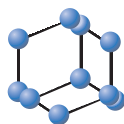


## RESEARCH ARTICLE


**BENTHAM  
SCIENCE**

# Predictive Value of Complete Blood Count Parameters for Alzheimer's Disease in Relation to Periodontal Status


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**Abstract: Introduction/Objective:** Given the role of inflammation in the development of both Alzheimer's disease (AD) and periodontal disease, it is plausible that periodontal disease may influence the progression of AD. Complete blood count (CBC) parameters may also serve as predictive indicators for this condition. This study investigated the predictive value of CBC parameters on the progression of AD in patients with periodontal disease.

**Methods:** Data from a prospective cohort study (n=90) with 6-month follow-up was analyzed. AD was assessed based on the Clinical Dementia Rating Scale. Records of C-reactive Protein (CRP) levels and CBC parameters measured within the 6 months preceding the participation date were evaluated. Cognitive assessments at the initial and 6<sup>th</sup>-month follow-up were performed using the Standardized Mini-Mental Test (SMMT). All patients underwent clinical periodontal examination.

**Results and Discussion:** The difference in SMMT score change ( $\Delta$ SMMT) and platelet distribution width (PDW) value between groups with and without periodontitis was statistically notable ( $p < 0.05$ ). The presence of periodontitis was found to be significantly associated with age,  $\Delta$ SMMT, and PDW values using the multivariate logistic regression model ( $p < 0.05$ ). Furthermore, having Stage II and Stage III AD, periodontitis, age factor, and mean platelet volume (MPV) value had a notable impact on  $\Delta$ SMMT ( $p < 0.05$ ). These findings may indicate that systemic inflammation as reflected by complete blood count parameters (such as PDW and MPV) may play a predictive role in cognitive decline in Alzheimer's disease patients with periodontitis.

**Conclusion:** PDW and MPV levels may have a predictive significance in clarifying the association between periodontitis and AD progression.

**Keywords:** Alzheimer's Disease, biomarkers, blood cell count, cognitive decline, complete blood count, periodontal disease, periodontitis.

## 1. INTRODUCTION

Alzheimer's disease is the most common and widely recognized form of dementia, accounting for the majority of cases worldwide [1, 2]. It is a progressive neurodegenerative condition that leads to extensive neuronal damage, significantly impacting large areas of the central nervous system and resulting in a gradual decline in both cognitive and functional abilities [1, 2]. This condition is characterized by an irreversible and continuous deterioration of cognitive functions, which worsens over time and severely affects an individual's quality of life [1-3]. While hallmark symptoms, such as memory impairment, language difficulties, and reasoning deficits, define Alzheimer's disease, research has established that pathological changes begin long before clinical manifestations appear, often decades earlier [1]. The acc-

umulation of extracellular amyloid beta plaques, the hyperphosphorylation of tau leading to neurofibrillary tangles, and neuroinflammation are identified as key factors in the disease's pathogenesis [4-11].

A definitive diagnosis of Alzheimer's disease depends on detecting specific pathological markers, including amyloid beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau proteins, typically through brain tissue analysis obtained *via* biopsy or autopsy [12]. Although these methods provide conclusive confirmation, they are invasive and primarily limited to postmortem studies or rare clinical cases requiring biopsy. Advances in medical technology have enabled the use of less invasive diagnostic tools, such as neuroimaging and biomarker analysis from body fluids like cerebrospinal fluid and blood plasma, allowing the identification of Alzheimer's disease-related changes in individuals during their lifetime [1]. Among these, phosphorylated tau and amyloid beta levels in cerebrospinal fluid are commonly recognized as essential biomarkers for differentiating Alzheimer's disease from other forms of dementia

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[13]. Additionally, neuroimaging techniques, including positron emission tomography and magnetic resonance imaging, are commonly used to identify disease-related changes [1]. Positron emission tomography imaging helps visualize amyloid beta accumulation in the brain, while magnetic resonance imaging is useful for identifying patterns of neuronal degeneration and brain atrophy associated with Alzheimer's disease [1]. A combination of these imaging methods and cerebrospinal fluid biomarker analysis provides a comprehensive approach to identifying the pathological features of Alzheimer's disease. However, despite their diagnostic value, these techniques face notable challenges. Positron emission tomography and magnetic resonance imaging scans are costly and require specialized equipment and trained personnel, making them less accessible in resource-limited settings. Furthermore, obtaining cerebrospinal fluid samples is an invasive procedure that can cause discomfort and potential complications, limiting its feasibility for routine clinical use. Given these limitations, the development of alternative diagnostic strategies that are non-invasive, cost-effective, and widely accessible has become a key focus in Alzheimer's disease research. Blood-based parameters present a promising alternative since blood samples are easier to collect, less invasive, and allow for repeated measurements. However, the lower concentration of amyloid beta and tau proteins in blood compared to cerebrospinal fluid necessitates the use of highly sensitive and often expensive analytical techniques. A meta-analysis investigating plasma amyloid beta levels in Alzheimer's disease has yielded inconsistent findings [14]. Chen *et al.* [15] conducted a meta-analysis reporting that total tau and phosphorylated tau levels in blood were elevated in Alzheimer's patients compared to individuals with mild cognitive impairment and cognitively normal individuals, indicating that biomarker detection methods significantly influence the results. Consequently, simpler and more accessible methods, such as complete blood count analysis, could offer clinical utility. Complete blood count tests provide key insights into systemic inflammation [16, 17], which is gaining recognition as a contributing factor in Alzheimer's disease. Specific complete blood count parameters, including neutrophil count, lymphocyte count, neutrophil percentage (%), lymphocyte percentage (%), and the neutrophil-to-lymphocyte ratio, have been linked to systemic inflammation and could offer insights into inflammatory mechanisms underlying Alzheimer's disease. Additionally, platelet indices, such as mean platelet volume and platelet distribution width, are associated with inflammatory responses, which may further highlight their relevance in Alzheimer's disease research.

