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EVALUATION OF SALIVARY IL-6, MMP-9, AND CYFRA 21-1 AS DIAGNOSTIC BIOMARKERS IN ORAL SQUAMOUS CELL CARCINOMA PATIENTS OF MARDAN

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is one of the main causes of cancer-related morbidity and mortality in Pakistan and poses a substantial public health burden.

Objective: To measure and compare salivary levels of CYFRA 21-1, MMP-9, and IL-6 in newly diagnosed OSCC patients to healthy controls; to correlate these biomarkers with tumor grade and stage; and to evaluate sensitivity and specificity separately and in combination**.**

Methodology: Total 30 biopsy-confirmed, untreated OSCC patients (Group A) and thirty age- and sex-matched healthy controls (Group B) from BKMC/BKCD, Mardan, were recruited for a 12-month comparative cross-sectional study. ELISA was used to measure the concentrations of biomarkers. ANOVA/Kruskal-Wallis, correlation analysis, t-test or Mann-Whitney U test, and ROC curve analysis (AUC, cutoff, sensitivity, and specificity) were among the statistical analyses.

Results: In OSCC patients, the mean salivary IL-6 was 85.4 ± 24.7 pg/mL, while in controls, it was 18.6 ± 7.8 pg/mL ($p < 0.001$). MMP-9 concentrations were 112.4 ± 40.1 ng/mL versus 298.2 ± 85.3 ng/mL ($p < 0.001$). CYFRA 21-1 levels were 1.45 ± 0.65 ng/mL versus 5.92 ± 1.95 ng/mL ($p < 0.001$). IL-6 and CYFRA were positively associated with higher TNM stage in OSCC patients ($\rho = 0.52$, $p = 0.004$; $\rho = 0.48$, $p = 0.006$, respectively).

Conclusion: Salivary IL-6, MMP-9, and CYFRA 21-1 were all markedly increased in OSCC, and they demonstrated good diagnostic accuracy. The combined biomarker panel enhanced discrimination even more.

Keywords: Biomarkers, CYFRA 21-1, IL-6, RO, Oral squamous cell carcinoma, Saliva

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a significant public health concern and is the most common subtype of head and neck squamous cell carcinoma (HNSCC). Most malignancies in the oral cavity occur in the form of oral squamous cell carcinoma (OSCC), which has a poor prognosis if detected too late (1). In many parts of Pakistan, OSCC is one of the most common cancers and is frequently linked to snuff, tobacco, and betel nut use (2). Early on, clinical signs might be subtle, which cause delays in diagnosis and raises morbidity and mortality. Biopsies are required for traditional diagnosis, which is time-consuming, invasive, and may discourage screening in environments with limited resources. Although the oral cavity is anatomically accessible, late-stage diagnoses persistently impede treatment

efficacy, leading to elevated morbidity and mortality rates worldwide (3). According to GLOBOCAN 2022, oral cancer is ranked among the top 20 malignancies globally, with approximately 390,000 new cases and 188,000 deaths per year (4). Risk factors like tobacco, alcohol abuse, areca nut chewing, and poor oral hygiene are significant contributing factors, especially in South Asia, where cultural practices intensify the disease burden (5,6). Furthermore, despite substantial strides in therapeutics, the 5-year survival rate for OSCC has stagnated below 60 % over the last two decades, emphasizing the need for novel diagnostic strategies (7,8). Currently, histopathological evaluation following tissue biopsy is considered the gold standard for OSCC diagnosis. This method is invasive, costly and time-consuming and frequently inaccessible in remote or economically challenged regions, resulting in diagnostic delays and increased disease burden (9,10). In these circumstances, there is urgent need for early and non-invasive diagnostic methods that are rapid, consistent, and feasible for point-of-care testing (POCT) to revolutionize the screening paradigm for OSCC (11). Therefore, there has been a lot of interest in non-invasive biomarkers in saliva. Saliva can reflect host and tumor responses because it comes into direct contact with oral lesions.

Numerous cytokines have been investigated as salivary biomarkers of OSCC, including IL-6, IL-8, and TNF-α; meta-analyses have confirmed that OSCC patients have significantly higher salivary IL-6 than controls (12). Additionally, salivary concentrations of MMP-9, an enzyme implicated in matrix degradation and tumor invasion, have been studied in OSCC and have demonstrated promising diagnostic potential (e.g. ROC AUC ~0.91) (13). Although there are fewer studies, CYFRA 21-1, a fragment of cytokeratin 19, is released when epithelial cells are damaged and has been studied in serum and saliva for epithelial cancers, including OSCC (14). However, limited data exist on salivary biomarker profiles in the Mardan population, where cultural and lifestyle factors differ from previously studied regions, the purpose of this study is to assess diagnostic performance both individually and in combination, as well as to evaluate salivary IL-6, MMP-9, and CYFRA 21-1 in OSCC patients there and investigate correlations with tumor stage/grade.

