The Journal of Prevention of Alzheimer's Disease 12 (2025) 100065

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Influence of *APOE* ε4 on performance of CSF biomarkers in differentiating clinical Alzheimer's disease ☆

Yan Wang [a,1], Fangyu Li [a,1], Qi Qin [a], Tingting Li [a], Qi Wang [a], Yan Li [a], Ying Li [a], Jianping Jia [a,b,c,d,*], Alzheimer's Disease Neuroimaging Initiative

[a] *Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases*
[b] *Beijing Key Laboratory of Geriatric Cognitive Disorders; Clinical Center for Neurodegenerative Disease and Memory Impairment, Capital Medical University*
[c] *Center of Alzheimer's Disease, Beijing Institute of Brain Disorders, Collaborative Innovation Center for Brain Disorders, Capital Medical University*
[d] *Key Laboratory of Neurodegenerative Diseases, Ministry of Education*

ARTICLE INFO

Keywords:
Alzheimer's disease
Apolipoprotein E
Mild cognitive impairment
Biomarker
Cognitive decline

ABSTRACT

Introduction: *Apolipoprotein E* ε4 (*APOE* ε4) bring the higher risk of Alzheimer' Disease (AD). It is essential to evaluate whether the diagnostic performances and critical values of cerebrospinal fluid (CSF) biomarkers are influenced by *APOE* ε4, which has guiding significance for the clinical practical application.

Methods: The differences in CSF biomarkers and their performances between *APOE* ε4 carriers and non-carriers in distinguishing AD, mild cognitive impairment (MCI) and preclinical AD from normal controls (NCs) were analyzed. The receiver operating characteristic (ROC) curves were generated to compare the area under the curve (AUC) between *APOE* ε4 carriers and non-carriers, as well as the critical values corresponding Youden Index.

Results: In a cross sectional convenience sample of 1610 participants, lower Aβ42 and Aβ42/Aβ40 and higher p-Tau 181/Aβ42 in CSF were observed among *APOE* ε4 carriers than non-carriers in NC, MCI, and AD groups ($P<$ 0.05). The performance of CSF p-tau/Aβ42 in distinguishing MCI from NC among *APOE* ε4 carriers was superior to non-carriers [AUC: 0.714 (95%CI: 0.673- 0.752) vs 0.600 (95%CI: 0.564- 0.634), $P<$ 0.001], although it was similar in distinguishing AD from NC between *APOE* ε4 carriers and non-carriers [AUC: 0.874 (95%CI: 0.835- 0.906) vs 0.876 (95%CI: 0.843- 0.904)]. In the longitudinal cohort of 254 participants, the association of CSF Aβ42, Aβ42/Aβ40 and p-Tau181/Aβ42 with cognitive decline were stronger in *APOE* ε4 carriers compared to non-carriers ($P<$ 0.05). Meanwhile, the critical values were different depending on *APOE* genotype.

Discussion: The CSF level of p-Tau181/Aβ42 was significantly different between *APOE* ε4 carriers and non-carriers at different stages of AD. The results indicate that the performances of CSF biomarkers are influenced by *APOE* ε4, which should be considered in the practical application.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease, severely affecting the physical and mental health of the elderly [1]. The early and accurate diagnosis of AD still remains one of the top priorities, enabling patients to initiate interventions before irreversible damage sets in. According to the "AT(N) framework" proposed and updated by the National Institute on Aging and Alzheimer's Association (NIA-AA) [2], fluid biomarkers of AD can be utilized to distinguish mild cognitive impairment (MCI) and AD from normal cognition and to identify the preclinical phase [2,3]. However, challenges persist regarding testing methodologies, critical values and applicable people. Various detec-

☆ 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.

* Corresponding author at: Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, 100053, Beijing, China.
E-mail address: jjp@ccmu.edu.cn (J. Jia).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.tjpad.2025.100065
Received 1 January 2025; Accepted 10 January 2025
Available online 17 January 2025

tion methods may employ different techniques and fragment lengths of polypeptide or protein as references, leading to divergent defined values across different testing approaches [4,5]. Disease onset and progression can vary significantly among populations with different disease risks, and the heterogeneity of biomarkers within the population was high, making it difficult to clearly define a unified critical value [6].

An increasing number of evidence has indicated that AD is a complex and heterogeneous disease with many factors contributing to its pathophysiology. The risk of developing AD is estimated to be 60–80% dependent on heritable factors [6]. Generally, AD is roughly classified into two subgroups, familial AD (FAD) and sporadic AD (SAD) [7]. FAD is often attributed to rare variants in known pathogenic genes, including *APP, PSEN1*, and *PSEN2*, while SAD is associated with multiple risk loci [7]. It is reported that over 40 risk loci have been identified in SAD, with *Apolipoprotein E* (*APOE*) ε4 allele showing the strongest association with AD [6]. Individuals with one ε4 allele have a 2-3-fold increased risk, while those with two ε4 alleles have a 10-15-fold increased risk [8,9]. The specific mechanisms by which *APOE* ε4 influences the occurrence and development of AD remains under investigation [10]. *APOE* ε4 exerts a vital role in the downstream effects of β-amyloid (Aβ) on the aggregation of phosphorylated tau in the living human brain [11–13]. Additionally, *APOE* genotype was correlated with cerebrospinal fluid (CSF) levels of biomarkers during the progression of AD. Higher levels of p-tau181 and lower levels of Aβ42 and Aβ42/40 are observed among *APOE* ε*4* carriers. Furthermore, *APOE* ε4 has been shown to affect the plasma levels of neurofilament light chain (NfL) and brain imaging measurements [14–17]. However, it remains uncertain whether the impact of *APOE* ε4 on biomarkers influences their performances in differentiating clinical AD, and whether the critical values of CSF biomarkers are consistent between *APOE* ε4 carriers and non-carriers.

In order to clarify the impact of *APOE* ε4 on biomarkers and its diagnostic performance, we conducted a comprehensive evaluation and comparison of the performance of CSF biomarkers in differentiating AD, MCI, and preclinical AD from normal controls (NCs) among *APOE* ε4 carriers and non-carriers in a large convenience sample. Concurrently, the corresponding critical values were calculated. Our findings revealed that p-Tau181/Aβ42 in CSF was significantly different between *APOE* ε4 carriers and non-carriers across different stages of AD. Furthermore, its diagnostic performance and critical value for MCI and preclinical AD varied depending on *APOE* ε4 status.

2. Methods

2.1. Cohorts

In this study, the used clinical and demographic data were acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI is a longitudinal multicenter study with convenience samples from specialty clinics to track and evaluate changes in cognition and biomarkers during the progression of MCI and AD. This study was approved by the institutional review board of all participating ADNI centers and written informed consent was acquired from all the participants (a complete list of ADNI sites can be found at http://adni.loni.usc.edu/about/centers-cores/study-sites/).

The inclusion and exclusion criteria for the NC, MCI, and AD cohorts can be obtained at http://adni.loni.usc.edu. In brief, NC participants were included if they had Mini- Mental State Examination (MMSE) scores $\geq$ 24 and Clinical Dementia Rating Scale (CDR) scores of 0, with no confounding neurological or psychological disorders. MCI participants had MMSE scores $\geq$ 23, abnormal memory function measured by the Wechsler Memory Scale Revised-Logical Memory II, CDR scores of 0.5, preserved activities of daily living and absence of dementia. If the participants met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD, reported MMSE scores of 20-26 and CDR scores of 0.5-1.0, they were considered AD dementia. Totally 1610 participants were involved in the cross sectional convenience sample (588 NC, 754 MCI, and 268 AD patients). For the longitudinal follow-up cohort, the cognitively normal (CN) and cognitive decline (CD) groups were included retrospectively in accordance with the following criteria. For the CN group, normal cognitive function was presented at baseline and during 120 months of follow-up. If the participants presented normal cognitive function at baseline, and MMSE $\leq$ 26 or CDR $\geq$ 0.5 during the follow-up, they were in the CD group. A total of 254 participants (188 within CN group and 66 within CD group) were included in the preclinical cohort. To explore the different effects of follow-up on the biomarkers between *APOE* ε4 carriers and non- carriers, this study included the participants with normal cognitive function at baseline and biomarker detections at least twice during the 120 months of follow-up. Publicly available metadata including age, sex, diagnosis at baseline, MMSE score, and *APOE* genotype were collected.

