Research Article

Comparative Evaluation of Serum C-Reactive Protein and Albumin Levels in Healthy Controls and Patients with Oral Potentially Malignant Disorders, and Oral Malignancy

Arooj Mahmood[1,*], Moghees Ahmad Baig[1], Ashfaq ur Rahim[2], Anum Abid[1], Khurshid Ali Ansari[1], Easha Tahir Butt[3]

[1]*Department of Oral and Maxillofacial Surgery, University of Lahore, Lahore, Pakistan.*
[2]*Department of Oral and Maxillofacial Surgery, Rahbar College of Dentistry, Lahore, Pakistan.*
[3]*Department of Physiology, Azra Naheed Dental College, Superior University Lahore, Lahore, Pakistan.*

Abstract: Background: Oral cancers, like oral squamous cell carcinoma (OSCC), are often preceded by oral potentially malignant disorders (OPMDs) and biomarkers like C-reactive protein (CRP) and serum albumin can be indicators for early detection of these disorders.

Objective: To evaluate and compare the levels of CRP and serum albumin in healthy individuals, patients with oral premalignant lesions, and OSCC, and identify their potential as biomarkers.

Materials and Methods: This comparative cross-sectional study was conducted at the University College of Dentistry from 1st January to 31st August 2025 after the IRB approval [(Ref: UCD/ERCA/24/1583), dated 13-12-2024]. A total of 180 participants, aged 18-80 years, were divided into 3 groups i.e., healthy individuals, patients with premalignant lesions, and OSCC, using consecutive sampling. Individuals with inflammatory and chronic disorders, pregnancy, recent surgery or transfusion were excluded. Fasting venous blood samples were assessed. SPSSv24 was used for data analysis and comparisons, using one-way-ANOVA, pairwise comparisons, t-test, and Pearson's correlation.

Result: The mean age was 43±12.4years, with 104 males (57.8%) and 76 females (42.2%). Mean CRP was 16.97±17.33mg/L, highest in pre-malignant lesions (36.67±15.04), followed by OSCC (13.04±4.46) and controls (1.20±1.12) ($p<0.001$). Albumin levels declined progressively (Normal 4.40±0.61; OSCC 2.90±0.45; Premalignant 2.18±0.55g/dL, $p<0.001$). No significant differences were observed by gender (CRP, $p=0.532$; Albumin, $p=0.221$) or age (CRP, $p=0.243$; Albumin, $p=0.144$). CRP and albumin showed inverse correlations in premalignant lesions ($p<0.001$).

Conclusion: Serum CRP and albumin levels are significantly altered in oral premalignant and malignant lesions. These inexpensive biomarkers may serve as adjuncts for early detection, and prognosis of patients with OPMDs and OSCC.

Keywords: C-reactive protein, Serum albumin, Oral squamous cell carcinoma, Biomarkers, Inflammation, Lesions.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a major type of oral cancer which is usually preceded by oral pre-malignant lesions like leukoplakia, erythroplakia, oral submucous fibrosis, and oral lichen planus [1, 2]. In a 2025, U.S. cohort of over four million individuals reported that malignant transformation rates were 8.4% for leukoplakia, 50.0% for erythroplakia, 5.1% for OSMF, and 0.2% for oral lichen-planus which highlight a measurable risk gradient along which objective biomarkers could help in surveillance [3].

Inflammation and nutrition is a key factor in the development of cancer and its progression. Among various parameters, C reactive protein (CRP) and serum albumin are routine tumor markers, CRP is a protein produced in response to proinflammatory cytokines, like interleukin 6 and its elevation indicates systemic inflammation, which is associated carcinogenesis and tumor progression [4]. Serum albumin, on the other hand, is a plasma protein which decreases in its concentration indicating chronic inflammation and malnutrition linked with carcinogenesis [5]. The CRP levels tend to rise and the albumin levels often decline in patients with malignancy, providing an overview of the host inflammatory and nutritional state [6].