Periodontal disease is a chronic inflammatory disease affecting the teeth and surrounding structures [18]. If left untreated, it can cause progressive tissue destruction, leading to tooth loss and other complications [19]. Beyond its impact on oral health, growing evidence suggests an association between periodontal disease and systemic conditions [20], including cognitive decline and neurodegenerative disorders, such as Alzheimer's disease [21, 22]. One of the primary pathological features of periodontal disease is the for-

mation of ulcerated periodontal pockets [23, 24], which act as entry points for proinflammatory cytokines, periodontal bacteria, and bacterial by-products into the systemic circulation [25]. These factors contribute to chronic low-grade systemic inflammation [26], often accompanied by elevated C-reactive protein levels, a well-established marker of systemic inflammation [17]. Furthermore, periodontal disease has been associated with alterations in complete blood count parameters, including changes in white blood cell count, the neutrophil-to-lymphocyte ratio, and other inflammatory markers [27-44]. These systemic inflammatory responses underscore the potential role of periodontal disease in the development and progression of systemic inflammatory conditions, including those impacting cognitive health.

Given that inflammation is a crucial part of both Alzheimer's disease and periodontal disease, research increasingly supports a potential connection between these conditions [25]. There is speculation that periodontal disease may accelerate the progression of Alzheimer's disease. Clinical studies suggest a possible correlation between periodontal health and the rate of progression of Alzheimer's disease [21, 22, 45]. Moreover, routine complete blood count parameters could serve as a practical and accessible means of investigating this link by offering valuable information on systemic inflammation and its contribution to neurodegeneration. As a result, this study aims to assess the predictive value of routine complete blood count parameters in evaluating how periodontal status may impact the rate of progression of Alzheimer's disease.

## 2. METHODS

### 2.1. Study Design and Participant Selection

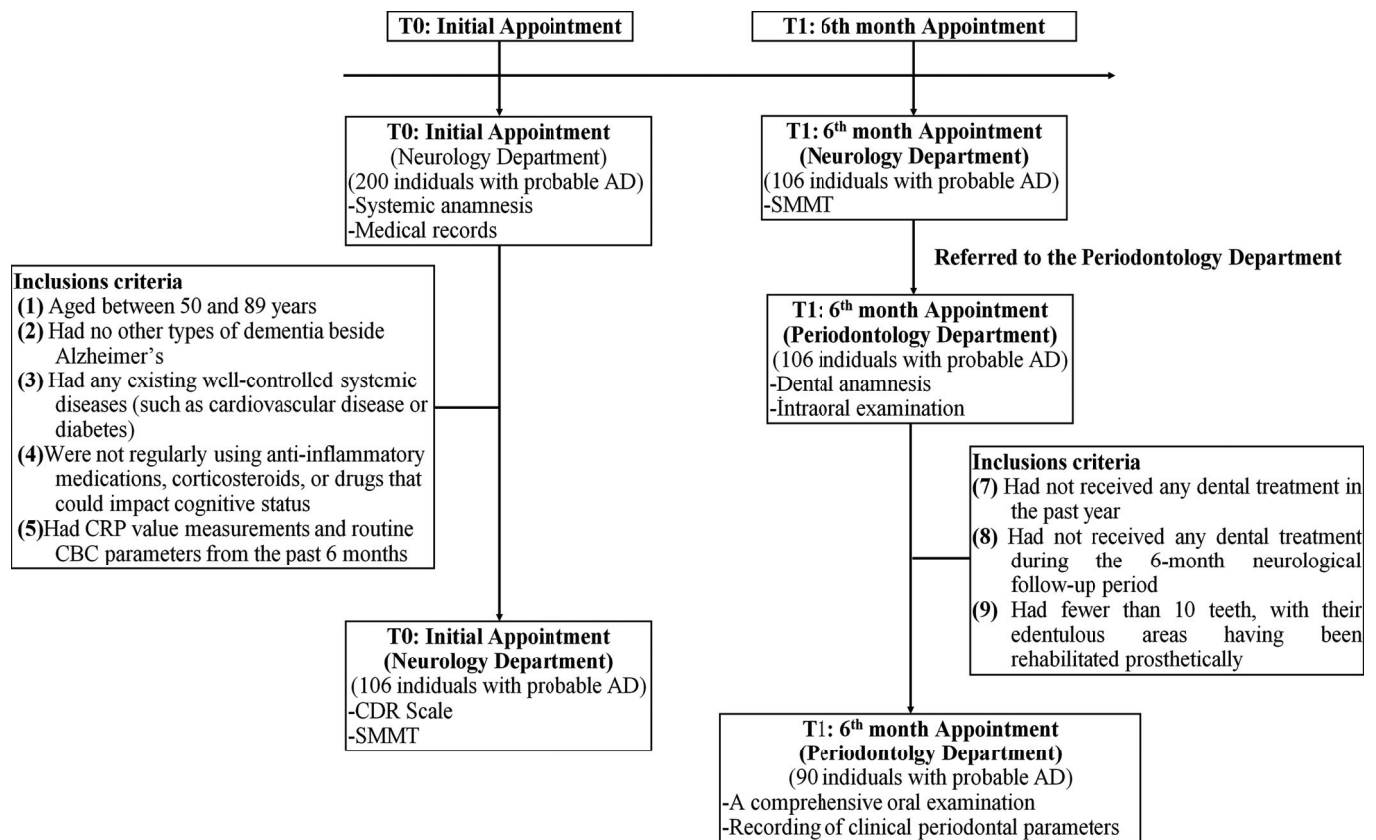
This observational study was based on data collected from a prospective cohort clinical trial [45] with a six-month follow-up period conducted from March 2022 to January 2023 at Bezmialem Vakif University. The sample size was determined based on clinical attachment level data (Cohen's  $d = 0.78$ ) obtained from our previous preliminary study investigating the relationship between Alzheimer's disease and periodontal conditions and approved by the Bezmialem Vakif University Clinical Research Ethics Committee (Approval Date and Number: 17.05.2021 E.163.12). Accordingly, 90 participants diagnosed with Alzheimer's disease were included.

