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RESEARCH ARTICLE

Plasma amyloid-β oligomerization tendency as a potential predictor for conversion from mild cognitive impairment to Alzheimer's dementia: Findings from the GMCII cohort

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Abstract

INTRODUCTION: This study aimed to explore the association between plasma amyloid-β oligomerization tendency (OAβ) and cognitive performance in Alzheimer's disease (AD) and determine its predictive value for outcomes of mild cognitive impairment (MCI).

METHODS: Plasma from 727 subjects (286 AD, 260 MCI, and 181 controls) in a case registry was analyzed using the multimer detection system (MDS) to measure plasma OAβ.

RESULTS: Elevated plasma OAβ was strongly correlated with multidomain cognitive performance in patients with MCI and AD. Patients with MCI with high baseline plasma OAβ demonstrated a higher risk of progressing to dementia (hazard ratio = 1.083, 95% confidence interval [CI] 1.032–1.137). Baseline plasma OAβ effectively predicted MCI-dementia conversion (area under the curve [AUC] = 0.824, 95% CI 0.752–0.897).

DISCUSSION: The real-world findings underscore the clinical relevance of plasma OAβ as a potential predictor for the conversion from mild cognitive impairment (MCI) to dementia.

KEYWORDS
Alzheimer's disease, amyloid, biomarker, mild cognitive impairment, oligomerization

Highlights

- We recruit study participants of Alzheimer's dementia (AD), mild cognitive impairment (MCI), and cognitively normal controls in a case registry.
- We use the multimer detection system (MDS) to measure plasma amyloid-β oligomerization tendency (OAβ).
- We observe that elevated plasma OAβ strongly correlates with multidomain cognitive performance in patients with MCI and AD.

Yuhan Xie and Xue Meng contributed equally to this study.

- MCI individuals with high baseline plasma OAβ demonstrate a higher risk of progressing to dementia.
- The real-world findings underscore the clinical relevance of plasma Oaβ as a potential predictor for the conversion from MCI to dementia.

1 | BACKGROUND

The biological underpinnings of Alzheimer's disease (AD) have drawn much attention since the proposal of the amyloid-β (Aβ), pathologic tau, and neurodegeneration (ATN) research framework in 2018.[1] However, the ATN framework is not widely used in routine clinical scenarios partially due to the barriers against cerebrospinal fluid (CSF) acquisition and positron emission tomography (PET) scans.[2] Conversely, peripheral blood collection presents a promising avenue for discovering new blood-based biomarkers.[3–6] Despite substantial investment in researching new blood biomarkers, our current understanding remains limited, particularly concerning clinical applications, owing to the complex pathogenesis of AD.

The amyloid cascade hypothesis, a cornerstone in AD pathology, suggests that AD arises from an imbalance in the production and clearance of Aβ.[7] Nonetheless, this hypothesis fails to fully explain various aspects of AD, prompting the recent consideration of amyloid oligomers.[8,9] Aβ oligomers, formed early in AD progression[10] preceding Aβ plaques and clinical symptoms, are believed to be the most toxic component during the Aβ pathogenesis.[11–13] The Aβ oligomerization tendency (OAβ) has yet to be recognized as a biomarker, partly due to insufficient research on their association with cognitive decline, particularly in the early stages.

Limited research exists on plasma Aβ oligomers as AD biomarkers, but findings generally indicate elevated levels in AD patients.[14,15] Despite promising results, studies suffer from small sample sizes and limitations in accurate assay of plasma Aβ oligomerization. Additionally, there is a paucity of research incorporating mild cognitive impairment (MCI) into the disease spectrum. Thus, further research with larger samples is warranted to validate the utility of plasma Aβ oligomerization, especially in MCI.

Cognitive decline is a pivotal indicator in AD management, with deficits manifesting in various domains during the early stages.[16] Combining blood biomarkers with cognitive assessments can aid disease monitoring and treatment guidance. However, research on the relationship between Aβ oligomerization and cognition remains scarce, particularly in the early stages.

While plasma Aβ levels have shown predictive value in MCI-to-AD progression,[17] studies on the role of Aβ oligomerization in this process are limited.[18] Jongbloed et al. conducted the only follow-up study on the ability of cerebrospinal fluid (CSF) Aβ-oligomer levels to predict the risk of MCI-to-AD conversion[18]; however, they obtained a negative result. Besides, the outcome of MCI remains heterogeneous.[19,20] Investigating the predictive value of OAβ on MCI-to-AD conversion is crucial for guiding clinical interventions.

Given these research gaps, our study aimed to explore the relationship between plasma OAβ and cognitive function along the MCI-to-AD spectrum. We hypothesize that plasma OAβ correlates with multidomain cognitive performance, particularly in early cognitive impairment stages, and predicts MCI-to-AD conversion outcomes.

2 | METHODS

2.1 | Participants

A total of 368 people with AD, 340 people with MCI, and 278 cognitively normal controls (NC) were recruited from the cohort of the Geriatric Mood and Cognitive Impairment Initiative (GMCII) at the Dementia Care and Research Centre, Peking University Institute of Mental Health. All subjects participated in a standardized research scheme, including demographic information collection, neuropsychological examination, and blood sample collection. A dementia specialist interviewed all participants prior to making each diagnosis. The enrollment process is shown in Figure 1.

The inclusion criteria for the AD group were as follows: (1) aged between 55 and 85 years; (2) met both the criteria for dementia according to the International Classification of Diseases, 10th Revision (ICD-10) and the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and the Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA); and (3) had more than 6 years of education. The inclusion criteria for the MCI group were as follows: (1) aged between 55 and 85 years; (2) met Petersen's criteria, that is, a memory complaint confirmed by an informant, normal general cognitive function, as defined by a global Clinical Dementia Rating (CDR) score of 0.5, and preserved activities of daily living; and (3) had more than 6 years of education. The inclusion criteria for the NC group were as follows: (1) aged between 55 and 85 years; (2) had no complaints of memory decline; (3) had more than 6 years of education; (4) a Mini-Mental State Examination (MMSE) score $\geq$ 24; and (5) had normal daily living abilities. Participants were excluded if they had a history of other psychiatric disorders (e.g., schizophrenia, bipolar disorder, major depressive disorder, alcohol or substance abuse/dependence), stroke, other focal brain injury or other neurodegenerative conditions, or any hearing or visual impairment that could prevent the efficient completion of an evaluation.

