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Evaluation of Serum C-Reactive Protein in Oral Malignancies and Premalignant Disorders

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ABSTRACT

Background: OSCC commonly occurs in the context of systemic inflammation and is secondary to OPMDs. CRP, an IL-6-mediated acute-phase protein secreted by hepatocytes, is a systemic inflammatory marker and may reflect cancer development and progression. **Objective:** To compare serum CRP among healthy subjects, OPMDs, and OSCC patients and evaluate its usefulness as an adjunct inflammatory biomarker. **Study Design:** Comparative cross-sectional study. **Settings:** Department of Oral and Maxillofacial Surgery, Dr Ishrat ul Ebad Khan Institute of Oral Health Sciences, DUHS Karachi Pakistan. **Duration:** Six months from 16-9-2025 to 16-03-2026. **Methods:** Involving 105 subjects, equally allocated to the healthy control group (Group I), OPMDs (Group II), and confirmed OSCC cases (Group III). Blood samples were collected and tested for serum CRP using the immunoturbidimetric method. The Kruskal–Wallis test was used to compare CRP levels among the three groups and the significance level was set at $p<0.05$. **Results:** The median CRP level was 2.40 mg/L (IQR: 1.10–5.20) in healthy controls, 2.80 mg/L (IQR: 1.50–6.40) in OPMD patients, and 22.50 mg/L (IQR: 9.80–48.00) in OSCC patients (Kruskal-Wallis H (2) = 42.18, $p<0.001$). Post-hoc pairwise comparisons using Dunn's multiple comparison test with Bonferroni correction showed that OSCC patients had significantly higher CRP levels than both healthy controls and OPMD patients, whereas the difference between OPMD patients and healthy controls was not statistically significant. **Conclusion:** The findings indicate that elevated CRP levels measured before diagnosis are linked to a higher likelihood of developing oral cancer later in life, suggesting that plasma CRP may serve as an adjunct inflammatory marker requiring validation.

Keywords: *C-reactive protein, Precancerous conditions, Biomarkers.*

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INTRODUCTION

Oral squamous cell carcinoma accounts for the largest percentage of oral cancer cases, diagnosed at a late stage where treatment becomes more challenging.[1] It is prevalent in Pakistan and other South Asian countries because of high tobacco usage, betel quid, areca nut, and gutka.[2] Early detection of these lesions through assessment and long-term follow-up is necessary to prevent the development of oral cancer.[3] Although traditional clinical assessment and histopathological diagnosis have proven their effectiveness over decades, it remains challenging to evaluate inflammation and malignant transformation easily, repeatably, and cost-effectively.[4]

Chronic irritation by various products, which includes tobacco smoking, betel quid, and areca nut chewing, induces a state of inflammation, resulting in the formation of premalignant lesions.[5] Among different biomarkers, which include ILs, TNF-α, LDH, miRNAs, oxidative stress markers, and C-reactive protein (CRP), the most effective markers for early detection, risk stratification, and prognosis in the case of OPMDs and OSCCs appear to be IL-1β, IL-6, and IL-8.[6]

The liver secretes CRP in response to the cytokine IL-6. When inflammation occurs in the body, CRP levels become elevated. In the context of OPMD and OSCC, CRP levels may increase with the inflammatory activity accompanying the development of premalignant lesions and the transition to invasive malignancies.[7] Studies demonstrate elevated serum CRP levels in OPMD patients compared with the control group, as well as a correlation between serum and salivary CRP levels.[8] Elevated

CRP (or CRP-to-albumin ratio) has been shown to correlate with poor prognosis in OSCC patients, and salivary CRP also varies with the inflammatory/malignant stage.[9,10]

Some studies focused on salivary CRP levels without proper clinicopathological correlations and evaluation of diagnostic characteristics. Additionally, data on CRP among patients from high-burden regions such as South Asia are scarce. Further research in the field requires a well-designed comparative study of serum CRP levels among the above-mentioned groups.

The proposed comparative study evaluates serum CRP in three groups – healthy controls, OPMD patients, and OSCC patients- to examine whether CRP serum levels increase progressively with disease progression, from healthy to OPMD to OSCC. The aim is to determine whether serum CRP could serve as a relatively easy and inexpensive adjunct biomarker for inflammatory activity and malignant transformation risk, offering a low-cost approach for OPMD and OSCC screening and risk stratification.

METHODS

The comparative cross-sectional study was conducted at Dr Ishrat ul Ebad Khan Institute of Oral Health Sciences, Dow Hospital Karachi, Pakistan in department of Oral and maxillofacial surgery after receiving approval from ethical committee institutional of Dow University of health sciences Karachi (Ref:4096/DUHS/Approval/2025/337) on date 15th September 2025 over six months' time duration (16-9-2025 to 16-03-2026) by employing non-probability convenience sampling. This study complies with the STROBE checklist as supplementary material.

