarkers in discriminating autopsy-confirmed Alzheimer's disease.

	Non-dementia					Dementia				
	Threshold	Sp	Se	AUC	95% CI	Threshold	Sp	Se	AUC	95% CI
Amyloid PET	1.2	1	1	1	1–1	1	0.75	1	0.90	0.7–1
CSF p-tau181/Aβ42	0.03	1	0.91	0.94	0.82–1	0.04	1	0.87	0.96	0.9–1
CSF Aβ42	1148.5	1	0.91	0.96	0.87–1	1068.6	0.33	1	0.59	0.27–0.91
CSF p-tau181	26	0.67	0.82	0.78	0.57–0.99	19.1	1	0.97	0.98	0.94–1
CSF t-tau	267.8	0.67	0.82	0.68	0.41–0.94	220.7	1	0.91	0.96	0.9–1
Plasma p-tau181	39.7	0.38	1	0.60	0.27–0.93	16	0.67	0.94	0.74	0.45–1
Plasma Aβ42/40	0.3	0.5	0.75	0.55	0.27–0.84	0.2	0.8	0.54	0.50	0.22–0.78
Plasma t-tau	2.1	0.56	0.88	0.71	0.46–0.94	2.6	1	0.77	0.77	NA[a]
Plasma NfL	143.2	0.17	1	0.51	0.26–0.76	50.7	0.86	0.4	0.54	0.37–0.79

Notes: The ROC was used to assess the probability of each biomarker predicting autopsy confirmed Alzheimer's disease. The optimal cutoff value of each biomarker (Threshold), specificity, sensitivity, areas under the curve (AUC), and 95% CI, were reported based on ROC curves.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADNC, Alzheimer's disease neuropathological change; AUC, area under the curve, CI, confidence interval; CSF, cerebrospinal fluid; NfL, neurofilament light chain; PET, positron emission tomography; p-tau181, tau phosphorylated at threonine 181; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity; t-tau, total tau.
[a]The control of participants with available plasma t-tau in the clinical dementia group was only one, and then CI was lacking.

(AUC = 0.96) than dementia group (AUC = 0.59, $P = 0.04$ for difference), while CSF p-tau181 and CSF t-tau performed well in the dementia group compared to the non-dementia group despite that no significant differences between AUCs were observed ($P > 0.05$ for the difference). Among plasma biomarkers, plasma p-tau181 had an acceptable accuracy in predicting autopsy-confirmed AD in the dementia group but not the non-dementia group, while plasma t-tau had an acceptable accuracy in both groups. No other plasma biomarkers were found to have an acceptable predictive accuracy in both groups. Furthermore, the AUCs of biomarkers were higher when combining *APOE* ε4 status, and a similar trend of diagnostic accuracy was observed with biomarkers alone (Figure 2B and Table S2 in supporting information). When further combined with age at death, sex, and years from last assessment to death as predictors, the diagnostic performances of each biomarker were better or slightly worse than the biomarker combined with *APOE* ε4 status, and a similar trend of diagnostic accuracy remained (Figure 2C and Table S3 in supporting information). Note that the AUCs of plasma biomarkers were significantly improved in the model combining covariates, reaching an excellent level.

3.4 | Association between biomarkers and neuropathological changes among clinical diagnosis groups

We used univariate ordinal logistic regression models to test the association between biomarkers and different neuropathologic scores (Table 4). The models demonstrated that amyloid PET and CSF p-tau/Aβ42 were associated with higher odds of more advanced Thal, Braak, and CERAD scores. Higher levels of CSF Aβ42 were associated with lower odds of all neuropathological scores in the non-dementia group and only with Thal phases in the dementia group. Among other CSF biomarkers, higher CSF p-tau181 concentrations were related to higher odds of neuropathological scores in both groups. In contrast, a similar association for CSF t-tau was shown in the dementia group. In the non-dementia group, higher CSF t-tau levels were only associated with high odds of Braak stages. For plasma biomarkers, higher levels of plasma p-tau181 corresponded to higher odds for all neuropathological scores in the dementia group but not the non-dementia group. No other plasma biomarkers were associated with neuropathological scores.

When adjusted for *APOE* ε4 status in the ordinal logistic regression model, the associations of the biomarkers remained mostly unchanged in the non-demented group, except for the association of CSF p-tau181 with all neuropathology scores, which became non-significant (Table S4 in supporting information). In the dementia group, biomarkers were only associated with the pathology they were related with, that is, Aβ42 and amyloid pathology, and p-tau181 and t-tau with tau pathology. Similar associations were observed when additionally adjusting for age at death, sex, and years from last assessment to death (Table S5 in supporting information).

