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Associations between neutrophil–lymphocyte ratio and risk of cognitive impairment among Chinese older adults

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Abstract

Background Associations between the neutrophil–lymphocyte ratio (NLR) and cognitive performance in older population are rarely reported. We investigated the associations between NLR and risk of cognitive impairment in Chinese community-dwelling older adults.

Methods Individuals aged ≥ 65 years from the 2011 and 2014 waves of the Chinese Longitudinal Healthy Longevity Survey were enrolled. We used the Chinese version of the Mini-Mental State Examination to evaluate cognitive function, with a score <18 indicating cognitive impairment. NLR was expressed as derived NLR (white blood cell count – lymphocyte count]/lymphocyte count). Logistic regression was used to evaluate the association between NLR levels and risk of cognitive impairment.

Results The study enrolled 2375 cognitively healthy participants and 838 with cognitive impairment. Significantly higher NLR values were noted in the latter than in the former group. In the cross-sectional analysis, NLR values in the highest than in the lowest quartile indicated significantly increased risk of cognitive impairment, after controlling for all confounding factors. During follow-up, 134 of the 1173 healthy participants at baseline developed cognitive impairment. NLR values in the highest two quartiles indicated higher risk of cognitive impairment than those in the lowest quartile. When NLR was classified into dichotomous groups, the risk of cognitive impairment was significantly higher in the high-inflammation than in the noninflammatory status group, regardless of the analysis used (cross-sectional or prospective).

Conclusions Elevated NLR status is associated with increased risk of cognitive impairment in Chinese community-dwelling older adults.

Keywords Neutrophil–lymphocyte ratio, Cognitive impairment, Inflammation, Alzheimer's disease, Older adults

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Background

Alzheimer's disease (AD), the most common neurodegenerative disorder, is characterized by progressive cognitive impairment. Approximately 15 million Chinese individuals aged 60 years or older currently lived with dementia, of whom ~ 9.8 million have been diagnosed with AD [1]. As the aging population grows and life expectancy improves, AD prevalence is projected to increase worldwide every year, imposing a heavy burden to society and families [2]. Early diagnosis and development of effective therapeutic methods are thus important. Current application of diagnostic biomarkers for AD, including amyloid-β (Aβ) and tau protein levels in the cerebrospinal fluid and neuroimaging assessments, in large-scale early population screening is challenging because of the invasive procedures involved, high cost, and harmful radiation to the human body.

A growing number of studies have demonstrated that neuroinflammation plays a significant role in AD pathogenesis [3–5]. In addition, the contribution of immune responses to the pathogenesis of AD cannot be ignored; in particular, the role of the peripheral immune system has received considerable attention in recent years [6–8]. Previous studies have shown that microglial activation occurs before Aβ deposition [9, 10]. And Liu et al. (2023) revealed that immune dysfunction in AD precedes neuropathological changes, including the formation of Aβ plaques and neurofibrillary tangles [6]. These studies indicate that neuroinflammation and immune responses may be early events in the onset of AD.

The neutrophil–lymphocyte ratio (NLR), calculated as the ratio of neutrophils to lymphocytes in peripheral blood, can reflect inflammatory burden and the presence of immune responses [11]. As a simple, easily available and cost-effective peripheral-blood index, NLR has been increasing studied in association with AD. Some studies have suggested that NLR is higher in patients with AD than in the healthy population [12–14]. In addition, Li et al. (2023) showed that elder Americans with elevated NLR values are in increased risk of developing cognitive impairment [15]. In contrast, other findings have suggested that no significant differences are present between NLR values in AD and in cognitively healthy populations [16, 17]. We speculate that the small sample size in previous studies may have limited the power to detect an association between NLR level and cognitive function. Other reasons for these inconsistent results include the difference of enrolled study population, confounding factors, evaluation criteria of cognitive impairment. In addition, the association between NLR and risk of cognitive impairment in the older adults is unclear (mean age was 80 years and older). Previous study has shown that the influencing factors of cognitive impairment in the older adults are different from those in the younger adults [18]. The older adults have a higher prevalence of dementia and a worse prognosis than the younger adults. Therefore, the clarifying of the relationship between NLR and cognitive impairment in the older adults, is important for the understanding pathogenesis, and preventing disease occurrence by reducing risk factors related to dementia.

