

Investigating the Correlation Between Neutrophil-to-Lymphocyte Ratio and Blood-Based Pathological Markers of Alzheimer's Disease and Cognitive Impairment

Chunhua Liang

Shenzhen Second People's Hospital

Xueqin Yan

Shenzhen Second People's Hospital

Guo Hong

Shenzhen Second People's Hospital

Yanxing Zhou

Shenzhen Second People's Hospital

Chengjie Li

Shenzhen Second People's Hospital

Jing Tian

Shenzhen Second People's Hospital

Cuimei Wei

Shenzhen Second People's Hospital

Jingyun Ding

Shenzhen Second People's Hospital

Guojun Yao

Shenzhen Second People's Hospital

Chen Liu

Shenzhen Second People's Hospital

Rendan Zhang

Shenzhen Second People's Hospital

Dongni Chen

Shenzhen Second People's Hospital

Ming Zeng

Shenzhen Second People's Hospital

Yunzhu Yang

Shenzhen Second People's Hospital

Yaohui Huang

Shenzhen Second People's Hospital

Xiaohua Xiao

tu_xi8888@163.com

Shenzhen Second People's Hospital

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Abstract

Background: Neuroinflammation is recognized as a critical factor in the pathogenesis of Alzheimer's disease (AD). The neutrophil-to-lymphocyte ratio (NLR) serves as a straightforward peripheral indicator of systemic inflammation; however, its association with blood-based biomarkers of AD and cognitive function remains inadequately understood.

Methods: A total of 228 participants, comprising 117 cognitively unimpaired individuals and 111 with AD-related cognitive impairment, aged between 46 and 84 years, were enrolled in this study. Each participant underwent comprehensive clinical and neuropsychological assessments, APOE genotyping, and fasting blood sampling. Plasma levels of amyloid- β 42/40 (A β 42/40), glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and phosphorylated tau181 (p-tau181) were quantified using the Simoa platform. The relationships between NLR, cognitive performance scores, and AD biomarkers were evaluated using Spearman correlation coefficients and multivariate regression models, with adjustments for potential confounding variables. Additionally, mediation analyses were conducted employing bootstrap methods.

Results: In comparison to the unimpaired group, individuals with cognitive impairment exhibited increased neutrophil counts, elevated NLR, and higher GFAP, NfL, and p-tau181, alongside a reduced A β 42/40 ratio. The NLR demonstrated a negative correlation with cognitive scores and a positive correlation with GFAP, NfL, and p-tau181, with the strongest correlation observed for NfL. Multivariate regression analysis indicated that NLR remained independently associated with GFAP, NfL, and p-tau181 after controlling for age, education, and other covariates. Mediation analysis suggested that NLR partially mediated the relationships between GFAP, NfL, and p-tau181 and cognitive performance, but not the relationship with A β 42/40.

Conclusion: Elevated NLR is linked to poorer cognitive function and higher plasma concentrations of GFAP, NfL, and p-tau181, with the most pronounced association observed for NfL. NLR has the potential to serve as a cost-effective peripheral biomarker for AD-related cognitive decline.

Background

Alzheimer's disease (AD) is the most prevalent form of dementia, currently affecting over 55 million individuals worldwide. With the rapid aging of the global population, the prevalence of AD is projected to surpass 115 million by 2050(1). In China, approximately 15.07 million individuals aged 60 years or older are estimated to have dementia, with 9.83 million diagnosed with Alzheimer's disease (AD), representing nearly one-quarter of the global prevalence. In 2015, the annual cost of treating AD patients in China was 167.74 billion USD, and this figure is projected to rise to 1.8 trillion USD by 2050, thereby exerting a significant economic burden on both families and society(2). The pathological mechanisms underlying AD are complex, with the most widely recognized processes involving the extracellular accumulation of misfolded amyloid- β (A β) plaques and the intracellular aggregation of tau protein into neurofibrillary tangles (NFTs)(3). Recent advancements in ultra-sensitive detection technologies, such as the Simoa

platform, have facilitated notable progress in identifying blood-based biomarkers for AD, including plasma A β 42/40, GFAP, NfL, and phosphorylated tau variants such as p-tau181 and p-tau217. These biomarkers exhibit diagnostic and prognostic capabilities comparable to those of cerebrospinal fluid markers, offering substantial potential for clinical application. In 2024, the National Institute on Aging and Alzheimer's Association (NIA-AA) expanded the A β /Tau/Neurodegeneration (A/T/N) framework by incorporating inflammation, vascular factors, and α -synuclein (I/V/S), thereby standardizing the evaluation of blood biomarkers in AD-related clinical research(4). The role of neuroinflammation in AD is well established(5–7), exhibiting a dualistic impact on the disease's trajectory. Neuroinflammation can accelerate the pathological progression of AD. Conversely, the deposition of A β and abnormal aggregation of tau protein within neurons can activate microglia and astrocytes, thereby triggering neuroinflammation. Peripheral inflammatory markers may also reflect central nervous system immune activity. Recent research has identified a correlation between elevated peripheral blood inflammatory markers, such as C-reactive protein, interleukin-6, and tumor necrosis factor- α , and neuropathological alterations in AD, including A β deposition and tau protein phosphorylation. This suggests a potential involvement of inflammation in the pathogenesis of AD(5). Nonetheless, the specific peripheral blood inflammatory markers indicative of AD progression remain unclear, necessitating further clinical investigations to elucidate their relationship with AD pathology.