The research involved collaboration between the Neurology Department of the Faculty of Medicine and the Periodontology Department of the Faculty of Dentistry. Ethical approval was obtained from the Bezmialem Vakif University Observational Research Ethics Committee (protocol number: 2022/54; Clinical Trials Identifier: NCT05807100), and all procedures were carried out in line with the 2013 Declaration of Helsinki's ethical principles. Before participation, all individuals or first-degree relatives signed a consent form. Additionally, the research adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies, ensuring accurate and transparent reporting of findings [46].

At the initial appointment in the Neurology Department, a specialist neurologist (OG) conducted a systemic anamnesis of 200 individuals determined to have probable Alzheimer's disease. Diagnoses were based on the criteria outlined by the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [1] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [47]. Medical records were also reviewed to confirm the diagnosis. The study included 106 Alzheimer's patients who met the following eligibility criteria: (1) aged between 50 and 89 years, (2) diagnosed exclusively with Alzheimer's disease without any other form of dementia, (3) had any existing well-controlled systemic conditions (such as diabetes or cardiovascular disease), (4) were not on regular anti-inflammatory medications, corticosteroids, or any drugs that might affect cognitive function, (5) had C-reactive protein value measurements and routine complete blood count parameters recorded within the past six months, and (6) were non-smokers and/or non-alcohol users. Clinical Dementia Rating Scale and Standardized Mini-Mental Test were used to assess cognitive status. Patients were scheduled for a follow-up appointment at the Neurology Department six months later. At this six-month follow-up, after the Standardized Mini-Mental Test scores were determined

by the doctors (OG), patients were referred to the Periodontology Department. Dental anamnesis of all patients was carried out in the Periodontology Department. Accordingly, 90 individuals who met the following additional criteria were included in the study: (7) had not received any dental treatment in the past year, (8) had not received any dental treatment during the 6-month neurological follow-up period, and (9) had fewer than 10 teeth, with their edentulous areas rehabilitated prosthetically. A comprehensive oral examination was conducted on all patients in the Periodontology Department, and clinical periodontal parameters were recorded. Periodontal measurements were performed by a single investigator (KK) using a Williams-marked periodontal probe (Hu-Friedy, Chicago, IL, USA) and Nabers probe (PQ2N, Hu-Friedy, Chicago, IL, USA). Before conducting the actual periodontal measurements, pocket depth and clinical attachment level measurements were repeated at 48-hour intervals in 10 non-study patients with similar periodontal status as in the study population. Accordingly, the intraclass correlation coefficient for clinical attachment level and pocket depth measurements ranged from 0.817 to 0.989, indicating that the measurements were sufficiently reproducible by the investigator.

The detailed study design and methodology are visually represented in the flowchart provided in Fig. (1).



**Fig. (1).** The flow chart of the study. **Abbreviations:** AD: Alzheimer's Disease; CBC: Complete Blood Count; CDR: Clinical Dementia Rating; CRP: C-Reactive Protein; SMMT: Standardized Mini-Mental Test.

## 2.2. Cognitive Assessment

The Clinical Dementia Rating Scale [48] was used to assess the stage of Alzheimer's disease in all participants. According to the scale, Stage I represents the earliest form of dementia, Stage II corresponds to an intermediate level of dementia, and Stage III indicates an advanced stage of dementia.

Cognitive function was measured with the Standardized Mini-Mental Test [49], known for its brief administration time. The maximum Standardized Mini-Mental Test score is 30, with 10 points corresponding to orientation questions, 3 points to recording memory, 5 points to attention and calculation, 3 points to recall, and 9 points to language. Both the initial and six-month follow-up Standardized Mini-Mental Test scores for all participants were recorded, and the change ( $\Delta$ ) in Standardized Mini-Mental Test scores was calculated.

## 2.3. Routine Peripheral Blood Biomarkers Assessment

The C-reactive protein levels measured in the six months prior to study participation and routine complete blood count parameters, including neutrophil count, lymphocyte count, neutrophil percentage (%), lymphocyte percentage (%), neutrophil-to-lymphocyte ratio, mean platelet volume and platelet distribution width, were recorded for all participants.

Biochemical analyses were conducted using the Coulter analyzer in the biochemistry laboratory of Bezmialem Vakif University Hospital. This analyzer is routinely calibrated twice a month. Peripheral blood samples were collected from each participant using standard tubes with ethylenediaminetetraacetic acid (EDTA). The available blood-based parameters were evaluated retrospectively.

## 2.4. Periodontal Assessment

The percentage of plaque (P%), percentage of bleeding on probing (BOP%), pocket depth, and clinical attachment level were measured on all teeth except the third molars. Additionally, the number of existing teeth, excluding third molars, was recorded. Measurements were taken at six sites per tooth: mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual. Each participant with teeth during this research was categorized as having stage III or stage IV periodontitis according to the current classification scheme [18] for periodontal and peri-implant diseases and conditions.

## 2.5. Statistical Analysis

The sample size was determined using clinical attachment level data (Cohen's  $d = 0.78$ ) from our previous preliminary study that investigated the connection between Alzheimer's disease and periodontal conditions. The research received approval from the Clinical Research Ethics

Committee of Bezmialem Vakif University (Approval date and number: 17.05.2021 E.163.12). Based on this calculation, it was planned to enroll 90 study participants diagnosed with Alzheimer's disease.

