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Evaluation of C-reactive Protein-Albumin-Lymphocyte (CALLY) Index in the Pathogenesis of Osteoporosis

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Abstract

Objective: To assess the relationship between bone mineral density (BMD) and the C-reactive protein-albumin-lymphocyte (CALLY) index in postmenopausal women.

Materials and Methods: A cross-sectional analysis of 337 postmenopausal women [107 with osteoporosis (OP), 144 with osteopenia, and 86 controls] was conducted from January 2023 to December 2024. Participants were stratified by BMD using DXA T-scores: normal ≥-1, osteopenia -1 to -2.5, OP ≤-2.5. Hematological parameters (C-reactive protein, albumin, lymphocyte counts) were analyzed, and the CALLY index was derived.

Results: No statistically significant difference in CALLY index scores was observed between groups ($p = 0.130$). However, albumin and lymphocyte levels were significantly lower in the OP group than in the normal group ($p = 0.002$).

Conclusion: Low albumin and lymphocyte levels observed in the OP group underscore the significance of these parameters in the pathogenesis of bone loss. However, the CALLY index, which integrates these parameters, does not offer sufficient discrimination for assessing the low-grade systemic inflammation associated with OP. Prospective studies with larger sample sizes may help clarify the role of the CALLY index in the etiology of OP.

Keywords: Bone mineral density, CALLY index, hematological index, inflammation, osteoporosis

Introduction

Osteoporosis (OP) is a systemic skeletal condition marked by a reduction in bone mass and significant changes in the structure of bone tissue. This condition significantly increases bone fragility, resulting in greater susceptibility to fractures. Its prevalence increases with age, making it a significant public health issue for individuals and society because of the fractures it causes. OP often starts insidiously and progresses without symptoms until bone fractures occur. With the extension of human life expectancy worldwide, OP has become a significant medical challenge. A 2010 report indicated that approximately 5 million men and more than 20 million women in European countries were diagnosed with OP. It is more prevalent among individuals of European ancestry and women. The prevalence of OP increases with age, particularly during the first few years after menopause, a period when bone loss accelerates (1).

OP has a complex etiopathogenesis, and recent literature suggests that it is influenced not only by hormonal and mineral imbalances but also by inflammatory processes. Proinflammatory cytokines, especially interleukin-6 and tumor necrosis factor-alpha, have been shown to accelerate bone resorption by increasing osteoclast activity. Furthermore, targeting inflammation in OP treatment has become an important focus for the development of new therapeutic strategies (2). Inflammation-related complex parameters, such as hemoglobin, albumin, lymphocytes, and platelets, the C-reactive protein (CRP)/albumin ratio (CAR), and the systemic immune-inflammation index (SII), have been used as indicators of inflammation (3,4). Recent research has introduced

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the C-reactive protein-albumin-lymphocyte (CALLY) index, a new composite measure that has demonstrated greater predictive ability for overall survival in patients with colorectal and gastric cancer compared with traditional prediction methods (5). The CALLY index is a non-invasive quantitative measure. A low CALLY index indicates significant active inflammation, which may compromise overall health. A compromised immune system is linked to an increased vulnerability to infections and various diseases. Additionally, a low index often reflects inadequate nutritional intake, leading to deficiencies that can adversely affect physical well-being and recovery.

The relationship between the CALLY index and OP has not been clearly established. This study sought to examine the potential correlation between the CALLY index and the development of OP. If the CALLY index proves to be a reliable predictive marker for OP, it could facilitate the identification of at-risk individuals and enhance measures to prevent its onset.

Materials and Methods

The research was conducted following ethical approval from the University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital Non-interventional Ethics Committee, which was obtained on (approval number: 2025/3-8, dated: 06.02.2025). We retrospectively reviewed the medical records of patients who visited the outpatient clinics of the departments of internal medicine and physical medicine and rehabilitation from January 2023 to December 2024. The selection criteria included a detailed anamnesis, physical examination findings, and demographic information such as age and gender, alongside laboratory parameters including albumin level, CRP, complete blood count, and T-scores. Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry (DEXA) in all subjects. The research was conducted in the Nuclear Medicine Department at University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital. This study measured BMD at the lumbar spine (L1–L4 and L2–L4) and at the proximal femur (total femur, femoral trochanter, and Ward's triangle). These measurements were obtained in the anteroposterior view using the Lunar GE device (MDL DPX Prodigy-tech. 150070, Madison, USA). The study employed a scanning voltage of 67 kV and a current of 1500 mA, resulting in a delivered dose of 20.0 µGy over approximately 3 minutes. The evaluation of results centered on BMD, measured in g/cm2, and associated T-scores for both examined regions. The diagnosis of OP adhered to the World Health Organization's classification criteria. Individuals with T-scores ≥-1.0 were categorized as normal; those with T-scores between -1.0 and -2.5 were classified as osteopenic; and individuals with T-scores ≤-2.5 were diagnosed with OP. This classification system underscores the importance of precise measurement in assessing bone health and the risk of OP.