With the aging Chinese population, cognitive impairment, the main clinical features of AD, has become an important public health concern in the country. In addition to previous small-sample studies that produced conflicting results, studies on the association of peripheral NLR levels with the risk of cognitive impairment in older Chinese adults are scarce. Herein, we explored the relationship between NLR and risk of cognitive impairment in a Chinese community-dwelling older population in this present study. We aimed to determine whether NLR can be serve as a predictive marker for cognitive impairment in cognitively healthy older adults.

Methods

Sample selection

In this study, data from the 2011 and 2014 waves of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) were used to explore the association between NLR levels in the peripheral blood and risk of cognitive impairment. CLHLS is an ongoing prospective cohort study exploring the health status of older adults in 23 provinces of China, covering approximately 85% of Chinese elderly population. The survey started in 1998 and the individuals were followed up every 2–3 years thereafter. The CLHLS tried to interview all centenarians who voluntarily agreed to participate in the study in the sampled counties and cities. Details of this survey have been described elsewhere [19]. The survey data are publicly available at: https://opendata.pku.edu.cn/dataverse/CHADS.

Of the 2357 and 2433 participants aged over 65 in the 2011 and 2014 waves, respectively, who received a blood test, 244 individuals without NLR or Mini-Mental State Examination (MMSE) data in the 2011 wave and 55 individuals in the 2014 wave were excluded. Collectively, data from 2113 individuals from the 2011 wave and 2378 individuals from the 2014 wave were included in this study. All participants of the 2011 wave were invited to participant in the 2014 wave. However, due to participants loss to follow-up and death, as well as a lack of complete data, only 60.48% of the 2011 wave participants had follow-up data in the 2014 wave. Among the 2014 cohort, 1278 participants were from the 2011 wave and 1100 were added in the 2014 wave. In this study, the data from the 2113 individuals from the 2011 wave and the 1100 individuals added in the 2014 wave were combined for the cross-sectional analyses. Among 1278 participants for whom prospective data were available, 1173 with healthy cognitive function provided data for the prospective analysis.

A flow chart depicting the screening and inclusion procedure is provided in Fig. 1. The CLHLS has been performed adhered to the Declaration of Helsinki and was sponsored by the Ethics Committee of Peking University (IRB00001052-13074). Each participant signed a written informed consent form.

Covariates

All participants were interviewed face-to-face by professionals using structured questionnaires. Data were collected regarding age, sex, ethnicity, marital status, education, history of smoking (past or current smoking greater than twenty pack years) or alcohol consumption (past or current drinking more than twice a week for more than one year), patterns of regular physical activity (regularly performing exercise for over thirty minutes at least twice a week), body mass index (BMI), and history of disease.

Cognitive function assessment

The Chinese version of the MMSE was utilized to assess cognitive function of all participants. The MMSE has a total score of 30, with higher scores suggesting better cognitive function [20]. All the questions were answered by the participants themselves. Considering that 82.22% of our study participants had no formal education, participants with MMSE scores < 18 were defined as having cognitive impairment, as described in several previous study [21–23].

NLR measurement

Fasting blood samples were obtained in the morning and sent to the local hospital for routine blood testing on the same day. In CLHLS, routine blood testing did not contain data on neutrophils counts. Therefore, we replaced NLR with a derived NLR (dNLR), which was calculated using the following formula: dNLR= (white blood cell count – lymphocyte count)/lymphocyte count [24]. We classified the NLR levels using two strategies. In the first approach, a cutoff value of 3 was chosen to subclassify NLRs. An NLR < 3 for NLR results within the reference range indicated noninflammatory status, while NLR ≥ 3 referred to NLR values beyond the reference range, indicating a high- inflammation status, as previously described [25]. The second strategy was quartile classification.