The GMCII cohort was formulated through the case registry of multiple studies approved by the Institutional Review Board of Peking University Sixth Hospital. All participants of these studies provided informed consent to participate in the formulation of the GMCII

cohort and consented that the blood sample could be analyzed anonymously.

2.2 | Neuropsychological tests

All participants were administered comprehensive neuropsychological tests, including the MMSE, Montreal Cognitive Assessment (MoCA), Cognitive Abilities Screening Instrument (CASI), Common Objects Memory Test (COMT), visual reproduction, verbal fluency, digit span, and figure completion tests.[21–26]

All neuropsychology tests were conducted in Mandarin. The COMT is a subtest of the Cross-Cultural Neuropsychological Test Battery (CCNB), which assesses participants' language ability and recent memory. The visual reproduction test consists of reproduction and recall and mainly evaluates visual-spatial memory function. The animal verbal fluency test mainly assessed the subjects' language ability. The forward and backward digit span tests assessed participants' attention. The picture completion tests mainly evaluated the individual's reasoning ability. Higher scores indicated better comprehension.

2.3 | Plasma preparation

Venous blood was collected in 6 mL BD Vacutainer ethylene diamine tetraacetic acid (EDTA) tubes; samples were then centrifugated at 850 × *g* for 30 min at room temperature (RT). Plasma separation was performed within 3 h of sample collection. The plasma was finally aliquoted into polypropylene tubes (1.5 mL) in volumes of 500 µL and stored at −80°C until assayed.

2.4 | Quantifying the plasma OAβ levels

The AlzOn^{+} assay kit (donated by PeopleBio, Inc., Korea) was used to quantify plasma OAβ. The antibodies used in the assay kit were the mouse monoclonal antibody 6E10 (BioLegend, San Diego, CA, USA) and the WO2-HRP antibody (Absolute Antibody Ltd., Oxford, UK). A well-trained technician blinded to the diagnostic information of the samples performed the experiments according to the manufacturer's protocol.

Before assay, aliquots of plasma samples were thawed at 37°C for 15 min. Ten microlitres of plasma, 4 µL of human anti-murine antibody (HAMA) blocker (Scantibodies Laboratory, Santee, CA, USA), and 90 µL of assay buffer were mixed. Ten microliters of PBR-1 (1% proprietary material + 1.25% dimethyl sulfoxide [DMSO] + 96.75% phosphate-buffered saline containing Tween 20 [PBST] + 1% ultra-pure water) was mixed into the plasma mixture. PBR-1 is a synthetic Aβ peptide produced by PeopleBio Inc. The 1% proprietary material is the concentrated stock solution of synthetic Aβ peptide.

Then, the EDTA-treated plasma mixtures were incubated for 1 h. 100 µL of the plasma sample mixture and serially diluted standards were added to separate wells of the plate. The plates were incubated at RT for 1 h. After washing three times with washing buffer, the detection antibody was added to the wells, and the plate was incubated for 1 h at RT. Finally, 100 µL of 3,3′,5,5′-tetramethylbenzidine (TMB) reagent was added as a substrate, and after 15 min, the reaction was stopped with 50 µL of 1 M H_2SO_4. Optical density (OD) values were measured at 450 nm using a Victor 3 multispectrophotometer. To minimize the intra-plate signal variance, high (Control A) and low (Control B) concentrations of oligomeric Aβ were loaded in row D of the assay plate. For example, Control A was loaded in row D of column 3 and Control B in row D of column 4. The concentration of oligomeric Aβ in the plasma samples, as well as in Controls A and B, was calculated using the standard curve. The ratio value for each sample in columns 3 and 4 was determined by dividing the oligomeric Aβ concentration of the sample by the mean oligomeric Aβ concentration of Controls A and B in the corresponding column. OAβ levels are expressed in MDS ratio value, where the concentration of a sample is divided by the mean concentration value of the internal controls (Controls A and B) in the corresponding column on the microplates. Samples were analyzed in singlicates.

The assay's coefficient of variation (CV%) is approximately 5%, validated through testing control materials at four concentrations (high positive, medium positive, low positive, and negative) across three different LOTs, two distinct instruments, and three different testers over 5 days, with each sample tested in five replicates. All 225 positive sample tests returned positive results, and all 75 negative sample tests returned negative results, demonstrating 100% reproducibility. The CV% of the OAβ level for total variability, as well as variability across LOTs, testers, and instruments, was approximately 5%.

RESEARCH IN CONTEXT

1. **Systematic review**: A literature review was conducted using traditional sources (e.g., PubMed). Although there have been studies on amyloid-β (Aβ) oligomers playing a crucial role in Alzheimer's disease (AD), Aβ oligomers have not yet become recognized markers. To date, there is not only a lack of comparative studies on continuous spectra with relatively large samples but also insufficient research on the correlation between the plasma Aβ oligomerization tendency (OAβ) and cognition, especially early, mild cognitive impairment (MCI). There is also no study on the follow-up queue of OAβ to observe MCI-to-AD conversion.
2. **Interpretation**: This study is one of the studies regarding real-world multimer detection system (MDS)-OAβ usefulness and systematically investigated the contribution of OAβ in MCI-to-AD conversion.
3. **Future directions**: In future follow-up studies, the sample size of the MCI population can be expanded to more deeply explore the pathogenesis mechanism.

