



Turkish Journal of Geriatrics  
2026; 29(1):14–24

DOI: 10.29400/tjgeri.2026.474

Emel SABAZ KARAKEÇİ<sup>1</sup>  
 Nesibe AYDOĞDU<sup>2</sup>  
 Serpil DOĞAN<sup>3</sup>

<sup>1</sup>Health Sciences University Fethi Sekin City Hospital, Department of Physical medicine and rehabilitation, Elazığ, Türkiye

<sup>2</sup>Health Sciences University Fethi Sekin City Hospital, Department of Internal medicines, Elazığ, Türkiye

<sup>3</sup>Health Sciences University Fethi Sekin City Hospital, Department of Neurology, Elazığ, Türkiye

#### Correspondence

Emel Sabaz Karakeçi  
Phone : +904246066000  
e-mail : emelsabaz@gmail.com

Received : Dec 29, 2025

Accepted: Feb 15, 2026

## ORIGINAL ARTICLE

# ROLES OF THE C-REACTIVE PROTEIN-ALBUMIN-LYMPHOCYTE INDEX AND PAN-IMMUNE-INFLAMMATION VALUE INDICES AS NEW INDICATORS OF DEMENTIA SEVERITY

## ABSTRACT

**Introduction:** Alzheimer's disease is a common condition that can be challenging to diagnose, primarily due to the high costs and limited availability of specific tests. This study aimed to explore the relationship between peripheral inflammation markers, such as pan-immune-inflammation-value and the C-reactive protein -albumin-lymphocyte and their ability to predict the severity of the disease.

**Materials and Method:** A total of 232 patients diagnosed with Alzheimer's-type dementia and 52 healthy individuals with no history of the disease were retrospectively included in the study conducted between January 2024 and November 2025. The patients were classified into five groups based on the Clinical Dementia Rating Scale. After a 10-12 hour fast, venous blood samples were collected from all participants, and demographic and clinical data were obtained from the hospital information system. The analysis included complete blood count parameters (leukocytes, neutrophils, lymphocytes, monocytes, and platelets), C-reactive protein levels, serum albumin levels, and routine biochemical parameters from the blood samples.

**Results:** Although there was no significant difference in pan-immune-inflammation values between the study groups ( $p = 0.721$ ), the C-reactive protein-albumin-lymphocyte index showed a significant decrease as the severity of dementia increased. Similarly, Albumin-Lymphocyte Ratio, Systemic Inflammatory Index, Neutrophil-Lymphocyte Ratio, and Platelet-Lymphocyte Ratio also showed significant differences between the groups ( $p < 0.05$ ).

**Conclusion:** The findings of this study highlight the attractiveness of the C-reactive protein-albumin-lymphocyte index and the albumin/lymphocyte ratio as potential screening tools for dementia risk assessment in clinical settings.

**Keywords:** Biomarkers; C-Reactive Protein; Lymphocytes; Prognosis; Dementia; Inflammation; Retrospective Studies.

#### Cite this article as:

Sabaz Karakeçi E, Aydoğdu N, Doğan S. Roles of the C-Reactive Protein-Albumin-Lymphocyte Index and Pan-Immune-Inflammation Value Indices as New Indicators of Dementia Severity . Turkish Journal of Geriatrics 2026; 29(1):14–24. doi: 10.29400/tjgeri.2026.474



## INTRODUCTION

Alzheimer's disease (AD) is among the most common and most devastating forms of dementia. It has become an increasingly pressing public health issue due to the ageing global population, with its prevalence projected to double in Europe and to triple worldwide by 2050 (1, 2). Clinically, AD is characterised by memory loss, language difficulties (aphasia), problems with recognising objects (agnosia), impaired visual-spatial skills, challenges with abstract thinking and problem-solving, and changes in personality and behaviour. Therefore, this disease significantly diminishes the quality of life of affected individuals and places a heavy burden on caregivers (3).

The primary neuropathological features of AD are amyloid- $\beta$  deposition, intraneuronal neurofibrillary tangles and synaptic loss. However, the biological mechanisms that trigger the onset and progression of the disease have yet to be fully understood (4). Multiple pathological processes – including vascular abnormalities, mitochondrial dysfunction, oxidative stress, reduced glucose metabolism and neuroinflammation – contribute to the complex nature of the disease (5). Recent research has intensely focused on the hypothesis that chronic inflammatory processes lead to cognitive decline by disrupting neuroglial cell signalling.

In this context, various biomarkers of systemic inflammation have been linked to AD. Among these, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR) and Systemic Inflammation Index are convenient, low-cost and widely utilised indicators of peripheral systemic inflammation. Multiple investigations have shown that elevations in these ratios may signal cognitive impairment and/or progression towards dementia in patients with AD (6). Additional parameters associated with inflammation and/or immunity have been introduced as potential predictors of dementia risk, such as the Pan-Immune-Inflammation Value

(PIV). PIV incorporates the initial aspects of both NLR and PLR, together with parameters from neutrophils, platelets, lymphocytes and monocytes, thereby enabling more comprehensive assessment of inflammatory and immune status than with the NLR and MLR (7). PIV has demonstrated prognostic potential in inflammatory and/or autoimmune disorders such as vasculitis and ischaemic stroke (8). Similarly, the C-reactive protein (CRP)-albumin-lymphocyte (CALLY) index, which incorporates multiple inflammatory markers, provides a more complete and reliable measure of systemic inflammatory, nutritional and immune status than previously described inflammation index (9). It has shown prognostic value in cancer, but its potential role in AD diagnosis has not yet been investigated (9, 10).