2.2. Biomarkers in cerebrospinal fluid

Roche Elecsys β amyloid(1-42) CSF, Elecsys Total-Tau CSF, and Elecsys Phospho-Tau(181P) CF immunoassays were employed to measure the levels of Aβ42, total-Tau(t-Tau), and Phospho-Tau181(p-Tau 181) in CSF based on the instructions of the preliminary kit manufacturer at the UPenn/ADNI Biomarker Laboratory [18]. 2D-UPLC tandem mass spectrometry was applied to test CSF Aβ42/Aβ40 and Aβ40 levels. Neurofilament light (NfL) in CSF was measured by a sensitive sandwich ELISA method (NF-light ELISA kit, UmanDiagnostics AB, Umeå, Sweden). Glial fibrillary acidic protein (GFAP) in CSF was measured through the CSF multiplex MRM panel which was developed by Caprion Proteomics in collaboration with the Biomarker Consortium Project Team.

2.3. Statistical analysis

The analytic approaches were designed to address the primary objectives, that is to estimate the differences in the performance of CSF biomarkers in distinguishing patients with AD, MCI or preclinical AD from NCs. The chi-square test was employed to explore categorical variables. Fluid biomarkers were compared between *APOE* ε4 carriers and non-carriers with Mann Whitney test or t test depending on whether the data conforms to a normal distribution. The abnormal data in each group deviated from the mean by over three times the standard deviation and were excluded. The linear mixed-effects (LME) models were adopted for examining the effects of different biomarkers and *APOE* ε4 status on longitudinal memory trajectories. Each model was adjusted for age at baseline, education, and sex variables (e.g., [biomarker~ age+ gender+ edu+ group+ time, data, random=~1|patientnumber]). Simple linear regression curve fits were drawn with Prism 8 to show the CSF biomarker trajectories along the MMSE. Receiver-operating characteristic (ROC) curves were used to quantify the area under the ROC curve (AUC), and the difference in the AUC was identified with DeLong statistics. The critical values were determined by the corresponding Youden index. P values < 0.05 represented statistical significance. Prism 8, SPSS Statistics 20.0 and MedCalc statistical software were used for all statistical analyses.

2.4. Data availability

Anonymized data will be available upon reasonable request from a qualified investigator following with ADNI data-sharing protocol (http://adni.loni.usc.edu).

3. Results

3.1. Cohort characteristics by available biomarkers

The cross sectional convenience sample involved 1610 participants (age 72.57 $\pm$ 7.31 years; education 16.18 $\pm$ 2.68 years) consisting of

Table 1
Demographic and clinical profile of the enrolled cohort from ADNI.

	All (n=1610)	CN (n=588)	MCI (n=754)	AD (n=268)
Age, mean (SD), year	72.57 (7.31)	72.40 (6.35)	72.12 (7.55)	74.19 (8.35)
Sex n (%)				
female	757 (47.02)	338 (57.48)	310 (41.11)	109 (40.67)
male	853 (52.98)	250 (42.52)	444 (58.89)	159 (59.33)
Educational attainment, mean (SD), year	16.18 (2.68)	16.58 (2.48)	16.09 (2.73)	15.54 (2.83)
APOE ε4, n (%)				
positive	727 (45.16)	178 (30.27)	365 (48.41)	184 (68.66)
negative	883 (54.84)	410 (69.73)	389 (51.59)	84 (31.34)
MMSE score, mean (SD)	27.50 (2.58)	29.10 (1.13)	27.75 (1.86)	23.29 (2.00)
Race, n (%)				
white	1489 (92.48)	526 (89.46)	707 (93.77)	256 (95.52)
black	69 (4.29)	40 (6.80)	22 (2.92)	7 (2.61)
Asian	23 (1.43)	9 (1.53)	10 (1.33)	4 (1.49)
others	29 (1.80)	13 (2.21)	15 (1.99)	1 (0.37)
Ethnic, n (%)				
Hisp/Latino	56 (3.48)	25 (4.25)	23 (3.05)	8 (2.99)
Not Hisp/Latino	1547 (96.09)	560 (95.24)	729 (96.68)	258 (96.27)
unknown	7 (0.43)	3 (0.51)	2 (0.27)	2 (0.75)

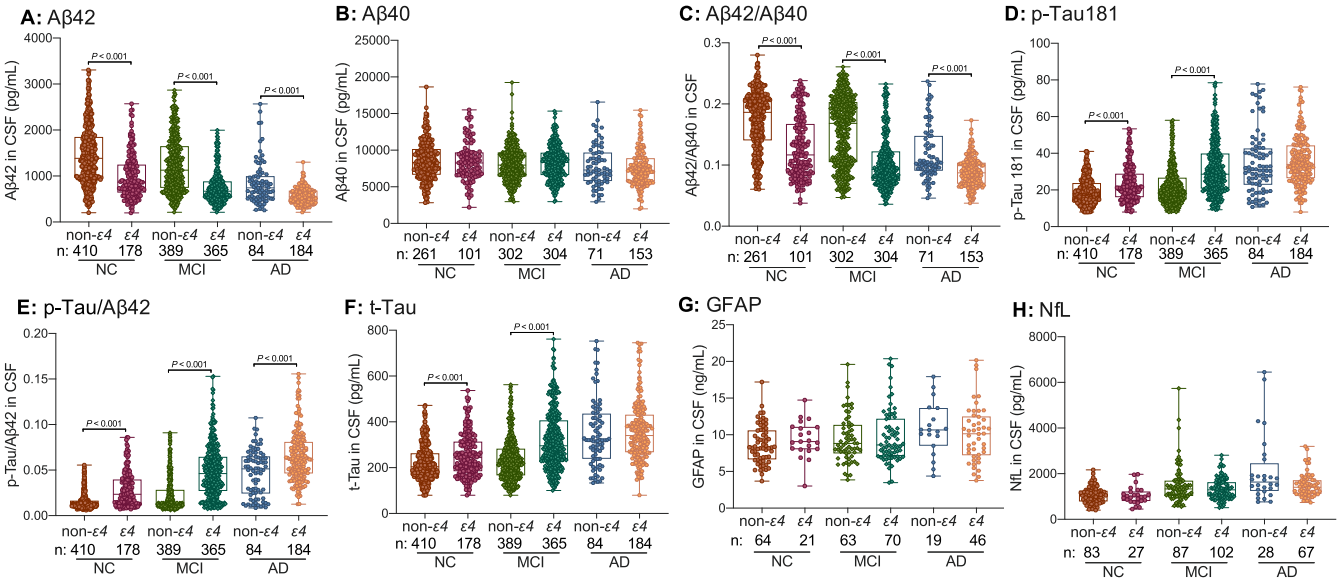


Fig. 1. CSF biomarkers in *APOE* ε4 carriers and non-carriers among NC, MCI and AD groups. Groups were compared using two-sided analysis of covariance with adjustment for age and sex as covariates, followed by Bonferroni corrected post hoc comparisons. All the points were shown from min to max, and the boxes showed median with interquartile range. A-H, The CSF levels of Aβ42, Aβ40, Aβ42/ Aβ40, p-Tau181, p-Tau/Aβ42, t-Tau, GFAP and NfL across groups.