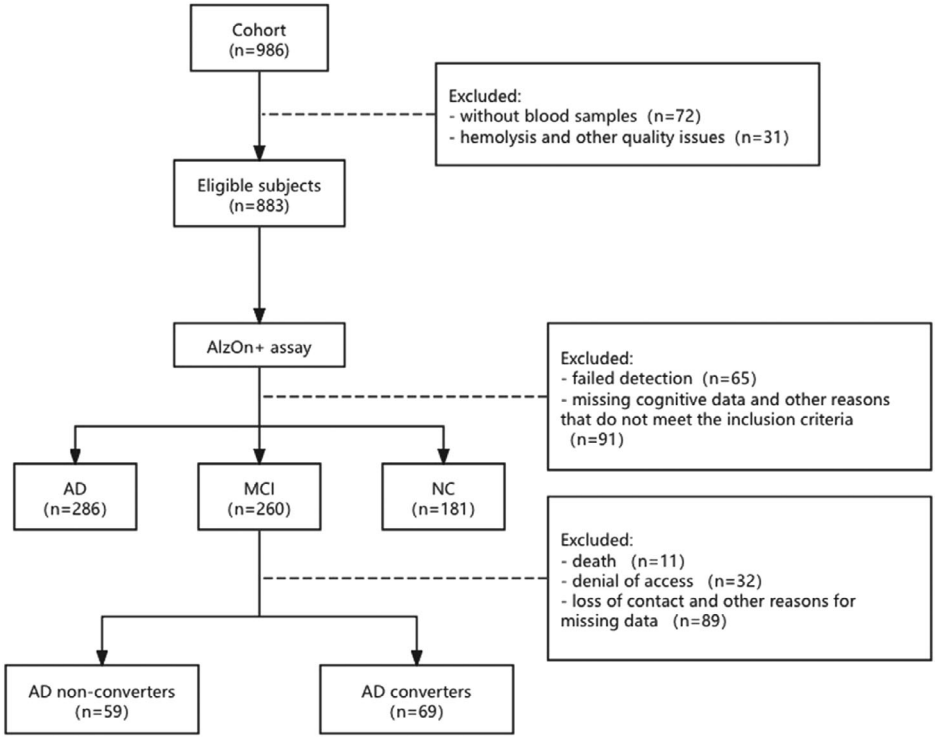

FIGURE 1 Flow chart of the subject enrolment process.

2.5 | Follow-up procedure

Participants were annually administered follow-up interviews with the same neuropsychological evaluation and consensus diagnosis methods as those performed at baseline. AD converters were defined as those with an incident AD dementia diagnosis at any follow-up interview. AD nonconverters included those who were clinically diagnosed as cognitively normal or having MCI throughout follow-up.

2.6 | Statistical analysis

Data analysis was performed with IBM SPSS Statistics 21.0 software. According to whether variables conformed to a normal distribution and homogeneity of variance, a single factor analysis of variance or nonparametric Wilcoxon test was used to evaluate comparisons among the NC, MCI, and AD groups. A pairwise comparison of post hoc analysis was performed using the least significant difference (LSD) method. Chi-squared (χ^2) tests were used to compare the sex ratio. To compare plasma OAβ among the NC group, MCI group, and AD group, covariance analysis was used while adjusting for age and years of education. Partial correlation analysis was used to analyze the correlation between cognitive scores and plasma OAβ while adjusting for years of education and age. Partial correlation analysis was also used to analyze the correlation between cognitive scores and plasma OAβ among the groups with different levels of AD, adjusting for years of education. According to the CDR score, patients with AD were divided into a mild AD group if they had a CDR score = 0.5/1, a moderate AD group with a CDR score = 2, and a severe AD group with a CDR score = 3.

Student's *t* test and the Mann–Whitney U test were used to compare continuous variables, while the Pearson χ^2 test was used to compare categorical variables between AD converters and nonconverters. Analysis of covariance was used to test the differences in the concentrations of biomarkers between these two groups. Patient outcomes were statistically classified as conversion of follow-up outcomes to dementia with a value of 1, while maintenance of MCI or restoration of normal cognition was recorded as 0. Using a median of 2.37 for binary grouping, we divided the MCI follow-up population into high-ratio and low-ratio groups. The Cox regression was used to present the cumulative AD incidence and estimate the risk (hazard ratio [HR] with 95% confidence interval [CI]) during the follow-up period. The predictive performance of plasma OAβ for MCI-to-AD progression was analyzed by receiver operating characteristic curve (ROC) analysis, and the sensitivity, specificity, and area under the curve (AUC) were investigated. Here, $p < 0.05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Characteristics of study participants

A total of 286 patients with AD, 260 patients with MCI, and 181 NC were enrolled in this study. Table 1 summarizes the demographic characteristics of these participants at baseline. There were significant differences in education level ($p < 0.001$) and age ($p < 0.001$) among the three groups. The general cognitive level in the AD group was significantly lower than that in the NC group ($p < 0.001$, Table 1).

TABLE 1 Demographic characteristics and general clinical features of the study participants.