Diagnosing AD remains a major challenge, as the limited availability and high cost of definitive tests often leads to delays. Therefore, this study aimed to investigate the association between traditional blood markers – particularly neutrophils – and peripheral inflammatory markers. Specifically, it examined correlations between PIV and CALLY index levels and the increased severity of classic clinical features of AD to determine whether these blood markers are linked to further cognitive deficits or impairments in patients diagnosed with AD.

## MATERIALS AND METHOD

This study was approved by the Non-Interventional Research Ethics Committee of Elazig Fethi Sekin City Hospital (Ethics Committee Decision No. 2025/5-13).

### Participant Recruitment

A total of 232 patients with AD-type dementia, classified according to the criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA), participated between January 2024 and November 2025. All patients were enrolled in the rehabilitation programme of Elazig Fethi Sekin

City Hospital via its neurology outpatient clinic and palliative care service. The inclusion criteria were age over 65 years, a diagnosis of AD-type dementia according to the NIA-AA criteria and receipt of care at a neurology outpatient clinic (11). Exclusion criteria included a history or presence of malignancy (cancer); decompensated renal, hepatic, or chronic heart failure; acute infection, decubitus ulcer, or major surgery within the past month; acute or chronic inflammatory disease; hematological disease; and any significant endocrine disorder requiring treatment; or use of corticosteroids or immunosuppressive drugs.

In addition, 52 healthy individuals – with no history of dementia or major neurological or psychiatric disorders and matched to the patients by age and sex – were recruited from the same outpatient clinic.

Thus, this study included 284 participants, divided into five groups according to the participants' Clinical Dementia Rating Scale (CDRS) scores (12). Group 1, with mild dementia ( $n = 64$ ); Group 2, with mild moderate dementia ( $n = 62$ ); Group 3, with moderate dementia ( $n = 49$ ); Group 4, with severe dementia ( $n = 57$ ); and Group 5, without dementia (control,  $n = 52$ ). Written informed consent was obtained from each participant or their caregiver.

### Data Collection

Demographic and clinical data were obtained from the Hospital Information System. Venous blood samples were collected following a 10–12 h fast. The blood samples were analyzed via complete blood count using a SYS/MAX 8000 Automated Hematology Analyzer (Sysmex Corporation, Kobe, Japan) which provides total leukocyte and leukocyte differential counts as well as counts for neutrophils, lymphocytes and monocytes. CRP and serum albumin levels were also measured, together with routine biochemical assays for Aspartate aminotransferase, Alanine aminotransferase, glucose, urea, creatinine and vitamin B12. CRP

and serum albumin levels were quantified using a Roche Cobas 8000 Biochemistry Analyzer (Roche Diagnostics, Basel, Switzerland). The reference ranges for albumin, lymphocytes and CRP in our laboratory are 3.5–5.2 g/dL, 1000–4000 cells/ $\mu$ L and 0–5 mg/L, respectively.

To assess inflammatory status, the PIV and CALLY indices were calculated using data from the complete blood count, CRP and albumin levels, according to the following equations:

$$\text{PIV} = (\text{Neutrophil} \times \text{Monocyte} \times \text{Platelet}) / \text{Lymphocyte}$$

$$\text{CALLY index} = (\text{Lymphocyte count [cells}/\mu\text{L}] \times \text{Albumin [g/dL]}) / (\text{CRP [mg/L]} \times 10^4)$$

$$\text{SII (Systemic Inflammatory Index)} = (\text{Platelet} \times \text{Neutrophil}) / \text{Lymphocyte}$$

$$\text{NLR (Neutrophil Lymphocyte ratio)} = \text{Neutrophil} / \text{Lymphocyte}$$

$$\text{PLR (Platelet Lymphocyte ratio)} = \text{Platelet} / \text{Lymphocyte}$$

Dementia severity was determined by the same experts based on the participants' clinical histories, neurological examinations and standardised cognitive tests, particularly the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment.

