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ORIGINAL RESEARCH

Serum Homocysteine as a Potential Dynamic Biomarker for Staging and Monitoring Progression in Alzheimer's Disease

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Background: Reliable biomarkers are urgently needed for the early diagnosis and dynamic monitoring of Alzheimer's disease (AD). Serum homocysteine (Hcy) has been increasingly investigated but with inconsistent association to AD severity.

Objective: To investigate the correlation between serum Hcy levels and AD severity/cognitive function, and to evaluate its clinical utility as a dynamic monitoring indicator for the disease.

Methods: This retrospective study enrolled 80 AD patients (stratified by Mini-Mental State Examination [MMSE] score: 40 mild, 28 moderate, 12 severe) and 80 healthy controls from the Cerebrovascular Disease outpatient and inpatient departments of our hospital between January 2022 and December 2024. Fasting serum Hcy was measured via chemiluminescent immunoassay. Correlation with cognitive scores and severity discrimination were analyzed.

Results: Serum Hcy levels were significantly higher in the AD group than controls (21.2 ± 6.6 vs 14.5 ± 4.8 μmol/L, $p < 0.05$), increasing with severity (mild: 16.8 ± 3.2, moderate: 21.2 ± 4.5, severe: 25.6 ± 5.8 μmol/L, $p < 0.001$). A strong inverse correlation with MoCA scores was observed ($r = -0.76$, $p < 0.01$). ROC analysis showed an AUC of 0.87 for discriminating AD severity, with an optimal cut-off of 17.5 μmol/L (sensitivity 78%, specificity 72%). After 6 months of B-vitamin intervention, Hcy decreased significantly with cognitive improvement.

Conclusion: Serum Hcy correlates strongly with AD severity and cognitive decline, supporting its potential as a dynamic biomarker for monitoring progression and treatment response.

Keywords: Alzheimer's disease, homocysteine, cognitive decline, biomarker, dynamic monitoring

Introduction

Alzheimer's disease (AD) ranks among the most prevalent neurodegenerative disorders, accounting for 60–80% of all dementia cases.[1] According to World Health Organization estimates, approximately 50 million individuals worldwide are affected by AD, a figure projected to triple by 2050.[2] The hallmark neuropathological features of AD include senile plaques formed by the deposition of amyloid-beta (Aβ) peptides, neurofibrillary tangles resulting from the hyperphosphorylation of tau protein, along with neuronal loss and synaptic degeneration.[3] These pathological alterations lead to progressive memory impairment, cognitive decline, and behavioral abnormalities, ultimately resulting in the loss of independent living capacity.[4,5]

Current AD diagnosis primarily relies on clinical symptom assessment, neuropsychological testing, and neuroimaging. However, the sensitivity and specificity of these methods are limited, particularly during the early disease stages.[6] Consequently, identifying reliable and readily accessible biomarkers is crucial for the early diagnosis and longitudinal monitoring of AD. In recent years, considerable attention has focused on the role of serum homocysteine (Hcy) in AD pathogenesis. Hcy is a sulfur-containing amino acid metabolite generated during the transmethylation of methionine.[7,8] Elevated Hcy levels are well-established as an independent risk factor for cardiovascular diseases.[9] A growing body of

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evidence suggests that hyperhomocysteinemia is not only strongly associated with cerebrovascular pathology but may also accelerate AD pathological progression through multiple mechanisms. These include interference with DNA methylation leading to increased Aβ accumulation, induction of neuronal apoptosis, disruption of the cholinergic system,[10,11] direct neurotoxicity via protein post-translational modification, promotion of oxidative stress, induction of neuroinflammation, and activation of glutamate receptors.[12–14] Notably, Hcy levels are influenced by various factors, including age, sex, deficiencies in vitamins B6, B12, and folate, as well as renal insufficiency[15] – factors that are themselves independently linked to AD risk. Elevated Hcy further contributes to increased blood-brain barrier permeability and disrupts the metabolism of glycine, folate, and vitamin B12, thereby compromising their neuroprotective properties.[7]

While cerebrospinal fluid (CSF) biomarkers (Aβ42, p-tau, t-tau) and amyloid/tau PET imaging offer high diagnostic specificity for AD pathology, their clinical utility is limited by high cost, invasiveness, and limited accessibility, particularly in primary care and resource-limited settings.[16,17] In contrast, serum homocysteine is a readily measurable, non-invasive, and cost-effective marker that reflects both vascular and neurodegenerative pathways implicated in AD. Moreover, unlike static pathological markers, Hcy is modifiable through B-vitamin supplementation—a feature that enhances its translational value for monitoring treatment response and guiding personalized interventions.[18,19] Therefore, while not a replacement for core AD biomarkers, Hcy serves as a practical complementary tool, especially for longitudinal tracking and risk stratification in early or pre-dementia stages.