Parameter	AD group ($n = 286$)	MCI group ($n = 260$)	NC group ($n = 181$)	F/χ2	p-value
Age (years), mean (SD)	73.87 (7.34)	73.46 (7.68)	69.43 (7.05)[a,b]	22.69	<0.001
Sex, F (%)	188 (65.73)	159 (61.15)	131 (72.40)	5.97	0.051
Education (years), mean (SD)	12.19 (3.78)	12.50 (3.61)	13.97 (2.66)[a,b]	15.60	<0.001
MMSE score	18.41 (5.80)[b]	26.94 (2.17)[a]	28.63 (1.28)[a,b]	490.11	<0.001
MoCA score	13.34 (5.32)[b]	21.63 (2.94)[a]	26.01 (2.40)[a,b]	628.76	<0.001
CASI score	62.62 (17.37)[b]	88.30 (6.14)[a]	96.11 (3.27)[a,b]	560.39	<0.001
Episodic memory					
COMT-IR score	4.50 (1.82)[b]	7.06 (1.33)[a]	8.05 (1.04)[a,b]	368.53	<0.001
COMT-DR5 score	3.96 (2.76)[b]	7.28 (1.89)[a]	8.56 (1.14)[a,b]	296.58	<0.001
COMT-DR30 score	4.10 (2.60)[b]	6.54 (1.87)[a]	8.68 (1.11)[a,b]	283.53	<0.001
Visuospatial function					
Visual reproduction score	17.45 (9.44)[b]	30.79 (6.91)[a]	35.41 (4.60)[a,b]	370.68	<0.001
Visual reproduction-recall score	11.12 (8.45)[b]	19.69 (9.91)[a]	30.36 (7.15)[a,b]	271.49	<0.001
Language function					
Verbal fluency test score	10.02 (4.15)[b]	17.14 (6.16)[a]	20.04 (4.57)[a,b]	252.32	<0.001
Attention					
Digit span total score	12.96 (4.05)[b]	15.82 (3.75)[a]	17.96 (3.60)[a,b]	99.13	<0.001
Digit forward score	8.47 (2.78)[b]	9.89 (2.36)[a]	10.88 (2.13)[a,b]	55.84	<0.001
Digit backward score	4.49 (1.86)[b]	5.95 (2.08)[a]	7.08 (2.28)[a,b]	92.4	<0.001
Comprehension					
Graphics completion score	5.90 (2.59)[b]	7.50 (1.81)[a]	8.31 (1.60)[a,b]	81.28	<0.001

Note: Continuous variables are presented as the mean (standard deviation). ANOVA was used to compare continuous variables among three groups. Categorical variables are presented as numbers (percentages). The chi-squared test was used for the statistical analysis of categorical variables.
Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating; COMT, Common Objects Memory Test; DR30, 30-min delayed recall test; DR5, 5-min delayed recall test; GDS, Geriatric Depression Scale; IR, immediate recall test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NC, normal controls.
[a]$p < 0.05$ vs. AD.
[b]$p < 0.05$ vs. MCI.

A total of 128 patients with MCI at baseline were followed up with at least one post-baseline cognitive test; among these patients, 69 (54%) converted to AD and 59 (46%) did not. Among participants who did not convert to AD, 7 recovered normal cognition, and 52 maintained MCI status. The follow-up time of AD converters was significantly longer than that of the AD nonconverters (mean (SD), 4.19 (3.03) vs. 3.14 (2.13), $p < 0.05$). The demographic characteristics of the follow-up participants are summarized in Table S1.

3.2 | Comparison of cognitive domain function among the AD, MCI, and NC groups

As expected, there were significant differences among the three groups in their scores reflecting various domains of cognition, including memory, executive function, visuospatial function, language function, attention, and comprehension ($p < 0.001$). The AD group showed the worst performance, followed by the MCI group, and the NC group had the highest scores (Table 1).

3.3 | Comparison of plasma OAβ among the AD, MCI, and NC groups

After adjusting for age and years of education, analysis of variance was conducted to compare plasma OAβ in the AD group, MCI group, and NC group; there was a significant difference in plasma OAβ among the three groups ($p < 0.001$, Figure 2). Additionally, plasma OAβ showed an increasing trend from the NC group to the MCI group and then to the AD group. Pairwise comparisons revealed significant differences between the AD and NC groups ($p < 0.001$), the MCI and NC groups ($p < 0.05$), and the AD and MCI groups ($p < 0.05$).

3.4 | Correlation between plasma OAβ and cognitive function

As shown in Figure 3, in the MCI group, there were significant associations between plasma OAβ and COMT 5-min ($r = -0.29$, $p < 0.001$) and 30-min ($r = -0.74$, $p < 0.001$) recall scores, verbal fluency scores

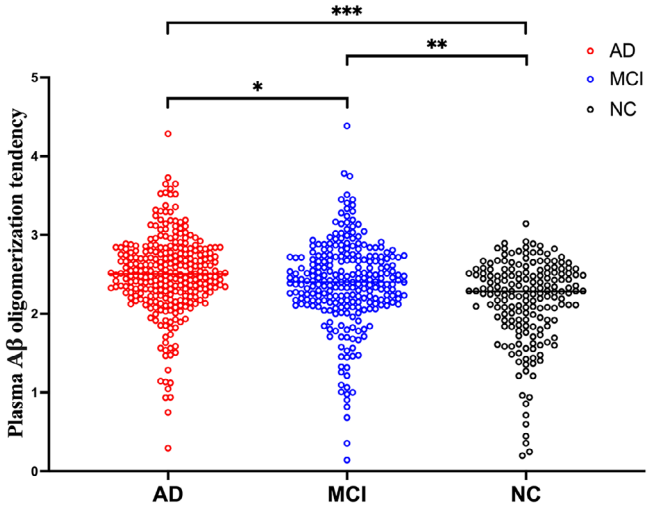

FIGURE 2 Comparison of plasma Aβ oligomerization tendency among the AD, MCI, and NC groups. Covariance analysis was used while adjusting for age and years of education. Aβ, amyloid-β; AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal controls.

($r = -0.33$, $p < 0.001$), and digit span-forward scores ($r = -0.16$, $p = 0.013$). In the AD group, there were significant associations between plasma OAβ and COMT 5-min ($r = -0.51$, $p < 0.001$) and 30-min ($r = -0.61$, $p < 0.001$) recall scores, verbal fluency scores($r = -0.20$, $p = 0.001$), and digit span-forward scores ($r = -0.28$, $p < 0.001$). The correlation results between plasma OAβ and scores in different cognitive domains are shown in Table S2.

3.5 | The predictive value of plasma OAβ for MCI-to-AD conversion

As shown in Figure 4A, the baseline plasma OAβ in the MCI-to-AD converters was significantly higher than those in the non-converters ($p < 0.001$). Meanwhile, there were no differences in cognitive domain scores between the two groups except for the episodic memory domain (Table S1).