Inclusion Criteria

- Patients who underwent bone measurement in the outpatient clinic with suspected OP
- Postmenopausal women diagnosed with OP
- Patients who had been followed or treated at our institution within the last two years
- Patients who underwent a DEXA scan at our institution within the last year

Exclusion Criteria

- History of inflammatory diseases
- Compression fractures
- Inability to mobilize independently
- Active malignancy, organ failure, critical illness, or pacemaker
- Diseases affecting bone metabolism (hyperparathyroidism, thyrotoxicosis, chronic renal failure, and malabsorption syndromes etc.)
- Secondary causes of OP (chronic systemic corticosteroid use, anticonvulsant use, and long-term alcohol and tobacco consumption.)
- Infection within the last 3 months
- Incomplete diagnostic or treatment information
- History of ischemic or hemorrhagic cerebrovascular disease
- Cognitive dysfunction diagnoses such as dementia, Alzheimer's disease, known organic brain damage such as Parkinson's disease (the ability to move independently can be significantly impaired in individuals with Alzheimer's disease or Parkinson's disease. This impairment can complicate accurate positioning during DEXA scanning, which may lead to less reliable measurements of BMD. Patients with advanced Parkinson's disease and dementia are particularly at risk for developing secondary OP or osteomalacia due to an increased risk of falls and nutritional deficiencies. Additionally, these neurological diseases are often associated with chronic low-grade systemic inflammation, which may impact certain components of the CALLY index, especially CRP and albumin levels).

Laboratory Measurements

Blood samples from all patients were collected during their initial evaluation upon presentation to our clinic, prior to the diagnosis of OP or the initiation of any specific anti-osteoporotic treatment. The samples were analyzed by complete blood count using the Sysmex XN-3000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). CRP and serum albumin levels were quantified using a Roche Cobas 8000 biochemistry analyzer (Roche Diagnostics, Basel, Switzerland). In our

laboratory, reference ranges for these biomarkers were defined as follows: serum albumin, 3.5–5.2 g/dL; lymphocyte counts, 1000–4000 cells/μL; and CRP, 0–5 mg/dL. These parameters offer essential information regarding the physiological and inflammatory conditions of the subjects studied.

CALLY Index

The CALLY index was determined using a specific formula that takes into account the serum albumin level (in g/dL), lymphocyte count (in cells/μL), and CRP level (in mg/dL). The formula is expressed as follows: [serum albumin level (g/dL) × lymphocyte count (cells/μL)/CRP (mg/dL) × 10^4.

Statistics

Statistical analyses were performed using IBM SPSS version 27 (IBM, Chicago, IL, USA) to ensure a comprehensive examination of the data. The Shapiro-Wilk test was used to assess whether the data follow a normal distribution. For quantitative data that did not follow a normal distribution, descriptive statistics were presented as median values, along with their corresponding minimum and maximum values. Categorical variables were reported as n (%). The Kruskal–Wallis test was used to analyze non-normally distributed data from two or more independent groups, followed by post hoc Dunn-Bonferroni tests to identify significant pairwise differences between groups. Spearman's rank correlation test was used to assess correlations in non-parametric data. A significance level of $\alpha = 0.05$ was set for all statistical tests conducted.

Results

The study included 337 female patients, all of whom underwent bone measurements. The participants were categorized into three distinct groups based on their bone health: 86 patients were classified as having normal bone density, 144 were identified as having osteopenia and 107 patients were diagnosed with OP, The mean ages of the OP, osteopenia, and control groups were 67.4 ± 10.1, 59.8 ± 11.2, and 55.2 ± 10.3, respectively ($p < 0.001$) (Table 1). In the normal group, 18 patients (20.9%) had no comorbidities. In the osteopenia group, 29 patients (20.1%) had no comorbidities, compared with 14 patients (13.1%) in the OP group. Patients in the study presented with various comorbid conditions, including diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and asthma. Statistical analysis indicated that lymphocyte levels, age, urea, T-score, and albumin levels were significantly reduced in the groups studied ($p < 0.05$). When comparing CALLY index scores, "no statistically significant difference was found in the CALLY index between the groups ($p = 0.130$) (Figure 1). T-scores, the standard measures derived from BMD assessments, play a crucial role in diagnosing and staging OP. In this context, we found low, non-significant correlation between the CALLY index and T scores ($r = 0.063$, $p = 0.251$).