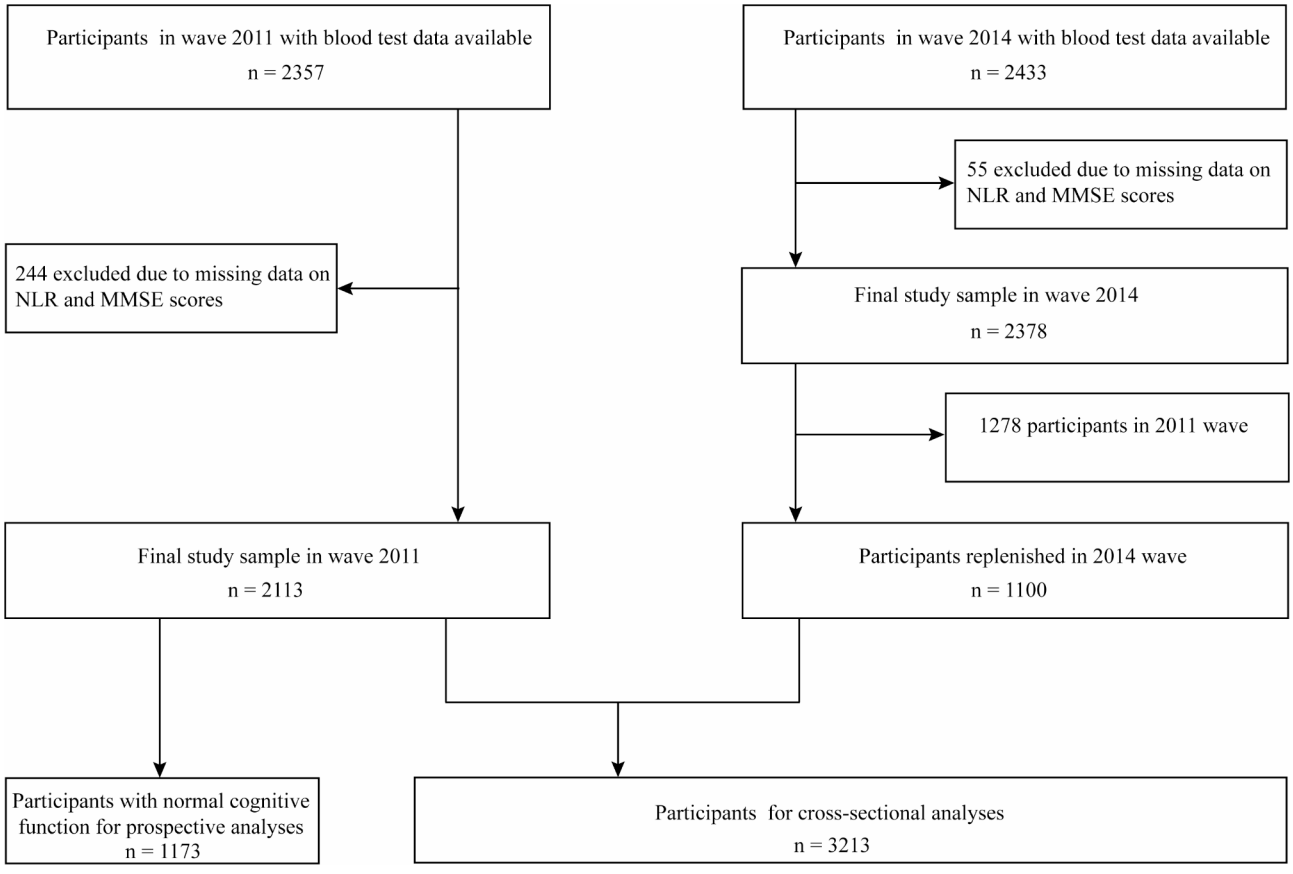

Fig. 1 Detailed flowchart of participant selection. MMSE, Mini-Mental State Examination; NLR, neutrophil–lymphocyte ratio

Statistical analyses

Group comparisons in data were performed utilizing the student's *t*-test, chi-squared tests, or non-parametric tests, as appropriate. Due to the skewed distribution, NLR values are presented as the median (interquartile range). The associations between peripheral NLR values and risk of cognitive impairment were assessed using four logistic regression models, adjusted for different confounding factors. To reduce the issue of multicollinearity, we calculated variance inflation factors (VIF) for final models for both the cross-sectional and longitudinal analyses. VIF scores higher than 5 indicate multicollinearity in a model. We do not observe the existence of multicollinearity issues, with all variance inflation factors < 5 (Supplementary Tables 2 and Table 1). When NLR levels were classified by quartiles, we evaluated the odds ratios (ORs) associated with other quartiles, with the first quartile serving as a reference. The statistical analyses were conducted using SPSS version 26.0 (IBM, Armonk, NY, USA), and a *P*-value less than 0.05 was considered significant.