While existing research has predominantly focused on establishing Hcy as a risk factor for AD, studies investigating the specific relationship between Hcy levels and AD severity remain relatively scarce. Therefore, this study aims to compare serum Hcy levels across AD patients stratified by disease severity, investigate its correlation with cognitive impairment, and evaluate the clinical value of Hcy as a potential biomarker for the dynamic monitoring and prediction of AD progression. The findings are anticipated to provide a theoretical foundation for early intervention and personalized management strategies in AD.

Materials and Methods

This study enrolled a total of 160 participants: 80 patients diagnosed with Alzheimer's disease (AD group) and 80 cognitively healthy individuals serving as controls (Control group). AD patients were recruited consecutively from the outpatient clinics and inpatient wards of the Cerebrovascular Disease Department at our hospital between January 2022 and December 2024. The diagnosis of AD was established according to the criteria outlined by the National Institute on Aging and Alzheimer's Association (NIA-AA) in 2011. Control participants were volunteers who underwent routine health examinations at the Physical Examination Center of our hospital during the same period. Controls were free from any neurological disorders or cognitive impairment. The study protocol received approval from the Medical Ethics Committee of Hangzhou Third People's Hospital (Approval No.:2022KA122). Written informed consent was obtained from all participants or their legal guardians prior to enrollment.

Inclusion and Exclusion Criteria

AD Group Inclusion Criteria

1) Age between 60 and 85 years. 2) Diagnosis of probable AD meeting NIA-AA 2011 criteria. 3) Other types of dementia ruled out by cranial magnetic resonance imaging (MRI) or computed tomography (CT). 4) Absence of major systemic diseases (eg, myocardial infarction, stroke, active cancer). 5) No intake of vitamin B complex or folic acid supplements within 3 months prior to enrollment. 6) Provision of written informed consent by the participant or legal guardian, and willingness to complete all study assessments.

AD Group Exclusion Criteria

1) Co-existing Parkinson's disease, vascular dementia, dementia with Lewy bodies, or other non-AD dementias. 2) Significant hearing, visual, or language impairments hindering reliable cognitive assessment. 3) History of major psychiatric disorders (eg, schizophrenia, bipolar disorder) or substance abuse. 4) Hematological diseases or severe hepatic/renal dysfunction (defined as serum creatinine >2.0 mg/dL or estimated glomerular filtration rate [eGFR]

<30 mL/min/1.73m^2). 5) Pregnancy or lactation. 6) Poor compliance anticipated, rendering completion of follow-up or assessments unlikely.

Control Group Inclusion Criteria

1) Age >60 years. 2) No subjective complaints of cognitive decline. 3) Cognitive function test scores within the normal range for age and education level.

Control Group Exclusion Criteria

1) Presence of cognitive impairment attributable to other disorders (eg, thyroid 2)dysfunction, vitamin B12 deficiency), as assessed by comprehensive laboratory 3) investigations including biochemistry, liver/kidney function, and thyroid function tests. 4) Severe systemic diseases (eg, significant cardiac, pulmonary, hepatic, renal disease, active cancer). 5) History of known central nervous system disorders (eg, stroke, epilepsy, multiple sclerosis, significant head trauma). 6) Sensory deficits (eg, deafness, blindness) severe enough to preclude valid cognitive or functional assessment.

Data Collection

Demographic information, medical history (including family history), physical examination findings, and cognitive assessment results were collected for all study participants using structured questionnaires. Patients were interviewed directly whenever possible. For patients, an additional interview was conducted with their primary caregiver. To ensure accurate reporting, caregivers were required to be intimately familiar with the patient's clinical status and provide daily care for a minimum of 2 hours. The questionnaires were designed to gather comprehensive data on participant characteristics, including:Age, sex, educational attainment, marital status.Smoking status, alcohol consumption, regular vitamin supplementation, general lifestyle habits.Past medical history (specifically diabetes mellitus, hypertension, heart disease, stroke), current medications.Family history of relevant disorders.