The sample size was calculated using G*Power version 3.1.9.7, based on the difference in mean serum C-reactive protein (CRP) levels reported in a previous comparative study by Vankadara *et al*.[13] Considering a 95% confidence level ($\alpha = 0.05$) and 80% statistical power, the required sample size was estimated to be 35 participants per group. Therefore, a total of 105 participants were enrolled, comprising 35 healthy controls, 35 patients with oral potentially malignant disorders (OPMDs), and 35 patients with oral squamous cell carcinoma (OSCC).

Participants were recruited using a consecutive (non-probability) sampling technique from patients attending the outpatient department who met the eligibility criteria.

Inclusion criteria were subjects' ≥20 years old with OPMDs, OSCCs, confirmed by histopathological examination and healthy individuals with no inflammatory or infectious diseases, or malignancy. The exclusion criteria included patients with active systemic inflammatory or infectious conditions, autoimmune diseases, cardiovascular diseases, liver diseases, renal diseases, and diabetes mellitus with complications, trauma, recent surgeries, other cancers, pregnant/lactating women, acute infections, periodontal abscesses, or severe caries with suppuration.

After obtaining informed consent from subjects, various clinical and demographic parameters, including age, gender, and other risk factors, were recorded. A clinical examination was conducted to document the presence of OPMD and OSCC. A histopathological confirmation was necessary for OSCCs.

To determine CRP level, 2 mL of venous blood was drawn, centrifuged to separate serum, and subjected to immunoturbidometric analysis for CRP levels in mg/L. Quality control was maintained throughout the testing process, and samples showing hemolysis, lipemia, insufficiency, or improper storage were either retested or replaced. Laboratory workers were blinded to group allocation wherever possible.

Primary outcome measure: Serum CRP level (mg/L). Secondary measures include age, gender, OPMD subtypes, lesion location, and tobacco/betel exposure.

Statistical analyses were done using SPSS software v26. Continuous variables such as age were assessed in mean ± SD and CRP was assessed in median, while categorical variables such as gender were reported as counts/percentages. Because serum CRP values showed significant deviation from normality (Shapiro–Wilk $p<0.001$), comparisons among the three groups were performed using the Kruskal–Wallis test. Pairwise comparisons were conducted using Dunn's test with Bonferroni adjustment. Age differences were compared using ANOVA. For significant Kruskal–Wallis tests, Dunn's multiple comparison test with Bonferroni correction was performed for post-hoc pairwise comparisons. Significant results were considered to have two-sided $P<0.05$.

RESULTS

Participant's age ranged from 20–76 years. Group I had a mean age of 43.63 ± 8.56 (confidence interval: 40.69–46.57; median: 43; interquartile range: 38- 49). Group II had a mean age of 43.67 ± 13.85 (confidence interval: 38.91-48.43; median: 42; interquartile range: 33-54). While in Group III, the mean age was 57.17 ± 10.29 (confidence interval: 53.64-60.70; median: 58; interquartile range: 49-65). Analysis of Variance (ANOVA) test revealed: $F(2,102) = 14.86$, $p<0.001$. A significant difference in age was observed among the study groups, with OSCC patients being older than the control and OPMD groups.

Table 1: Age distribution across the studied groups

Group	n	Minimum	Maximum	Mean ± SD	p-value
Group I: Healthy controls	35	20	75	43.63 ± 8.56	<0.001
Group II: OPMDs	35	20	75	43.67 ± 13.85	
Group III: OSCC	35	40	76	57.17 ± 10.29	

The gender distribution of participants across the three study groups is presented in Table 2. Among healthy controls, 18 (51.4%) participants were female and 17 (48.6%) were male. In the OPMD group, 12 (34.3%) participants were female and 23 (65.7%) were male. In the OSCC group, 23 (65.7%) participants were female and 12 (34.3%) were male.

Table 2: Gender distribution across the studied groups

Gender	Group I: Healthy controls n (%)	Group II: OPMDs n (%)	Group III: OSCC n (%)
Female	18 (51.4%)	12 (34.3%)	23 (65.7%)
Male	17 (48.6%)	23 (65.7%)	12 (34.3%)
Total	35 (100%)	35 (100%)	35 (100%)

Serum C-reactive protein (CRP) levels demonstrated considerable variation among the three study groups and showed a non-normal distribution (Shapiro–Wilk test, $p<0.001$). Therefore, CRP concentrations were summarized using the median and interquartile range (IQR). The median CRP level was 2.40 mg/L (IQR: 1.10–5.20) in healthy controls, 2.80 mg/L (IQR: 1.50–6.40) in OPMD patients, and 22.50 mg/L (IQR: 9.80–48.00) in OSCC patients. Overall, CRP levels differed significantly among the three groups (Kruskal–Wallis test, $p<0.001$), with the highest levels observed in the OSCC group.