3.5 | Replication and sensitivity analysis

For a replication and sensitivity analysis, we repeated all of the above analyses and performed stratified analyses in a lower sample (19 participants) and a larger sample (100 participants). Due to the limitation of participants in the lower sample, each biomarker performed worse than the previous results, but similar trends were observed. However, in the larger sample, the results of the above analyses were better or similar to the previous results. Additional details of the results are reported in Supplementary Results.

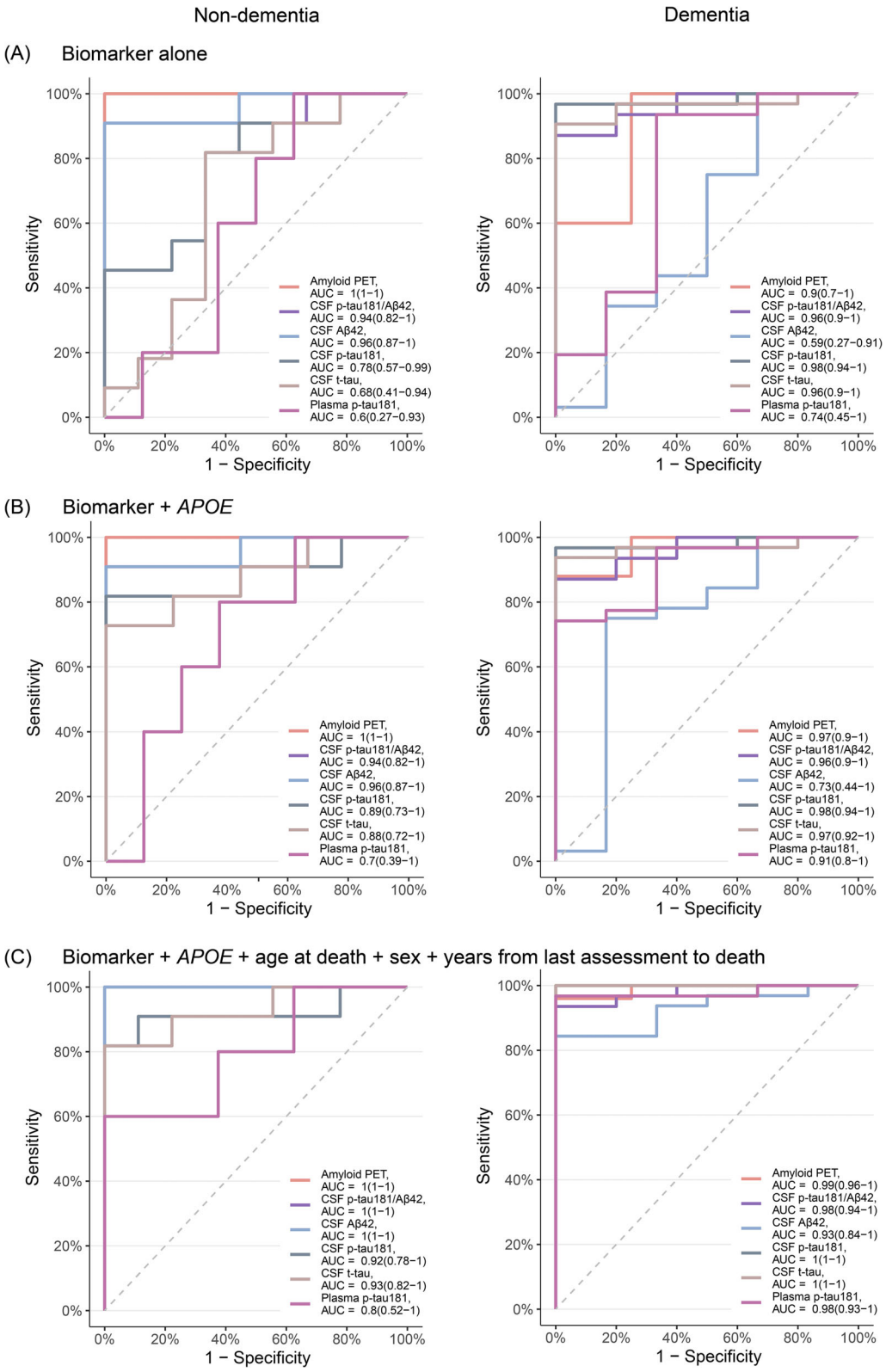

FIGURE 2 Accuracy of biomarkers in predicting autopsy-confirmed AD across clinical diagnoses. According to the National Institute on Aging-Reagan Institute criteria, the ROC curves were used to assess the predictive accuracy of PET, CSF, and plasma biomarkers for autopsy-confirmed AD versus non–autopsy-confirmed AD in individuals with non-dementia and dementia. AUC statistic and 95% CI were calculated based on biomarker alone (A) and using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status (0 = non-carriers, 1 = ε4 carriers) (B), as well as using predicted probabilities from multivariable binary logistic regression that included *APOE* ε4 status, age at death, sex, years from last assessment to death (C). AD, Alzheimer's disease; *APOE*, apolipoprotein E; AUC, area under the curve; CFS, cerebrospinal fluid; CI, confidence interval; PET, positron emission tomography; ROC, receiver operating characteristic.