The neutrophil-to-lymphocyte ratio (NLR) serves as a readily accessible peripheral marker of inflammation, indicative of the equilibrium between systemic inflammatory activity and adaptive immune responses. Due to its simplicity and clinical availability, NLR holds potential as a complementary tool to existing plasma biomarkers, contributing to a cost-effective screening panel for AD risk stratification. Previous research has demonstrated a robust association between NLR and a variety of conditions, such as ischemic stroke, acute coronary syndrome, pneumonia, multiple system atrophy, Parkinson's disease, various cancers, aging, and dementia(8, 9). With the increasing acknowledgment of neuroinflammation's involvement in AD pathogenesis, the relevance of NLR in the context of AD has gained substantial attention in recent years. Elevated NLR has been linked to an increased risk of dementia in older adults(10). Baseline NLR levels may predict the onset of dementia(11), and heightened NLR levels have been observed in individuals with AD-related Mild Cognitive Impairment (MCI) and AD itself(12). Nonetheless, heterogeneity within AD cohorts limits current evidence, and NLR has yet to be firmly established as a reliable peripheral biomarker of neuroinflammation across the AD spectrum.

Although peripheral blood inflammatory indicators represent a promising avenue in AD research, they have not yet been widely adopted as standalone diagnostic markers. Future research should prioritize multi-marker integration to improve the accuracy of early diagnosis. Consequently, this study utilized real clinical data to assess the relationship between NLR, AD blood markers, and cognitive function, with the aim of identifying additional indicators for the early prediction of AD.

Materials and methods

Subject population

The study population comprised individuals aged 46 to 84 years, recruited from the Geriatrics Department of Shenzhen Second People's Hospital between January 2023 and April 2025. A total of 228 participants were included, consisting of 117 individuals with cognitively unimpaired (CU) and 111 individuals with cognitively impaired (CI). All participants underwent thorough clinical and cognitive assessments, ensuring the availability of complete baseline data. Fasting blood samples were collected for comprehensive blood cell counts, detection of AD blood markers, and analysis of the *APOE* genotype. The CU group was characterized by meeting the following criteria: a Mini-Mental State Examination (MMSE) score of 27 or higher, a Montreal Cognitive Assessment (MoCA) score of 26 or higher, and normal daily living abilities. The CI group met the diagnostic criteria for MCI due to AD and AD, as jointly established by the NIA-AA in 2011. Exclusion criteria encompass cognitive impairment from other causes, brain tumors, Parkinson's disease, history of head trauma or surgery, severe stroke, significant organ dysfunction, mental illness, acute inflammatory or stress conditions, blood and immune system disorders, and medications affecting the immune system or inflammatory response. The Ethics Committee of Shenzhen Second People's Hospital has reviewed and approved this study. All research was performed in accordance with relevant guidelines/regulations. In addition, Written informed consent was obtained from all participants and/or their legal guardians at inclusion.

Blood detection

Informed written consent was secured from all participants or their legal guardians. Venous blood samples were collected from participants in a fasting state during the morning hours. Whole blood was drawn into EDTA tubes, and an automated blood cell analyzer was employed to quantify various cell types, including white blood cells, eosinophils, neutrophils, and lymphocytes. The neutrophil-to-lymphocyte ratio (NLR) was subsequently calculated.

Blood samples were centrifuged at 2000 rpm (radius 15 cm) for 10 minutes within a 2-hour timeframe, and plasma was aliquoted (0.5 ml) into polypropylene tubes for storage at -80°C. The samples were later thawed at room temperature and subjected to centrifugation at 10,000×g for 10 minutes. Quantitative analysis of plasma Aβ_{42/40}, GFAP, NfL, and p-tau₁₈₁ levels was conducted using the Simoa platform (Quanterix) with commercially available kits. All samples were analyzed in a single batch, with operators blinded to clinical information. Quality control was ensured using kit-provided controls, and intra-assay coefficients of variation were maintained at less than 10% for all analytes.