757 (47.02%) females and 853 (52.98%) males; 727/1610 (45.16%) are *APOE* ε4 carriers. Table 1 presents the baseline sociodemographic characteristics of participants separated by cognitive function (588 NC, 754 MCI and 268 AD).

3.2. Comparison of CSF biomarkers between APOE ε4 carriers and non-carriers in the cross sectional convenience sample

A comparison of the differences in CSF biomarkers between *APOE* ε4 carriers and non-carriers at different stages of AD indicated lower Aβ42 and Aβ42/ Aβ40 and higher p-Tau181/Aβ42 in the CSF of *APOE* ε4 carriers than in that of non-carriers in the NC, MCI and AD groups (Fig. 1A, C, and E). The CSF t-Tau and p-Tau181 levels were higher among *APOE* ε4 carriers than those among non-carriers in NC and MCI groups, while they were similar between *APOE* ε4 carriers and non-carriers in AD group (Fig. 1D and F). For GFAP and NfL in CSF, no significant differences were found between *APOE* ε4 carriers and non-carriers across disease progression (Fig. 1G and H). The impact of *APOE* genotype on the biomarkers was still found in female group and male group (Fig. S1 and S2), which was similar with that in whole population.

To analyze dose response relation between *APOE* ε4 and CSF biomarker, the levels of CSF biomarker in *non*-ε4, one ε4 and two ε4 carriers were compared in NC, MCI, and AD groups. It was shown that higher p-Tau181/Aβ42 and lower Aβ42 were in two ε4 carriers than those in one ε4 carriers in the NC, MCI and AD groups (Fig. S3A and D). CSF level of Aβ42/Aβ40 was significantly lower in two ε4 carriers than those in one ε4 carriers in MCI and AD groups (Fig. S3B). No significant difference was observed in CSF t-tau and p-Tau181 between one and two ε4 carriers (Fig. S3C and E).

3.3. Effect of APOE genotype on fluid biomarker trajectories along with cognitive decline

The stratified analyses by *APOE* genotype and the curve simulation model including a cognitive function test MMSE and CSF biomarkers were presented in Fig. 2. There were several important observations. At first, during the decline in cognitive function, the level of CSF Aβ42 and Aβ42/Aβ40 among *APOE* ε4 carriers were below those in non-carriers (MMSE ≥ 19) ($P < 0.001$, Fig. 2A and B). Second, from normal cognition to initial cognitive decline (MMSE ≥ 24), the trajectories of CSF t-Tau

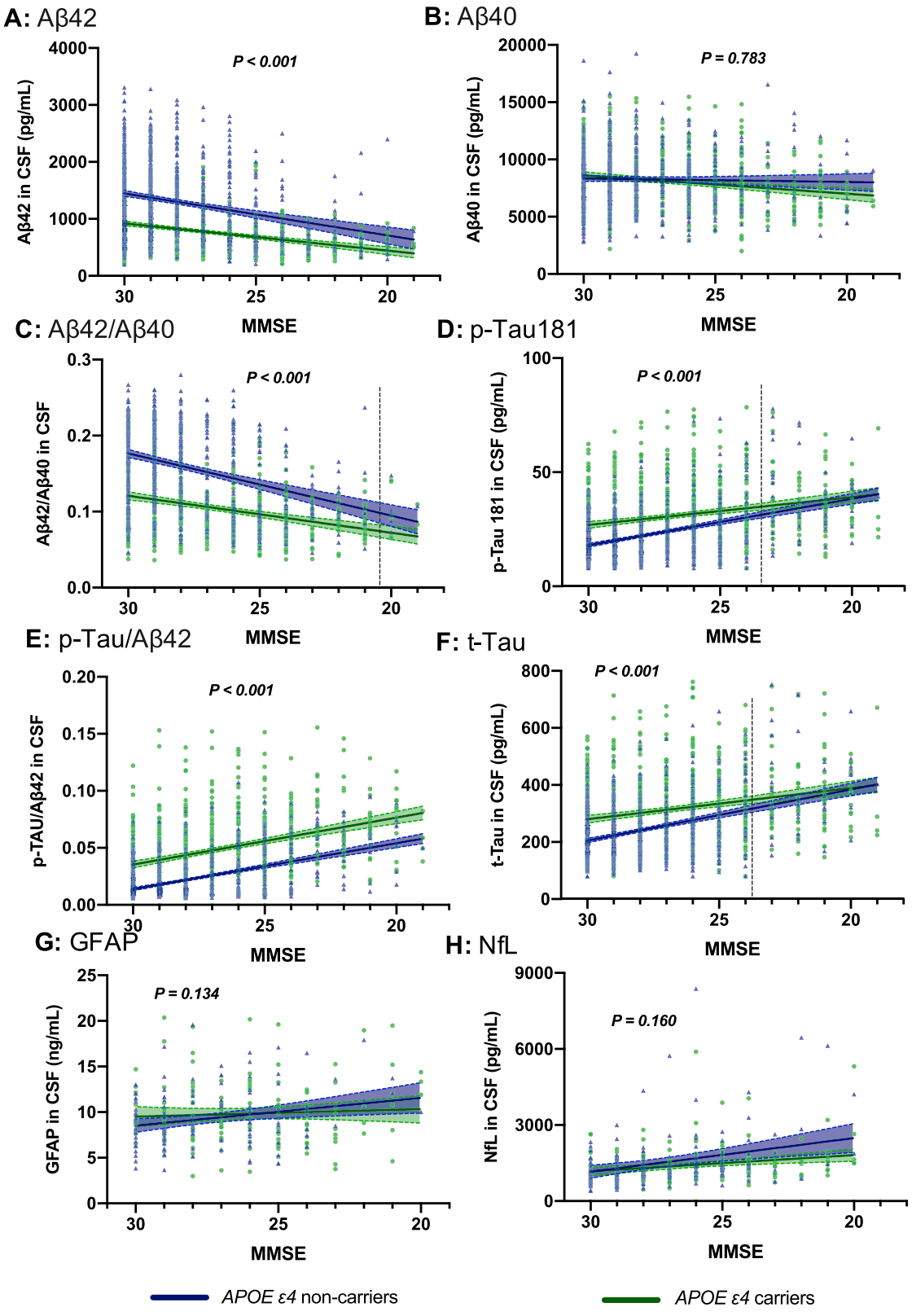


Fig. 2. CSF biomarkers trajectories along with the changes in cognitive function stratified by *APOE* ε4 status. Simple linear regression curve fit showing changes of CSF biomarkers Aβ42(A), Aβ40(B), Aβ42/Aβ40(C), p-Tau181(D), t-Tau(E), p-Tau/Aβ42(F), GFAP(G) and NfL(H), with cognitive decline across *APOE* groups. Shaded areas represent 95% confidence intervals.

and p-Tau181 were different between *APOE* ε4 carriers and non-carriers ($P < 0.05$, Fig. 2D and F). Third, p-Tau181/Aβ42 in CSF was different between *APOE* ε4 carriers and non-carriers ($P < 0.001$, Fig. 2E). Fourth, the trajectories of Aβ40, GFAP and NfL across cognitive decline were largely overlapping in *APOE* ε4 carriers and non-carriers (Fig. 2B, G and H). Furthermore, the trajectories of CSF Aβ42, Aβ42/Aβ40 and p-Tau181/Aβ42 were significantly different between one and two ε4 carriers in dose-response characteristics (Fig. S4A, C and E). However, the trajectories of CSF Aβ40, t-Tau, p-Tau181, GFAP and NfL were similar between one and two ε4 carriers (Fig. S4B, D, F, G and H).