### Statistical Analysis

IBM SPSS Statistics (version 22) and G\*Power (version 3.1) were used for data analysis. In the descriptive analysis, categorical variables were reported as counts and percentages, while non-parametric continuous variables were expressed as medians and ranges (minimum to maximum). Spearman's correlation was applied to assess the relationship between the CALLY index values and MMSE scores. For the comparison of non-parametric continuous variables across groups, the Kruskal-Wallis test was employed. Where global significance was observed, post-hoc pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni correction for multiple testing. Pair-



wise comparisons were performed with *p*-values adjusted for multiple testing. To examine the independent association between the CALLY index values and dementia severity, as measured by MMSE, a multivariate ordinal regression model was constructed, adjusting for confounding variables including age, sex, and comorbidities. The diagnostic performance of the inflammatory indices and their ability to discriminate dementia severity were evaluated using Receiver Operating Characteristic (ROC) curve analysis. The Comparison of the Area Under the Curves (AUC) was performed using the DeLong method, and the Z statistic was utilized to determine the significance of the differences between the AUC values of the CALLY index and other markers (NLR, PLR, Albumin, etc.). The optimal cut-off values for achieving the highest diagnostic accuracy of each analytical parameter were established using the Youden index formula: "sensitivity + specificity – 1. Statistical significance was set at *p* < 0.05. To reduce the risk of Type II errors, all analyses were powered at > 80%.

## RESULTS

The study included a total of 284 participants, stratified into five groups based on Clinical Dementia Rating Scale (CDRS) scores. No dementia (control, *n* = 52), mild dementia (*n* = 64), mild to moderate dementia (*n* = 62), moderate dementia (*n* = 49), and severe dementia (*n* = 57). No statistically significant differences were found between the groups regarding gender, total white blood cell (WBC), platelet, Neutrophil count, glucose, AST or vitamin B12 levels. However, significant differences were observed in urea (*p*=0.008), creatinine (*p*=0.009), and ALT (*p*=0.003) levels across the groups. CRP levels showed a significant and notable increase from the control group to the severe dementia group. In contrast, serum albumin levels displayed a significant decreasing trend as dementia severity progressed. Regarding white blood cell parameters, Lymphocyte and Monocyte counts also

showed a significant differences. The Lymphocyte and Monocyte percentage considerably decreased with worsening dementia, indicating a shift in the immune cell profile.

No significant difference was noted in PIV values between the study groups (*p*= 0.721). However, the CALLY index showed a significant decline with increasing dementia severity. This indicates a strong inverse relationship with dementia stages. Similarly, the Albumin-to-Lymphocyte Ratio decreased significantly between the groups (*p* < 0.001). On the other hand, it was found that SII, NLR, and PLR values increased statistically significantly in correlation with the severity of dementia. ( Table 1).

The analyses revealed significant differences in CALLY index values among patients grouped according to their CDR scores. In particular, patients in the severe dementia stage had significantly lower CALLY index scores than all groups included in the study. (Figure 1).

In the comparative analysis of dementia groups, the CALLY and ALB/LYM indices were identified as the parameters with the highest statistical significance in distinguishing the severe dementia group from all other groups. (Table 2).

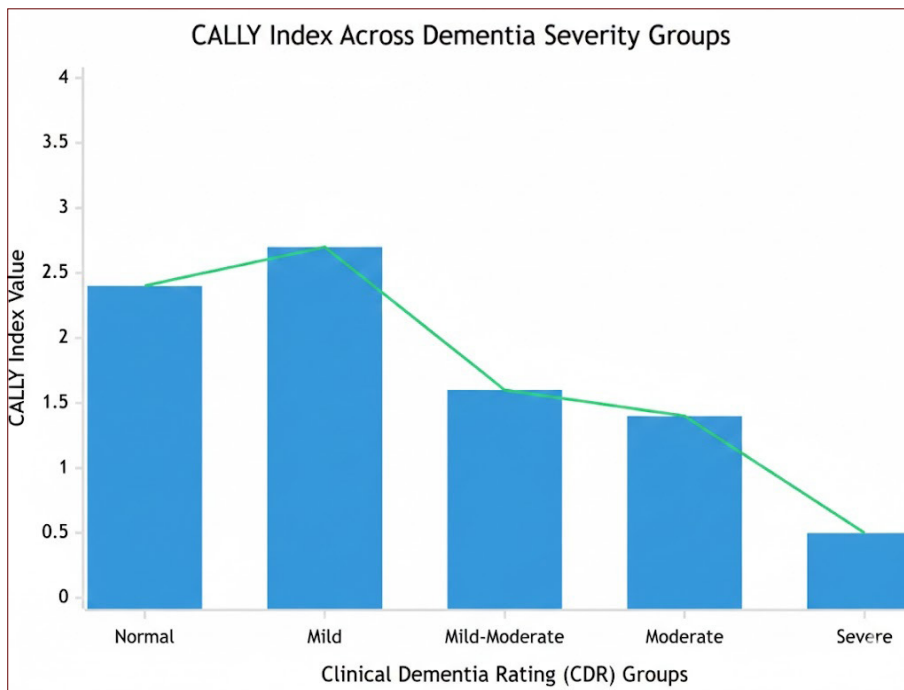
A multivariate logistic regression model was applied to identify independent determinants associated with severe dementia. The results revealed that CALLY, ALB/LYM ratio, Albumin, and CRP were significant independent factors. The diagnostic efficacy of these indices, including threshold values, sensitivity, specificity, AUC, and 95% confidence intervals, is shown in Table 3 via ROC analysis.