Table 1 The detailed demographic and clinical characteristics of all participants

Characteristics	Total (*N* = 3213)	Cognitively healthy (*N* = 2375)	Cognitive impairment (*N* = 838)	*P*-value
Age (years), mean (SD)	86.92(11.62)	83.66 (10.96)	96.17 (7.85)	**< 0.001**
Men (vs. women), n (%)	1399(43.54)	1199(50.48)	200 (23.87)	**< 0.001**
Ethnicity (Han vs. others), n (%)	2849(88.67)	2115 (89.05)	734 (87.59)	0.251
Marital status, n (%)				0.628
Married	1224(38.10)	900 (37.89)	324 (38.66)	
Widowed	1906(59.32)	1410(59.37)	496 (59.19)	
Other	83(2.58)	65 (2.74)	18 (2.15)	
Years of schooling, mean (SD)	2.11(0.06)	2.21 (0.07)	1.84 (0.10)	**0.038**
Smoking history, n (%)	748(23.28)	526(22.18)	222(26.49)	**0.011**
Drinking history, n (%)	680(21.16)	452 (19.03)	228 (27.21)	**< 0.001**
Regular physical activity, n (%)	556(17.30)	402 (16.93)	154 (18.38)	0.340
BMI (kg/m2)	21.08(3.44)	20.90(3.41)	21.59(3.47)	**< 0.001**
Hypertension, n (%)	816(25.40)	575 (24.21)	241 (28.76)	**0.009**
Diabetes, n (%)	78(2.43)	62 (2.61)	16 (1.91)	0.257
Stroke, n (%)	219(6.82)	152 (6.40)	67 (8.00)	0.115
Cardiovascular disease, n (%)	245(7.63)	193 (8.13)	52 (6.21)	0.072
Respiratory diseases, n (%)	272(8.47)	199 (8.38)	73 (8.71)	0.766
Cancer, n (%)	18(0.56)	14 (0.59)	4 (0.48)	0.708
Lymphocytes count [M, (P25, P75)]	1.70 (1.30, 2.15)	1.70 (1.30, 2.20)	1.55 (1.14, 2.00)	**< 0.001**
Leukocyte count [M, (P25, P75)]	5.50 (4.50, 6.64)	5.59 (4.60, 6.71)	5.20 (4.20, 6.38)	**< 0.001**
NLR [M, (P25, P75)]	2.21(1.67, 3.00)	2.17 (1.65, 2.92)	2.30 (1.69, 3.22)	**0.004**
Abnormal NLR, n (%)	805(25.05)	554(23.33)	251(29.95)	**< 0.001**

NOTE. Significant results in bold

Abbreviations: BMI, body mass index; SD, standard deviation; M, median; P25, 25% quartile, P75, 75% quartile; NLR, neutrophil–lymphocyte ratio

Results

Study participants

The cross-sectional analysis of the combined samples included data from 3213 participants aged 65 – 112, of whom 2375 were designated as cognitively healthy and 838 presented with cognitive impairment. No notable differences were observed between the group with cognitive impairment and the healthy group in terms of ethnicity, marital status, patterns of regular physical activity, and history of diabetes, stroke, cardiovascular disease, respiratory diseases, or cancer. Compared to the healthy group, the group with cognitive impairment comprised significantly older individuals, more women, and adults with fewer years of schooling, more frequent history of smoking and alcohol consumption, higher BMI, and more adults live with hypertension. The group with cognitive impairment had significant lower leukocyte count (5.20 [4.20, 6.38] vs. 5.59 [4.60, 6.71], respectively; $P < 0.001$), lower lymphocytes count (1.55 [1.14, 2.00] vs. 1.70 [1.30, 2.20], respectively; $P < 0.001$), and higher NLR values than the healthy group (2.30 [1.69, 3.22] vs. 2.17 [1.65, 2.92], respectively; $P = 0.004$). Lastly, in the group with cognitive impairment, NLR values outside of the reference range were significantly higher than those in the healthy group (29.95% vs. 23.33%, respectively; $P < 0.001$). The detailed demographic features of this cohort are listed in Table 1.

NLR levels classified by quartiles and risk of cognitive impairment

The logistic regression models (Table 2) suggested that peripheral NLR values were significantly correlated with risk of cognitive impairment ($P < 0.05$). In the cross-sectional analysis, compared to the participants in the lowest quartile, those of in the highest quartile regarding NLR levels had a significantly higher risk of cognitive impairment after controlling for all confounding factors (OR = 1.506, 95% confidence intervals [CI]: 1.163–1.950). During follow-up, 134 of the 1173 participants in the healthy group developed cognitive impairment. Participants with NLR values in the highest two quartiles were at a higher risk of cognitive impairment than participants with values in the lowest quartile (OR = 2.010, 95% CI: 1.103–3.664 for Q3, and OR = 2.709, 95% CI: 1.529–4.799 for Q4).