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TABLE 4 Effect of biomarkers on cumulative odds of higher degrees of neuropathological changes.

	Non-dementia						Dementia					
	Thal		Braak		CERAD		Thal		Braak		CERAD	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Amyloid PET SUVR	2.26 (1.24–4.09)	0.025	2.36 (1.61–3.45)	0.002	3.36 (2.19–5.14)	<0.001	1.67 (1.36–2.04)	<0.001	1.4 (1.13–1.72)	0.004	1.53 (1.06–2.2)	0.031
CSF p-tau181/Aβ42	2.51 (1.94–3.23)	<0.001	2.64 (2.19–3.18)	<0.001	3.79 (3.13–4.58)	<0.001	1.73 (1.45–2.06)	<0.001	1.6 (1.33–1.91)	<0.001	1.76 (1.35–2.29)	<0.001
CSF Aβ42	0.43 (0.32–0.58)	<0.001	0.43 (0.32–0.58)	<0.001	0.31 (0.22–0.44)	<0.001	0.75 (0.6–0.95)	0.02	0.91 (0.71–1.15)	0.43	0.93 (0.66–1.3)	0.68
CSF p-tau181	1.73 (1.13–2.65)	0.021	2 (1.39–2.88)	0.002	2.49 (1.53–4.05)	0.002	1.5 (1.21–1.86)	<0.001	1.57 (1.3–1.88)	<0.001	1.77 (1.36–2.31)	<0.001
CSF t-tau	1.4 (0.88–2.24)	0.17	1.64 (1.07–2.52)	0.036	1.78 (0.99–3.2)	0.071	1.38 (1.11–1.73)	0.008	1.49 (1.23–1.81)	<0.001	1.7 (1.31–2.22)	<0.001
Plasma p-tau181	0.79 (0.42–1.48)	0.47	1.01 (0.6–1.69)	0.98	0.9 (0.51–1.58)	0.71	1.27 (1.01–1.59)	0.04	1.36 (1.1–1.68)	0.007	1.61 (1.17–2.21)	0.006
Plasma Aβ42/40	1.1 (0.69–1.77)	0.69	0.96 (0.62–1.48)	0.86	1.1 (0.6–2.01)	0.75	1.11 (0.94–1.3)	0.23	1.05 (0.8–1.37)	0.75	1.12 (0.8–1.56)	0.52
Plasma t-tau	1.46 (1–2.13)	0.06	1.29 (0.88–1.88)	0.20	1.45 (0.86–2.42)	0.17	1.04 (0.89–1.21)	0.62	1.08 (0.8–1.46)	0.62	1.12 (0.71–1.78)	0.63
Plasma NfL	0.92 (0.58–1.46)	0.72	1.15 (0.76–1.76)	0.51	0.95 (0.54–1.68)	0.86	0.91 (0.76–1.09)	0.31	1.02 (0.84–1.23)	0.84	1.02 (0.76–1.35)	0.91

Notes: The univariate ordinal logistic regression model was used to assess the probability of each biomarker in predicting advanced degrees of neuropathological changes at autopsy. The OR and its 95% CI and *P*-value were reported from the logistic regression model.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADNC, Alzheimer's disease neuropathological change; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; NfL, neurofilament light chain; OR, odds ratio; PET, positron emission tomography; p-tau181, tau phosphorylated at threonine 181; SUVR, standardized uptake value ratio; t-tau, total tau.

4 | DISCUSSION

This prospective study aimed to assess the difference between PET, CSF, and plasma biomarkers measured at the non-dementia and dementia stages in predicting AD neuropathology at autopsy. We found that levels of amyloid PET, CSF biomarkers (Aβ42/p-tau181, Aβ42, p-tau181, and t-tau), and plasma p-tau181 changed with the progression of AD. These biomarkers showed high discriminative accuracy in differentiating individuals with and without autopsy-confirmed AD and were associated with high odds of advanced stages of different AD neuropathology at autopsy. However, they performed significantly different when measured in individuals with non-dementia and dementia.