Analysis of the diagnostic performance of the CALLY index, comparing it to various inflammatory markers along with other indices to assess its effectiveness in discriminating dementia severity, showed that the CALLY index had significantly higher diagnostic accuracy compared to NLR, PLR, and Albumin levels. Although the CALLY index

**Table 1.** Demographic and laboratory findings of patients

| Variables                       | Normal   | Mild Dementia                                   | Mild-Moderate Dementia                           | Moderate Dementia                               | Severe Dementia                                 | P       |
|---------------------------------|--|---|--|---|---|---------|
| Mean Age (years) ±SD (Min-Max)  | 73±7.34 (59-95)                                  | 81.5±8.29 (63-107)                              | 81.9±7.0 (67-100)                                | 81.4±7.62 (67-100)                              | 83.5±6.02 (69-95)                               | <0.001  |
| Gender                          | Male:26<br>Female:26                             | Male:22<br>Female:42                            | Male:22<br>Female:40                             | Male:25<br>Female:24                            | Male:16<br>Female:41                            | 0.174   |
| Comorbid Diseases               | HT:37<br>DM:23<br>IHD:18<br>COLD:18<br>Others:31 | HT:50<br>DM:27<br>IHD:27<br>COLD:8<br>Others:35 | HT:42<br>DM:19<br>IHD:26<br>COLD:16<br>Others:37 | HT:32<br>DM:13<br>IHD:9<br>COLD:13<br>Others:33 | HT:38<br>DM:22<br>IHD:13<br>COLD:9<br>Others:37 |         |
| WBCx103/µL ±SD (Min-Max)        | 7.7±2.29 (4.3-14.7)                              | 7.1±2.53 (2.6-18.0)                             | 7.9±4.40 (3.1-31.0)                              | 7.8±3.35 (2.50-20.0)                            | 7.8±3.10 (3.40-17.20)                           | 0.357   |
| PLTx103/µL±SD (Min-Max)         | 261.4±90.04 (133-620)                            | 251.5±104.8 (14.1-690.0)                        | 267.5±130.8 (94-792)                             | 228.5±86.93 (14-522)                            | 269.2±112.5 (23-593)                            | 0.178   |
| NEU(103/µL)±SD (Min-Max)        | 5.0±2.15 (1.89-12.90)                            | 4.7±2.16 (1.57-13.0)                            | 5.1±3.09 (1.73-24.0)                             | 5.2±2.97 (1.12-17.0)                            | 5.7±3.12 (1.76-15.0)                            | 0.430   |
| LYM103/µL ±SD (Min-Max)         | 1.90±0.90 (0.89-5.28)                            | 1.60±0.76 (0.33-4.10)                           | 1.90±2.70 (0.35-22.0)                            | 1.80±0.79 (0.66-3.99)                           | 1.40±0.77 (0.06-4.54)                           | 0.027   |
| MONOCYTE103/µL ±SD (Min-Max)    | 0.79±0.95 (0.20-7.37)                            | 0.59±0.24 (0.20-1.36)                           | 0.73±1.11 (0.22-8.95)                            | 0.82±1.24 (0.15-8.95)                           | 0.48±0.48 (0.02-0.81)                           | <0.001  |
| CRP (mg/L) ±SD (Min-Max)        | 18.9±36.37 (0.70-236)                            | 28.3±30.39 (0.30-386)                           | 20.4±30.86 (0.44-179)                            | 24.6±40.79 (1.0-181)                            | 69.1±99.91 (2.07-456)                           | <0.001  |
| Glucose (mg/dL) ±SD (Min-Max)   | 145.1±86.75 (65-400)                             | 136.2±71.06 (57-499)                            | 130.9±58.51 (62-340)                             | 118.3±71.19 (46-536)                            | 131.9±58.61 (59-398)                            | 0.320   |
| Urea (mg/dL) ±SD (Min-Max)      | 46.3±27.72 (11-163)                              | 49.2±28.02 (2.6-210)                            | 45.97±22.68 (17-152)                             | 50±41.60 (15-307)                               | 73.58±50.52 (21-208)                            | 0.008   |
| Creatinine (mg/dL)±SD (Min-Max) | 0.9±0.36 (0.30-2.20)                             | 0.9±0.66 (0.40-5.30)                            | 0.9±0.36 (0.40-2.20)                             | 0.8±0.33 (0.30-2.09)                            | 0.9±0.82 (0.20-5.60)                            | 0.009   |
| Albumin (g/dL) ±SD (Min-Max)    | 3.8±0.56 (2.0-4.80)                              | 3.6±0.49 (2.4-4.70)                             | 3.4±0.54 (2.2-4.40)                              | 3.5±0.65 (2.0-5.1)                              | 2.9±0.56 (1.70-4.10)                            | <0.001  |
| AST (U/L) ±SD (Min-Max)         | 22.8±11.42 (9.0-75.0)                            | 22.1±11.27 (10.0-90.0)                          | 26.1±29.99 (7.0-209.0)                           | 24.4±18.71 (9.0-122.0)                          | 34.0±69.20 (9.0-534.0)                          | 0.727   |
| ALT (U/L) ±SD (Min-Max)         | 19.3±11.47 (5.0-60.0)                            | 15.3±11.46 (4.0-68.0)                           | 15.1±19.14 (2.0-151.0)                           | 18.4±17.85 (4.0-109.0)                          | 26.4±52.0 (2.0-388.0)                           | 0.003   |
| B12 (pg/mL) ±SD (Min-Max)       | 241.4±152.82 (57.0-710.0)                        | 315.4±359.46 (64.0-1565.0)                      | 266.50±280.69 (50.0-1500.0)                      | 299.60±364.40 (50.0-1500.0)                     | 233.3±203.57 (50.0-1123.0)                      | 0.691   |
| PIV                             | 612.3±563.17 (54.37-2509.41)                     | 602.80±767.95 (11.52-4469.20)                   | 1004.6±2409.40 (8.78-17697.10)                   | 762.4±1300.05 (4.34-7580.19)                    | 775.0±1063.18 (51.49-6393.60)                   | 0.721   |
| ALB/LYM                         | 7.43±3.75 (1.78-21.41)                           | 5.78±3.01 (0.89-16.81)                          | 6.73±10.87 (0.84-88.00)                          | 6.25±3.22 (1.47-15.01)                          | 4.2±2.89 (0.13-17.71)                           | P<0.001 |
| CALLY                           | 2.38±3.41 (0.01-15.84)                           | 2.72±6.43 (0.00-37.80)                          | 1.60±2.72 (0.01-16.77)                           | 1.41±1.61 (0.01-6.51)                           | 0.52±0.83 (0.00-3.68)                           | P<0.001 |
| SII                             | 826.72±610.67 (93.76-2884.38)                    | 894.48±672.66 (22.59-3464.50)                   | 1131.70±1128.88 (21.96-6554.48)                  | 814.54±782.59 (28.99-3228.99)                   | 1793.40±2677.41 (234.08-15984.00)               | 0.017   |
| NLR                             | 3.16±2.31 (0.39-14.49)                           | 3.71±2.82 (0.85-13.98)                          | 3.98±2.96 (0.15-15.17)                           | 3.73±3.83 (0.60-24.29)                          | 7.92±12.17 (1.04-65.00)                         | 0.019   |
| PLR                             | 162.32±85.13 (36.95-412.60)                      | 187.83±99.27 (5.44-495.12)                      | 196.08±105.31 (6.86-454.26)                      | 152.35±88.80 (16.11-456.72)                     | 266.12±220.04 (61.23-1110.00)                   | 0.003   |