Multivariate Cox proportional risk regression analysis showed that, for every 0.10 increase in plasma OAβ in the MCI follow-up population, the risk of AD conversion also increased 1.083-fold (HR, 1.083; 95% CI, 1.032–1.137; $p = 0.001$). The risk of AD conversion at high plasma OAβ (≥ 2.37) was 2.161 times higher than that at low levels (< 2.368) (HR, 2.161; 95% CI, 1.236–3.776, Figure 5). The plasma OAβ could be used to differentiate between the MCI-to-AD converters and non-converters with an AUC of 0.824 (0.752–0.897, Figure 4B).

4 | DISCUSSION

In the present study, plasma OAβ was lowest in the NC group and highest in the AD group. Meanwhile, elevated plasma OAβ is strongly correlated with decreased general cognitive ability and multidomain cognition scores, especially with early cognitive impairment. MCI individuals with high OAβ were more likely to convert to AD dementia than those with low OAβ. Plasma OAβ showed predictive value for AD conversion, suggesting it might be an accessible and feasible indicator of clinical AD prognosis.

The observed trends in plasma OAβ in AD patients are consistent with previous studies, which showed that the Aβ oligomerization levels in AD patients are higher than those in the NC group, whether in the blood or CSF.[16,18,27,28] However, few studies on Aβ oligomerization include patients in the MCI stages, and their conclusions vary. A few studies that considered the full MCI-to-AD disease spectrum did not show significant results despite a continuous trend.[18,29–32] Jongbloed et al. found that baseline CSF Aβ-oligomer levels do not differ between cognitively normal, MCI, and AD subjects.[18] Although some researchers have found significant differences in oligomer levels between AD or MCI and controls, they cannot distinguish between AD and MCI well.[29–32] The reasons for these different experimental results may include small sample sizes, insufficient advanced detection methods, and different types of oligomers detected. Therefore, our comparative study on the MCI-to-AD continuous spectra with a relatively large sample size adopted more accurate detection methods, resulting in more significant and generally better results.

One of the most exciting findings from the present study was that plasma OAβ was highly correlated with multidomain cognitive performance in MCI-to-AD patients, especially in areas related to early cognitive impairment, such as episodic memory, language function, and attention. Previous studies have demonstrated that the level of soluble Aβ oligomers is correlated with the extent of synaptic loss, which in turn restricts hippocampal function.[33] Increased levels of Aβ oligomers were also described by Fukumoto et al. In that study, the AUC for Aβ oligomers was greater than that for CSF Aβ42, suggesting that Aβ oligomers may serve as a candidate marker for discriminating between AD/MCI and normal controls.[34] Although it has become apparent that the plasma Aβ42/40 ratio, rather than absolute levels of these peptides, is a better indicator of AD risk, there is a lack of comparative studies between Aβ oligomers and Aβ42/40 ratio so far. The present study could be the first to report the correlation between plasma OAβ and episodic memory, attention, and language function in MCI and AD. Episodic memory and executive deficits occur in the very early stage of AD.[21] In many paradigms evaluating learning, memory, and recall, delayed recall is a characteristic feature for detecting MCI and AD. As a detection approach that excludes cultural differences, COMT is widely used in memory testing.[22] Although easily overlooked, a change in attention is also one of the early manifestations of AD patients.[23] Investigations in MCI have also revealed evidence of impairment in attention.[35] The Digit Span subtest from the Wechsler Scales measures distractibility and attention.[24] Here, observing the significant changes in attention tested by digit span in MCI and AD is consistent with previous studies. In addition, we also focused on the changes to language function in AD and MCI patients. Decreased vocabulary size may be an early indicator of cognitive impairment.[25] Verbal fluency impairments, closely related to overall language function, occur early in AD and, to a lesser extent, in normal aging.[26] The strong correlations between