3.4. *Effect of* APOE *genotype on the abilities of biomarkers to distinguish MCI and AD patients from NCs*

The ROC curves of Aβ42, Aβ42/Aβ40, p-Tau181, p-Tau/Aβ42 and t-Tau in CSF were constructed to compare their performances in distinguishing individuals with AD or MCI from NCs between *APOE* ε4 carriers and non-carriers (Fig. 3). Regarding MCI versus NC in *APOE* ε4 carriers, the AUCs of Aβ42, Aβ42/Aβ40, p-Tau181, p-Tau/Aβ42, t-Tau and NfL in CSF were 0.660 (96%CI: 0.618-0.700), 0.650 (96%CI: 0.602-0.697), 0.670 (96%CI: 0.629-0.710), 0.714 (96%CI: 0.673-0.752), and 0.653 (96%CI: 0.611-0.693), respectively. However, in *APOE* ε4 non-carriers, the AUCs were 0.599 (96%CI: 0.564-0.634), 0.588 (96%CI: 0.546-0.629), 0.562 (96%CI: 0.527-0.597), 0.600 (96%CI: 0.564-0.634), and 0.551 (96%CI: 0.515-0.586), respectively. To distinguish MCI from NCs, the AUCs of p-Tau181, p-Tau/ Aβ42 and t-Tau in *APOE* ε4 carriers were significantly higher than those in non- carriers ($P < 0.01$, Fig. 3C, D and E). For AD versus NC, no significant difference in AUCs of these biomarkers was found between *APOE* ε4 carriers and non-carriers (Fig. 3). When analyzing the effect of *APOE* ε4 dose on the ROCs, it was shown that there was no significance in AUC of these biomarkers in differentiating MCI or AD from NC between one ε4 and two ε4 carriers (Fig. S5).

Then, the critical values corresponding to the Youden index for CSF biomarkers in distinguishing individuals with MCI or AD from NCs between *APOE* ε4 carriers and non-carriers were calculated. As shown in the tables below each figure in Fig. 3, the critical values of Aβ42 and Aβ42/Aβ40 for distinguishing patients with AD or MCI from NC were similar between *APOE* ε4 carriers and non-carriers (Fig. 3). The critical values of p-Tau 181 and t-Tau for MCI were 24.59 pg/mL and 266.9 pg/mL in *APOE* ε4 carriers, which were approximately 1.25 and 1.23 times greater than those in non-carriers, respectively (Fig. 3C and E). The critical values of p-Tau 181 and t-Tau for AD patients versus NCs were approximately equal between *APOE* ε4 carriers and non-carriers. The critical values of p-Tau/Aβ42 in CSF in *APOE* ε4 carriers were 0.0407 and 0.0422 for MCI and AD, which were 2.09 and 1.71 times greater than those in non-carriers, respectively (Fig. 3D).

3.5. *Effect of* APOE *genotype on the association of CSF biomarkers with cognitive decline*

APOE ε4 is related to earlier onset of cognitive impairment and amyloidosis accumulation [19]. Combined with the above-mentioned analysis, the association of CSF biomarkers with cognitive decline at the cognitively unimpaired stage may vary widely depending on *APOE* genotype. Totally 254 participants were involved in the longitudinal follow-up cohorts to investigate the impact of *APOE* genotype on the association of biomarkers with cognitive decline (Table S1). There were 66 individuals experiencing cognitive decline during the follow-up. Among them, 21 individuals (31.8%) were *APOE* ε4 carriers. In addition, 188 individuals remained cognitive normal (CN). Compared with the CN group, lower Aβ42 and Aβ42/Aβ40 and higher p-Tau/Aβ42, p-Tau 181 and t-Tau at baseline were observed in cognitive decline (CD) group (Fig. S6).

Furthermore, in stratification analysis by *APOE* genotype, the Aβ42 and Aβ42/Aβ40 levels were lower and p-Tau/Aβ42 were higher among *APOE* ε4 carriers than those among non-carriers in both CN and CD groups (Fig. S7). No significant difference was observed in CSF levels of t-Tau and p-Tau 181 between *APOE* ε4 carriers and non- carriers in either CN or CD groups. When compared with CN group, significant decreases in CSF Aβ42/Aβ40 and increases in p-Tau 181 and p-Tau/Aβ42 were observed in both *APOE* ε4 carriers and non- carriers in CD groups ($P < 0.05$, Fig. S7B-D). The significant decrease in CSF Aβ42 was only found in *APOE* ε4 carriers through the comparison between CN and CD individuals (Fig. S7). Compared with CN groups, a slight increase was observed in t-Tau among *APOE* ε4 non- carriers in CD groups, but not *APOE* ε4 carriers (Fig. S7E).

ROC curve analysis was performed to assess whether the association of CSF biomarkers with cognitive decline could be influenced by *APOE* genotype (Fig. 4). The AUCs of Aβ42, Aβ42/Aβ40 and p-Tau181/Aβ42 for identifying cognitive decline were significantly greater in *APOE* ε4 carriers when compared with non-carriers (0.866 vs 0.571 for Aβ42, 0.853 vs 0.618 for Aβ42/Aβ40, and 0.843 vs 0.654 for p-Tau181/Aβ42, respectively). In addition, no significant difference was observed in the AUCs of p-tau 181 or t-Tau for cognitive decline between *APOE* ε4 carriers and non-carriers. Furthermore, we determined the critical values of biomarkers for identifying cognitive decline in *APOE* ε4 carriers and non-carriers (Fig. 4). The critical value of Aβ42 in CSF was 739.4 pg/mL for the CD versus CN group among *APOE* ε4 carriers, while it was 1345 pg/mL among non-carriers. The critical values of Aβ42/Aβ40 in CSF were 0.117 for *APOE* ε4 carriers and 0.155 for non-carriers. Regarding the CD group versus CN group, the critical values of p-Tau181/Aβ42 in CSF were 0.0175 and 0.0166 among *APOE* ε4 carriers and non-carriers, respectively. The critical values of Aβ42 and Aβ42/Aβ40 in CSF among *APOE* ε4 non-carriers for cognitive decline were nearly 1.82 and 1.32 times greater than those among *APOE* ε4 carriers, respectively.

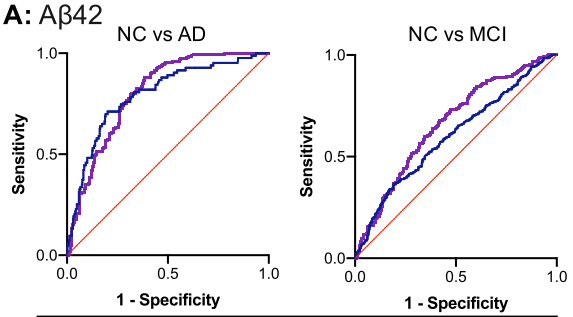
The mean concentration of Aβ42, Aβ42/Aβ40 and p-Tau/ Aβ42 in CSF over time in *APOE ε4* carriers were persistently different from the mean concentration in non- carriers (Fig. S8A, B and D). Compared with non-carriers, CSF p-Tau/ Aβ42 increased faster while Aβ42 and Aβ42/Aβ40 decreased over time in *APOE* ε4 carriers ($P < 0.001$). In addition, CSF p-Tau and t-Tau were gradually converging over time between *APOE ε4* carriers and non- carriers (Fig. S8C and E).