METHODOLOGY

The Bacha Khan Medical Complex and Bacha Khan College of Dentistry (BKMC/BKCD), Mardan, were the sites of this 12-month comparative cross-sectional analytical study. The BKMC/BKCD Institutional Review Board (IRB) granted ethical clearance for the study protocol. All participants gave their written informed consent before being included in the study, and they were made aware of their freedom to leave at any moment without facing any repercussions. Sample size of the study was calculated through open epi Two groups made up the study population: sample size of the study was calculated through open epi. Thirty (n = 30) recently diagnosed, histopathological confirmed cases of oral squamous cell carcinoma (OSCC) who had not yet received treatment were included in Group A. The oncology, ENT, and dental outpatient clinics at BKMC/BKCD were the successive sources of these patients. The thirty (n = 30) healthy individuals in Group B were matched for age and sex and had no prior history of malignancy, systemic illness, or oral lesions.

All participants had to be at least eighteen years old to be considered. The control group comprised healthy people without oral or systemic pathology, whereas the OSCC group only included untreated cases. Those with a history of cancer (radiation, chemotherapy, or surgery); autoimmune or chronic inflammatory diseases; salivary gland diseases; and tobacco use, smoking, or betel nut use within two hours before saliva collection was excluded. A structured questionnaire that had been pre-made was used to collect data. Demographic information like age and sex as well as behavioral risk factors like tobacco use, chewing betel nut, and snuff consumption were among the data that were documented. OSCC patients' clinical data was recorded using the tumor–node–metastasis (TNM) classification system. The World Health Organization's (WHO) classification criteria were followed when histopathological grading the tumors.

To minimize diurnal variations in salivary composition, unstimulated whole saliva was collected between 8:00 and 10:00 a.m. For a minimum of one hour prior to collection, participants were advised to refrain from eating, drinking, or engaging in any oral hygiene activities. Saliva was collected using the passive drooling technique, which involves allowing at least 2 mL of saliva to accumulate in sterile polypropylene tubes, after participants rinsed their mouths with water to remove any remaining debris. The samples were immediately placed on ice and transported to the laboratory for processing. To eliminate cellular debris, samples were centrifuged in the lab at 3000 × g for 10 minutes at 4°C. Before being subjected to biochemical analysis, the clarified supernatants were aliquoted into sterile microtubes and kept at -80°C. ELISA kits (Medix Biochemica) were used to quantify the biomarkers interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), and cytokeratin fragment 21-1 (CYFRA 21-1). The optical densities were measured using a microplate reader at the recommended wavelengths, and concentrations were calculated from the standard curves generated for each biomarker. Results were expressed in pg/mL for IL-6 and in ng/mL for MMP-9 and CYFRA 21-1.

Data was analyzed using Statistical Package for the Social Sciences (SPSS) software version 24. The normality of distribution for continuous variables was assessed using the Shapiro–Wilk test. Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-parametric data. Comparisons between OSCC and control groups were performed using independent t-tests or Mann–

Whitney U tests, as appropriate. For multiple group comparisons based on tumor stage or grade, analysis of variance (ANOVA) or the Kruskal–Wallis test was applied, followed by relevant post hoc tests. The Pearson's or Spearman's correlation coefficients were used to assess the relationships between biomarker levels and clinical factors like tumor stage and histological grade. The diagnostic performance of each biomarker, including the area under the curve (AUC), ideal cutoff values (based on the Youden index), sensitivity, and specificity, was assessed using Receiver Operating Characteristic (ROC) curve analysis. In addition, a logistic regression model was built to assess the combined diagnostic accuracy of CYFRA 21-1, MMP-9, and IL-6. To evaluate the increase in diagnostic efficiency, the ROC curves of this combined panel and individual biomarkers were compared. Throughout the investigation, a p-value of less than 0.05 was regarded as statistically significant.

RESULTS

The study included 60 participants, 30 of whom had OSCC confirmed by biopsy and 30 of whom were healthy controls. OSCC patients were 52 ± 10.4 years old on average, whereas controls were 50 ± 9.8 years old. There was no statistically significant difference between the two groups ($p = 0.68$). Male-to-female ratios in both groups were equal (18:12), indicating successful sex-matching. Yet, with a highly significant p-value (<0.001), the prevalence of tobacco or betel nut use was significantly higher among OSCC patients (80%) than among controls (13%). The tongue accounted for 40 percent of OSCC patients' tumors, with the buccal mucosa (26.7%), floor of the mouth (16.7%), and other sites (16.7%) following closely behind. Clinically, 13.3% of patients were in Stage I, 26.7% were in Stage II, 33.3% were in Stage III, and 26.7% were in Stage IV. 33.3% of patients had good histological differentiation, 46.7% had moderate differentiation, and 20% had poor differentiation as shown in table 1.