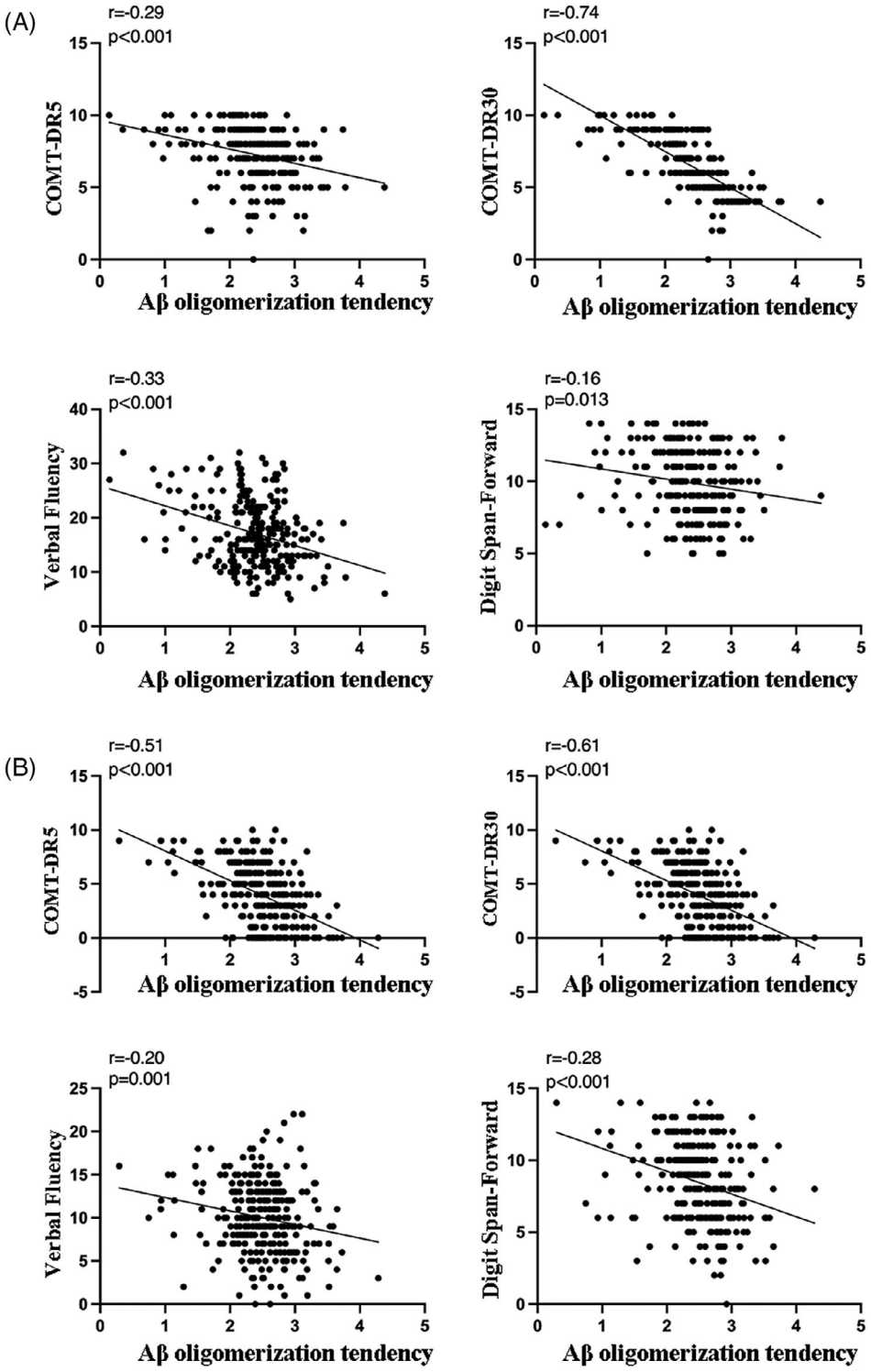

FIGURE 3 Correlation analysis between plasma Aβ oligomerization tendency and cognitive function in the MCI group (A) and AD group (B). Partial correlation analysis was used to analyze the correlation between cognitive scores and plasma Aβ oligomerization tendency while adjusting for years of education and age. AD, Alzheimer's disease; Aβ, amyloid-β; MCI, mild cognitive impairment.

plasma OAβ and the delayed recall scores on the COMT, verbal fluency, and digit span revealed that the increased plasma OAβ paralleled the earliest cognitive changes in patients with AD. The significance of plasma OAβ parallel with the earliest cognitive changes could present additional evidence supporting plasma OAβ as a potential blood-based biomarker for AD screening or diagnosis.

One of the most important results in our study is that MCI individuals with higher plasma OAβ at baseline demonstrated a higher AD risk

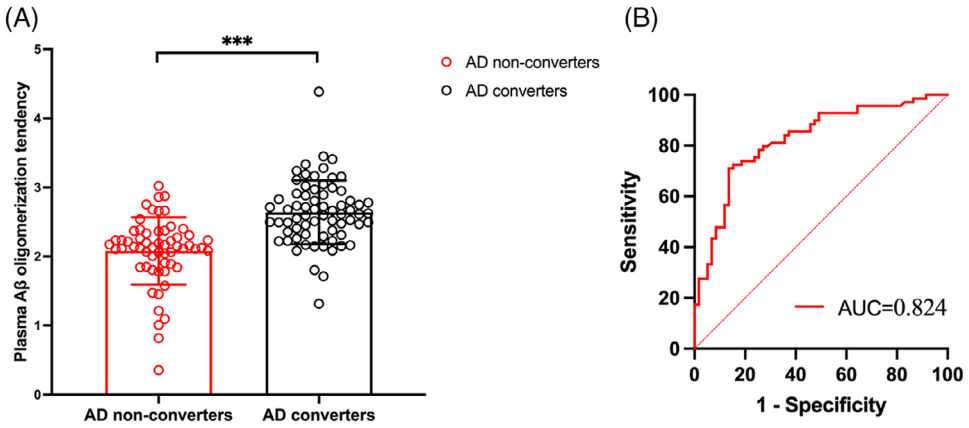

FIGURE 4 (A) Comparison of baseline plasma Aβ oligomerization tendency between MCI-to-AD converters and non-converters. (B) The ROC curve of plasma Aβ oligomerization tendency in differentiation between MCI-to-AD converters and AD non-converters. Analysis of covariance was used to test the differences in plasma Aβ oligomerization tendency between these two groups. The predictive performance of plasma Aβ oligomerization tendency for MCI-to-AD was analyzed by ROC curve analysis, and the sensitivity, specificity, and AUC were investigated. Aβ, amyloid-β; AD, Alzheimer's disease; AUC, area under the curve; MCI, mild cognitive impairment; ROC, receiver operating characteristics.