Table 2 NLR levels classified by quartiles and risk of cognitive impairment

Analysis	NLR	Odds ratios (95% Confidence interval)				*P*-value
		Q1	Q2	Q3	Q4	
Cross-sectional	NLR (μg/mL)	0.500-1.667	1.667–2.208	2.211-3	3-21.667	
	Model 1	1	0.901(0.716,1.133)	1.034(0.825,1.295)	1.380(1.109,1.718) **	**0.001**
	Model 2	1	1.016(0.781,1.322)	1.230(0.946,1.598)	1.576(1.222,2.032) ***	**0.001**
	Model 3	1	1.041(0.797,1.358)	1.197(0.919,1.560)	1.512(1.169,1.957) **	**0.007**
	Model 4	1	1.046(0.801,1.365)	1.176(0.902,1.534)	1.506(1.163,1.950) **	**0.008**
Prospective	NLR (μg/mL)	0.543–1.667	1.667–2.182	2.187-2.9	2.909–10.923	
	Model 1	1	1.180(0.667,2.088)	1.521(0.880,2.627)	2.141(1.272,3.606) **	**0.018**
	Model 2	1	1.438 (0.776,2.664)	2.001(1.010,3.635) *	2.747(1.553,4.860) ***	**0.004**
	Model 3	1	1.439 (0.775,2.673)	2.020(1.109,3.682) *	2.725(1.538,4.827) ***	**0.004**
	Model 4	1	1.425 (0.766,2.649)	2.010(1.103,3.664) *	2.709(1.529,4.799) ***	**0.004**

NOTE. Significant results appear in bold

Abbreviations: NLR, neutrophil–lymphocyte ratio; Q1 (2,3,4), quartile (2,3,4)

Model1: Unadjusted

Model2: Adjusted for age, sex, education, and body mass index

Model3: Adjusted as in Model 2 and additionally adjusted for smoking, drinking status

Model4: Adjusted as in Model 3 and additionally adjusted for medical history of hypertension

Table 3 NLR levels classified by dichotomous groups and risk of cognitive impairment

	Model	β	$S_β$	Wald χ2	Odds ratios (95% Confidence interval)	*P*-value
Cross-sectional	Model 1	0.340	0.090	14.409	1.406 (1.179,1.676)	**< 0.001**
	Model 2	0.377	0.119	12.933	1.458 (1.187,1.790)	**< 0.001**
	Model 3	0.337	0.106	10.031	1.400 (1.137,1.724)	**0.002**
	Model 4	0.336	0.106	9.963	1.399 (1.136,1.724)	**0.002**
Prospective	Model 1	0.565	0.200	7.973	1.759 (1.189,2.603)	**0.005**
	Model 2	0.650	0.222	8.565	1.915 (1.239,2.959)	**0.003**
	Model 3	0.639	0.223	8.239	1.894 (1.225,2.929)	**0.004**
	Model 4	0.635	0.222	8.161	1.888 (1.221,2.920)	**0.004**

NOTE. Significant results appear in bold

Model1: Unadjusted

Model2: Adjusted for age, sex, education, and body mass index

Model3: Adjusted as in Model 2 and additionally adjusted for smoking, drinking status

Model4: Adjusted as in Model 3 and additionally adjusted for medical history of hypertension

NLR levels classified by dichotomous groups and risk of cognitive impairment

When NLR values were categorized into dichotomous groups, 805 participants had NLR values outside of the reference range and 2408 had NLR values within the reference range in the cross-sectional analysis; additionally, the NLR values of 263 and 910 participants were outside and within the reference range, respectively, in the prospective analysis. In all four logistic regression models, the risk of cognitive impairment in the group with high-inflammation status was significantly higher than in the group with noninflammatory status, regardless of whatever cross-sectional or prospective analysis was performed (Table 3).

Discussion

This large-sample study used 2011 and 2014 CLHLS data to evaluate the relationship between NLR values and risk of cognitive impairment in an older Chinese population. We found higher NLR value in the group with cognitive impairment than in the healthy group. In addition, higher NLR levels correlated with increased risk of cognitive impairment.

It has been reported that NLR is significantly associated with the levels of C-reactive protein, interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α) [25]. Thus, we speculated that measurements of peripheral NLR could serve as a parameter of systemic inflammatory load. In addition, a previous study showed that NLR is a superior marker for reflecting immune responses than neutrophil or lymphocyte alone [26]. Higher NLR values suggest the presence of non-specific inflammatory status and a relatively insufficient immune response [27].

Because of NLR was defined as the ratio of neutrophils to lymphocytes, the higher NLR values in the group with cognitive impairment recorded in this study can be attributed to the increased neutrophil numbers in peripheral blood. AD is complex multifactorial disease.