Table 1-Study Participants' Demographic and Clinical Features

Characteristic	OSCC Patients (n = 30)	Controls (n = 30)	p-value
Age (years, mean ± SD)	52 ± 10.4	50 ± 9.8	0.68
Gender (male: female)	18: 12	18: 12	—
Tobacco/betel habit (%)	24/30 (80%)	4/30 (13%)	< 0.001
Tumor site	Tongue: 12, Buccal mucosa: 8, Floor of mouth: 5, Others: 5	—	—
Clinical stage (TNM)	Stage I: 4; II: 8; III: 10; IV: 8	—	—
Histological grade	Well differentiated: 10; Moderately: 14; Poorly: 6	—	—

OSCC patients had significantly higher mean salivary concentrations of IL-6, MMP-9, and CYFRA 21-1 than controls. In OSCC cases, IL-6 levels were almost five times higher (85.4 ± 24.7 pg/mL) than in controls (18.6 ± 7.8 pg/mL). These findings are shown in Table 2, which shows that all three biomarkers have a high capacity for discrimination.

Table 2- The levels of salivary biomarkers in OSCC patients and controls

Biomarker	OSCC (mean ± SD)	Controls (mean ± SD)	p-value
IL-6 (pg/mL)	85.4 ± 24.7	18.6 ± 7.8	<0.001
MMP-9 (ng/mL)	298.2 ± 85.3	112.4 ± 40.1	<0.001
CYFRA 21-1 (ng/mL)	5.92 ± 1.95	1.45 ± 0.65	<0.001

Salivary concentrations were examined based on TNM stage and histological grade to investigate the connection between biomarker levels and disease severity. Table 3 illustrates how CYFRA 21-1, MMP-9, and IL-6 levels gradually rose as the tumor stage advanced. For all three markers, the highest mean concentrations were found in Stage IV patients. Likewise, as histological differentiation deteriorated, biomarker levels increased, peaking in tumors with poorer differentiation. A significant increase in IL-6 ($p < 0.01$), MMP-9 ($p = 0.03$), and CYFRA 21-1 ($p = 0.02$) was found by trend analysis. CYFRA 21-1 also showed a positive correlation with stage ($\rho = 0.48$, $p = 0.006$), while IL-6 showed a positive correlation with both stage ($\rho = 0.52$, $p = 0.004$) and grade ($\rho = 0.46$, $p = 0.01$), according to correlation analysis. The correlation for MMP-9 was lower ($\rho = 0.38$, $p = 0.06$).

Table 3-Levels of Biomarkers by Histological Grade and Tumor Stage

Parameter	IL-6 (pg/mL)	MMP-9 (ng/mL)	CYFRA 21-1 (ng/mL)
By TNM stage			
Parameter	**IL-6 (pg/mL)**	**MMP-9 (ng/mL)**	**CYFRA 21-1 (ng/mL)**
Stage I/II (n = 12)	62.1 ± 15.8	235.5 ± 60.2	4.20 ± 1.1
Stage III (n = 10)	89.8 ± 20.5	298.7 ± 79.4	6.12 ± 1.6
Stage IV (n = 8)	115.7 ± 25.4	360.3 ± 91.7	7.85 ± 2.0
p (trend)	<0.01	0.03	0.02
By histological grade			
Well differentiated (n = 10)	72.5 ± 18.2	260.4 ± 68.3	5.10 ± 1.3
Moderately (n = 14)	88.6 ± 22.7	305.2 ± 82.1	6.05 ± 1.7
Poorly (n = 6)	105.3 ± 28.0	342.3 ± 95.4	7.30 ± 2.1
p (ANOVA)	0.04	0.08	0.03

Receiver Operating Characteristic (ROC) analysis was done for each biomarker separately and in combination to evaluate diagnostic accuracy. Table 4 indicates that IL-6 had the highest individual AUC (0.91), closely followed by MMP-9 (0.88), and CYFRA 21-1 (0.89). For IL-6, CYFRA 21-1, and MMP-9, the ideal cutoff values, as established by the Youden index, produced sensitivities of 83.3%, 85.0%, and 80.0%, respectively, with matching specificities ranging from 80% to 86.7%. With an AUC of 0.96, sensitivity of 90.0%, and specificity of 93.3%, a logistic regression model that combined all three biomarkers yielded improved diagnostic performance. The potential of this combined biomarker panel as a reliable, non-invasive diagnostic tool for OSCC detection was highlighted by the fact that it performed better than anyone marker alone.