Cognitive Assessment

Global cognitive function was assessed in all participants using the Mini-Mental State Examination (MMSE).[20] The MMSE is a widely employed and well-validated screening tool for cognitive impairment. It evaluates five key cognitive domains through a series of 16 tasks, yielding a total score ranging from 0 to 30 points. Higher scores indicate better cognitive performance.Based on established MMSE cut-off scores reflecting disease severity,[20] the 80 AD patients were stratified into three severity groups:Mild AD Group (n=40): MMSE score ≥21 and ≤26.Moderate AD Group (n=28): MMSE score ≥10 and ≤20.Severe AD Group (n=12): MMSE score ≤9.

Biochemical Indicator MeasurementVenous blood samples (5 mL) were collected from all participants under fasting conditions in the morning. Blood was drawn directly into plain vacuum tubes (without anticoagulant). Samples were allowed to clot at room temperature for 30 minutes. Subsequently, serum was separated by centrifugation at 3000 revolutions per minute (rpm) for 15 minutes. The separated serum was immediately aliquoted and stored at −80°C until analysis to prevent multiple freeze-thaw cycles.Serum Hcy concentrations were measured using a chemiluminescent immunoassay (CLIA) performed on the IMMULITE 2000 automated analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA), strictly following the manufacturer's protocols.Additional biochemical parameters, including neuron-specific enolase (NSE), ferritin, low-density lipoprotein (LDL), creatinine, and uric acid, were assayed using a modular biochemistry/immunoassay analyzer (Roche Diagnostics, Basel, Switzerland). Reagents for these assays were supplied by Hangzhou Nova Biomedical Engineering Co., Ltd. (Hangzhou, China).To ensure analytical reliability and minimize inter-assay variation, all procedures (sample processing and biochemical analyses) were performed by certified laboratory personnel. Crucially, all samples were analyzed within a single assay batch.

Statistical Analysis

Data analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (Mean ± SD). Intergroup comparisons for normally distributed data were conducted using one-way analysis of variance (ANOVA), while the Kruskal–Wallis test was applied for non-normally distributed data. Categorical variables were summarized as frequencies (n) and percentages (%), and intergroup

differences were evaluated using the chi-square (χ^2) test or Fisher's exact test, as appropriate.Pearson correlation analysis was used to assess the relationship between serum homocysteine (Hcy) levels and continuous variables, whereas Spearman rank correlation analysis was employed for ordinal or non-normally distributed data. Multiple linear regression analysis was conducted to explore the association between Hcy levels and the severity of Alzheimer's disease (AD) after adjusting for potential confounding factors. Logistic regression models were used to evaluate the association between elevated Hcy levels and different stages of AD severity.All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were constructed to assess the discriminatory performance of serum Hcy levels in distinguishing between different severities of AD.

Results

Comparison of Baseline Characteristics

Baseline demographic and clinical characteristics of the AD group and the healthy control group are summarized in Table 1. The two groups demonstrated no significant differences in age, sex, years of education, history of hypertension, history of diabetes mellitus, smoking status, alcohol consumption, serum levels of neuron-specific enolase (NSE), ferritin, low-density lipoprotein (LDL), creatinine, uric acid, or vitamin B12 levels (all p > 0.05), indicating comparability between the groups at baseline.

Comparison of Serum Homocysteine Levels Across Groups

Serum Hcy levels in the Alzheimer's disease (AD) patient group and the healthy control group are presented in Figure 1. The mean serum Hcy level was significantly higher in the AD group (21.2 ± 6.6 μmol/L) compared to the healthy control group (14.5 ± 4.8 μmol/L) (p < 0.05).Further analysis revealed a progressive elevation in serum Hcy levels corresponding with increasing AD severity. As illustrated in Figure 2, Hcy levels were highest in the severe AD group (25.6 ± 5.8 μmol/L), followed by the moderate AD group (21.2 ± 4.5 μmol/L), and lowest in the mild AD group (16.8 ± 3.2 μmol/L). Pairwise comparisons using Bonferroni post-hoc analysis demonstrated statistically significant differences in Hcy levels