All statistical analyses were carried out using the SPSS software (IBM SPSS Statistics for Windows, version 28.0, IBM Inc., USA). Data normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The values of descriptive statistics are presented as median, minimum, and maximum values. Group comparisons were conducted using the Kruskal-Wallis test, with post hoc pairwise comparisons carried out after the analysis using the Mann-Whitney U test, with a Bonferroni adjustment applied. Categorical data were assessed using the chi-square test. Logistic and linear regression models were developed to explore associations between periodontal health, cognitive decline, and blood biomarkers. No missing data were present in the dataset. Binary logistic regression was employed to assess the relationship between periodontitis and non-periodontitis groups, adjusting for potential confounders (age, gender, systemic condition, stages of Alzheimer's disease, SMMT-T1, SMMT-T2,  $\Delta$ SMMT, CRP, neutrophil%, lymphocyte%, neutrophil count, lymphocyte count, NLR, MPV, and PDW). The final model included age, change ( $\Delta$ ) in the Standardized Mini-Mental Test, and PDW as confounders, with a significance threshold set at a  $p$ -value of  $<0.05$ . Odds ratios (OR) and 95% confidence intervals (CI) were calculated. The association between Alzheimer's disease progression, as measured by changes ( $\Delta$ ) in the Standardized Mini-Mental Test, and potential confounders was assessed using multiple linear regression. A  $p$ -value of  $<0.05$  was considered statistically significant.

## 3. RESULTS

### 3.1. Participants Characteristics

Ninety individuals diagnosed with Alzheimer's disease, 65 participants with periodontal disease, and 25 participants without teeth and active periodontal disease were enrolled in this study. Table 1 presents a summary of the demographic characteristics, systemic conditions, cognitive status, and biochemical parameters of the study population.

Based on the periodontal status of the participants, results revealed a significant difference in the change ( $\Delta$ ) in Standardized Mini-Mental Test scores and platelet distribution width levels between the groups ( $p < 0.05$ ). However, the other parameters did not differ between the groups ( $p > 0.05$ ).

### 3.2. Relationship between Biochemical Parameters and Alzheimer's Disease Stage

Table 2 presents the distribution of biochemical data among Alzheimer's patients according to the stages of Alzheimer's disease. The analysis revealed that serum C-reactive protein levels were notably elevated in Stage III Alzheimer's patients as opposed to those in Stage I ( $p < 0.05$ ).

Table 1. Characteristics of the study population.

	All Participants (n=90)		p
	Presence of Periodontal Disease (n=65)	Absence of Periodontal Disease (n=25)	
Age	76 (53-88) 75.01±7.64	79 (68-89) 78.80±5.97	0.051 <sup>†</sup>
Gender Female/Male	42/23	15/10	0.684 <sup>‡</sup>
Systemic Status	-	-	-
No DM and/or CVD	17 (26.15%)	7 (28%)	0.792 <sup>‡</sup>
Under control DM	4 (6.15%)	3 (12%)	
Under control CVD	28 (43.07%)	9 (36%)	
Under control DM + CVD	16 (24.61%)	6 (24%)	
AD Stage	-	-	-
Stage I AD	31 (47.69%)	11 (44%)	0.568 <sup>‡</sup>
Stage II AD	19 (29.23%)	10 (40%)	
Stage III AD	15 (23.07%)	4 (16%)	
SMMT-T0	19 (8-24)	21 (12-22)	0.867 <sup>†</sup>
SMMT-T1	17 (5-22)	19.95 (11-21)	0.762 <sup>†</sup>
ΔSMMT	2 (1-5)	1 (1-3)	<b>0.001<sup>†*</sup></b>
CRP (mg/l)	2 (0.20-16.76)	1.51 (0.20-9.86)	0.437 <sup>†</sup>
Neutrophil%	60.13 (39.09-87.16)	60.20 (33-81.70)	0.662 <sup>†</sup>
Lymphocyte%	28.12 (6.27-46.80)	27.96 (9.80-51.02)	0.871 <sup>†</sup>
Neutrophil count (10*3/uL)	4.30 (1.90-8.76)	4.17 (1.53-12.01)	0.604 <sup>†</sup>
Lymphocyte count (10*3/uL)	1.86 (0.54-3.62)	1.84 (1.03-3.32)	0.567 <sup>†</sup>
NLR	2.13 (0.88-14.02)	2.13 (0.65-8.33)	0.917 <sup>†</sup>
MPV (fL)	7.84 (5.43-13.67)	8.31 (6.12-10.70)	0.254 <sup>†</sup>
PDW (fL)	19.93 (10.60-24.20)	18.77 (9.30-21.04)	<b>0.002<sup>†*</sup></b>

Note: †: Bonferroni-adjusted Mann-Whitney U test. Bonferroni correction  $\alpha = 0.05/2 = 0.025$ . Data are expressed as the median (minimum-maximum), mean±standard deviation. ‡: Pearson Chi-square test. \*:  $p < 0.05$ ; indicates statistically significant. **Abbreviations:** n: number of individual; %: percentage; DM: Diabetes Mellitus; CVD: Cardiovascular Disease; AD: Alzheimer's disease; SMMT: Standardized Mini Mental Test; T0: initial; T1: 6<sup>th</sup> month; Δ: change (T0-T1) CRP: C-Reactive protein; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; PDW: platelet distribution width..

Table 2. Biochemical parameters of the study population in terms of AD stage.