In head-and-neck oncology several studies have reported CRP, albumin, and other indices to OSCC progression [5, 6]. Moreover, combined indices such as ratio of CRP: albumin (CAR) and the Glasgow Prognostic Score (GPS), have shown tumor progression and overall outcome [4, 7, 8]. Previous studies have also suggested that changes in CRP and albumin can be detected in patients with pre-malignant lesions, indicating that systemic inflammation is already present before malignant transformation [5, 9,10]. A meta-analysis on OSCC reported that the CRP-to-albumin ratio (CAR) can independently predicts overall survival, aligning with the literature [11].

* Address correspondence to this author at the Department of Oral and Maxillofacial Surgery, University of Lahore, Lahore, Pakistan.
Email: arooj.mahmood@ucd.uol.edu.pk

Recent population-based data like 2024 National Health and Nutrition Examination Survey (NHANES) cancer cohort analysis reported that lower serum albumin levels (≤4.2 g/dL) are associated with increased mortality in cancers, indicating albumin as a negative prognostic marker [12]. Inflammatory and nutritional changes can be detectable even before malignant transformation [7]. Patients with oral pre-malignant lesions have reportedly shown higher CRP levels, with some studies observing a gradual rise in CRP from normal mucosa to pre-malignant lesions and then to OSCC [13, 14].

Despite these findings, only a limited number of studies have directly compared CRP and albumin levels across healthy individuals, patients with OPMDs, and patients with OSCC in a single study framework [3]. The findings could be useful in resource-limited areas, where access to advanced diagnostic tools is restricted.

The study aims to perform a comparative analysis of serum CRP and albumin levels among three groups: healthy controls, patients with oral pre-malignant lesions, and patients with OSCC.

MATERIALS AND METHODS

This comparative cross-sectional study was performed at Dental and Maxillofacial Center in University College of Medicine and Dentistry (UCMD) Hospital in Lahore from 1st January 2025 to 31st August 2025, after the approval from the Institutional Review Board of University College of Dentistry, University of Lahore (UCD/ERCA/24/1583). Written informed consent was obtained from all participants.

A total sample size of 180 individuals was calculated using 90% power of study and 5% desired level of significance, anticipated frequency. σ=13% [15], using formula: $n=2(Z1-\alpha/2+Z1-\beta)2\sigma2/d2$, where d=mean difference. The participants were allocated equally to three groups (n=60 per group), using consecutive sampling technique. The first group was normal healthy individuals without clinical signs, and with no history of prior oral cancer or pre-cancer, and no active systemic inflammatory illness. The second group was premalignant group including patients with clinically suspected lesions (e.g., leukoplakia, erythroplakia, OSMF, oral lichen planus) confirmed by standard clinical diagnostic criteria with documentation. The third group was OSCC group with histopathologically confirmed primary OSCC cases prior to definitive therapy (surgery/radiation/systemic therapy).

The inclusion criteria were patients aged 18–80 years who agreed to be included in the study with newly diagnosed or previously documented active lesion or lesions. The newly diagnosed patients with OSCC with no prior oncologic treatment were also included. The exclusion criteria were patients with acute infection within 2 weeks; chronic inflammatory or autoimmune disease; chronic liver or renal failure, nephrotic syndrome; active tuberculosis; pregnancy; current systemic corticosteroids or immunosuppressants; recent major surgery/trauma (<4 weeks); known hereditary or acquired hypoalbuminemia; recent blood transfusion (<3 months). For healthy individuals current tobacco and alcohol intake were excluded.

Blood and laboratory analysis was performed after an overnight fast (8–12 hours), 5 mL of venous blood was drawn between 8:00–12:00 a.m. to limit diurnal and post-prandial variation. Samples were collected into plain vacutainers, centrifuged at 3000g for 10 minutes. Serum was visually inspected to exclude hemolysis or lipemia; aliquots were stored at −80°C and were analyzed, logged and documented.

Serum albumin and CRP levels were measured in the laboratory at UCMD. The serum albumin (g/dL) was measured on an automated chemistry analyzer using the bromocresol green method. Analytical imprecision was targeted at <3% CV and the serum CRP (mg/L) was measured using an immunoturbidimetric assay.

STATISTICAL ANALYSIS

Data was entered and cross-validated. Pre-analytical variables (time of draw, fasting status, transport time, storage temperature) were documented; samples with gross hemolysis or pre-specified QC failures were re-drawn where feasible or excluded. Analyses were performed using SPSS version 24. The Continuous variables were summarized as mean±SD. Shapiro–Wilk normality testing was done; data was normally distributed. Group comparisons used one-way ANOVA with post-hoc Tuckey tests for pairwise comparison. Pearson's correlation was applied for CRP and Albumin levels for various groups. p-values ≤ 0.05 were taken as significant.