Table 1 General Characteristics of Participants

Characters	AD [n=80]	HC [n=80]	*P*
Age (years)	73.4±6.3	74.7±5.2	0.752
Gender [n (%)]			0.615
Male	42 (52.5%)	40 (50%)	
Female	38 (47.5%)	40 (50%)	
Smoking [n (%)]	36 (45%)	34 (42.5%)	0.327
Drinking [n (%)]	28 (35%)	32 (40%)	0.513
Hypertension [n (%)]	52 (65%)	47 (58.7%)	0.432
Diabetes [n (%)]	38 (47.5%)	37 (46.2%)	0.299
Hyperlipidemia [n (%)]	34 (42.5%)	30 (37.5%)	0.837
Years of Education [n (%)]			0.648
Primary school or below	52 (65%)	55 (68.7%)	
Junior high school	12 (15%)	14 (17.5%)	
Senior high school	12 (15%)	8 (10)	
College or above	4 (5)%	3 (3.7%)	
NSE (ng/mL)	10.6±4.2	11.3±3.8	0.072
Ferritin (ng/mL)	202.5±106.2	205.7±115.6	0.392
LDL (mmol/L)	2.84±1.2	2.56±0.9	0.442
Cr (μmol/L)	71.63±45.6	74.38±51.1	0.612
UA (mg/dL)	320±80.3	334±74.7	0.865
Vitamin B12 (pg/mL)	280.73±134.1	267.45±152.9	0.878
Hcy (μmol/L)	21.2±6.6	14.5±4.8	0.014
MMSE	14.35±6.3	25.43±2.15	0.032

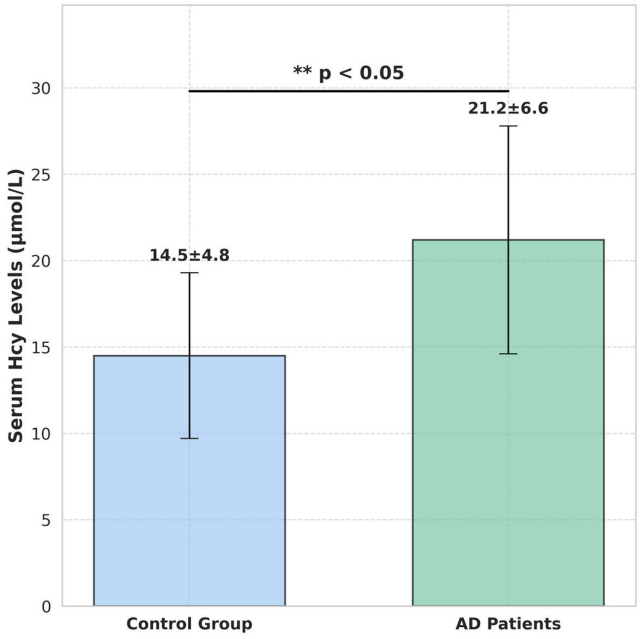

Figure 1 Comparison of Serum Hcy Levels between AD Patients and Control Group.
Notes: Data are presented as mean ± standard deviation. The difference between groups was analyzed using an independent samples *t*-test. ** < 0.05 indicates a statistically significant difference.