4. Discussion

The diagnostic performances of AT(N) biomarkers in CSF were assessed and compared between *APOE* ε4 carriers and non-carriers among NC, MCI and AD, as well as preclinical AD patients. The findings indicated that the core AD biomarkers, specifically Aβ and p-Tau in CSF, showed significant differences between *APOE* ε4 carriers and non-carriers at different stages of the disease, especially in the early stages. In contrast, nonspecific biomarkers such as NfL and GFAP did not exhibit such disparities. The performance of biomarkers in differentiating individuals with MCI from NCs and identifying cognitive decline was more pronounced among *APOE* ε4 carriers compared to non-carriers. Additionally, the critical values corresponding to the Youden index were different between *APOE* ε4 carriers and non-carriers, providing strong evidence for optimizing the clinical diagnostic model based on the *APOE* genetic risk factors.

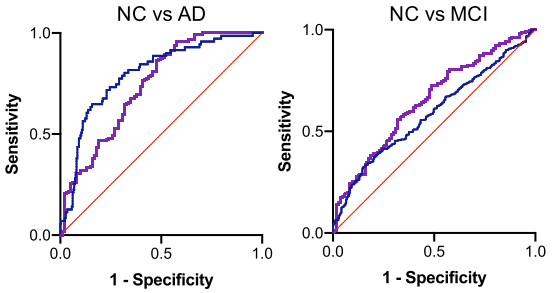
The Aβ proteinopathy defines AD and can therefore be used for diagnosing the disease, among which, abnormal Aβ42 and Aβ42/Aβ40 in CSF specifically represent dysregulated Aβ metabolism and processing [20]. The CSF levels of Aβ42 and Aβ42/Aβ40 can be used to diagnose and identify clinical progression. Earlier and faster Aβ accumulation was observed in *APOE* ε4 carriers than non-carriers [21], which could be reflected by CSF biomarkers. CSF Aβ42 and Aβ42/Aβ40 in *APOE* ε4 carriers remained at lower levels than those in non-carriers among NC, MCI and AD groups, consistent with other studies [21]. Different from others, we further compared the performance of CSF Aβ42 and Aβ42/Aβ40 in differentiating MCI or AD from NCs between *APOE* ε4 carriers and non-carrier. Furthermore, the AUCs and critical values of

A: Aβ42



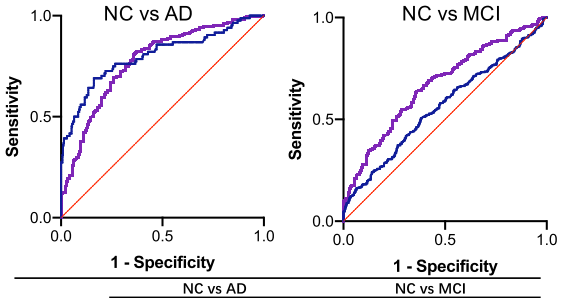
Aβ42	NC vs AD		NC vs MCI	
	ε4 carriers (n= 362)	ε4 non-carriers (n= 494)	ε4 carriers (n= 543)	ε4 non-carriers (n= 799)
AUC (95%CI)	0.803 (0.758-0.843)	0.795 (0.756-0.830)	0.660 (0.618-0.700)	0.599 (0.564-0.634)
critical value (pg/mL)	769.7	910.3	802.6	892.1
sensitivity	87.43	71.08	67.98	36.36
specificity	61.36	79.90	57.95	80.88
PPV	70.18	41.84	76.58	64.22
NPV	82.44	93.14	47.22	57.39

B: Aβ42/Aβ40



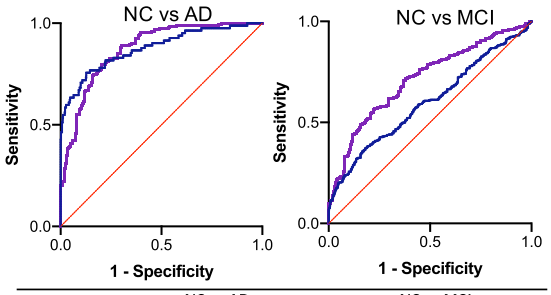
Aβ42/Aβ40	NC vs AD		NC vs MCI	
	ε4 carriers (n= 254)	ε4 non-carriers (n= 332)	ε4 carriers (n= 405)	ε4 non-carriers (n= 563)
AUC (95%CI)	0.743 (0.684 -0.795)	0.798 (0.750 -0.840)	0.650 (0.602-0.697)	0.588 (0.546- 0.629)
critical value	0.115	0.115	0.098	0.114
sensitivity	86.18	64.79	55.92	32.45
specificity	52.48	84.29	68.32	85.06
PPV	73.18	52.87	84.16	71.53
NPV	71.62	89.79	33.99	52.11

C: p-Tau181



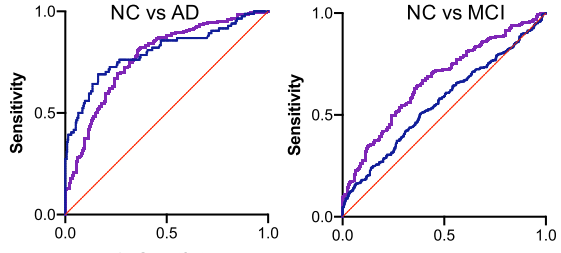
p-Tau 181	NC vs AD		NC vs MCI	
	ε4 carriers (n= 362)	ε4 non-carriers (n= 494)	ε4 carriers (n= 543)	ε4 non-carriers (n= 799)
AUC (95%CI)	0.774 (0.727-0.816)	0.800 (0.762-0.835)	0.670 (0.629-0.710)	0.562*** (0.527 -0.597)
critical value (pg/mL)	24.59	26.30	24.59	19.69
sensitivity	80.66	69.05	63.23	50.66
specificity	64.41	83.79	64.41	61.60
PPV	69.86	47.15	78.28	55.62
NPV	76.51	92.82	46.34	56.78

D: p-Tau/Aβ42



p-Tau/Aβ42	NC vs AD		NC vs MCI	
	ε4 carriers (n= 362)	ε4 non-carriers (n= 494)	ε4 carriers (n= 543)	ε4 non-carriers (n= 799)
AUC (95%CI)	0.874 (0.835-0.906)	0.876 (0.843- 0.904)	0.714 (0.673- 0.752)	0.600*** (0.564- 0.634)
critical value	0.0422	0.0247	0.0407	0.0195
sensitivity	80.66	75.61	56.42	37.2
specificity	64.41	87.25	77.84	82.00
PPV	69.86	54.87	83.82	66.2
NPV	76.51	94.58	46.76	57.95

E: t-Tau



t-Tau	NC vs AD		NC vs MCI	
	ε4 carriers (n= 362)	ε4 non-carriers (n= 494)	ε4 carriers (n= 543)	ε4 non-carriers (n= 799)
AUC (95%CI)	0.750 (0.702-0.794)	0.787 (0.748- 0.823)	0.653 (0.611- 0.693)	0.551** (0.515- 0.586)
critical value (pg/mL)	264.7	273	266.9	217.8
sensitivity	78.02	72.29	59.83	53.40
specificity	63.48	79.16	64.61	59.06
PPV	68.60	41.67	77.42	55.28
NPV	73.86	93.27	44.23	57.21