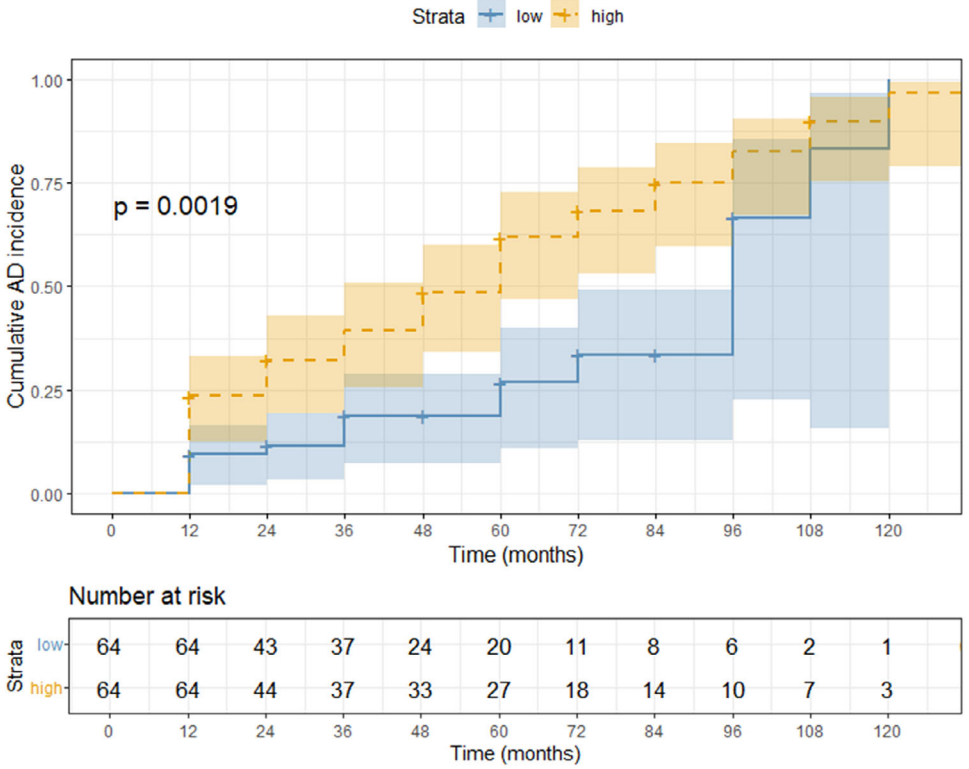

FIGURE 5 Cumulative AD incidence in participants with low and high plasma Aβ oligomerization tendency. The Cox regression model was used to present the cumulative AD incidence and estimate the risk (hazard ratio [HR] with 95% confidence interval) during the follow-up period. Aβ, amyloid-β; AD, Alzheimer's disease.

and that plasma OAβ had good performance in predicting AD conversion. Previously, only Jongbloed et al. had conducted a follow-up study on CSF Aβ-oligomer levels of participants with MCI to predict the risk of converting into AD.[18] However, in their study, the levels of CSF Aβ oligomers did not differ between the groups of MCI-to-AD converters and non-converters. Moreover, there was no association between CSF Aβ-oligomer levels and cognitive performance at baseline in any group. The discrepancy may be primarily attributed to the insufficient sample size in the studies. Human and animal models have shown that Aβ oligomer formation occurs before Aβ plaques and clinical symptoms

appear.[36] Assuming that soluble Aβ oligomers in Aβ plaques are free and exist under certain conditions, the diffusion of soluble Aβ oligomers onto synaptic membranes and other cell surfaces[37] may trigger harmful cascade reactions, damaging neurons and synapses.[38] In addition, if the presence of Aβ oligomers precedes the formation of Aβ plaques, Aβ oligomerization may represent the initial stage of Aβ plaque formation. Previous studies have shown that the severity of the disease is not related to the level of Aβ plaques but rather to the level of soluble Aβ oligomers in the brain.[39] Thus, the consideration of Aβ oligomers may more closely reflect the pathogenic mechanism of AD.

Several limitations of this study should be noted. First, while performing the Kaplan–Meier curve with the log-rank test, we categorized OAβ into binary high/low levels based on their median values. Since no universally accepted cutoff values are available and other studies each used their own criteria to categorize biomarker levels, our results may not be directly comparable to previous studies. Second, the difference in follow-up time between converters and non-converters to AD in the MCI group is big. To address this concern, we supplemented the analysis of AD conversion rates at 3-year time points. We found that the conversion rate in the group with high plasma OAβ is significantly higher than in the low tendency group (Figure S1). However, our study is a clinical natural observational cohort study. The adherence to follow-up depends on the willingness of the patients. The potentially high drop-out rate inevitably contributed to the big difference in the follow-up duration. Therefore, our findings should be interpreted cautiously. Third, in Figure 5, at follow-up time ≥ 96 months, the incidence appears to increase more rapidly in the low strata compared to the high. This observation is relevant to the relatively small number of cases with follow-up time exceeding 96 months. Meanwhile, the trend shown in Figure 5 is visually remarkable, but not statistically significant at 8-, 9-, 10-, and 11-year time points. Therefore, our results may be more applicable to younger than older elderly participants. Last, compared to longitudinal studies in ADNI and BioFINDER cohorts,[40,41] the sample size of this study was relatively small, and the follow-up time was relatively short. Further large-sample prospective studies are needed to verify the utility of various blood biomarkers on MCI-to-AD conversion with different ethnic backgrounds.

5 | CONCLUSION

Plasma OAβ is elevated across the continuum of AD and strongly correlates with the performance of multiple cognitive domains, especially episodic memory, language function, and attention. MCI individuals with high OAβ are more likely to convert to AD dementia. Therefore, plasma OAβ may be a candidate biomarker for AD. However, future large-sample studies with longer follow-up duration and higher adherence to follow-up are warranted.

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CONFLICT OF INTEREST STATEMENT

We have no conflict of interest with any commercial or other association connected with the submitted article. The funding agency had no role in the design of the study, in the collection, analysis, or interpretation of the data, in the writing, and approval of the paper, or decision to submit the manuscript for publication. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All study participants provided informed consent before they participated in the study.

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REFERENCES

1. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535-562.
2. Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol*. 2021;20:739-752.
3. Hampel H, O'Bryant SE, Castrillo JI, et al. PRECISION MEDICINE—the golden gate for detection, treatment and prevention of Alzheimer's disease. *J Prev Alzheimers Dis*. 2016;3:243-259.
4. Hampel H, O'Bryant SE, Durrleman S, et al. A Precision Medicine Initiative for Alzheimer's disease: the road ahead to biomarker-guided integrative disease modeling. *Climacteric*. 2017;20:107-118.
5. Hampel H, Lista S, Teipel SJ, et al. Perspective on future role of biological markers in clinical therapy trials of Alzheimer's disease: a long-range point of view beyond 2020. *Biochem Pharmacol*. 2014;88:426-449.
6. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med*. 2018;284:643-663.
7. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297:353-356.
8. Villemagne VL, Pike KE, Chételat G, et al. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. *Ann Neurol*. 2011;69:181-192.
9. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol*. 2012;71:362-381.
10. Lambert MP, Barlow AK, Chromy BA, et al. Diffusible, nonfibrillar ligands derived from $A\beta_{1\text{-}42}$ are potent central nervous system neurotoxins. *Proc Natl Acad Sci USA*. 1998;95:6448-6453.
11. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8:595-608.
12. Hayden EY, Teplow DB. Amyloid β-protein oligomers and Alzheimer's disease. *Alzheimers Res Ther*. 2013;5:60.