Table 3: Comparison of serum C-reactive protein levels across the studied groups

Group	n	Minimum	Maximum	Median (IQR)	p-value
Group I: Healthy controls	35	0.1	18.3	2.40 (1.10–5.20)	<0.001
Group II: OPMDs	35	0.8	53.9	2.80 (1.50–6.40)	
Group III: OSCC	35	3.3	96.0	22.50 (9.80–48.00)	

DISCUSSION

Serum CRP levels were compared among healthy controls, OPMD patients, and OSCC patients. Patients with OSCC exhibited highly elevated levels of CRP when compared with both control individuals and patients with OPMD. Post hoc analysis revealed a highly significant increase in CRP among OSCC patients, whereas differences between controls and OPMD were not statistically significant.

Elevated serum CRP levels were associated with systemic inflammation mediated by pro-inflammatory cytokines such as interleukin-6. As the tumor develops, it triggers inflammatory processes driven by its growth and stromal infiltration.[12] This inflammation plays a role in the tumor's initiation, development, angiogenesis, invasion, and metastasis. Hence, the increase in CRP seen among patients with OSCC can be attributed to inflammation generated by malignant epithelial growth, stromal invasion, and interactions between the tumor and the host immune system.[13]

This observation is consistent with the results of previous studies demonstrating increased CRP during the transition from premalignant to malignant states. For instance, Mounesh Kumar et al.[9] reported CRP levels of 2.1 ± 1.6 mg/dL for control individuals, 5.5 ± 4.8 mg/dL for leukoplakia, 6.1 ± 4.9 mg/dL for OSMF, and 10.5 ± 2.4 mg/dL for OSCC. Similarly, Sharma et al.[12] reported significantly increased CRP in OPMD and OSCC cases relative to control, with OSCC having the highest value. The higher levels of CRP observed in the current study may be due to the greater tumor burden, advanced disease stage, and exposure to tobacco products and/or betel nut, which is characteristic of populations in South Asia.[13]

Unlike several other studies, the current study failed to demonstrate a significant difference between CRP levels in OPMD patients and control individuals. For instance, according to the report by Thakar et al.,[8] CRP levels were significantly increased in OPMD (5.91 ± 3.11 mg/L) vs the control group (2.18 ± 0.66 mg/L), and there was also a positive correlation between serum and salivary CRP levels. Possible explanations include OPMD patients having an early-stage disease, relatively mild inflammation, or a different distribution of OPMD type.[14-16]

In the current study, CRP levels varied across OPMD types (leukoplakia, OLP, OSMF), with the latter exhibiting the highest levels, though a single outlier drove this. Median CRP level of 4.20 mg/L indicates limited discriminative ability of this test.

Clinically, CRP can be useful since it is easily measurable, inexpensive, and standardized.[17] However, this test is nonspecific and may show an elevation in cases of infections, trauma, autoimmune, cardiovascular, and metabolic conditions.[18-20] Therefore, CRP should be employed as part of a diagnostic approach along with other diagnostic techniques (including clinical examination, histopathological biopsy, radiological imaging, and risk factors).

Further research using a prospective longitudinal design and including larger samples, detailed clinicopathologic information, history of harmful habits, and diagnostic accuracy analysis is required to validate the findings of the current study. The highly elevated serum CRP levels detected in OSCC cases suggest the use of CRP as an adjunct inflammatory marker. Its limited ability to discriminate between OPMD and controls suggests limited utility as a screening test. Overall, serum CRP could be useful as part of an extensive diagnostic panel, alongside traditional diagnostics.

CONCLUSION

Significantly increased serum levels of C-reactive protein were noted in OSCC subjects compared to controls or subjects with OPMDs. Patients with OPMD showed only a mild increase in serum CRP compared with controls. OSCC was associated with increased systemic inflammatory response. Serum CRP is a simple and affordable biomarker that could assist in detecting OSCC alongside other diagnostic methods like physical examination, histopathology, and assessment of habits. More extensive longitudinal studies should be conducted to determine its significance in oral malignancy screening and prognosis.

LIMITATIONS

This was a single-center cross-sectional study with a relatively small sample size and non-probability convenience sampling, which may limit the generalizability of the findings. Furthermore, serum CRP is a non-specific inflammatory marker and may be influenced by factors other than oral malignancy. The study groups differed in age and sex distribution; therefore, potential confounding by these demographic factors cannot be excluded and the findings should be interpreted with caution.

SUGGESTIONS / RECOMMENDATIONS

Future multicenter prospective longitudinal studies with larger sample sizes are recommended to validate the diagnostic and prognostic value of serum CRP in OPMDs and OSCC. Further research should evaluate CRP in combination with other inflammatory and molecular biomarkers to improve diagnostic accuracy. Additionally, studies assessing the relationship between CRP levels, tumor stage, histopathological grade, treatment response, and long-term survival are warranted.

CONFLICT OF INTEREST / DISCLOSURE

The authors declare that they have no conflict of interest.

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