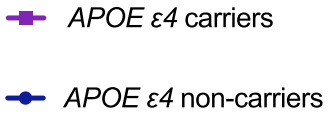
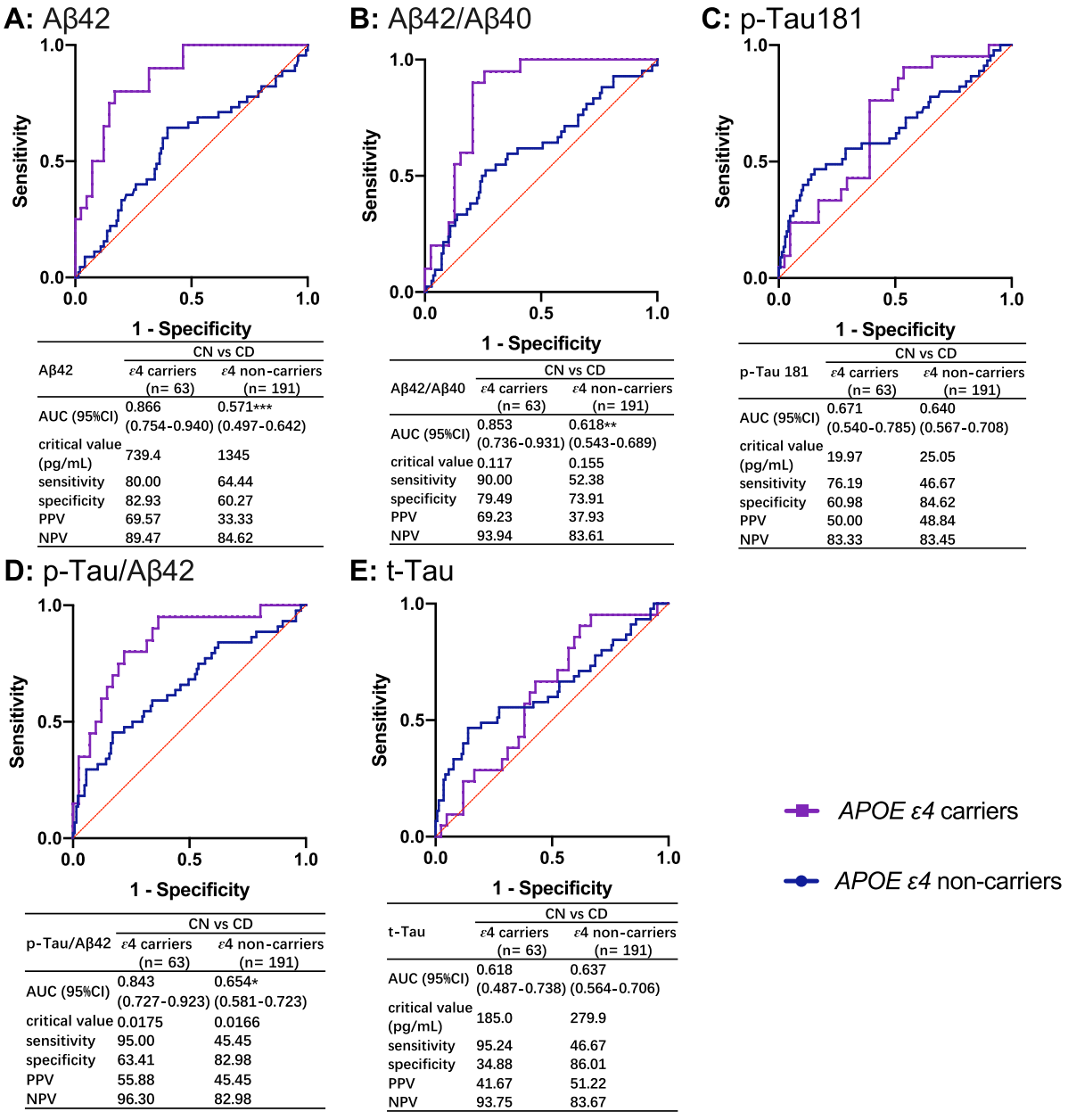


Fig. 3. The distinguish capacity of CSF biomarkers in *APOE* ε4 carriers and non-carriers. Receiver operating curves (ROCs) showed the performance of CSF biomarkers for distinguishing AD and MCI from CN, and the below tables corresponding each ROC showed the area under the curves and the critical values corresponding to Youden Index. Comparisons of ROC curves between *APOE* ε4 carriers and non-carriers were using DeLong test. A-E, The CSF biomarkers of Aβ42, Aβ42/Aβ40, p-Tau181, p-Tau/Aβ42, and t-Tau. PPV, Positive Predictive Value; NPV, Negative Predictive Value. *, $P < 0.05$. **, $P < 0.01$.



Aβ42	CN vs CD	
	ε4 carriers (n= 63)	ε4 non-carriers (n= 191)
AUC (95%CI)	0.866 (0.754-0.940)	0.571*** (0.497-0.642)
critical value (pg/mL)	739.4	1345
sensitivity	80.00	64.44
specificity	82.93	60.27
PPV	69.57	33.33
NPV	89.47	84.62

Aβ42/Aβ40	CN vs CD	
	ε4 carriers (n= 63)	ε4 non-carriers (n= 191)
AUC (95%CI)	0.853 (0.736-0.931)	0.618** (0.543-0.689)
critical value	0.117	0.155
sensitivity	90.00	52.38
specificity	79.49	73.91
PPV	69.23	37.93
NPV	93.94	83.61

p-Tau 181	CN vs CD	
	ε4 carriers (n= 63)	ε4 non-carriers (n= 191)
AUC (95%CI)	0.671 (0.540-0.785)	0.640 (0.567-0.708)
critical value (pg/mL)	19.97	25.05
sensitivity	76.19	46.67
specificity	60.98	84.62
PPV	50.00	48.84
NPV	83.33	83.45

p-Tau/Aβ42	CN vs CD	
	ε4 carriers (n= 63)	ε4 non-carriers (n= 191)
AUC (95%CI)	0.843 (0.727-0.923)	0.654* (0.581-0.723)
critical value	0.0175	0.0166
sensitivity	95.00	45.45
specificity	63.41	82.98
PPV	55.88	45.45
NPV	96.30	82.98

t-Tau	CN vs CD	
	ε4 carriers (n= 63)	ε4 non-carriers (n= 191)
AUC (95%CI)	0.618 (0.487-0.738)	0.637 (0.564-0.706)
critical value (pg/mL)	185.0	279.9
sensitivity	95.24	46.67
specificity	34.88	86.01
PPV	41.67	51.22
NPV	93.75	83.67

Fig. 4. The identification ability of CSF biomarkers in *APOE* ε4 carriers and non-carriers. Receiver operating curves (ROCs) showed the performance of CSF biomarkers in identification for longitudinal cognitive decline in preclinical AD, and the below tables corresponding each ROC showed the area under the curves and the critical values corresponding to Youden Index. Comparisons of ROC curves between *APOE* ε4 carriers and non-carriers were using DeLong test. A-E, The CSF biomarkers of Aβ42, Aβ42/Aβ40, p-Tau181, p-Tau/Aβ42, and t-Tau. PPV, Positive Predictive Value; NPV, Negative Predictive Value. *, $P < 0.05$. **, $P < 0.01$.

CSF Aβ42 and Aβ42/Aβ40 were similar between two groups, suggesting that they could be applied to *APOE* ε4 carriers and non-carrier without distinction.

The p-Tau abnormality, as an early event in AD pathogenesis, was related to amyloid-β accumulation [22]. In the revised criteria for diagnosis and staging of AD, phosphorylated tau which included p-Tau181, p-Tau217 and p-Tau 231 was the core T1 biomarker [23]. We discovered that p-Tau181 in CSF was higher in *APOE* ε4 carriers than non-carrier among NC and MCI groups, similar to those observed in the cognitively unimpaired adults and MCI [22,24,25]. While the discrepancy of p-Tau181 reduced between *APOE* ε4 carriers than non-carrier in AD group, which was similar to the influence of *APOE* ε4 on plasma p-tau181 [26]. It is probably because the disease process is active at the stage of clinically manifested AD, and as a genetic risk factor, the impact of *APOE* ε4 on tau burden diminished [26,27]. There was difference in the impact *APOE* ε4 on p-Tau at the early and late stages of AD, while the key mechanism needed to be further explored.