APOE genotype detection

The *APOE* genotype in blood samples was determined through real-time fluorescence quantitative PCR technology. Genomic DNA was extracted from blood samples following the protocol provided by the Quanterix Human Blood Genomic Extraction Kit, and the concentration of the extracted DNA was measured using the NanoDrop One microspectrophotometer. Genotyping for human *APOE* ε₂/ε₃/ε₄ alleles was conducted targeting the rs429358 (ε₄) and rs7412 (ε₂) single nucleotide polymorphisms in accordance with the instructions of a commercial fluorescence PCR detection kit, using the Hongshi

SLAN 96-s real-time fluorescence quantitative PCR instrument. Negative controls and known genotype controls were included in each run, and replicate consistency was 100%.

Statistical analysis

Data analysis was executed using SPSS version 26, while chart design was accomplished with GraphPad Prism version 9. Continuous variables were represented as mean $\pm$ standard deviation or median (interquartile range), whereas categorical variables were presented as the number of cases (percentage). An independent samples t-test (for normally distributed data with equal variances) or Mann-Whitney U test (for non-normally distributed data) was employed to compare continuous variables between groups, while the chi-square test (χ^2) was utilized for comparing categorical variables between groups. Spearman's rank correlation analysis was conducted to assess the association between two indicators. Multivariate linear regression models were used to examine the independent associations of NLR with AD blood markers, with adjustments for age, sex, years of education, smoking history, hypertension, and diabetes. The bootstrap test (5,000 resamples) was applied to determine the significance of the mediating effect of NLR on the relationship between AD blood markers and cognitive function. All statistical analyses were conducted using two-tailed tests, with a p-value of less than 0.05 considered indicative of statistical significance. Correction for multiple comparisons was performed using the Bonferroni method.

Results

Characteristics of the subject population, expression of NLR, and blood pathological markers

A total of 228 participants, aged 46 to 84 years, were included, comprising individuals with cognitive unimpaired (CU, n = 117) and cognitive impaired (CI, n = 111) conditions. The CI group was older and had a lower educational attainment compared to the CU group. No significant differences were observed between the two groups in terms of sex, body mass index (BMI), history of smoking and alcohol consumption, history of hypertension and diabetes, or the prevalence of APOE ϵ 4 carriers. However, the CI group exhibited elevated complete blood cell counts, including white blood cells, eosinophils, neutrophils, lymphocytes, and NLR, relative to the CU group. Notably, significant differences were identified in neutrophil counts and NLR between the groups. Additionally, Significant differences were observed in plasma levels of A β 42/40, GFAP, NfL, and p-tau181 between the two groups, with the CI group showing lower A β 42/40 and higher GFAP, NfL, and p-tau181 levels compared to the CU group (Table 1).

Table 1
General characteristics of the sample.

Men	CU(n = 117)	CI(n = 111)	p
	52(44.44%)	45(40.54%)	0.644
age (years)	60(54, 69)	67(60, 73)	<0.001
BMI	23.589(21.398, 25.712)	23.880(21.716, 25.952)	0.595
Years of education	12(12, 16)	12(6, 12)	<0.001
Smoking behavior	29(24.79%)	25(22.52%)	0.806
Drinking behavior	30(25.64%)	24(21.62%)	0.577
Hypertension	55(47.01%)	50(45.45%)	0.869
Diabetes	30(20.64%)	36(32.43%)	0.325
<i>APOE ε4</i> carrier	21(17.95%)	26(23.42%)	0.391
MMSE (score)	29(28, 30)	25(20, 27)	<0.001
MoCA (score)	27(26, 28)	20(15, 23)	<0.001
White blood cells (×10 ⁹ /L)	5.540(4.730, 6.490)	5.760(4.860, 7.130)	0.075
Eosinophils(×10 ⁹ /L)	0.140(0.100, 0.225)	0.150(0.110, 0.250)	0.477
Neutrophil (×10 ⁹ /L)	2.980(2.345, 3.765)	3.370(2.730, 4.750)	0.003
Lymphocyte (×10 ⁹ /L)	1.830(1.560, 2.300)	1.850(1.390, 2.240)	0.459
NLR	1.522(1.202, 2.087)	1.978(1.446, 2.645)	0.001
Aβ 42 (pg/mL)	6.235(4.691, 7.248)	6.130(4.592, 7.665).	0.994
Aβ 40 (pg/mL)	99.699(86.927, 119.340)	105.186(88.000, 130.089)	0.308
Aβ42/40	0.060(0.054, 0.069)	0.057(0.047, 0.066)	0.019
GFAP (pg/mL)	118.459(85.921, 159.841)	146.287(80.510, 198.890)	0.036
NfL (pg/mL)	15.318(10.637, 23.474)	18.679(11.610, 29.020)	0.020
p-tau181 (pg/mL)	1.893(1.167, 2.739)	2.175(1.422, 3.510)	0.034

Note: Continuous variables were expressed as Median (interquartile range, IQR), and Mann–Whitney U test was used for comparison between groups. Categorical variables were expressed as the number of cases (%), and chi-square test (χ^2) was used for comparison between groups. CU cognitively unimpaired, CI cognitively impaired, BMI body mass index, *APOE ε4* carrier status refers to carrying at least one *APOE4* allele. NLR neutrophil to lymphocyte, MMSE Mini-Mental State Examination, MoCA Montreal Cognitive Assessment, GFAP glial fibrillary acidic protein, NfL neurofilament light, p-tau181 phosphorylated tau181.