All Participants (n=90)	Stage I AD (n=42)	Stage II AD (n=29)	Stage III AD (n=19)	p
CRP (mg/l)	1.52 (0.20-9.86)	2 (0.20-16.76)	4 (0.20-10.41) <sup>a</sup>	<b>0.044*</b>
Neutrophil%	61.89 (33.00-87.16)	60.13 (47.00-85.08)	59.50 (41.50-75.84)	0.870
Lymphocyte%	26.85 (6.27-51.02)	28.35 (9.91-41.90)	29.50 (14.38-46.80)	0.510
Neutrophil count (10*3/uL)	4.22 (1.53-12.01)	4.60 (2.39-8.76)	4.26 (2.15-6.45)	0.507
Lymphocyte count (10*3/uL)	1.77 (0.54-3.62)	1.95 (0.80-3.12)	1.91 (1.06-3.32)	0.629
NLR	2.29 (0.65-14.02)	2.04 (1.12-8.59)	2.03 (0.89-3.67)	0.525
MPV (fL)	7.70 (5.43-12.28)	8.27 (5.68-10.60)	8.26 (6.16-13.67)	0.417
PDW (fL)	19.58 (9.30-22.36)	19.79 (10.70-21.34)	19.44 (10.60-24.20)	0.826
Presence of Periodontal Disease (n=65)	Stage I AD (n=31)	Stage II AD (n=19)	Stage III AD (n=15)	p
CRP (mg/l)	1.16 (0.20-6.73)	2 (0.20-16.76)	4 (0.20-10.41) <sup>a</sup>	<b>0.003*</b>
Neutrophil%	61.79 (39.09-87.16)	61.32 (47.09-85.08)	59.36 (41.50-69.08)	0.443
Lymphocyte%	27.42 (6.27-44.31)	28.12 (9.91-39.30)	29.50 (20.82-46.80)	0.585
Neutrophil count (10*3/uL)	4.33 (1.90-8.76)	4.64 (2.43-8.76)	4.02 (2.15-6.45)	0.135

(Table 2) Contd.....

Presence of Periodontal Disease (n=65)	Stage I AD (n=31)	Stage II AD (n=19)	Stage III AD (n=15)	<i>p</i>
Lymphocyte count (10*3/uL)	1.86 (0.54-3.62)	1.92 (0.80-3.12)	1.91 (1.06-2.97)	0.937
NLR	2.22 (0.88-14.02)	2.26 (1.22-8.59)	2.02 (0.89-3.22)	0.538
MPV (fL)	7.38 (5.43-12.28)	7.37 (5.68-9.92)	9.12 (6.16-13.67)	0.100
PDW (fL)	20 (17.41-22.36)	19.79 (10.70-21.34)	19.44 (10.60-24.20)	0.285
Absence of Periodontal Disease (n=25)	Stage I AD (n=11)	Stage II AD (n=10)	Stage III AD (n=4)	<i>p</i>
CRP (mg/l)	1.95 (0.20-9.86)	1.70 (0.20-6.73)	1.18 (0.59-1.51)	0.727
Neutrophil%	62.63 (33.81-81.70)	58.90 (47-75.45)	69.06 (55.76-75.84)	0.330
Lymphocyte%	26.69 (9.80-51.02)	30.83 (16.32-41.90)	30.68 (14.38-38.87)	0.234
Neutrophil count (10*3/uL)	3.50 (1.53-12.01)	4.12 (2.39-6.57)	4.88 (4.39-5.77)	0.371
Lymphocyte count (10*3/uL)	1.47 (1.03-2.37)	2.08 (1.42-2.90)	2.36 (1.41-3.32)	<b>0.041*</b>
NLR	2.35 (0.65-8.33)	1.87 (1.12-4.63)	2.35 (1.38-3.67)	0.371
MPV (fL)	8.90 (6.12-10.70)	8.65 (6.36-10.60)	7.63 (6.53-8.26)	0.406
PDW (fL)	18.77 (9.30-21.04)	18.34 (10.70-20.38)	19.63 (18.63-20.36)	0.466

Note: Data are expressed as the median (minimum-maximum). Kruskal-Wallis/Bonferroni-adjusted Mann-Whitney U test. Bonferroni correction  $\alpha = 0.05/3 = 0.016$ . (a: Difference according to Stage I AD, b: Difference according to Stage II AD). \*:  $p < 0.05$  indicates statistically significant. **Abbreviations:** n: number of individual; AD: Alzheimer's Disease; CRP: C-Reactive protein; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; PDW: platelet distribution width.

An analysis of biochemical parameters in relation to periodontal disease status revealed that serum C-reactive protein levels were substantially elevated in patients diagnosed with Stage III Alzheimer's disease in comparison to those in Stage I ( $p < 0.05$ ). Furthermore, a statistically significant difference in lymphocyte count was observed across the various stages of Alzheimer's disease among edentulous individuals without active periodontal disease ( $p < 0.05$ ).

### 3.3. Relationship between Periodontal Status and Clinical Parameters

Multivariate analysis employing a binary logistic regression model was performed to estimate the OR for patients with active periodontal disease *versus* those without active periodontal disease. The relationship between each confounding factor and periodontal status was evaluated (Table S1), and factors with  $p < 0.05$  were included in the final model. Consequently, factors, such as age, the change ( $\Delta$ ) in the Standardized Mini-Mental Test score, and the platelet distribution width, were carefully considered and subsequently included in the multivariable binary logistic regression analysis. A detailed overview of these variables is presented in Table 3.

As indicated by the results of multivariate binary logistic regression analysis, Alzheimer's patients had an increased risk of active periodontal disease with advancing age (OR-adjusted=0.907; 95% CI: 0.829-0.992,  $p = 0.033$ ). It was also determined that those with active periodontal disease had a higher likelihood of developing change ( $\Delta$ ) in the Standardized Mini-Mental Test (OR-adjusted= 2.484; 95% CI: 1.325-4.656,  $p = 0.005$ ). Furthermore, Alzheimer's patients with active periodontal disease had 1.426 times higher platelet distribution width values, a routine peripheral blood biomarker, than Alzheimer's patients with absence of perio-

dontal disease (OR-adjusted= 1.426; 95% CI: 1.170-1.738,  $p = 0.000$ ).

### 3.4. Relationship between Cognitive Decline and Clinical Parameters

A multiple linear regression model was used to analyze the association between the confounding variables assessed and the change ( $\Delta$ ) in the Standardized Mini-Mental Test scores. The detailed results derived from this analysis are presented in Table 4.