RESULT

A total of 180 individuals were included in the study and divided into three groups (n=60 per/group) i.e., normal (healthy individuals), patients with premalignant lesions, and OSCC group. The mean age was 43±12.4 years. The study included 57.8% (n=104) males and 42.2% (n=76) females. The mean CRP level was 16.97±17.33mg/L, while the mean serum albumin was 3.16±1.07g/dL.

The biomarker were compared among the three groups (Normal, Premalignant, OSCC) using one-way ANOVA, reporting a highly significant difference among the groups ($p<0.001$). Post hoc pairwise comparison showed that each comparison was significant, grading the groups as Premalignant>OSCC>Normal (Table **1**).

The serum albumin showed a gradual decline across groups. There was a statistically significant difference between the groups ($p<0.001$). Post hoc pairwise comparisons showed that all pairwise differences were significant, with the pattern; Normal>OSCC>Premalignant (Table **1**).

Comparison between genders reported no statistically significant differences. Male participants had a mean CRP of 17.66±16.95 mg/L compared to 16.02±17.90 mg/L in females. Mean albumin

was slightly lower in males compared with females. There was no statistically significant age wise differences observed in either biomarker indicating findings indicate that age did not exert a significant effect on either biomarker (Table **2**).

A significant inverse relationship between serum CRP and albumin levels was found within each group using Pearson correlation (Table **3**). The findings support the hypothesis that elevated systemic inflammation is associated with reduced serum albumin, particularly in precancerous oral lesions.

Table 1. Comparison of Serum CRP and Albumin.

Biomarkers	Group (n=60)	Mean±SD	F	p	Tukey Post Hoc Result
CRP (mg/L)	Normal	1.20±1.12	237.2	<0.001	All pairwise comparisons were significant (Premalignant > OSCC >Normal)
	OSCC	13.04±4.46			
	Premalignant	36.67±15.04			
Albumin (g/dL)	Normal	4.40±0.61	264.2	<0.001	All pairwise comparisons were significant (Normal > OSCC > Premalignant)
	OSCC	2.90±0.45			
	Premalignant	2.18±0.55			

p-values were obtained using One way ANOVA.

Table 2. Comparison of Serum CRP and Albumin by Gender and Age.

Biomarker	Gender	Mean ± SD	t	p
CRP (mg/L)	Male (n=104)	17.66 ± 16.95	0.63	0.532
	Female (n=76)	16.02 ± 17.90		
Albumin (g/dL)	Male (n=104)	3.08 ± 1.04	−1.23	0.221
	Female (n=76)	3.27 ± 1.10		
Biomarker	**Age Category**	**Mean ± SD**	**F**	**p**
CRP (mg/L)	Younger Age (n=8)	8.64 ± 9.07	1.42	0.243
	Middle Age (n=148)	17.86 ± 17.61		
	Older Age (n=24)	14.25 ± 17.06		
Albumin (g/dL)	Younger Age (n=8)	3.84 ± 0.87	1.96	0.144
	Middle Age (n=148)	3.11 ± 1.05		
	Older Age (n=24)	3.27 ± 1.17		

p-values were obtained using independent sample t-test and ANOVA.

Table 3. Correlation between CRP and Albumin within Groups.

Group	Pearson r	p	n	Interpretation
Normal	−0.383	0.003	60	Moderate inverse correlation
Premalignant	−0.873	<0.001	60	Strong inverse correlation
OSCC	−0.532	<0.001	60	Moderate inverse correlation

Correlation analyses were performed using Pearson Correlation.

DISCUSSION

The current study found that CRP levels were higher in patients with premalignant lesions compared to those with OSCC and healthy individuals. These findings were in agreement with the previous studies where elevated CRP were found in both oral pre malignant disorders (OPMDs) and OSCC compared to controls [13, 16, 17]. A more recent diagnostic study also confirmed that salivary CRP could reliably differentiate OPMD and OSCC from healthy mucosa [18]. However, some studies reported the highest CRP in OSCC rather than premalignant lesions [7, 16, 17]. These inconsistencies may be related to the type of lesions, cancer stage, and differences in biological samples (serum vs saliva). The results of this study suggest that systemic inflammation is already prominent in the precancerous stage and may act as an early marker of malignant risk [4].