The correlation between NLR or blood AD pathological markers and cognitive scores

Furthermore, significant differences were evident in the NLR, as well as in plasma A β 42/40, GFAP, NfL, and p-tau181 levels between the CI and CU groups. The Spearman correlation analysis results between the aforementioned indicators and cognitive scores revealed that the plasma A β 42/40 level was significantly positively correlated with both the MMSE and MoCA cognitive scale scores, with correlation coefficients (r) of 0.251 and 0.190, respectively. Notably, the plasma A β 42/40 level exhibited a stronger correlation with the MMSE score. Conversely, the levels of NLR, plasma GFAP, NfL, and p-tau181 were significantly negatively correlated with cognitive scores, with all p-values being less than 0.05. Among these, the correlation coefficient (r) between NLR and the MoCA score was the highest, at -0.277. We integrated the MMSE and MOCA scores to form the Z-score, which is a more representative indicator of global cognitive function. From Table 2, we can see that, except for A β 42/40, NLR, GFAP, NfL and p-tau181 are all significantly negatively correlated with Z-score. All correlations remained significant after Bonferroni correction (Table 2).

Table 2
Correlation Analysis Between Blood Biomarkers and Cognitive Performance Scores

	MMSE		MoCA		Z-score	
	r	p	r	p	r	p
NLR	-0.213	0.001	-0.277	<0.001	-0.255	<0.001
A β 42/40	0.251	<0.001	0.190	0.004	0.229	<0.001
GFAP	-0.211	0.001	-0.234	<0.001	-0.213	0.001
NfL	-0.240	<0.001	-0.222	0.001	-0.220	0.001
p-tau181	-0.203	0.002	-0.224	0.001	-0.201	0.002
Note: r indicates the correlation coefficient in Spearman correlation analysis. Z-score=(Z _{MMSE} +Z _{MoCA})/2, Z _{MMSE} =(Primitive-Mean)/Standard deviation, Z _{MoCA} =(Primitive-Mean)/Standard deviation.						

Baseline characteristics and expression of blood markers in the NLR subgroups

Within the cohort of 228 subjects, the NLR ranged from 0.601 to 6.587, with an average of 1.990 $\pm$ 1.062 and a median of 1.672. Subjects were categorized into two groups based on the median NLR value of 1.672, resulting in 114 subjects in both the low and high NLR groups. An analysis comparing the two groups indicated that, relative to the low NLR group, the high NLR group exhibited a higher proportion of males, older age, lower educational attainment, and a greater prevalence of smokers. Conversely, no

significant differences were observed between the groups concerning baseline characteristics such as BMI, alcohol consumption history, hypertension, diabetes, and *APOE* $\epsilon 4$ carrier status. Notably, the MMSE and MoCA cognitive scores were significantly lower in the high NLR group compared to the low NLR group ($p < 0.001$). The high NLR group demonstrated elevated levels of plasma NfL, and p-tau181 (Table 3).

Table 3
Comparison of baseline data between the Low NLR group and the High NLR group

Men	Low NLR (n = 114)	High NLR (n = 114)	<i>p</i>
	37(32.46%)	60(52.63%)	0.002
age (years)	61(55,69)	68(58, 73)	0.010
BMI	23.789(21.194, 26.020)	23.814(21.760, 25.746)	0.842
Years of education	12(9, 16)	12(6, 12)	0.001
Smoking behavior	17(14.91%)	37(32.46%)	0.003
Drinking behavior	24(21.05%)	30(26.32%)	0.350
Hypertension	48(42.11%)	57(50.00%)	0.288
Diabetes	28(24.56%)	38(33.33%)	0.144
<i>APOE</i> $\epsilon 4$ carrier	25(21.93%)	22(19.30%)	0.623
MMSE (score)	28(27, 29)	27(23, 29)	0.011
MoCA (score)	26(22, 27)	24(17, 26)	0.001
A β 42 (pg/mL)	6.133(4.768, 7.264)	6.355(4.502, 7.517).	0.356
A β 40 (pg/mL)	100.671(88.357, 120.846)	107.504(85.787, 130.930)	0.417
A β 42/40	0.058(0.053, 0.068)	0.060(0.048, 0.067)	0.613
GFAP (pg/mL)	116.430(79.989, 178.194)	138.804(93.923, 184.194)	0.190
NfL (pg/mL)	15.244(10.648, 21.759)	19.716(11.578, 33.176)	0.010
p-tau181 (pg/mL)	1.797(1.231, 2.628)	2.261(1.408, 3.548)	0.024
Note: The low NLR group was < median 1.672, and the high NLR group was > median 1.672. Continuous variables were expressed as Median (interquartile range, IQR), and Mann–Whitney U test was used for comparison between groups. Categorical variables were expressed as the number of cases (%), and chi-square test (χ^2) was used for comparison between groups.			