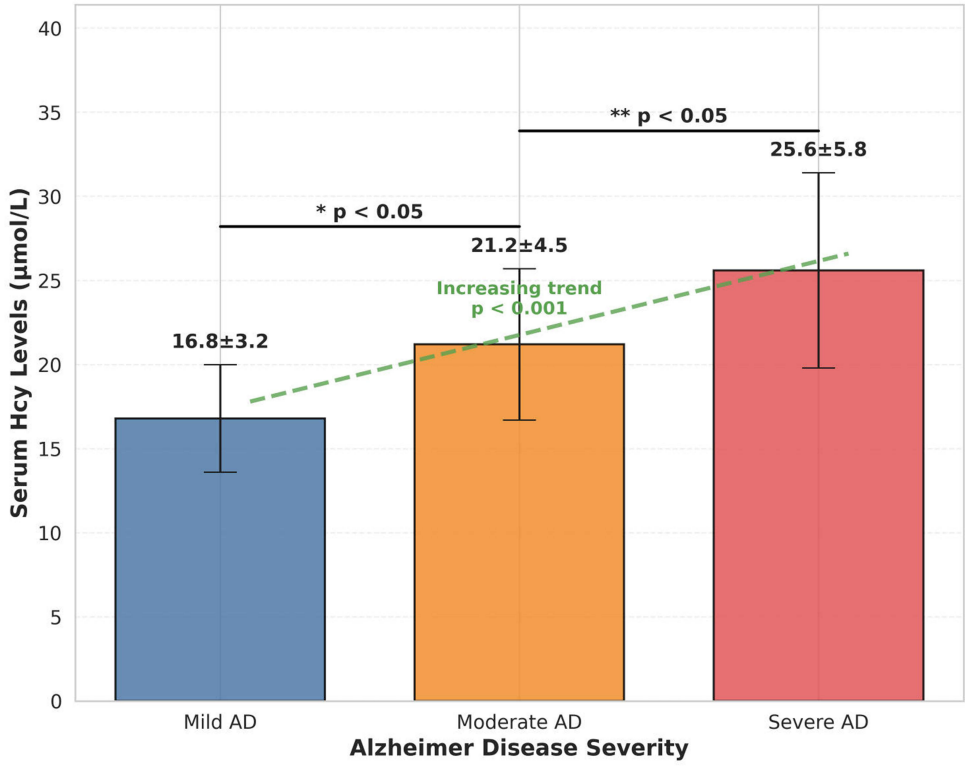

Figure 2 Serum Hcy Levels Across Different Stages of AD.
Notes: Data are presented as mean ± standard deviation. AD severity was stratified by MMSE scores (Mild: ≥21; Moderate: 10–20; Severe: ≤9). Group comparisons were performed using one-way ANOVA followed by Bonferroni post-hoc test. *p< 0.001 for all pairwise comparisons between severity groups.

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between all severity groups: severe vs moderate ($p < 0.001$), severe vs mild ($p < 0.001$), and moderate vs mild ($p < 0.001$).

These findings indicate a strong association between elevated serum Hcy levels and AD, as well as a quantitative relationship between Hcy concentration and disease severity.

Correlation Between Hcy and MMSE Scores and Dynamic Changes

Pearson correlation analysis revealed a significant inverse correlation between serum homocysteine (Hcy) levels and Mini-Mental State Examination (MMSE) scores (*r* = −0.76, $P < 0.01$), indicating that elevated Hcy levels are strongly associated with cognitive decline (Figure 3).

Furthermore, all AD patients underwent a standardized B-vitamin intervention regimen for 6 months. Follow-up assessments demonstrated a significant decrease in serum Hcy levels across all AD severity groups post-intervention compared to baseline levels ($P < 0.05$). Concurrently, cognitive function, as measured by MMSE scores, showed significant improvement in all groups. These changes are detailed in Table 2.Critically, baseline serum Hcy levels (measured at admission) exhibited a significant correlation with MMSE scores assessed at the 6-month follow-up ($P < 0.05$). This finding further supports the potential utility of serum Hcy as a dynamic monitoring indicator for tracking disease progression and treatment response in AD.

ROC Curve Analysis of Serum Hcy for Discriminating AD Severity

The receiver operating characteristic (ROC) curve assessing the ability of serum homocysteine (Hcy) levels to discriminate between different levels of Alzheimer's disease (AD) severity (mild, moderate, severe) is presented in Figure 4. The analysis yielded an area under the curve (AUC) of 0.87 (95% confidence interval [CI]: 0.76–0.89; $P < 0.001$), indicating good discriminatory power of serum Hcy levels for distinguishing AD severity stages.The optimal cut-off value for serum Hcy, determined by maximizing the Youden index, was 17.5 μmol/L. At this threshold, the sensitivity