Serum albumin levels in the present study showed a significant decrease across the groups with highest in healthy controls, lower in OSCC, and lowest in the premalignant lesions. Hypoalbuminemia is recognized as a biomarker of inflammatory status and is associated with poor survival outcomes in oral cancer

[19]. A population based study by Tang *et al.*, reported that lower albumin level is linked with increased mortality in different cancer types [20]. In oral disease, serum albumin reportedly decrease in both premalignant and malignant lesions as compared to controls [21]. The lower levels seen in premalignant cases in this study may suggest high inflammatory burden even before cancer develops.

The correlation analysis in this study showed a significant inverse relationship between CRP and albumin and it was strongest in the premalignant group. This is consistent with the literature which report that the CRP/albumin ratio (CAR) and indices like CALLY index (CRP, albumin, lymphocyte count) predict disease and overall survival in OSCC [12, 14]. A study of hypopharyngeal cancer also confirmed the prognostic value of the CALLY index [22]. These finding suggest that systemic inflammation is linked to early carcinogenesis and these combined markers may help identify OPMDs in patients at higher risk of malignant transformation.

There was no significant difference in CRP or albumin levels were observed between males and females and this is in agreement with the previous studies reporting that changes in these biomarkers are primarily influenced by tumor stage, nodal involvement, and oral health status rather than gender [23, 24]. Similarly, no differences were observed in age groups reporting that CRP and albumin remain stable across age groups; prior studies report mixed outcomes [14, 24, 25].

The present study adds important findings to the literature linking systemic inflammatory biomarkers with oral disease progression. By demonstrating that serum CRP increases and serum albumin decreases significantly across the groups; normal mucosa to premalignant lesions and OSCC, this study reports the potential importance of these simple, cost-effective laboratory markers in routine clinical practice [12]. The exceptionally strong inverse correlation between CRP and albumin in premalignant lesions suggests that these biomarkers may be useful in identifying high-risk OPMD cases, thereby facilitating earlier intervention [16]. Furthermore, as per current study findings, these markers are not influenced by gender or age, they can be applied universally across populations without complex adjustment.

LIMITATIONS

The study has several limitations like cross-sectional type of the study. The sample was drawn from a single tertiary care center, which may limit generalizability. Although systemic diseases and confounders were excluded, effects of oral health, periodontitis, or lifestyle may influence CRP and albumin levels. Future studies should use longitudinal designs determine the predictive findings for malignant transformation. Grouping by lesion subtype, stage, and histopathological grade may provide deeper understandings of biomarker behavior [12]. Multi center studies with larger and diverse samples are suggested to improve the findings.

CONCLUSION

The CRP and albumin levels are simple and cost effective biomarkers that can help in the risk assessment for premalignant and malignant lesions. The CRP levels were raised in the patients with premalignant lesions and OSCC, with larger levels in cases with premalignant. The serum albumin levels reported a progressive decline and were lowest in the premalignant lesions group. A significant inverse correlation between CRP and albumin levels was observed, especially in premalignant lesion group, indicating the effectiveness of these tests for early detection of malignancy. No significant differences in biomarker levels was observed in age and gender, Longitudinal and multi center studies are recommended in future to further validate these findings.

LIST OF ABBREVIATIONS

CALLY Index: C-reactive Protein–Albumin–Lymphocyte Index.

CAR: C-reactive Protein to Albumin Ratio.

CRP: C-reactive Protein.

GPS: Glasgow Prognostic Score.

NHANES: National Health and Nutrition Examination Survey.

OPMD: Oral pre-Malignant Disorder.

OSCC: Oral Squamous Cell Carcinoma.

AUTHORS' CONTRIBUTION

Arooj Mahmood: Conceptualization, Study design.

Moghees Ahmad Baig: Final approval, final proof to be published.

Ashfaq ur Rahim: Critical review and revision the manuscript.

Anum Abid: Methodology, Data analysis and interpretation.