Discussion

The current paradigm of OP pathogenesis has evolved beyond mechanical considerations to encompass complex inflammatory interactions. While traditionally associated with aging, this systemic skeletal disorder demonstrates variable onset patterns, which are influenced by a complex interplay among metabolic, endocrine, and inflammatory factors (6,7). Particularly compelling is the growing evidence implicating chronic low-grade inflammation as a key driver of accelerated bone remodeling and microarchitectural deterioration (8). Clinical observations consistently reveal spatial associations between inflammatory states and bone loss patterns, where systemic

Table 1. Distribution of variables by group

	Normal	Osteopenia	Osteoporosis	Total	p-value
Age (year)	55.2 ± 10.3	59.8 ± 11.2	67.4 ± 10.1	62.0 ± 12.1	**p < 0.001**
Urea (mg/dL)	30.43 ± 11.11	35.47 ± 15.47	38.94 ± 14.60	35.24 ± 14.51	**p < 0.001**
Creatinine (mg/dL)	0.71 ± 0.18	0.76 ± 0.34	0.72 ± 0.26	0.73 ± 0.28	0.728
Ca (mg/dL)	9.49 ± 0.42	9.44 ± 0.48	10.34 ± 9.64	9.74 ± 5.45	0.534
Vitamin D (ng/mL)	19.31 ± 8.78	21.53 ± 10.21	21.24 ± 11.10	20.87 ± 10.18	0.378
Height (meter)	1.55 ± 0.6	1.54 ± 0.5	1.53 ± 0.6	1.54 ± 0.6	0.328
Weight (kg)	78.90 ± 13.55	76.47 ± 12.03	74.45 ± 13.77	76.45 ± 13.07	0.148
BMI (kg/m^2)	32.90 ± 6.94	32.34 ± 5.26	31.94 ± 5.90	32.35 ± 5.93	0.812
T-score	-0.01 ± 0.7	-1.6 ± 0.6	-3.1 ± 0.9	-1.7 ± 1.4	**p < 0.001**
Kymphocyte (cells/μL)	2.60 ± 2.62	2.28 ± 0.76	1.96 ± 0.73	2.26 ± 1.48	**0.001**
CRP (mg/L)	7.28 ± 13.22	5.53 ± 6.60	7.83 ± 19.02	6.71 ± 13.34	0.771
Albumin (g/dL)	4.15 ± 0.26	4.03 ± 0.34	3.97 ± 0.38	4.04 ± 0.34	**0.003**
CALLY index	0.38 ± 0.49	0.34 ± 0.31	0.33 ± 0.38	0.35 ± 0.38	0.130
Comorbid diseases, n (%)	68 (79.9%)	115 (79.1%)	93 (86.9%)	336 (81.9%)	

BMI: Body mass index, Ca: Calcium, CRP: C-reactive protein, CALLY: C-reactive protein-albumin-lymphocyte

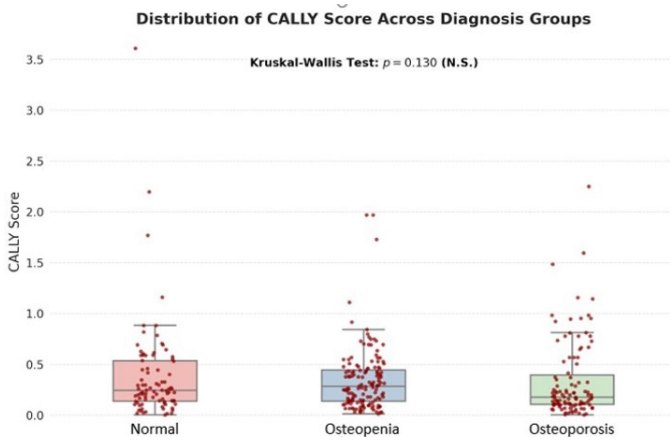

Figure 1: Relationship of CALLY index values between the groups

CALLY: C-reactive protein-albumin-lymphocyte

inflammation is associated with generalized OP, while localized inflammatory processes are associated with regional reductions in bone density (7).