13. Taneja V, Verma M, Vats A. Toxic species in amyloid disorders: oligomers or mature fibrils. *Ann Indian Acad Neurol*. 2015;18:138.
14. Zhou L, Chan KH, Chu LW, et al. Plasma amyloid-β oligomers level is a biomarker for Alzheimer's disease diagnosis. *Biochem Biophys Res Commun*. 2012;423:697-702.
15. Wang MJ, Yi S, Han J, et al. Oligomeric forms of amyloid-β protein in plasma as a potential blood-based biomarker for Alzheimer's disease. *Alzheimers Res Ther*. 2017;9:98.
16. Meng X, Li T, Wang X, et al. Association between increased levels of amyloid-β oligomers in plasma and episodic memory loss in Alzheimer's disease. *Alzheimers Res Ther*. 2019;11:89.
17. Xiao Z, Wu W, Ma X, et al. Plasma Aβ42/Aβ40 and p-tau181 predict long-term clinical progression in a cohort with amnestic mild cognitive impairment. *Clin Chem*. 2022;68:1552-1563.
18. Jongbloed W, Bruggink KA, Kester MI, et al. Amyloid-β oligomers relate to cognitive decline in Alzheimer's disease. *J Alzheimers Dis*. 2015;45:35-43.
19. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica*. 2009;119:252-265.
20. Rockwood K, Chertkow H, Feldman HH. Is mild cognitive impairment a valid target of therapy. *J Neurol Sci*. 2007;34:S90-S96.
21. Baudic S, Barba G, Thibaudet M, Smagghe A, Remy P, Traykov L. Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Arch Clin Neuropsychol*. 2006;21:15-21.
22. Kempler D, Teng EL, Taussig M, Dick MB. The common objects memory test (COMT): a simple test with cross-cultural applicability. *J Int Neuropsychol Soc*. 2010;16:537-545.
23. Greenwood PM, Parasuraman R, Haxby JV. Changes in visuospatial attention over the adult lifespan. *Neuropsychologia*. 1993;31:471-485.
24. Bowden SC, Petrauskas VM, Bardenhagen FJ, Meade CE, Simpson LC. Exploring the dimensionality of digit span. *Assessment*. 2013;20:188-198.
25. Aramaki E, Shikata S, Miyabe M, Kinoshita A. Vocabulary size in speech may be an early indicator of cognitive impairment. *PLoS ONE*. 2016;11:e0155195.
26. Rodríguez-Aranda C, Waterloo K, Johnsen SH, et al. Neuroanatomical correlates of verbal fluency in early Alzheimer's disease and normal aging. *Brain Lang*. 2016:24-35.
27. Savage MJ, Kalinina J, Wolfe A, Tugusheva K, Korn R, Cash-Mason T, et al. A sensitive Aβ oligomer assay discriminates Alzheimer's and aged control cerebrospinal fluid. *J Neurosci*. 2014;34:2884-2897.
28. Tomic JL, Pensalfini A, Head E, Glabe CG. Soluble fibrillar oligomer levels are elevated in Alzheimer's disease brain and correlate with cognitive dysfunction. *Neurobiol Dis*. 2009;35:352-358.
29. Zhang J, Peng M, Jia J. Plasma amyloid-β oligomers and soluble tumor necrosis factor receptors as potential biomarkers of AD. *Curr Alzheimer Res*. 2014;11:325-331.
30. Klaver AC, Coffey MP, Smith LM, et al. ELISA measurement of specific non-antigen-bound antibodies to Aβ1-42 monomer and soluble oligomers in sera from Alzheimer's disease, mild cognitively impaired, and noncognitively impaired subjects. *J Neuroinflammation*. 2011;8:93.
31. Youn YC, Kang S, Suh J, et al. Blood amyloid-β oligomerization associated with neurodegeneration of Alzheimer's disease. *Alzheimers Res Ther*. 2019;11:40.
32. Yang T, O'Malley TT, Kanmert D, et al. A highly sensitive novel immunoassay specifically detects low levels of soluble Aβ oligomers in human cerebrospinal fluid. *Alzheimers Res Ther*. 2015;7:14.
33. Lacor PN, Buniel MC, Chang L,et al. Synaptic targeting by Alzheimer's-related amyloid β oligomers. *J Neurosci*. 2004;24:10191-10200.
34. Fukumoto H, Tokuda T, Kasai T, et al. High-molecular-weight β-amyloid oligomers are elevated in cerebrospinal fluid of Alzheimer patients. *FASEB J*. 2010;24:2716-2726.
35. Saunders NLJ, Summers MJ. Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. *Neuropsychology*. 2011;25:237-248.
36. Lesné SE, Sherman MA, Grant M, et al. Brain amyloid-β oligomers in ageing and Alzheimer's disease. *Brain*. 2013;136:1383-1398.
37. Hong S, Ostaszewski BL, Yang T, et al. Soluble Aβ oligomers are rapidly sequestered from brain ISF in vivo and bind GM1 ganglioside on cellular membranes. *Neuron*. 2014;82:308-319.
38. Morris GP, Clark IA. Vissel B. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. *Acta Neuropathol Commun*. 2014;2:135.
39. DaRocha-Souto B, Scotton TC, Coma M, et al. Brain oligomeric β-Amyloid but not total amyloid plaque burden correlates with neuronal loss and astrocyte inflammatory response in amyloid precursor protein/tau transgenic mice. *J Neuropathol Exp Neurol*. 2011;70:360-376.
40. Palmqvist S, Tideman P, Cullen N, , et al. Alzheimer's Disease Neuroimaging Initiative. Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. *Nat Med*. 2021;27:1034-1042.
41. Cullen NC, Leuzy A, Palmqvist S, et al. Individualized prognosis of cognitive decline and dementia in mild cognitive impairment based on plasma biomarker combinations. *Nat Aging*. 2020;1:114-123.

SUPPORTING INFORMATION

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

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