Khurshid Ali Ansari: Study design.

Easha Tahir Butt: Writing draft.

ACKNOWLEDGEMENTS

Declare none.

ETHICAL DECLARATIONS

Data Availability

The data will be available from the corresponding author upon request.

Ethical Approval

This study was approved by the Institutional Review Board of the University College of Dentistry (Ref: UCD/ERCA/24/1583), dated 13-12-2024.

Consent to Participate

Written informed consent was obtained from all participants prior to inclusion in the study.

Consent for Publication

All authors provided consent for the publication.

Conflict of Interest

Declared none.

Competing Interest / Funding

Declared none.

Use of AI-Assisted Technologies

None.

REFERENCES

[1] Kumari P, Debta P, Dixit A. Oral potentially malignant disorders: Etiology, pathogenesis, and transformation into oral cancer. Front Pharmacol 2022; 13: 825266. https://doi.org/10.3389/fphar.2022.825266

[2] Manzar E, Zaidi AH, Muhammad A, Hassan H, Aziz MS, Anwar W, *et al.* Awareness and perception of nicotine pouches and e-cigarettes among dental students in Lahore. Pak J Med Health Sci 2021; 15(12): 3681-8. https://doi.org/10.53350/pjmhs2115123681

[3] Villa A, Lodolo M, Ha P. Oncological outcomes of patients with oral potentially malignant disorders. JAMA Otolaryngol Head Neck Surg 2025; 151(1): 65-71. https://doi.org/10.1001/jamaoto.2024.3719

[4] Sambataro D, Politi MR, Messina A, Scarpello L, Messina S, Guggino R, *et al.* Relationship of inflammatory parameters and nutritional status in cancer patients. Anticancer Res 2023; 43(6): 2821-9. https://doi.org/10.21873/anticanres.16451

[5] Kim YR, Choi CK, Lee Y-H, Choi S-W, Kim H-Y, Shin M-H, *et al.* Association between albumin, total bilirubin, and uric acid serum levels and the risk of cancer: A prospective study in a Korean population. Yonsei Med J 2021; 62(9): 792. https://doi.org/10.3349/ymj.2021.62.9.792

[6] Zhang C-l, Gao M-q, Jiang X-c, Pan X, Zhang X-y, Li Y, *et al.* Research progress and value of albumin-related inflammatory markers in the prognosis of non-small cell lung cancer: A review of clinical evidence. Ann Med 2023; 55(1): 1294-307. https://doi.org/10.1080/07853890.2023.2192047

[7] Luan C-W, Yang H-Y, Tsai Y-T, Hsieh M-C, Chou H-H, Chen K-S. Prognostic value of c-reactive protein-to-albumin ratio in head and neck cancer: A meta-analysis. Diagnostics 2021; 11(3): 403. https://doi.org/10.3390/diagnostics11030403

[8] Di Rosa M, Sabbatinelli J, Giuliani A, Carella M, Magro D, Biscetti L, *et al.* Inflammation scores based on C-reactive protein and albumin predict mortality in hospitalized older patients independent of the admission diagnosis. Immun Ageing 2024; 21(1): 67-75. https://doi.org/10.1186/s12979-024-00471-y

[9] Vogl M, Rosenmayr A, Bohanes T, Scheed A, Brndiar M, Stubenberger E, *et al.* Biomarkers for malignant pleural mesothelioma—A novel view on inflammation. Cancers 2021; 13(4): 658-82. https://doi.org/10.3390/cancers13040658

[10] Chauhan R, Trivedi V. Inflammatory markers in cancer: Potential resources. Front Biosci (Schol Ed) 2020; 12(1): 1-24. https://doi.org/10.2741/S537

[11] Wu T-H, Tsai Y-T, Chen K-Y, Yap W-K, Luan C-W. Utility of high-sensitivity modified Glasgow prognostic score in cancer prognosis: A systemic review and meta-analysis. Int J Mol Sci 2023; 24(2): 1318. https://doi.org/10.3390/ijms24021318

[12] Zhu D, Lin Y-D, Yao Y-Z, Qi X-J, Qian K, Lin L-Z. Negative association of C-reactive protein-albumin-lymphocyte index (CALLY index) with all-cause and cause-specific mortality in patients with cancer: Results from NHANES 1999–2018. BMC Cancer 2024; 24(1): 1499. https://doi.org/10.1186/s12885-024-13261-y