Amyloid PET can detect aggregated cerebral amyloid deposition with very high accuracy[25] and is recommended in clinical utility for diagnosing AD[26] and predicting the development of cognitive decline.[27,28] *Ante mortem* amyloid PET measured in CN participants could accurately predict AD neuropathology at autopsy.[11] However, amyloid deposition is estimated to reach a plateau level in later disease stages.[29] In this study, amyloid PET level was markedly increased in early clinical stage of AD compared to control but was not significantly different compared to late clinical stage. Thus, the accuracy of amyloid PET in predicting AD pathology might be poor in the late stage. Our results suggested that *ante mortem* amyloid PET was highly predictive of autopsy-confirmed AD in both stages. However, the AUC of amyloid PET was slightly higher in early than late clinical stages, yielding the amyloid PET cutoff of 1.1 and 1.4, respectively, for predicting autopsy-confirmed AD in the larger sample. In comparison, in the ADNI cohort, the cutoff of abnormal amyloid PET (18F-florbetapir) for describing Aβ positivity was 1.11.[18] In addition, previous studies demonstrated that *ante mortem* amyloid PET was associated with Thal and CERAD scores.[30] Extending these findings, we found an association between amyloid PET and Braak stages both in the early and late clinical stages.

CSF biomarkers (Aβ, p-tau181, and t-tau) are considered promising biomarkers for detecting the concordance with amyloid or tau PET measures in AD.[31–33] However, few CSF-to-autopsy studies investigated its levels in detecting neuropathological changes.[23,34] We found that CSF biomarkers increase or decrease rapidly in the early stage of AD and change slowly in the later stage. Indeed, CSF biomarkers might not be suited for monitoring the progress of neuropathological changes in later stages of AD,[12] as their levels reach a plateau during the dementia stage.[9] Our study supported this notion and found that CSF Aβ42 performed better in the early clinical stage for predicting autopsy-confirmed AD, and CSF p-tau and CSF t-tau performed better in the late clinical stage. Our findings further demonstrated that CSF biomarkers were associated with an increased risk of neuropathological changes at autopsy and that the ORs were higher in the early clinical stage than in the late clinical stage. In addition, we found that CSF Aβ42/p-tau181 showed excellent performance for differentiating autopsy-confirmed AD and predicting the risk of neuropathological changes in both stages. This result was in line with previous autopsy

studies that CSF Aβ42/p-tau181 had high sensitivity, specificity, and diagnostic performance for AD.[23,34]

Blood biomarkers in recent years have been developed in AD because they offer a cost-effective and non-invasive assessment for diagnosing AD.[35–38] Previous plasma-to-autopsy studies demonstrated that plasma p-tau181 levels were significantly associated with neuropathological changes and accurately differentiated autopsy-confirmed AD and other pathologies.[23,38] However, a 17-year follow-up study suggested that plasma p-tau181 may not be well suited for early diagnosis of AD.[39] In the present study, we observed that plasma p-tau181 levels were not different in individuals with control and early AD. Our study showed that plasma p-tau181 alone had high predictive accuracy for autopsy-confirmed AD at a late clinical stage and was associated with increased risk of Thal, Braak, and CERAD stage only at the late clinical stage. In addition, we did not find an association between plasma Aβ42/40 alone and neuropathological change at autopsy, which may be explained by the low inherent dynamic range of plasma Aβ42/40 and analytical errors and measurement biases limiting its routine clinical use.[40] Although plasma t-tau performed better than plasma p-tau181 and plasma Aβ42/40, the limited number of participants may have increased the choice to broaden statistical bias; thus, future large autopsy studies are required to validate our results. Furthermore, our findings and previous studies did not find associations between plasma NfL alone and AD-related neuropathological changes at autopsy.[14,23] The possible explanation may be that NfL is a neurodegenerative biomarker that is elevated in multiple neurodegenerative diseases but may not be a specific marker for AD. In addition, the low performance of plasma biomarkers in this study might also be explained by the platform used, as the performance of plasma biomarkers may be platform dependent.[41,42]

Our results demonstrated that *APOE* ε4 genotypes were an essential predictor for diagnosing AD. *APOE* ε4 is known as a genetic risk factor for AD and has modulatory effects on Aβ and tau pathology.[1] However, little is known about its performance in predicting AD neuropathology at autopsy. Our findings suggest that the diagnostic performance of AD-related biomarkers in predicting autopsy-confirmed AD was significantly improved when combined with *APOE* ε4 status. The diagnostic accuracy of each biomarker was somewhat smaller or improved when additionally combining age at death, sex, and years from last assessment to death, implying that *APOE* ε4 genotypes is the key driver of improvement of diagnostic performance. Moreover, after controlling *APOE* ε4 status, the significance of associations between AD-related biomarkers with AD neuropathology decreased or disappeared. These results provide important implications for future clinical settings to combine *APOE* ε4 genotypes to improve the predictive accuracy of AD-related biomarkers. In particular, in the present study, we found that the diagnostic performance of plasma biomarkers, in combination with *APOE* ε4 status and other covariates, has improved significantly from no discrimination to excellent discrimination. This finding suggests that plasma biomarkers may need to be combined with *APOE* ε4 genotypes and AD-related risk factors, rather than biomarkers alone, to improve their accuracy in predicting AD pathology in the clinical setting.