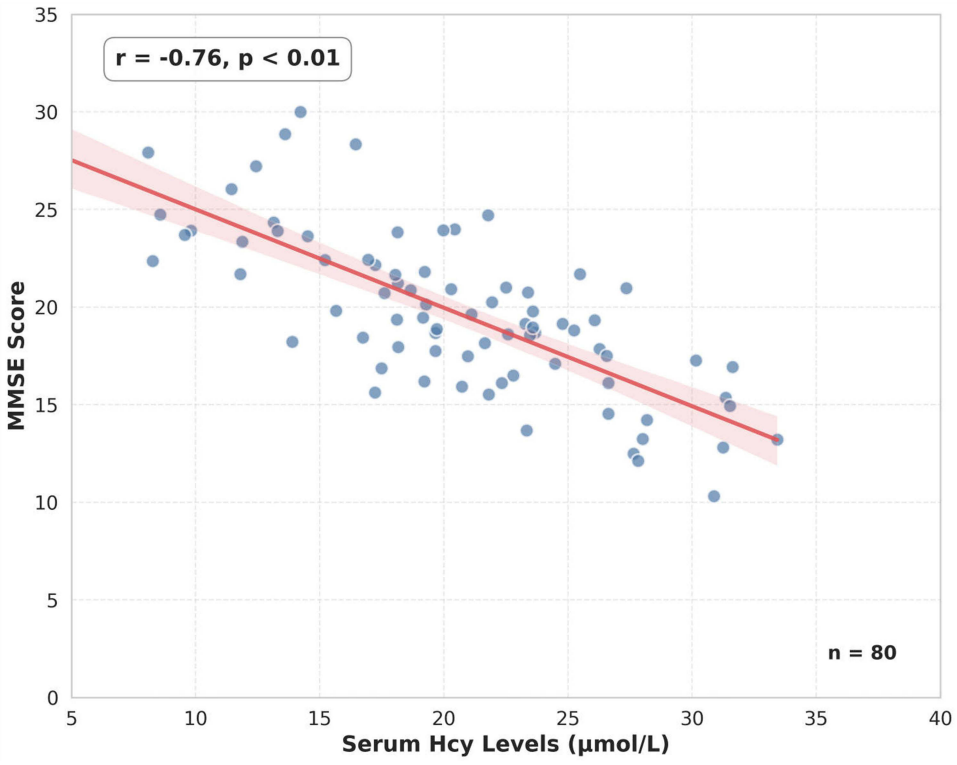

Figure 3 Correlation Between Hcy Levels and MMSE Scores in AD Patients.
Notes: The correlation between serum homocysteine (Hcy) levels and Mini-Mental State Examination (MMSE) scores was assessed using Pearson correlation analysis. The solid line represents the line of best fit, and the shaded area indicates the 95% confidence interval.

Table 2 Before and After 6 months of Treatment, Serum Hcy Levels in Each Group Were Correlated with the MMSE Scale Score

MMSE Scale Score (point)	21≤MMSE≤26	10≤MMSE≤20	MMSE≤9	*P*
On admission				
Patient (case)	40 (50%)	28 (35%)	12 (15%)	
Serum Hcy level (μmol/L)	16.8 ± 3.2	21.2 ± 4.5	25.6 ± 5.8	<0.05
6 months after treatment				
Patient (case)	47 (58.7%)	24 (30%)	9 (11.2%)	
Serum Hcy level (μmol/L)	12.9 ± 4.2	17.9 ± 3.8	22.1 ± 6.2	<0.05

was 78% and the specificity was 72%.These results demonstrate that serum Hcy level is a promising biomarker for assessing AD severity, offering significant potential for predictive assessment and monitoring in clinical practice.

Discussion

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, and its early diagnosis and dynamic monitoring of disease status remain major clinical challenges. In recent years, the role of elevated homocysteine (Hcy) levels in the pathogenesis of AD has garnered widespread attention. This study compared Hcy levels between AD patients of varying severities and healthy controls, explored its relationship with cognitive impairment, and evaluated the potential value of Hcy as a biomarker for the dynamic monitoring of AD progression.