The association between NLR and blood pathological markers of AD

In the correlation analysis between NLR and AD-related blood biomarkers, NLR demonstrated positive associations with three out of the four biomarkers, with the exception of plasma Aβ42/40. Although the overall strength of these correlations was modest, the association between NLR and NfL was statistically significant ($r = 0.243$, $p = 0.0002$). The correlation between NLR and GFAP was weaker but still significant ($r = 0.149$, $p = 0.025$) (Fig. 1). Multivariate linear regression adjusting for age, sex, education, smoking, hypertension, and diabetes revealed that NLR remained independently associated with GFAP ($\beta = 0.143$, $p = 0.039$), NfL ($\beta = 0.194$, $p = 0.005$) and p-tau181 ($\beta = 0.151$, $p = 0.030$) (Table 4).

Note

r indicates the correlation coefficient in Spearman correlation analysis

Table 4

Multivariable Linear Regression Analysis of Associations Between NLR and AD Blood Biomarkers

Dependent Variable	Independent Variable	β (95% CI)	Standardized β	SE	t	p
GFAP (pg/mL)	NLR	11.742(0.578, 22.905)	0.143	5.664	2.073	0.039
NfL (pg/mL)	NLR	4.421 (1.359, 7.483)	0.194	1.554	2.846	0.005
p-tau181 (pg/mL)	NLR	0.205 (0.020, 0.390)	0.151	0.094	2.182	0.030
Aβ42/40	NLR	-0.001 (-0.003, 0.001)	-0.084	0.001	-1.193	0.234

Notes: All models were adjusted for age, sex, years of education, smoking history, hypertension, and diabetes. β = unstandardized regression coefficient; 95% CI = 95% confidence interval; SE = standard error.

The mediating role of NLR between blood pathological markers of AD and cognitive scores

While plasma Aβ42/40 was found to have a significant positive impact on cognitive scores, the other AD blood markers and NLR were associated with significant negative effects on cognitive scores. To investigate the potential mediating role of the NLR in the relationship between AD blood markers and cognitive function, this study utilized the Z-score as dependent variables, while AD blood markers served as independent variables. The analysis revealed a significant mediating effect of NLR on the association between plasma GFAP, NfL, p-tau181, and cognitive function. The results showed that NLR did not exhibit a significant mediating effect on the relationship between plasma Aβ42/40 and cognitive function. However, it did show a significant partial mediating effect on the relationships between the other three AD blood markers (plasma GFAP, NfL, and p-tau181) and cognitive function, especially in the NfL,

suggesting that NLR can partially explain the associations between these markers and cognitive scores (Fig. 2).

Note

$Z\text{-score} = (Z_{\text{MMSE}} + Z_{\text{MoCA}}) / 2$, $Z_{\text{MMSE}} = (\text{Primitive-Mean}) / \text{Standard deviation}$, $Z_{\text{MoCA}} = (\text{Primitive-Mean}) / \text{Standard deviation}$. c: The total effect is calculated as the sum of the direct effect and the indirect effect. a: Regression analysis was conducted using the β values of the independent variable and the dependent variable. b: Regression analysis of the independent variable, mediating variable NLR, and dependent variable for β values. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. A 95% bootstrap confidence interval that includes zero suggests that the mediating effect is not statistically significant, whereas a 95% Bootstrap CI that does not include zero indicates a statistically significant mediating effect.

Discussion

This study conducted a systematic investigation into the relationships among NLR, AD blood biomarkers, and cognitive function. The principal findings are as follows: (1) Individuals with CI exhibited significantly elevated levels of NLR, GFAP, NfL, and p-tau181, alongside reduced A β 42/40 ratios, in comparison to CU individuals; (2) NLR demonstrated a negative correlation with cognitive function and a positive correlation with GFAP, NfL, and p-tau181, with the most pronounced association observed with NfL; (3) NLR partially mediated the relationships between GFAP, NfL, and p-tau181 and cognitive performance. These findings imply that NLR could serve as an economical peripheral biomarker indicative of AD-related neuroinflammation and neuronal damage.