Previous studies using biomarker evidence for AD have covered only one of these measures of abnormal amyloid in PET or CSF.[3,43,44] However, solely abnormal amyloid deposition may not accurately reflect the presence of AD pathology, and up to 27% of individuals with abnormal amyloid markers but normal tau markers do not have AD at autopsy.[8] Possibly, AD biomarker cutoffs may need recalibration and validation based on autopsy-confirmed cases. In addition, our results showing the different performance of AD biomarkers in different clinical stages prompted us to re-examine the definition of biomarker cutoffs. The time from preclinical stage to prodromal stages to dementia stage was more than 20 years,[45] and longer intervals may have altered neuropathology to such an extent. Thus, the cutoff of biomarkers based on the overall participants does not accurately reflect brain pathology at each clinical stage. Specific cutoffs for each clinical stage may have to be applied for diagnosing AD.

The strength of this study is that this is one of few studies that also had autopsy evidence for individuals with intact clinical diagnosis and the most promising biomarkers of AD at present. To our best knowledge, this is the first study to simultaneously assess the predictive and diagnostic accuracy of three modalities of biomarkers in PET, CSF, and plasma for detecting AD neuropathology at autopsy. This study has several limitations. First, the number of participants in the non-dementia group was relatively small, even in the larger sample, which impedes us from investigating the predictive performance of biomarkers in each clinical stage, that is, CN and MCI. Moreover, the small sample size may have contributed to the limited statistical power in each subgroup.[46] Second, we studied PET analysis based on amyloid PET only, and the lack of tau PET limits the exploration of direct association between neuropathological changes and brain tau deposition. Third, plasma biomarkers of glial fibrillary acidic protein (GFAP) and phosphorylated tau at Thr217 (p-tau217) and Thr231 (p-tau231) have shown high diagnostic accuracy in distinguishing AD from other neurodegenerative disorders in recent studies.[37,39] However, data for these biomarkers were lacking in this study. Fourth, studies have demonstrated the high prevalence of coexistent CAA, LB, and TDP-43 in AD participants.[47–49] In the present study, the proportion of co-pathologies ranged from 17.3% to 49.4% in total samples, and individuals with co-pathologies were more prevalent in dementia than non-dementia participants. However, our study did not exclude individuals with co-pathologies at autopsy due to the limited number of samples, which may influence the interpretation of our results. Additional autopsy studies are needed using different populations to include all clinical stages and biomarker modalities to explore and directly compare biomarker performance in predicting neuropathological changes at each clinical stage of AD after excluding the influence of co-pathologies.

In conclusion, our study demonstrated that *ante mortem* biomarkers of PET, CSF, and plasma in early and late clinical stages are associated with the risk of AD neuropathology at autopsy and are highly predictive and diagnostic of autopsy-confirmed AD. However, their performances were significantly different in each clinical stage, and this needs to be considered in clinical settings, clinical trial enrollment, and research design.

ACKNOWLEDGMENTS

Data used in preparation for this paper were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). The authors thank all participants who donated their brains to the ADNI Neuropathology Core Center. The authors also thank all researchers who collected and processed specimens and performed neuropathological assessments in the ADNI. This work is supported by grants from the Science and Technology Innovation 2030 Major Projects (2022ZD0211600), National Natural Science Foundation of China (82071201 and 81971032), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01), Research Start-up Fund of Huashan Hospital (2022QD002), Excellence 2025 Talent Cultivation Program at Fudan University (3030277001), and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University, China.

We express appreciation to contributors of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; BristolMyers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICTS OF INTERESTS STATEMENT

The authors declare no competing interests. ADNI was approved by the institutional review boards of all participating institutions. All participants provided written informed consent according to the Declaration of Helsinki before study enrollment. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

How to cite this article: Wang Z-B, Tan L, Wang H-F, et al. Differences between *ante mortem* Alzheimer's disease biomarkers in predicting neuropathology at autopsy. *Alzheimer's Dement*. 2023;1-12. https://doi.org/10.1002/alz.12997