Based on these findings, the change ( $\Delta$ ) in the Standardized Mini-Mental Test scores was identified as statistically noteworthy in participants with moderate and advanced stages of Alzheimer's disease, in those of advanced age, in those with active periodontal disease, and in those with high mean platelet volume values ( $p < 0.05$ ). Compared to the Stage I group, being in the Stage II group was associated with an increase in change ( $\Delta$ ) in the Standardized Mini-Mental Test by 0.272 units, while being in the Stage III Alzheimer's disease was associated with an increase of 0.652 units. In Alzheimer's patients, each 1 unit increase in the age of onset was linked to a reduction of 0.031 units in the change ( $\Delta$ ) of the Standardized Mini-Mental Test score. In contrast, the presence of active periodontal disease was related to an increase of 0.551 units in the change ( $\Delta$ ) of the Standardized Mini-Mental Test score. Additionally, a 1 unit increase in mean platelet volume value was associated with an increase in change ( $\Delta$ ) in the Standardized Mini-Mental Test by 0.109 units. As opposed to that, the effects of other complete blood count parameters and C-reactive protein levels on change ( $\Delta$ ) in the Standardized Mini-Mental Test were not found to be statistically notable ( $p > 0.05$ ).

A comprehensive summary of all key findings is presented in Table 5.

**Table 3. Results of binary logistic regression analysis regarding presence of active periodontal disease.**

Presence versus Absence of Active Periodontal Disease	$\beta$ Coefficients (SE)	Odds Ratio [OR]	95% Confidence Interval for B (Lower Bound/ Up Bound)	<i>p</i>
Age	-0.098 (0.046)	0.907	0.829/0.992	<b>0.033*</b>
$\Delta$ SMMT	0.910 (0.321)	2.484	1.325/4.656	<b>0.005*</b>
PDW (fL)	0.355 (0.101)	1.426	1.170/1.738	<b>0.000*</b>

Note: \*:  $p < 0.05$  indicates statistically significant. Abbreviations: SMMT: Standardized Mini Mental Test; T0: initial; T1: 6<sup>th</sup> month;  $\Delta$ : change (T0-T1); PDW: platelet distribution width.

**Table 4. Multiple linear regression analysis results according to  $\Delta$ SMMT scores.**

		Coefficients Standard Error	Unstandardized B Value	95% Confidence Interval for B (Lower Bound/ Up Bound)	<i>p</i>
Group	Stage II AD	0.096	0.272	0.080/0.464	<b>0.006*</b>
	Stage III AD	0.085	0.652	0.482/0.822	<b>0.000*</b>
Age	-	0.013	-0.031	-0.057/-0.005	<b>0.020*</b>
Gender	Female	0.179	0.153	-0.203/0.509	0.394
Systemic Condition	The presence of systemic disease under control	0.195	0.308	-0.080/0.696	0.118
Presence of Periodontal Disease	Periodontitis	0.223	0.551	0.107/0.994	<b>0.016*</b>
CRP (mg/l)	-	0.031	-0.019	-0.080/0.041	0.527
Neutrophil%	-	0.028	-0.039	-0.096/0.018	0.175
Lymphocyte%	-	0.030	0.008	-0.052/0.068	0.792
Neutrophil count (10 <sup>3</sup> /uL)	-	0.104	0.186	-0.022/0.394	0.079
Lymphocyte count (10 <sup>3</sup> /uL)	-	0.233	-0.441	-0.905/0.022	0.062
NLR	-	0.092	-0.015	-0.200/0.169	0.868
MPV (fL)	-	0.053	0.109	0.004/0.214	<b>0.042*</b>
PDW (fL)	-	0.033	-0.016	-0.079/0.046	0.603

Note: \*:  $p < 0.05$  indicates statistically significant. Abbreviations: AD: Alzheimer’s Disease; %: percentage; SMMT: Standardized Mini Mental Test; T0: initial; T1: 6<sup>th</sup> month;  $\Delta$ : change (T0-T1) CRP: C-Reactive protein; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; PDW: platelet distribution width.

**Table 5. A comprehensive summary of the key findings in the study population.**

Category	Findings
Cognitive Function & Platelet Distribution Differences	- Significant difference in $\Delta$ SMMT and PDW between groups with and without periodontitis ( $p < 0.05$ ).
Biochemical Parameters & AD Stage	- Higher serum CRP in Stage III vs. Stage I Alzheimer’s patients ( $p < 0.05$ ). - Significant difference in lymphocyte count across AD stages among edentulous patients ( $p < 0.05$ ).
Periodontal Status & Clinical Parameters	- Advanced age increases risk of active periodontal disease (OR = 0.907, 95% CI: 0.829/0.992) ( $p < 0.05$ ). - Active periodontal disease was associated with higher $\Delta$ SMMT (OR = 2.484, 95% CI: 1.325/4.656) ( $p < 0.05$ ). - Alzheimer’s patients with active periodontal disease had 1.426 times higher PDW values (OR = 1.426, 95% CI: 1.170/1.738) ( $p < 0.05$ ).
Cognitive Decline & Clinical Parameters	- Stage II AD increased $\Delta$ SMMT by 0.272 units; Stage III AD by 0.652 units ( $p < 0.05$ ). - Every 1-year increase in age reduced $\Delta$ SMMT by 0.031 units ( $p < 0.05$ ). - Presence of active periodontal disease increased $\Delta$ SMMT by 0.551 units ( $p < 0.05$ ). - A 1-unit increase in MPV increased $\Delta$ SMMT by 0.109 units ( $p < 0.05$ ).

Note:  $p < 0.05$ : indicates statistically significant. Abbreviations: AD: Alzheimer’s Disease; CRP: C-reactive protein; MPV: mean platelet volume; PDW: platelet distribution width; OR: odds ratio; CI: confidence interval; SMMT: Standardized Mini Mental Test; T0: initial; T1: 6<sup>th</sup> month;  $\Delta$ : change (T0-T1).