[13] Salema H, Joshi S, Pawar S, Nair VS, Deo VV, Sanghai MM, *et al.* Evaluation of the role of C-reactive protein as a prognostic indicator in oral pre-malignant and malignant lesions. Cureus 2024; 16(5): e60812. https://doi.org/10.7759/cureus.60812

[14] Yamagata K, Fukuzawa S, Ishibashi-Kanno N, Uchida F, Bukawa H. Association between the C-reactive protein/albumin ratio and prognosis in patients with oral squamous cell carcinoma. Sci Rep 2021; 11(1): 5446. https://doi.org/10.1038/s41598-021-83362-2

[15] Mustafa E, Parmar S, Praveen P. Premalignant lesions and conditions of the oral cavity. In: Bonanthaya K, Panneerselvam E, Manuel S, Kumar VV, Rai A, Eds. Oral and Maxillofacial Surgery for the Clinician. USA: Springer 2021; pp. 1845-52. https://doi.org/10.1007/978-981-15-1346-6_80

[16] Metgud R, Bajaj S. Altered serum and salivary C-reactive protein levels in patients with oral premalignant lesions and oral squamous cell carcinoma. Biotech Histochem 2016; 91(2): 96-101. https://doi.org/10.3109/10520295.2015.1077393

[17] Vankadara S, Padmaja K, Balmuri PK, Naresh G, Reddy V. Evaluation of serum C-reactive protein levels in oral premalignancies and malignancies: A comparative study. J Dent (Tehran) 2018; 15(6): 358-64.

[18] Uppal MK, Iyengar AR, Subash B, Patil S, Sharma ML, Thakar S. Estimation and correlation of serum and salivary C-reactive

protein in oral potentially malignant disorders. J Indian Acad Oral Med Radiol 2021; 33(1): 47-52. https://doi.org/10.4103/jiaomr.jiaomr_261_20

[19] Almasaudi AS, Dolan RD, Edwards CA, McMillan DC. Hypoalbuminemia reflects nutritional risk, body composition and systemic inflammation and is independently associated with survival in patients with colorectal cancer. Cancers 2020; 12(7): 1986. https://doi.org/10.3390/cancers12071986

[20] Tang Q, Li X, Sun C-R. Predictive value of serum albumin levels on cancer survival: a prospective cohort study. Front Oncol 2024; 14: 1323192. https://doi.org/10.3389/fonc.2024.1323192

[21] Metgud R, Patel S. Serum and salivary levels of albumin as diagnostic tools for oral pre-malignancy and oral malignancy. Biotech Histochem 2014; 89(1): 8-13. https://doi.org/10.3109/10520295.2013.793394

[22] Cetinayak HO, Aydin B, Semiz V, Atac Kutlu E, Basan U, Aksoy RA. Prognostic value of the CALLY index in hypopharyngeal cancer treated with definitive chemoradiotherapy: A Retrospective Cohort Study. Diagnostics 2025; 15(17): 2237. https://doi.org/10.3390/diagnostics15172237

[23] Keinänen A, Uittamo J, Marinescu-Gava M, Kainulainen S, Snäll J. Preoperative C-reactive protein to albumin ratio and oral health in oral squamous cell carcinoma patients. BMC Oral Health 2021; 21(1): 132. https://doi.org/10.1186/s12903-021-01516-0

[24] Park H-C, Kim M-Y, Kim C-H. C-reactive protein/albumin ratio as prognostic score in oral squamous cell carcinoma. J Korean Assoc Oral Maxillofac Surg 2016; 42(5): 243-50. https://doi.org/10.5125/jkaoms.2016.42.5.243

[25] Fang K-H, Lai C-H, Hsu C-M, Huang E, Tsai M-S, Chang G-H, *et al.* A retrospective study on the prognostic value of preoperative C-reactive protein to albumin ratio in patients with oral cavity squamous cell carcinoma. Peer J 2020;8: e9361. https://doi.org/10.7717/peerj.9361

Received: September 24, 2025 Revised: January 08, 2026 Accepted: January 12, 2026