WBC: White blood cells, PLT: Platelet, NEU: Neutrophil, LYM: Lymphocyte, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine transaminase, PIV: Pan-immune-inflammation-value, CALLY: C-reactive protein-albumin-lymphocyte, ALB: Albumin, HT: Hypertension, DM: Diabetes mellitus, IHD: Ischemic heart disease, COLD: Chronic obstructive lung disease, SII: Systemic Inflammatory Index, NLR: Neutrophil Lymphocyte ratio, PLR: Platelet Lymphocyte ratio



**Figure 1.** The CALLY index shows a significant decreasing trend with increasing dementia severity.

**Table 2.** Comparison of inflammatory indices between groups

| Intergroup Comparison:<br>PIV, ALB/LYM, CALLY, SII, PLR, NLR | Normal | Mild Dementia                                      | Mild-Moderate Dementia                             | Moderate Dementia                                  | Severe Dementia  |
|--|--------|--|--|--|--|
| <b>Normal</b>  | -      | 0.418<br>0.010<br>0.454<br>0.545<br>0.170<br>0.310 | 0,868<br>0.001<br>0.159<br>0.333<br>0.101<br>0.098 | 0.274<br>0.146<br>0.240<br>0.459<br>0.598<br>0.659 | 0.865<br>p<0.001<br>p<0.001<br>0.007<br>0.004<br>0.002   |
| <b>Mild Dementia</b>   | -      | -  | 0.539<br>0.638<br>0.485<br>0.636<br>0.626<br>0.581 | 0.715<br>0.438<br>0.677<br>0.163<br>0.033<br>0.487 | 0.364<br>p<0.001<br>p<0.001<br>0.029<br>0.113<br>0.025   |
| <b>Mild-Moderate Dementia</b>                                | -      | -  | -  | 0.412<br>0.222<br>0.831<br>0.130<br>0.019<br>0.252 | 0.768<br>0.004<br>p<0.001<br>0.132<br>0.205<br>0.118     |
| <b>Moderate Dementia</b>                                     | -      | -  | -  | -  | 0.255<br>p<0.001<br>p<0.001<br>0.002<br>p<0.001<br>0.009 |
| <b>Severe Dementia</b>                                       | -      | -  | -  | -  | -  |

PIV: Pan-immune-inflammation-value, CALLY: C-reactive protein-albumin-lymphocyte, ALB: Albumin, LYM: Lymphocyte, SII: Systemic Inflammatory Index, NLR: Neutrophil Lymphocyte ratio, PLR: Platelet Lymphocyte ratio

**Table 3.** AUC, sensitivity, specificity, confidence intervals of the cut-off values for predicting dementia severity based on ROC analysis.