**3.5. Result of Post-Hoc Power Analysis**

In our study, a post-hoc power analysis was performed to compare Alzheimer’s disease progression, assessed by the change in Standardized Mini-Mental Test scores, between patients with and without active periodontal disease. The analysis yielded an effect size (Cohen’s d) of 0.69 and a sta-

tistical power of 0.89, indicating a high probability of detecting a true difference.

**4. DISCUSSION**

As per our knowledge, this is the first clinical research that investigated the potential predictive value of routine

complete blood count parameters on the progression rate of Alzheimer's disease in the presence of current periodontitis. Our results suggest that mean platelet volume levels might serve as a marker for the progression of Alzheimer's disease. Additionally, our study highlights the potential link between periodontitis and the rate of progression of Alzheimer's disease and indicates that Alzheimer's patients with periodontitis might have elevated platelet distribution width levels.

Complete blood count parameters testing is commonly used in clinical practice, and the relationship between these parameters and Alzheimer's disease has been investigated in numerous studies [50-62]. Research has reported that individuals with Alzheimer's disease often exhibit higher neutrophil count and/or lower lymphocyte count, increased neutrophil-to-lymphocyte ratio, and alterations in parameters, such as mean platelet volume and platelet distribution width compared to healthy controls [50-58]. Wu *et al.* [59] investigated the association between routine blood parameters and cognitive impairment, finding that changes in these parameters in the cognitive impairment group, compared to the group with normal cognitive function, may be linked to cognitive decline. Fu *et al.* [62] analyzed differences in peripheral platelet markers between Alzheimer's patients and healthy controls, reporting significantly lower platelet levels in the AD group, while mean platelet volume, platelet large cell ratio, and platelet distribution width were significantly higher. Additionally, Algul *et al.* [61] demonstrated that the neutrophil-to-lymphocyte ratio is strongly correlated with the severity of Alzheimer's disease. However, some studies have found non-significant results, leading to no definitive conclusion about the relationship between routine complete blood count parameters and Alzheimer's disease [58, 60]. Our study did not reveal significant variations in routine complete blood count parameters across different Alzheimer's disease stages, either in the overall patient cohort or among those with periodontitis, suggesting that these parameters may not be directly linked to disease severity. Conversely, among Alzheimer's patients without active periodontal disease, we found that lymphocyte counts increased with the severity of Alzheimer's disease. This finding indicated that alterations in immune response markers, such as lymphocyte count, may play a role in the progression of Alzheimer's disease, even in the absence of active periodontal disease.

It has been reported that periodontitis can lead to changes in the cellular and molecular components of peripheral blood due to inflammatory processes in the periodontal tissues [26]. Singh *et al.* [27] conducted a clinical investigation involving 100 patients with and without periodontitis and found that elevated lymphocyte counts and neutrophil-to-lymphocyte ratio levels might reflect the inflammatory state associated with periodontitis. Anand *et al.* [39] reported significantly higher neutrophil counts and percentages, as well as significantly lower lymphocyte counts and percentages, in the periodontitis group compared to the controls. Meanwhile, Mutthineni *et al.* [43] found an increase in mean platelet volume and platelet distribution width values among individuals with moderate to severe periodontitis.

Moreover, Zhou *et al.* [63] identified a relationship between mean platelet volume levels and periodontal disease in individuals living in the United States. Similarly, Bhattacharya *et al.* [44] conducted a cross-sectional hematologic study that revealed significant variations in leukocyte, lymphocyte, red cell distribution width, mean corpuscular volume, platelet count, and neutrophil-to-lymphocyte ratio levels in individuals with periodontitis. Additionally, a meta-analysis by Botelho *et al.* [64] reported that higher neutrophil counts and lower mean platelet volume levels are common complete blood count findings in individuals with periodontitis compared to healthy individuals. In our study, every Alzheimer's patient with natural teeth was diagnosed with Stage III or Stage IV periodontitis, classified as severe, based on periodontal assessments. The majority of Alzheimer's patients with teeth had stage III periodontitis, while those with fewer than 10 teeth had undergone prosthetic rehabilitation. Additionally, edentulous Alzheimer's patients who managed their edentulism with prostheses were also included. As a result, the findings of this study may not be directly comparable with existing literature, as we specifically investigated the predictive value of complete blood count parameters in relation to the current periodontal condition in Alzheimer's patients.

Studies have reported that inflammation caused by periodontal disease leads to changes in neutrophil and lymphocyte parameters, which may link periodontitis to systemic diseases [27, 39, 64]. In our research, no significant differences were found in neutrophil count, neutrophil percentage, lymphocyte count, or lymphocyte percentage between Alzheimer's patients with periodontitis and edentulous Alzheimer's patients without active periodontal disease. Neutrophil-to-lymphocyte ratio, an inflammatory biomarker that reflects peripheral inflammation by combining neutrophil and lymphocyte counts, was higher in the presence of periodontal disease in our study; however, this difference was not statistically significant. Inflammatory and infectious conditions, such as periodontal disease, are known to increase platelet activity [26], which can be assessed using indices like mean platelet volume and platelet distribution width. In our study, no significant differences were found between the group without active periodontal disease and the periodontitis group in terms of mean platelet volume values, nor between the stages of Alzheimer's disease in terms of platelet distribution width values. Clinical studies have reported varying results regarding mean platelet volume levels in the context of periodontal disease [27, 43, 64]. Conversely, platelet distribution width values were notably higher in Alzheimer's disease patients with periodontitis, as opposed to those without active periodontal disease, which aligns with findings reported in similar studies in the literature [43].