The peripheral immune system is categorized into innate immunity, primarily associated with neutrophils, and adaptive immunity, primarily associated with lymphocytes. Innate immunity is hypothesized to be linked with neuronal dysfunction, the secretion of inflammatory factors, and decreased cerebral blood flow, whereas adaptive immunity is considered to exert a more neuroprotective effect(13). The NLR serves as an indicator of the balance between innate and adaptive immunity and is recognized as an effective marker of systemic inflammation. It can be derived from a complete blood cell count and is characterized by its low cost, convenience, and non-invasiveness. Previous studies have established a correlation between NLR and the risk of AD as well as the degree of cognitive impairment in the population(11, 13, 14). Emerging evidence from AD mouse models indicates that neutrophils undergo heightened activation, exhibiting increased migratory capacity and adhesion to cerebral microvessels, thereby facilitating their infiltration across the blood–brain barrier and accumulation in the brain(15, 16). Similarly, in AD patients, neutrophils show dysregulated activity and tend to aggregate in regions vulnerable to AD pathology, including the temporal cortex and hippocampus, particularly near A β plaques and sites of blood–brain barrier disruption(17, 18). Lymphocytes also contribute to neuroinflammation and disease progression. For instance, CD4⁺ helper T cells release pro-inflammatory cytokines, activate microglia, and compromise blood–brain barrier integrity(19, 20). Notably, Th17 cells are elevated in patients with mild cognitive impairment, and CD8⁺ T cell infiltration has been observed in

the brains of AD patients despite low circulating levels(21). Collectively, these findings underscore the central role of both innate and adaptive immune cells in AD pathogenesis, highlighting the importance of investigating peripheral immune markers as potential indicators of disease progression and cognitive decline. Furthermore, research indicates that NLR is significantly elevated in individuals with MCI and AD compared to CU individuals(11, 22). However, it does not effectively differentiate between dementia subtypes such as AD, vascular dementia, mixed dementia, and frontotemporal dementia(23). Our study found that the levels of white blood cells, eosinophils, neutrophils, and lymphocytes were elevated in the CI group compared to the CU group, with statistically significant differences observed in the counts of neutrophils between the two groups. Additionally, the NLR was significantly higher in the CI group than in the CU group ($p = 0.001$). These findings support previous evidence linking higher NLR and neutrophil counts to cognitive decline(11). To further investigate the relationship between the NLR and cognitive function, we conducted a Spearman correlation analysis between the NLR and cognitive scores. The analysis indicated that NLR is significantly negatively correlated with MMSE, MoCA and Z-score scores (all $p < 0.05$). These results suggest a strong association between NLR and cognitive function, indicating that NLR may serve as a risk factor for cognitive impairment. Specifically, higher NLR values were linked to poorer cognitive performance.

In recent years, advancements in testing techniques have enabled the detection of AD through blood markers. Our team's prior research demonstrated that plasma levels of GFAP, NfL, and p-tau181 exhibit an upward trend across the AD continuum, effectively distinguishing elderly AD patients and serving as reliable indicators for predicting AD(24). Plasma pathological markers such as A β 42/40, GFAP, NfL, and p-tau181 are recognized blood markers associated with AD and are closely linked to cognitive function. Research indicates that plasma levels of A β 42, p-tau181, and NfL may aid in predicting AD in the Chinese population up to eight years prior to clinical onset(25), and are intimately connected to AD pathology and cognitive function(26–29). Similarly, our study revealed significant differences in plasma levels of A β 42/40, GFAP, NfL, and p-tau181 between the CU and CI groups. Plasma A β 42/40 showed a significant positive correlation with cognitive scores, whereas the other three AD biomarkers—GFAP, NfL, and p-tau181—exhibited significant negative correlations with cognitive performance. However, research examining the relationship between NLR and AD-related blood markers remains limited. In this study, participants were divided into two groups according to the median NLR value. The results showed that plasma levels of NfL and p-tau181 were significantly higher in the high NLR group than in the low NLR group, whereas no significant differences were observed in plasma GFAP or A β 42/40 levels between the two groups. Correlation analysis revealed that NLR was positively correlated with GFAP, NfL, and p-tau181, all of which reached statistical significance ($p < 0.05$). Notably, the association between NLR and plasma NfL was particularly robust ($r = 0.243$, $p = 0.0002$), while no significant correlation was found between NLR and plasma A β 42/40 ($r = 0.059$, $p = 0.427$). NfL is a non-specific marker of axonal injury and is elevated in AD as well as in other neurodegenerative diseases. The strong link between NLR and NfL suggests that systemic inflammation may contribute to cognitive decline, at least in part, by promoting neuronal damage. In the present study, after multivariate adjustment, NLR remained independently associated with GFAP, NfL, and p-tau181. Mediation analysis revealed that NLR

significantly mediated the associations between plasma GFAP, NfL, and p-tau181 and cognitive function. Specifically, a partial mediation was identified, indicating that NLR partially accounted for the relationships between these plasma biomarkers and cognitive performance, whereas no significant mediating effect was observed for plasma A β 42/40. These findings suggest that systemic inflammation may contribute to AD pathology through astrocytic activation, axonal injury, and tau phosphorylation. Generally, within the AD continuum, an elevated NLR is correlated with an increased risk of A β deposition and cognitive decline^(14, 30, 31). In this study, we did not observe a significant association between NLR and A β 42/40. Potential explanations include the following: A β deposition is an early pathological event in AD, whereas the inflammatory response reflected by NLR may be more prominent in later stages. Additionally, the relationship between A β metabolism and inflammatory responses is complex and may be modulated by multiple factors. The lack of mediation by NLR in the A β 42/40–cognition relationship further supports this view. Nonetheless, the precise role of NLR in mediating the association between AD blood biomarkers and cognitive function remains unclear and warrants further investigation through in-depth foundational pathological research.