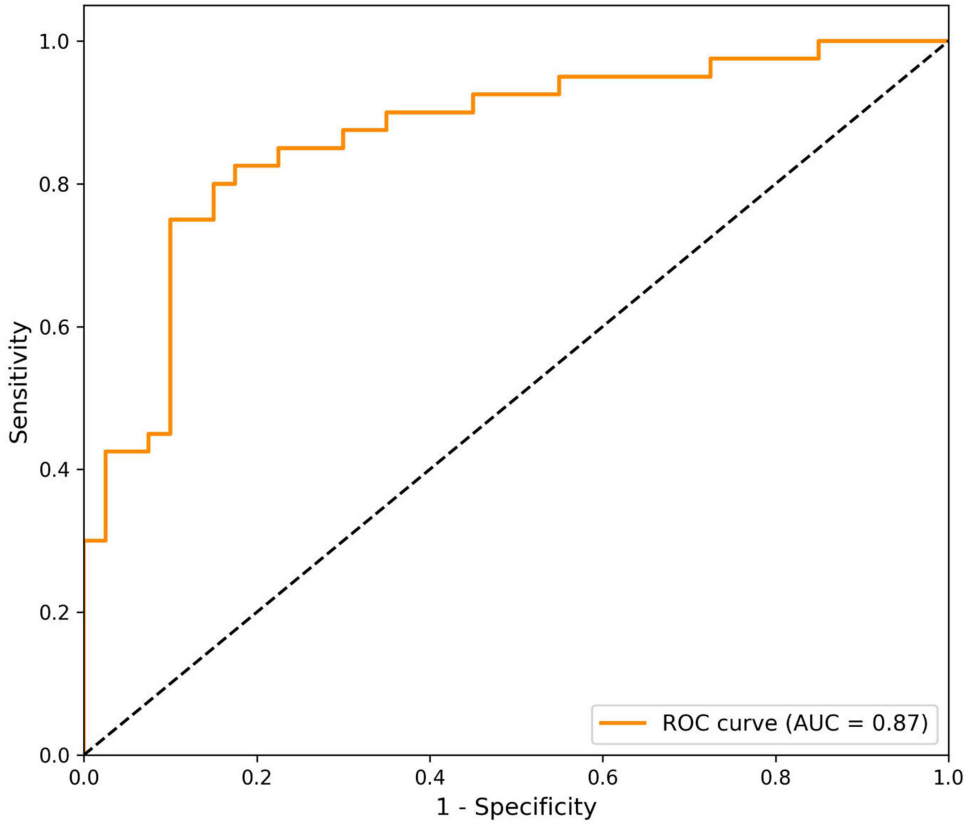

Figure 4 ROC Curve of Serum Homocysteine for Predicting AD Severity.
Notes: ROC curve analysis demonstrating the ability of serum homocysteine (Hcy) to discriminate between different severity stages of Alzheimer's disease (mild, moderate, and severe). The optimal cut-off value was determined by maximizing the Youden index.
Abbreviations: AUC, area under the curve; CI, confidence interval.

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From a biological mechanism perspective, Hcy is involved in multiple pathological pathways in the onset and progression of AD. Firstly, the positive feedback effect of Aβ deposition: Hcy promotes Aβ generation by upregulating BACE1 and PSEN1 expression, while Aβ can inhibit the activity of key enzymes in Hcy metabolism (such as cystathionine β-synthase), forming a pathological cascade.[21,22] Secondly, high Hcy levels generate superoxide anions, hydrogen peroxide, and hydroxyl radicals, which act as promoters of neurodegenerative events, leading to endothelial damage and neuronal death.[23,24] Thirdly, hyperhomocysteinemia, by increasing the susceptibility of hippocampal neurons to excitotoxic injury and amyloid peptide toxicity, is associated with increased hippocampal and cortical atrophy. Hcy may also exert neurotoxic effects on neurons by stimulating the activation of N-methyl-D-aspartate (NMDA) glutamate receptors, thereby causing cell death. Furthermore, hyperhomocysteinemia also affects the synthesis of methionine and S-adenosylmethionine, which can inhibit methylation reactions, neurotransmitter metabolism, and membrane phospholipids.[8,25] Finally, high Hcy levels can lead to the generation of β-amyloid peptide through the hydrolysis of amyloid precursor protein. This may contribute to the formation of amyloid plaques in neurons.[26,27] Therefore, hyperhomocysteinemia may play multiple roles in cognitive impairment, and its complex mechanisms warrant exploration. Concurrently, folate also plays an important role in cognitive function. Folate deficiency leads to oxidative stress and generates reactive oxygen species, which are responsible for neuronal degeneration and cell death in AD-associated brain regions.[28] Diets deficient in folate have been reported to promote hippocampal neurodegeneration in transgenic mice expressing mutant amyloid precursor protein.[26] The specific mechanisms linking Hcy and folate to the occurrence and development of AD are still not fully elucidated, necessitating further exploration to find effective treatments to delay the progression of cognitive decline and dementia.