Clinical studies have indicated that periodontitis can lead to an increased systemic inflammatory response and elevated C-reactive protein levels [26, 35, 65, 66]. In our study, C-reactive protein levels showed a significant difference between Alzheimer's disease stages when evaluated in all participants, as well as specifically in Alzheimer's patients with

periodontitis. This suggests that the stage of Alzheimer's disease may be related to higher C-reactive protein levels in the presence of active periodontal disease. Conversely, the lack of a statistically significant difference in C-reactive protein levels between Alzheimer's patients with periodontitis and those without active periodontal disease suggests that there may not be a direct relationship between periodontitis and elevated C-reactive protein levels.

Chronic conditions and uncontrolled diseases affecting peripheral organs have been associated with Alzheimer's disease [67-69]. As a result, individuals with poorly managed systemic health issues, as well as smokers, were not included in the study population. Current research suggests that the low-grade systemic inflammatory response caused by periodontal disease may be linked to a higher risk of Alzheimer's disease and may accelerate its progression [70]. Chen *et al.* [71] reported that individuals aged 50 and older with a history of periodontal disease lasting 10 years have an increased risk of developing Alzheimer's disease compared to those without periodontal disease. Similarly, Tzeng *et al.* [72] found that individuals aged 70 and over with periodontal disease demonstrated an elevated probability of dementia onset than those without periodontal disease. In our study, it was found that Alzheimer's disease patients with periodontitis showed a notably greater change ( $\Delta$ ) in Standardized Mini-Mental Test scores compared to those without active periodontal disease, suggesting that the current state of periodontal health may impact the rate of progression of Alzheimer's disease. However, since our study population did not include Alzheimer's patients with gingivitis or a healthy periodontium, the generalizability of these results may be limited.

Several clinical studies suggest an association between periodontitis and poor cognitive status [21, 22, 45, 71-80]. Kim *et al.* [78] found a strong association between periodontal disease and cognitive impairment. Similarly, Gu *et al.* [80] reported a significant relationship between poor periodontal health and poorer cognitive performance. Additionally, some research has investigated how periodontal conditions may impact the rate of Alzheimer's disease progression [21, 22, 45]. In their meta-analysis, Dziedzic *et al.* determined that there is insufficient direct evidence to establish a causal link between periodontal disease and dementia [81]. They also noted that the clinical data available are not strong enough to confirm a cause-and-effect relationship [81]. In our research, the progression rate of Alzheimer's disease was evaluated using the change ( $\Delta$ ) in the Standardized Mini-Mental Test. Our findings suggest that periodontitis and increased mean platelet volume levels may influence the progression rate of Alzheimer's disease, indicating that mean platelet volume could serve as a potential predictor of disease progression. Furthermore, the significant association between change ( $\Delta$ ) in the Standardized Mini-Mental Test and high platelet distribution width levels in individuals having Alzheimer's disease highlights a potential link between periodontitis and the progression of Alzheimer's disease. This relationship indicates that periodontitis in Alzheimer's patients could be related to higher platelet distribution width

levels. These findings may reflect the comprehensive evaluation of parameters affecting both Alzheimer's disease and periodontitis in our study.

This study has several limitations, including the lack of participants with gingivitis and active periodontal disease in the study population, as well as a limited sample size, which may affect the generalizability of the findings. Future research should involve a larger and more diverse group of participants representing different stages of periodontal disease, including gingivitis and healthy periodontal conditions, to gain deeper insights into the potential connection between systemic inflammation, periodontal health, and Alzheimer's disease. Moreover, further investigations should assess how periodontal disease treatment influences the progression of Alzheimer's disease, with special attention to its effects on complete blood count parameters and C-reactive protein levels.

## CONCLUSION

In summary, periodontal disease may be associated with elevated platelet distribution width levels. Additionally, mean platelet volume levels, a component of routine complete blood count parameters, could serve as a predictive marker for understanding the relationship between the rate of progression of Alzheimer's disease and periodontitis.

These findings highlight the need for large-scale, long-term research to further investigate the role of systemic inflammation in neurodegenerative disease progression. The insights gained from this study may also contribute to refining early diagnostic strategies in clinical settings. Specifically, incorporating routine complete blood count parameters into Alzheimer's disease monitoring could support the development of more accessible, cost-effective, and non-invasive biomarkers.

From a clinical perspective, assessing and treating periodontal conditions may offer crucial insights into the systemic factors that contribute to the progression of Alzheimer's disease. Therefore, strengthening interdisciplinary collaboration between neurology and periodontology is essential for enhancing early detection and optimizing disease management.

## AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Visualization and writing-original draft: K.K. Visualization and writing-review: A.A., S.G. Conceptualization, data collection and data interpretation: O.G., K.K. Conceptualization, data analysis and data interpretation: A.A., S.G. Supervision: S.G.

## LIST OF ABBREVIATIONS

T0	=	Initial
T1	=	6 <sup>th</sup> Month
$\Delta$	=	Change (T0-T1)

%	=	Percentage
AD	=	Alzheimer's Disease
BOP%	=	Percentage of Bleeding on Probing
CBC	=	Complete Blood Count
CI	=	Confidence Intervals
CRP	=	C-Reactive Protein
CVD	=	Cardiovascular Disease
DM	=	Diabetes Mellitus
EDTA	=	Ethylenedi-aminetetraacetic Acid
MPV	=	Mean Platelet Volume
NLR	=	Neutrophil-to-lymphocyte Ratio
OR	=	Odds Ratios
P%	=	Percentage of Plaque
PDW	=	Platelet Distribution Width
SMMT	=	Standardized Mini-mental Test
ΔSMMT	=	SMMT Score Change

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Observational Research Ethics Committee, Bezmialem Vakif University (decision number: 2022/54; decision date: 02.03.2022). Clinical Trials Identifier: NCT05807100).

#### HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were followed in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

#### CONSENT FOR PUBLICATION

All participants and/or their first-degree relatives provided their written informed consent form for this study.

#### STANDARDS OF REPORTING

STROBE guidelines were followed.

#### AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

#### FUNDING

None.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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#### SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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