| Criteria*,** | Sensitivity | Specificity | AUC   | 95% Confidence interval |       | P value |
|--------------|-------------|-------------|-------|-------------------------|-------|---------|
|              |             |             |       | Lower                   | Upper |         |
| CALLY ≤0.355 | 73.68       | 70.48       | 0.736 | 0.680                   | 0.786 | p<0.001 |
| ALB/LYM≤3.41 | 45.61       | 84.14       | 0.702 | 0.645                   | 0.755 | p<0.001 |
| NLR>3.88     | 50.88       | 74.01       | 0.626 | 0.567                   | 0.683 | 0.003   |
| PLR>125      | 82.46       | 38.33       | 0.621 | 0.562                   | 0.678 | 0.004   |
| CRP>11.68    | 70.18       | 66.08       | 0.713 | 0.657                   | 0.765 | p<0.001 |
| Albumin≤3.3  | 78.95       | 78.95       | 0.800 | 0.749                   | 0.845 | p<0.001 |

\*The cut-off levels of were calculated based on ROC-AUC analysis and the Youden index

\*\* Cut-off values were calculated for the data that were identified as significant in the logistic regression analysis.

OR: odds ratio, CALLY: C-reactive protein-albumin-lymphocyte, ALB: Albumin, LYM: Lymphocyte, CRP: C-reactive protein, NLR: Neutrophil Lymphocyte ratio, PLR: Platelet Lymphocyte ratio.

performed numerically better than the ALB/LYM ratio and CRP, the differences were not statistically significant (Table 4).

## DISCUSSION

This study explored the relationship between dementia severity and systemic inflammatory markers, specifically PIV and the CALLY index. To our knowledge, this is the first study to directly associate the CALLY index with dementia severity. Our key finding is a significant decrease in the CALLY index with increasing dementia severity, whereas no comparable relationship was observed with PIV.

There is growing evidence that inflammation contributes substantially to the development of dementia. Neuroinflammation can be triggered when microglia, the cells responsible for protecting the central nervous system from infections by clearing dysfunctional neurons, structural components and plaques, release inflammatory substances under pathological conditions (13). In the acute phase, microglial neuron loss due to inflammatory mediators leads to synaptic dysfunction, and in later stages, to cognitive decline (14). Animal studies have also demonstrated that peripheral cytokines can initiate neuroinflammation in the central nervous system when inflammatory

**Table 4.** Pairwise comparison of Receiver Operating Characteristic (ROC) curves

| Compared indices  | Z     | P      |
|-------------------|-------|--------|
| CALLY vs. NLR     | 2.673 | 0.007  |
| CALLY vs. PLR     | 2.640 | 0.008  |
| CALLY vs. Albumin | 2.166 | 0.030  |
| CALLY vs. ALB/LYM | 1.140 | 0.254  |
| CALLY vs. CRP     | 1.617 | 0.106  |
| ALB/LYM vs. NLR   | 2.292 | 0.022  |
| ALB/LYM vs. PLR   | 2.301 | 0.021  |
| NLR vs. Albumin   | 3.970 | <0.001 |
| PLR vs. Albumin   | 4.054 | <0.001 |
| CRP vs. Albumin   | 2.474 | 0.013  |
| NLR vs. PLR       | 0.136 | 0.891  |

CALLY: C-reactive protein-albumin-lymphocyte, ALB: Albumin, LYM: Lymphocyte, CRP: C-reactive protein, NLR: Neutrophil Lymphocyte ratio, PLR: Platelet Lymphocyte ratio.

mediators cross regions where the blood–brain barrier is compromised (15).

Alongside neuroinflammation, systemic inflammation is believed to play a major role in disease progression (16). Geng et al. (17) suggested that systemic inflammation indices, such as the Systemic Inflammation Index and PIV, can predict cognitive decline. Tondo et al. (18) reported that high



neutrophil counts, reflecting chronic inflammation, and low lymphocyte counts, indicating reduced responsive to foreign pathogens, can serve as neuroinflammatory markers in early dementia screening. They also noted that changes in these parameters might be associated with a rapid decline in cognitive function. The observation of elevated CRP levels in moderate to severe dementia further suggests that systemic inflammation increases with disease progression.

Understanding the inflammatory burden in patients with dementia, including AD, may help identify those who would benefit most from anti-inflammatory treatments. Long-term use of nonsteroidal anti-inflammatory drugs has been associated with reduced dementia risk, supporting the potential role of anti-inflammatory therapies in alleviating dementia-related neuroinflammation, improving certain pathological features and even treating the disease (16).

Largescale studies corroborate these findings. A study conducted in the United Kingdom, which included approximately 500,000 participants, found an inverse relationship between CRP – a biomarker of inflammation measured using WBC counts – and cognitive function (19). The study revealed particularly high CRP levels in groups with moderate and severe dementia, indicating that systemic inflammation increases as the disease progresses. This suggests that the elevated CRP levels observed in the severe dementia patients in the present study may play a role in the development of dementia. Borda et al. (20) reported that patients newly diagnosed with dementia who had higher CRP levels experienced greater functional deterioration over five years. Our findings of elevated CRP in severe dementia align with these reports, suggesting that severe infections (sepsis) significantly influence disease progression and functional decline in dementia (21).