Our findings further demonstrate that male sex, advanced age, lower educational attainment, and a history of smoking are correlated with elevated NLR. This correlation implies that socioeconomic and lifestyle factors, such as education and smoking, may constitute modifiable risk factors, meriting additional investigation. In alignment with previous studies, the MMSE and MoCA scores were lower in individuals with high NLR, reinforcing the link between elevated NLR and reduced cognitive function. Moreover, increased NLR levels are associated with a heightened risk of cognitive impairment^(22, 23). Peripheral blood NLR, a simple and readily available inflammatory marker, is significantly associated with core biomarkers of AD and cognitive impairment. These findings provide robust human evidence linking peripheral immune responses to the neuroinflammatory hypothesis of AD. Given its cost-effectiveness and ease of measurement, NLR holds promise as a supplementary tool in precision medicine for AD, aiding in disease assessment and prognostic evaluation.

Limitations

First, the single-center, cross-sectional design limits the ability to draw causal inferences and precludes the assessment of temporal changes in NLR and their association with cognitive decline. Second, cognitive classification relied on clinical criteria without confirmation via positron emission tomography (PET) or cerebrospinal fluid biomarkers, potentially introducing misclassification bias. Third, the study's sample size was relatively modest, and no independent validation cohort was included. Fourth, although we adjusted for multiple confounders, residual confounding (e.g., detailed medication use, chronic inflammatory conditions) cannot be excluded. Future multi-center, prospective cohort studies incorporating neuroimaging and cerebrospinal fluid biomarkers are warranted to clarify the dynamic changes and mechanisms underlying NLR in the AD continuum.

Conclusion

Elevated NLR was also linked to poorer cognitive performance and higher levels of plasma GFAP, NfL, and p-tau181, with the most significant association observed with NfL. NLR partially mediates the relationships between GFAP, NfL, and p-tau181 and cognitive function, indicating that systemic inflammation may contribute to AD-related cognitive decline through mechanisms involving astrocytic activation, axonal injury, and tau phosphorylation. As a simple and widely accessible marker, NLR could complement emerging plasma biomarkers in risk stratification and disease monitoring; however, validation in longitudinal, multi-center studies is necessary.

Abbreviations

AD Alzheimer's disease

NLR neutrophil-to-lymphocyte ratio

A β 42/40 amyloid- β 42/40

GFAP glial fibrillary acidic protein

NfL neurofilament light chain

p-tau181 phosphorylated tau181

NFTs neurofibrillary tangles

NIA-AA National Institute on Aging and Alzheimer's Association

CU cognitively unimpaired

CI cognitively impaired

MCI Mild Cognitive Impairment

MMSE Mini-Mental State Examination

MoCA Montreal Cognitive Assessment

PET positron emission tomography

Declarations

Ethics approval and consent to participate

The Ethics Committee of Shenzhen Second People's Hospital has reviewed and approved this study. In addition, Written informed consent was obtained from all participants and/or their legal guardians at inclusion.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare no competing interests.

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Authors' contributions

CL, XY, GH, YZ, CL, JT, CW, JD, GY, CL, RZ, DC, and MZ contributed to the analysis and interpretation of the data. CL, XY, and GH conduct draft writing and revision of the manuscript. JT, YH and YY conduct data management and research quality control. YH and XX contributed to reviewing and editing. All authors read and approved the final manuscript.