It has been reported that p-tau/Aβ42 is optimized to diagnose AD and MCI from NC, which can reflect the two proteinopathies once defined as AD [3,28]. The CSF p-tau/Aβ42 ratio remained higher in *APOE* ε4 carriers than that in non-carriers among NC, MCI and AD, similar to previous reports among Alzheimer's continuum, AD, and non-AD patients. The *APOE* genotype influences not only the level of CSF p-Tau/Aβ42 but also its capability of distinguishing MCI and AD from NC. Using ROC analysis, CSF p-Tau/Aβ42 was more appropriate for distinguishing MCI from NCs for *APOE* ε4 carriers. The critical values for both MCI and AD patients were different between *APOE* ε4 carriers and non-carriers. Therefore, a clinical diagnostic model needs to be constructed according

to *APOE* genotype when CSF p-Tau/Aβ42 is used to distinguish individuals with MCI or AD from NCs.

For the biomarkers that were nonspecific but important in AD pathogenesis, GFAP and NfL in CSF were overlapping across disease progression. However, the change in CSF t-Tau was similar to CSF p-tau 181 between *APOE* ε4 carriers and noncarriers among the NC, MCI and AD groups. It has been indicated that t-tau in CSF begins to increase early in autosomal dominant AD, consistent with the previous study [29]. The performance of CSF t-Tau in distinguishing MCI from NCs was better in *APOE* ε4 carriers than that in noncarriers, indicating that it was more suitable for *APOE* ε4 carriers. Furthermore, the critical values corresponding to the Youden index differed based on the *APOE* genotype.

As the increased risk with *APOE* ε4 dose [30], we found these CSF levels of Aβ42, Aβ42/Aβ40, and p-Tau/Aβ42 were in a ε4 dose-dependent manner. When performing the ROCs of these biomarkers in differentiating AD and MCI from NC, there was no significantly different between one ε4 and two ε4 carriers. While the ROCs among two ε4 carriers were not as robust as that among one ε4 carriers, this may be due to the small sample size after subgrouping. Due to the relatively small sample size in *APOE* ε4 homozygous population in NC group, the critical values were calculated between *APOE* ε4 positive and negative populations. In the future, it would be valuable that more ε4 heterozygous and homozygous individuals were further stratified to improve the clinical performance of biomarkers.

CSF biomarkers levels were changed 20 years prior to the onset of AD, which were also the key pathological proteins promoting cognitive impairment [31]. Changes in these biomarkers may serve as indicators to identify future cognitive decline [31,32]. Based on the changes in cognitive scale scores after 4 to 10 years, the group of individuals with normal cognition was further divided into those who experienced future cognitive decline and those who remained cognitively stable. There was obviously different in these biomarkers between the two groups. The CSF levels of Aβ42, Aβ42/ Aβ40, and p-Tau/Aβ42 were particularly influenced by *APOE* ε4 status. The AUCs were significantly higher for *APOE* ε4 carriers compared to non-carriers, and the critical values of Youden Index were also different. The findings suggested the importance of considering *APOE* ε4 status when employing these biomarkers and setting cut points for the detection of cognitive decline. As scale scores were mainly employed to determine the cognitive decline in this study, a larger longitudinal cohort with diagnostic systems or cognitive composites is warranted to further validate the influence of *APOE* genotype on the ability of biomarkers to identify clinical cognitive decline in future.

Ideally, there should be no overlap in the levels of biomarkers between disease group and normal group. However, the overlap and spread of biomarkers always exist [31]. The potential reason is that biomarkers are naturally present in the body and are primarily altered by diseases [31]. However, they might also be influenced by heterogeneity of the disease, complications and other factors [23,33–35]. The solution is to explore more specific and sensitive biomarkers and/or to combine some biomarkers simultaneously [36,37]. In this study, we found the level of CSF biomarkers was different between *APOE* ε4 carriers and non-carriers at different stages of disease. After subdividing people into *APOE* ε4 carriers and non-carriers, the overlap and spread of biomarkers was reduced to some extent. Rational subgrouping was also a possible solution.

This was an interesting preliminary finding from the ADNI cohort, while this study still had the following limitations. At first, the ADNI subjects were relatively young age, relatively high educational achievement, and relatively high frequency of *APOE* ε4. Therefore, it needs to be further verified in a wide variety of people with different races, socioeconomic status and social stratification to determine generalizability of the results. Secondly, AT(N) biomarkers, but not other new biomarkers, were selected for this study. More biomarkers should be identified by omics techniques to enhance the accurate diagnosis. Thirdly, the sample size for preclinical AD patients with *APOE* ε4 alleles was limited. Fourthly, individuals with MCI in this study might not be all due to AD dementia. The heterogeneity in MCI might lower AUC of ROC. The population with amyloid and tau PET would be needed to verify the impact of *APOE* ε4 on the performance of CSF biomarkers in differentiating clinical AD in a larger cohort in the future. Some performance characteristics were not as good as expected, such as PPV and NPV, which may be due to the limited clinical discriminative power of using a single biomarker. A combination of multiple biomarkers may significantly enhance these performance characteristics. Nevertheless, significant differences were observed between the two groups. Therefore, further study among a larger population is still needed.

In conclusion, this was a comprehensive and in-depth analysis to clarify the impact of *APOE* ε4 on the core biomarkers of AD. This study indicated that *APOE* ε4 influenced the core biomarkers of AD in CSF starting from the asymptomatic stage. Moreover, the identification capabilities of the CSF biomarkers for the early stage of the disease in *APOE* ε4 carriers were much better relative to those in non-carriers, with different critical values corresponding to the Youden index. The findings demonstrate that diagnostic model for clinical AD based on core biomarkers and critical values can be considered according to *APOE* ε4 status, which can therefore enhance the accuracy of its clinical application.

Declaration of competing interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Yan Wang: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Fangyu Li:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Qi Qin:** Data curation, Formal analysis, Software. **Tingting Li:** Formal analysis, Methodology, Validation. **Qi Wang:** Project administration, Visualization, Writing – original draft. **Yan Li:** Software, Validation, Writing – review & editing. **Ying Li:** Data curation, Methodology, Writing – review & editing. **Jianping Jia:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Acknowledgments

The data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). The authors thank all participants and all investigators for this project.

Funding

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.

This study was funded by STI2030-Major Projects (No. 2021ZD0201802); Beijing Brain Initiative from Beijing Municipal Science & Technology Commission (Z201100005520017); the Key Project of the National Natural Science Foundation of China (U20A20354); the grant from the Chinese Institutes for Medical Research (CX23YZ15); the National Key Scientific Instrument and Equipment Development Project (31627803); and the Key Project of the National Natural Science Foundation of China (81530036).

Data sharing

The data that support the findings of this study will be available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100065.