However, some studies have found no direct correlation between CRP or interleukin-6 and dementia. To assist in addressing these discrepancies,

composite indices have been explored (22, 23). The CALLY index is unique because it integrates multiple physiological pathways – CRP (inflammation), albumin (nutritional status) and lymphocytes (immune regulation) – thereby providing a more comprehensive and accurate measure of the relationship between inflammatory markers and dementia than single-parameter markers can.

The present study revealed a reverse relationship between CALLY index values and dementia severity. The severe dementia group exhibited markedly reduced CALLY index values with decreased albumin and increased CRP. We interpret this finding as further evidence that systemic inflammatory catabolism and malnutrition accompany late-stage dementia. It highlights that a peripheral index such as CALLY can provide a deeper explanation of the complex pathophysiology of dementia than CRP or albumin alone.

Platelets, while central to clotting, also mediate inflammation through their interactions with WBCs. Evidence suggests that they may serve as systemic biomarkers for neurodegenerative disorders (24). By evaluating the use of platelets as a multiplier, we can predict the inflammatory potential of diseases based on their PIV value (8). However, Algul et al. found a strong positive correlation between dementia severity and NLR but not PLR, possibly due to the lack of other prognostic markers associated with platelet counts (25). Consistent with this, the present study found no significant differences in PIV across the groups, suggesting that PIV is a more specific indicator of acute-phase responses or oncohaematological pathologies than the chronic neurodegenerative inflammation associated with dementia.

This study found that the PLR showed a significant association with the severity of dementia, whereas the PIV did not reach statistical significance. This discrepancy may stem from the multi-parametric nature of PIV, which incorporates neutrophil, monocyte, and platelet counts simultaneously.

While this comprehensive structure allows PIV to effectively reflect acute-phase systemic responses, it may be less sensitive to the chronic, low-grade neuroinflammation characteristic of Alzheimer's type dementia. In contrast, PLR more specifically highlights the role of platelet-mediated inflammatory pathways in neurodegeneration, suggesting it as a more focused marker for monitoring disease progression in this population. We observed significant differences among the dementia groups in the basic haematological and biochemical indices – albumin, CRP, and monocyte and lymphocyte counts – underscoring the importance of the biological factors of nutrition and systemic inflammation in the development of dementia. Furthermore, because lymphocytes and monocytes can cross the blood–brain barrier and interact with glia, their relative concentrations in blood may more accurately reflect ongoing neuroinflammation than assay-validated serum markers.

Platelet counts, as measured by PIV, are likely poor indicators of dementia pathology, as they are influenced by multiple physiological stressors and therefore cannot be directly correlated to dementia-related pathologies. Other systemic inflammatory markers – monocytes, lymphocytes and neutrophils – may exert greater influence on composite indices.

This study has several limitations. First, its cross-sectional design prevents the establishment of causality between dementia and systemic inflammation. Second, while peripheral blood markers indicate systemic inflammation, they may not directly reflect central nervous system inflammation. Third, the single centre design, limited sample size and absence of comparisons with other inflammatory markers restrict the generalisability of the findings. A notable limitation of our study is the statistically significant difference in mean age between the control group and the dementia groups. Although we aimed to match participants by age and sex, the higher average age in the severe dementia group reflects the clinical reality of disease progression.

Since inflammatory markers can be influenced by the aging process itself, this age disparity should be considered when interpreting the systemic inflammation indices. Finally, it is important to note that inflammatory parameters can be influenced by multiple factors, including infections, metabolic disorders and even ageing.

## CONCLUSION

This study provides valuable insights into the predictive value of inflammatory markers in dementia by comparing their levels across patients with varying levels of dementia severity and healthy controls. The main finding is that the CALLY index is strongly linked to the severity of AD, whereas PIV does not appear to be an independent marker of dementia risk. Our results suggest that the CALLY index may provide better diagnostic utility than other inflammatory indices because it is clinically more comprehensive; it assesses the overall immuno-nutritional status of the patient rather than simply focusing on an isolated inflammatory response.

These results suggest that the CALLY index and albumin-to-lymphocyte measurements are promising screening tools for dementia risk in clinical practice. Both are widely available, simple to calculate, inexpensive, and derived from routine laboratory parameters.

To further clarify the causal relationship between these markers and dementia risk, prospective longitudinal cohort studies and validation studies with larger sample sizes are needed. Additionally, the prognostic performance of the CALLY index should be compared with that of other commonly used indices, such as NLR.