Among the investigated inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) provides unique insights by simultaneously reflecting two immune pathways: neutrophilia, indicating active inflammation, and lymphopenia, suggesting an impaired stress response. Multiple research groups have reported significantly elevated NLR in osteoporotic patients compared with both osteopenic individuals and healthy controls, lending credence to the inflammation-OP hypothesis (9). However, the inflammatory landscape appears more complex when examining other hematological indices. Kim et al. (10) and colleagues identified a positive correlation between platelet count and BMD specifically in postmenopausal women, while Fang et al. (11) team observed concurrent elevations in the platelet-to-lymphocyte (PLR), monocyte-to-lymphocyte (MLR), and NLR ratios in patients with OP. These findings were extended by Zhang et al.(12) who demonstrated negative correlations of PLR, SII, MLR, and NLR with BMD measurements.

Not all studies support these associations, however. Eroglu et al. (13) reported a significantly increased PLR but an unchanged NLR in their OP cohort, while Dost Sürücü et al. (14) found no meaningful differences in either NLR or PLR between the study groups. Similarly, SII failed to show significant discriminatory value in assessing OP risk (15). These inconsistent findings have driven the search for more reliable inflammatory biomarkers in bone health evaluation.

The CRP-albumin axis has emerged as particularly promising in this context. Multiple lines of evidence confirm that elevated CRP levels not only correlate with reduced bone density but also independently predict osteoporotic fracture risk (16). Concurrently, research demonstrates that decreased serum albumin levels are significantly associated with reduced BMD (17,18). When combined to form the CAR, these markers show an enhanced predictive capacity for bone loss, with particularly strong negative correlations observed in postmenopausal women undergoing DXA assessment (19). Collectively, these findings strongly support the involvement of subclinical systemic inflammation in the development of OP (20).

Building on this evidence, our study investigated the novel CALLY index in postmenopausal OP. To our knowledge, this represents the first evaluation of this inflammatory marker in bone health assessment. Our analysis found no statistically significant difference in the CALLY index between the OP and control groups. However, we identified significant differences in other parameters, including age, urea levels, albumin levels, lymphocyte counts, and T-score. Several factors may explain the lack of a significant difference in the CALLY index. These include the presence of a low-grade, subclinical inflammatory process associated with OP, the limited discriminative ability of the index components (especially CRP) in this context, and the potential impact of various comorbid conditions on inflammatory processes and, consequently, on the CALLY index. Additionally, OP is recognized not only as an inflammatory condition but also as one affected by hormonal and mineral imbalances. The CALLY index may have limited diagnostic value in non-inflammatory subtypes of OP.

The older age of the OP group indicates that the prevalence of OP increases with age. Additionally, the lower T score validates the study's diagnostic criteria and confirms the reliability of the grouping.

We observed significant differences in albumin and lymphocyte levels between the groups. Notably, the OP group had the lowest median values for both parameters. Low albumin levels indicate the presence of subclinical inflammation and suggest metabolic and inflammatory interactions that contribute to the development of OP linked to malnutrition. Additionally, the significantly lower lymphocyte count observed in the OP group, which tends to decrease during chronic inflammation, reflects the influence of inflammatory and immunological processes on bone metabolism.

Study Limitations

The limitations of our study include its single-center, retrospective design and relatively small sample size. Additionally, we were unable to control for all potential confounding factors, such as medication use and comorbidities. We also did not conduct parallel assessments of other inflammatory markers, including NLR, PLR, SII, and CAR. Furthermore, the lack of a comprehensive correlation analysis between the CALLY index and T scores at various anatomical sites represents a significant limitation of the study.

Conclusion

Significantly lower levels of albumin and lymphocytes in the OP groupcompared with the normal groupunderscore the importance of these parameters in bone loss. However, the CALLY index, which combines these parameters, does not seem to provide adequate differentiation for assessing the low-grade systemic inflammation associated with OP. Prospective studies with larger sample sizes will help clarify the role of the CALLY index with respect to subclinical inflammation in the etiology of OP.

Ethics

Ethics Committee Approval: The research was conducted following ethical approval from the University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital Non-interventional Ethics Committee, which was obtained on (approval number: 2025/3-8, dated: 06.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.S.K., Concept: E.S.K., N.A., Design: E.S.K., N.A., Data Collection or Processing: E.S.K., N.A., Analysis or Interpretation: N.A., Literature Search: E.S.K., N.A., Writing: E.S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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