References

[1] Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. Lancet Public Health 2020;5(12):e661–ee71. doi:10.1016/s2468-2667(20)30185-7.
[2] Bianchetti A, Ikeda M, Mateos R, et al. The NIA-AA revised clinical criteria for Alzheimer's disease: are they too advanced? Int Psychogeriatr 2023;35(12):679–81. doi:10.1017/S1041610223000868.
[3] Mattsson-Carlgren N, Salvadó G, Ashton NJ, et al. Prediction of longitudinal cognitive decline in preclinical Alzheimer disease using plasma biomarkers. JAMA Neurol 2023;80(4):360–9. doi:10.1001/jamaneurol.2022.5272.
[4] Dakterzada F, Cipriani R, Lopez-Ortega R, et al. Assessment of the correlation and diagnostic accuracy between cerebrospinal fluid and plasma Alzheimer's disease biomarkers: a comparison of the Lumipulse and Simoa platforms. Int J Mol Sci 2024;25(9). doi:10.3390/ijms25094594.
[5] Lim HJ, Park JE, Kim BC, et al. Comparison of two analytical platforms in cerebrospinal fluid biomarkers for the classification of Alzheimer's disease spectrum with amyloid PET imaging. J Alzheimers Dis 2020;75(3):949–58. doi:10.3233/JAD-191331.
[6] Scheltens P, Strooper BD, Kivipelto M, et al. Alzheimer's disease. Lancet 2021;397(10284):1577–90. doi:10.1016/s0140-6736(20)32205-4.
[7] Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 2019;51(3):404–13. doi:10.1038/s41588-018-0311-9.
[8] Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. Nat Genet 2019;51(3):414–30. doi:10.1038/s41588-019-0358-2.
[9] Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 2013;45(12):1452–8. doi:10.1038/ng.2802.
[10] Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol 2021;20(1):68–80. doi:10.1016/S1474-4422(20)30412-9.
[11] Ferrari-Souza JP, Bellaver B, Ferreira PCL, et al. APOEε4 potentiates amyloid β effects on longitudinal tau pathology. Nat Aging 2023;3(10):1210–18. doi:10.1038/s43587-023-00490-2.
[12] Lautner R, Insel PS, Skillbäck T, et al. Preclinical effects of APOE ε4 on cerebrospinal fluid Aβ42 concentrations. Alzheimers Res Ther 2017;9(1):87. doi:10.1186/s13195-017-0313-3.
[13] Wang HF, Shen XN, Li JQ, et al. Clinical and biomarker trajectories in sporadic Alzheimer's disease: a longitudinal study. Alzheimers Dement (Amst) 2020;12(1):e12095. doi:10.1002/dad2.12095.
[14] Tato-Fernandez C, Ekblad LL, Pietila E, et al. Cognitively healthy APOE4/4 carriers show white matter impairment associated with serum NfL and amyloid-PET. Neurobiol Dis 2024;192:106439. doi:10.1016/j.nbd.2024.106439.
[15] Langella S, Bonta K, Chen Y, et al. Impact of APOE epsilon4 and epsilon2 on plasma neurofilament light chain and cognition in autosomal dominant Alzheimer's disease. Alzheimers Res Ther 2024;16(1):208. doi:10.1186/s13195-024-01572-y.
[16] Nemes S, Logan PE, Manchella MK, et al. Sex and APOE epsilon4 carrier effects on atrophy, amyloid PET, and tau PET burden in early-onset Alzheimer's disease. Alzheimers Dement 2023;19(Suppl 9):S49–63 Suppl 9. doi:10.1002/alz.13403.
[17] Malek-Ahmadi M, Su Y, Ghisays V, et al. Plasma NfL is associated with the APOE epsilon4 allele, brain imaging measurements of neurodegeneration, and lower recall memory scores in cognitively unimpaired late-middle-aged and older adults. Alzheimers Res Ther 2023;15(1):74. doi:10.1186/s13195-023-01221-w.
[18] Berger M, Cooter M, Roesler AS, et al. APOE4 copy number-dependent proteomic changes in the cerebrospinal fluid. J Alzheimer's Dis. JAD 2021;79(2):511–30. doi:10.3233/jad-200747.
[19] Williams OA, An Y, Armstrong NM, et al. Apolipoprotein E epsilon4 allele effects on longitudinal cognitive trajectories are sex and age dependent. Alzheimers Dement 2019;15(12):1558–67. doi:10.1016/j.jalz.2019.07.011.
[20] Almkvist O, Nordberg A. A biomarker-validated time scale in years of disease progression has identified early- and late-onset subgroups in sporadic Alzheimer's disease. Alzheimers Res Ther 2023;15(1):89. doi:10.1186/s13195-023-01231-8.
[21] Polsinelli AJ, Lane KA, Manchella MK, Logan PE, Gao S, Apostolova LG. APOE ε4 is associated with earlier symptom onset in LOAD but later symptom onset in EOAD. Alzheimer's & Dement. J. Alzheimer's Assoc. 2023;19(5):2212–17. doi:10.1002/alz.12955.
[22] Therriault J, Vermeiren M, Servaes S, et al. Association of phosphorylated tau biomarkers with amyloid positron emission tomography vs tau positron emission tomography. JAMA Neurol 2023;80(2):188–99. doi:10.1001/jamaneurol.2022.4485.
[23] Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's association workgroup. Alzheimers Dement 2024;20(8):5143–69. doi:10.1002/alz.13859.
[24] Weigand AJ, Ortiz G, Walker KS, et al. APOE differentially moderates cerebrospinal fluid and plasma phosphorylated tau181 associations with multi-domain cognition. Neurobiol Aging 2023;125:1–8. doi:10.1016/j.neurobiolaging.2022.10.016.
[25] Lim YY, Yassi N, Bransby L, et al. CSF Abeta(42) and tau biomarkers in cognitively unimpaired Abeta- middle-aged and older APOE epsilon4 carriers. Neurobiol Aging 2023;129:209–18. doi:10.1016/j.neurobiolaging.2023.05.009.
[26] Salami A, Adolfsson R, Andersson M, et al. Association of APOE varepsilon4 and Plasma p-tau181 with Preclinical Alzheimer's disease and longitudinal change in hippocampus function. J Alzheimers Dis 2022;85(3):1309–20. doi:10.3233/JAD-210673.
[27] Jack CR Jr. Preclinical Alzheimer's disease: a valid concept. Lancet Neurol 2020;19(1):31. doi:10.1016/S1474-4422(19)30440-5.
[28] Salvadó G, Larsson V, Cody KA, et al. Optimal combinations of CSF biomarkers for predicting cognitive decline and clinical conversion in cognitively unimpaired participants and mild cognitive impairment patients: A multi-cohort study. Alzheimer's & Dement J Alzheimer's Assoc 2023;19(7):2943–55. doi:10.1002/alz.12907.
[29] Barthélemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 2020;26(3):398–407. doi:10.1038/s41591-020-0781-z.
[30] Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. Nat Med 2024;30(5):1284–91. doi:10.1038/s41591-024-02931-w.
[31] Jia J, Ning Y, Chen M, et al. Biomarker changes during 20 years preceding Alzheimer's disease. N Engl J Med 2024;390(8):712–22. doi:10.1056/NEJMoa2310168.
[32] Jia J, Ning Y, Chen M, et al. Biomarker Changes during 20 years preceding Alzheimer's disease. N Engl J Med 2024;390(8):712–22. doi:10.1056/NEJMoa2310168.
[33] Lee WP, Choi SH, Shea MG, et al. Association of common and rare variants with Alzheimer's disease in more than 13,000 diverse individuals with whole-genome sequencing from the Alzheimer's Disease Sequencing Project. Alzheimers Dement 2024. doi:10.1002/alz.14283.
[34] Alemany S, Crous-Bou M, Vilor-Tejedor N, et al. Associations between air pollution and biomarkers of Alzheimer's disease in cognitively unimpaired individuals. Environ Int 2021;157:106864. doi:10.1016/j.envint.2021.106864.
[35] Iulita MF, Bejanin A, Vilaplana E, et al. Association of biological sex with clinical outcomes and biomarkers of Alzheimer's disease in adults with Down syndrome. Brain Commun 2023;5(2) fcad074. doi:10.1093/braincomms/fcad074.
[36] Wang X, Zhang X, Liu J, et al. Synaptic vesicle glycoprotein 2 A in serum is an ideal biomarker for early diagnosis of Alzheimer's disease. Alzheimers Res Ther 2024;16(1):82. doi:10.1186/s13195-024-01440-9.
[37] Shen Y, Timsina J, Heo G, et al. CSF proteomics identifies early changes in autosomal dominant Alzheimer's disease. Cell 2024;187(22):6309–26 e15. doi:10.1016/j.cell.2024.08.049.