**Acknowledgements:** The authors have no acknowledgements to declare.

**Conflict of Interest:** The authors declare no conflict of interest.

**Funding Sources:** The authors received no financial support for the present study.



## REFERENCES

1. Crous-Bou M, Minguillon C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. *Neurology* 1984;34(7):939-44. (Doi: 10.1212/wnl.34.7.939)
2. Wang C, Zong S, Cui X, et al. The effects of microglia-associated neuroinflammation on Alzheimer's disease. *Front Immunol* 2023;14:1117172. (Doi: 10.3389/fimmu.2023.1117172)
3. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939-44. (Doi: 10.1212/wnl.34.7.939)
4. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell* 2019;179(2):312-339. (Doi: 10.1016/j.cell.2019.09.001)
5. Rostagno AA. Pathogenesis of Alzheimer's Disease. *Int J Mol Sci* 2022;24(1):107. (Doi: 10.3390/ijms24010107)
6. Dong X, Nao J, Shi J, Zheng D. Predictive Value of Routine Peripheral Blood Biomarkers in Alzheimer's Disease. *Front Aging Neurosci* 2019;11:332. (Doi: 10.3389/fnagi.2019.00332)
7. Ligorio F, Fuca G, Zattarin E, et al. The Pan-Immune-Inflammation-Value Predicts the Survival of Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer Treated with First-Line Taxane-Trastuzumab-Pertuzumab. *Cancers (Basel)* 2021;13(8):1964. (Doi: 10.3390/cancers13081964)
8. Wang S, Zhang L, Qi H, Zhang F L, Fang Q, Qiu L. Pan-Immune-Inflammatory Value Predicts the 3 Months Outcome in Acute Ischemic Stroke Patients after Intravenous Thrombolysis. *Curr Neurovasc Res* 2023;20(4):464-471. (Doi: 10.2174/0115672026276427231024045957)
9. Iida H, Tani M, Komeda K, et al. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. *HPB (Oxford)* 2022;24(1):101-115. (Doi: 10.1016/j.hpb.2021.06.414)
10. Liu XY, Zhang X, Zhang Q, et al. The value of CRP-albumin-lymphocyte index (CALLY index) as a prognostic biomarker in patients with non-small cell lung cancer. *Support Care Cancer* 2023;31(9):533. (Doi: 10.1007/s00520-023-07997-9)
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association work groups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):263-9. (Doi: 10.1016/j.jalz.2011.03.005)
12. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43(11):2412-4. (Doi: 10.1212/wnl.43.11.2412-a)
13. Khan MA, Khan ZA, Shoeb F, Fatima G, Khan RH, Khan MM. Role of de novo lipogenesis in inflammation and insulin resistance in Alzheimer's disease. *Int J Biol Macromol* 2023;242(Pt 2):124859. (Doi: 10.1016/j.ijbiomac.2023.124859)
14. Jia S, Yang H, Huang F, Fan W. Systemic inflammation, neuroinflammation and perioperative neurocognitive disorders. *Inflamm Res* 2023;72(9):1895-1907. (Doi: 10.1007/s00011-023-01792-2)
15. Wang RP, Ho YS, Leung WK, Goto T, Chang RC. Systemic inflammation linking chronic periodontitis to cognitive decline. *Brain Behav Immun* 2019;81:63-73. (Doi: 10.1016/j.bbi.2019.07.002)
16. Fakhoury M. Inflammation in Alzheimer's disease. *Curr Alzheimer Res* 2020;17:959-961. (Doi: 10.2174/156720501711210101110513)
17. Geng C, Chen C. Association between elevated systemic inflammatory markers and the risk of cognitive decline progression: a longitudinal study. *Neurol Sci* 2024;45(11):5253-5259. (Doi: 10.1007/s10072-024-07654-x)
18. Tondo G, Aprile D, De Marchi F, et al. Investigating the Prognostic Role of Peripheral Inflammatory Markers in Mild Cognitive Impairment. *J Clin Med* 2023;12(13):4298. (Doi: 10.3390/jcm12134298)
19. Mekli K, Lophatananon A, Maharani A, Nazroo JY, Muir KR. Association between an inflammatory biomarker score and future dementia diagnosis in the population-based UK Biobank cohort of 500,000 people. *PLoS One* 2023;18(7):e0288045. (Doi: 10.1371/journal.pone.0288045)
20. Borda MG, Cederholm T, Salazar-Londono S, et al. C-reactive protein predicts functional decline in older adults newly diagnosed with dementia: A 5-year follow-up study. *Rev Esp Geriatr Gerontol* 2025;60(6):101722. (Doi: 10.1016/j.regg.2025.101722)

21. Sun M, Li F, Wang Y, et al. Sepsis on dementia risk: A population-based cohort study with dose-dependent analysis. *J Crit Care* 2025;89:155100. (Doi: 10.1016/j.jcrc.2025.155100)
22. Ozben T, Ozben S. Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. *Clin Biochem* 2019;72:87-89. (Doi: 10.1016/j.clinbiochem.2019.04.001)
23. Su C, Zhao K, Xia H, Xu Y. Peripheral inflammatory biomarkers in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *Psychogeriatrics* 2019;19(4):300-309. (Doi: 10.1111/psyg.12403)
24. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med* 2018;284(6):643-663. (Doi: 10.1111/joim.12816)
25. Algul FE, Kaplan Y. Increased Systemic Immune-Inflammation Index as a Novel Indicator of Alzheimer's Disease Severity. *J Geriatr Psychiatry Neurol* 2025;38(3):214-222. (Doi: 10.1177/08919887241280880)