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Figures

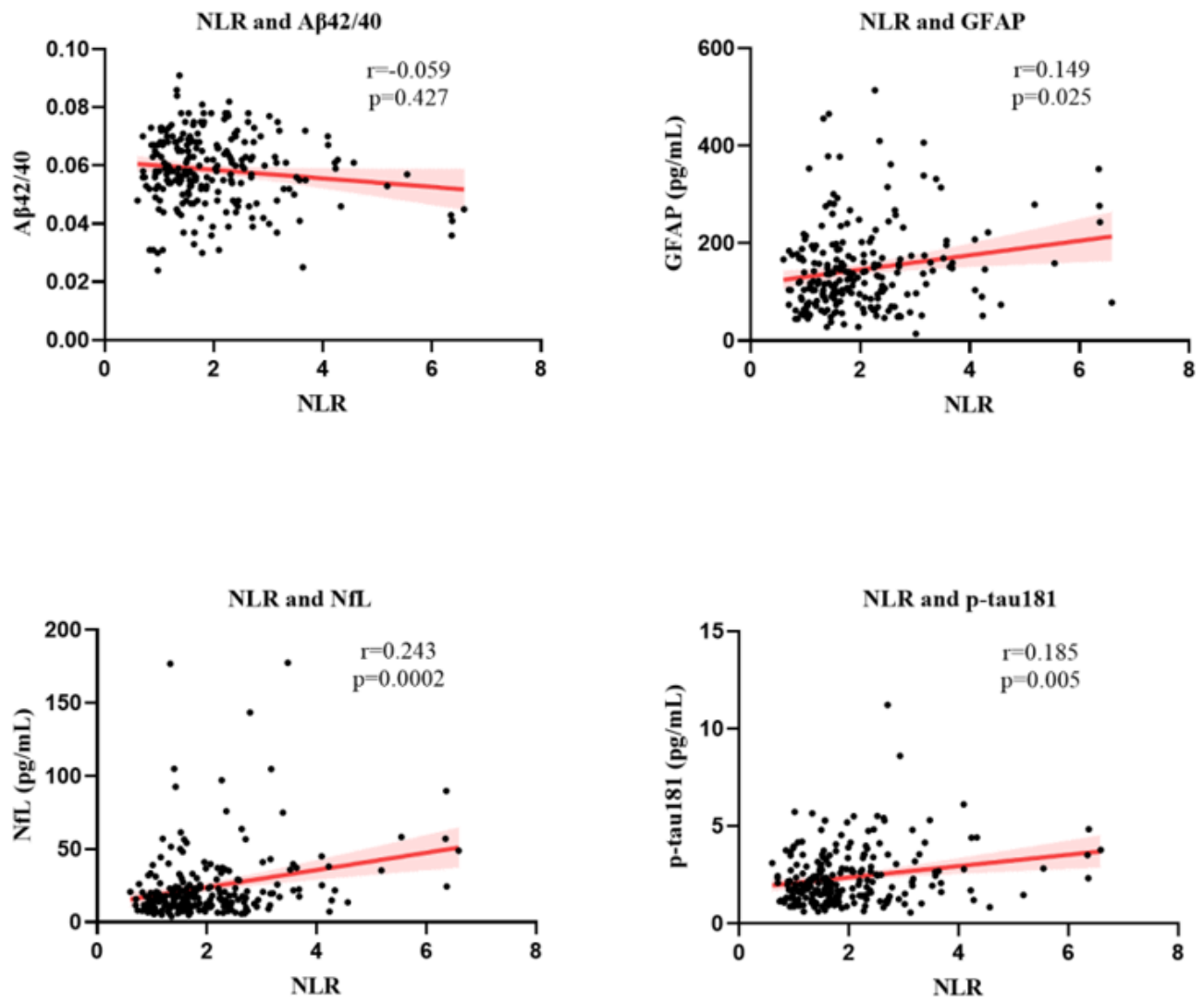


Figure 1

Baseline associations between the NLR and AD Blood Biomarkers.

Note: r indicates the correlation coefficient in Spearman correlation analysis

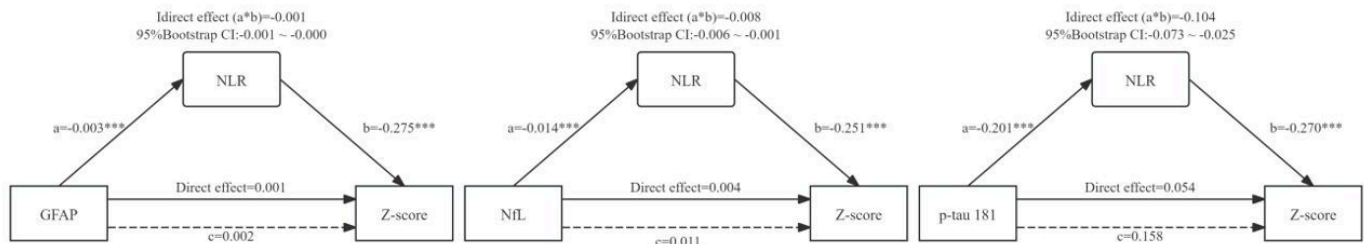


Figure 2

Test for the mediating effect of NLR between AD Blood Biomarkers and cognitive function

Note: $Z\text{-score} = (Z_{\text{MMSE}} + Z_{\text{MoCA}}) / 2$, $Z_{\text{MMSE}} = (\text{Primitive-Mean}) / \text{Standard deviation}$, $Z_{\text{MoCA}} = (\text{Primitive-Mean}) / \text{Standard deviation}$. c: The total effect is calculated as the sum of the direct effect and the indirect effect. a: Regression analysis was conducted using the β values of the independent variable and the dependent variable. b: Regression analysis of the independent variable, mediating variable NLR, and dependent variable for β values. $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$. A 95% bootstrap confidence interval that includes zero suggests that the mediating effect is not statistically significant, whereas a 95% Bootstrap CI that does not include zero indicates a statistically significant mediating effect.