Compared with previous studies, this research not only reaffirmed the positive correlation between high Hcy levels and AD risk but also refined the understanding of the dynamic changes of this biomarker through severity stratification. Multiple large meta-analyses, such as Zhang et al[29]'s pooled analysis of 12 prospective studies and Smith et al[30]'s systematic review covering 28 cross-sectional and cohort studies, consistently reported significantly higher Hcy levels in AD patients compared to healthy controls, with hazard ratios (HR) for AD risk ranging from 1.32 to 1.45 associated with high Hcy. These findings are highly consistent with the differences in Hcy levels between the AD and control groups and the gradient changes with severity observed in our study. More importantly, this study is the first to reveal a stepwise increase in Hcy levels from mild to severe AD in a clinical AD population based on MMSE stratification, suggesting that Hcy may dynamically reflect the activity of the neurodegenerative process. This finding provides new clinical support for Hcy as an indicator of disease activity.

Furthermore, Pearson correlation analysis revealed a significant negative correlation between serum homocysteine (Hcy) levels and Mini-Mental State Examination (MMSE) scores, indicating that elevated serum Hcy is closely associated with cognitive decline. This further supports the potential role of serum Hcy in reflecting the progression of Alzheimer's disease (AD). According to the results presented in Table 2, it can be observed that after receiving standardized B-vitamin intervention therapy, serum Hcy levels decreased in AD patients across all severity groups, accompanied by concurrent improvements in cognitive function. This finding underscores that Hcy is not merely a static risk factor but an important biomarker capable of dynamically reflecting disease progression. This study further validated the potential value of Hcy in monitoring AD progression through ROC curve analysis. Elevated Hcy possesses the potential to reflect dynamic disease changes: ROC curve analysis demonstrated that serum Hcy levels can effectively distinguish between AD patients of different severities with good discriminatory performance. The optimal cut-off value of 17.5 μmol/L provides a preliminary reference threshold for clinical application. The proposal of this threshold and its dynamic monitoring capability hold significant clinical practical implications. Firstly, as a convenient and non-invasive stratification tool, serum Hcy testing is simple to perform and low-cost, making it suitable as a non-invasive method for rapid risk stratification and disease assessment in AD patients. Secondly, this threshold offers a quantitative basis for initiating targeted interventions. When a patient's serum Hcy level consistently exceeds this threshold, it strongly suggests the presence of hyperhomocysteinemia (HHcy), which is not only a risk marker for AD progression but also itself a potential modifiable target. Based on this, clinicians can consider initiating intervention strategies aimed at lowering Hcy, among which supplementation with B vitamins (especially folate, vitamin B12, and vitamin B6) is the preferred option with robust evidence-based support and safety. Thirdly, compared to traditional methods relying on

single, expensive, or invasive tests such as neuroimaging or cerebrospinal fluid biomarkers, the dynamic monitoring capability of Hcy is more suitable for long-term follow-up. It not only aids in evaluating the effectiveness of therapeutic interventions like B-vitamin supplementation but can also more sensitively reflect trends in the risk of disease progression. Finally, continuous dynamic monitoring of Hcy levels, particularly during the early disease stages or mild cognitive impairment (MCI) phase, may help identify individuals at high risk for rapid disease progression, providing a critical time window for early intensive intervention and preventive strategies.

Our study also has several limitations. Firstly, as a single-center observational study with a relatively small sample size, it may be subject to certain biases. Future research should expand the sample size and conduct multi-center validation to further verify the clinical application value of serum Hcy levels in predicting AD severity. Secondly, the biomarker was singular, focusing only on serum Hcy levels. While serum Hcy testing is simple, cost-effective, and highly acceptable to patients compared to traditional invasive methods relying on neuroimaging or cerebrospinal fluid analysis, this study did not integrate core AD biomarkers such as cerebrospinal fluid Aβ42, p-tau, or neuroimaging (eg, PET). Future studies will delve deeper into the intrinsic link between Hcy levels and AD-specific pathological changes. Finally, Hcy levels are influenced by factors such as age, renal function, and B-vitamin status. Although this study controlled for some confounding variables, more stringent standardized testing protocols are needed to minimize errors.

Conclusion

This study provides preliminary evidence that serum homocysteine (Hcy) levels are positively correlated with the severity of AD and closely associated with cognitive decline. The reduction in Hcy levels following intervention, accompanied by cognitive improvement, suggests its potential value in monitoring disease progression and treatment response.

Copyright Acknowledgement and Statement

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Data Sharing Statement

All data and figures were obtained from clinical trials in our center and are absolutely true and valid, the data that support the findings of this study are available from the corresponding author upon reasonable request.

Informed Consent Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board. Informed consent was obtained from all participants involved in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflicts of interest related to this work.

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