Among other factors, neuroinflammation plays a crucial role in AD development. A previous study has shown that increased Aβ deposition can activate microglia by binding to cell-surface receptors of microglia, and lead to the release of a variety of pro-inflammatory cytokines including TNF-α in AD [28]. By releasing IL-9, TNF-α promotes the survival of neutrophil via activation of the NF-κß pathway [13], leading to an increase of the population of peripheral neutrophils. Peripheral neutrophils across the disrupted blood-brain barrier and migrate to the vicinity of Aβ deposition, subsequently generating reactive oxygen species (ROS), which cause neuronal dysfunction and cognitive impairment [29].

The immune system has also been involved in AD pathogenesis. Bettcher et al. have confirmed that there is a crosstalk in peripheral and the central immunity [30]. Thus, alterations in the peripheral blood can reflect immune responses in the brain. The higher NLR values in the group with cognitive impairment may also have been caused by the decreased lymphocyte count, further suggesting that immune dysregulation is important in AD pathogenesis. There are several reasons that contribute to the decrease of lymphocyte count. First, the activated microglia can promote peripheral lymphocyte migrate to the central nervous system through a disrupted blood-brain barrier; consequently, the lymphocyte count increases in the brain, while the peripheral count decreases, which in turn leads to Aβ deposition in the brain and subsequent cognitive impairment [31, 32]. Second, Hou et al. have shown that an increased neutrophils count is associated with high ROS production, which subsequently leads to increased lymphocyte DNA damage and lymphocyte death [33]. Because lymphocytes are more sensitive to ROS in disease than in the normal population, their peripheral counts decrease in patients with AD [34]. Lastly, presenilin 1, a gene associated with the development of AD, mediates hypersensitivity to cell death in peripheral lymphocytes [35].

The peripheral inflammatory response and activation of immune components in AD indicates that NLR may have potential clinical diagnostic value. The present study had several advantages. First, our study included a large amount of population data and applied cross-sectional and prospective analyses, which is consistent with the chronic and progressive course of AD. Second, all participants were older than 65 years, which has important implications for an aging society. In addition, all data derived from CLHLS, thereby avoiding the risk of selection bias. Several limitations should also be taken into consideration. First, because limited information was collected from CLHLS, we did not investigate any associations between other peripheral blood indicators and cognitive impairment, including neutrophil count, platelet-to-lymphocyte ratio, systemic immune-inflammation index. Second, the absolute value of NLR between the cognitively healthy and impaired seemed little. However, the significantly statistical difference still indicated that NLR might be a valuable, easily applicable peripheral blood indicators for AD. Third, the sample population in this present study was the Chinese older adults with low level of education, thus, generalizing to other populations must be done with caution. In addition, follow-up studies in larger cohorts are required to validate our results. Lastly, CLHLS relied on individual interviews, and information may have been subject to recall bias.

Conclusions

The current study corroborated the association between NLR values and cognitive function in older Chinese adults. This study reminds us that, to a certain extent, inherent pathological changes in AD may be reflected in the changes in peripheral blood indicators. Consequently, inclusion of measurements of peripheral blood indicators, especially NLR, is beneficial to understanding the pathophysiology of AD and to providing novel prevention and treatment strategies for the disease.

Abbreviations

AD	Alzheimer's disease
Aβ	amyloid-β
BMI	body mass index
CLHLS	Chinese Longitudinal Healthy Longevity Survey
dNLR	derived NLR
IL	interleukin
MMSE	Mini-Mental State Examination
NLR	neutrophil–lymphocyte ratio
ORs	odds ratios
ROS	reactive oxygen species
TNF-α	tumor necrosis factor-alpha

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05763-6.

Supplementary Material 1

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Author contributions

Xin Wang: Conceptualization, Formal Analysis, Funding acquisition, Methodology, Writing - Review & Editing. Binbin Wang: Conceptualization, Funding acquisition, Methodology. Xueqing Du: Methodology, Project administration. Peng Liu: Software; Validation. Fuwen Yang: Writing - Original Draft. Jiao Su: Writing - Original Draft. Yue Zhang: Formal analysis, Software, Supervision, Validation.

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Data availability
The data supporting the findings of this study are openly available at https://opendata.pku.edu.cn/dataverse/CHADS.

Declarations

Ethics approval and consent to participate
The CLHLS has been performed adhered to the Declaration of Helsinki and was sponsored by the Ethics Committee of Peking University (IRB00001052-13074). Each participant signed a written informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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