Table 4-Individual and Combined Biomarker Diagnostic Accuracy

Biomarker / Panel	AUC	Cutoff	Sensitivity (%)	Specificity (%)
IL-6	0.91	45.0 pg/mL	83.3	86.7
MMP-9	0.88	180.0 ng/mL	80.0	83.3
CYFRA 21-1	0.89	3.2 ng/mL	85.0	80.0
Combined Panel (IL-6 + MMP-9 + CYFRA)	0.96	–	90.0	93.3

The paragraph explaining MMP-9 function is too detailed. Can you add more on the study's implications instead?
12. Highlight clinical applicability with statements such as
"These results support the use of salivary biomarker panels as non-invasive adjuncts for OSCC screening in community dental settings."
13. Add a paragraph on why IL-6 and CYFRA 21-1 correlate more strongly with stage and grade.

DISCUSSION

The study examines salivary IL-6, MMP-9, and CYFRA 21-1 as diagnostic biomarkers in OSCC and presents the first data from a Mardan (BKMC/BKCD) cohort. The findings align with previously reported data from other populations matching the observations to a Pakistani cohort. The study found that OSCC patients had a significantly higher mean salivary IL-6 level (~85 pg/mL) than controls (~18 pg/mL, $p < 0.001$). According to meta-analytic data, salivary IL-6 is elevated in OSCC, with a pooled mean difference of approximately 122 pg/mL (15). Salivary IL-6 had a high discriminatory ability (AUC = 0.982), according to a recent Indian study, and levels increased as tumor aggressiveness increased (16). The findings also showed a significant association between IL-6 and tumor grade and stage, indicating that salivary IL-6 may reflect changes in the local inflammatory microenvironment and tumor burden. According to biology, IL-6 is a proinflammatory cytokine that is generated by tumors and stromal cells. It promotes angiogenesis, cell division, and apoptosis, all of which support tumor growth and immune evasion (17). Furthermore, IL-6 can promote proliferation and malignancy (i.e., an oncogenic role) in OSCC by activating the JAK2/STAT3/Sox4/NLRP3 inflammasome pathway (18). About MMP-9, the mean salivary level in OSCC (~298 ng/mL) was significantly higher than that of controls (~112 ng/mL, $p < 0.001$). This supports earlier findings that MMP-9 is elevated in oral potentially malignant disorders (OPMDs) and OSCC (19).The study had a significantly higher salivary CYFRA 21-1 level (~5.9

ng/mL) than the controls (~1.45 ng/mL, $p < 0.001$) (8).In a Pakistani study, salivary CYFRA 21-1 and MMP-9 levels were higher and correlated with habit duration and histological grade (19). Along with CA125 and TPA, the early classic study by St. John et al. reported that salivary CYFRA 21-1 increased by approximately 400% in patients with oral cancer (12). In our cohort, CYFRA 21-1 levels were significantly associated with poorer differentiation and higher stage ($p = 0.02$), indicating that more advanced disease is associated with increased cytokeratin fragment shedding and epithelial damage.

ROC analyses were used to evaluate diagnostic performance. With AUCs ranging from 0.88 to 0.91, CYFRA 21-1, MMP-9, and IL-6 each demonstrated strong discriminatory power. These results are consistent with the literature, which lists MMP-9 and IL-6 as two of the most promising salivary biomarkers for OSCC. In diverse populations, however, a single marker might not be enough to provide strong sensitivity and specificity. To increase diagnostic accuracy, a few authors recommend combining biomarkers (20). Salivary biomarker panels are non-invasive adjuncts for OSCC screening particularly in low-resource areas, according to these results. Early identification of high-risk individuals through routine screening with salivary IL-6, MMP-9, and CYFRA 21-1 may enable timely biopsy and intervention (21). This study has limitations such as sample size ($n = 30$ per group) is moderate and may limit the power of subgroup (stage/grade) comparisons. The cross-sectional design precludes assessment of longitudinal biomarker dynamics or prognostic utility. Being a single-center study, generalizability to other populations is constrained. Additionally, confounding factors such as subclinical oral inflammation, periodontal disease, or minor mucosal lesions unaccounted for here could influence salivary biomarker levels. Finally, post-treatment or serial sampling to examine biomarker decline or recurrence monitoring was not included. Despite these limitations, the findings support the feasibility of using salivary IL-6, MMP-9, and CYFRA 21-1 as a noninvasive biomarker panel for early OSCC detection, particularly in resource-constrained regions such as Mardan. Future studies should involve larger, multicenter cohorts, longitudinal follow-up (pre- and post-treatment), inclusion of additional salivary markers (e.g. IL-8, TNF-α, CD44, microRNAs) for panel refinement, and development of standardized protocols for saliva collection, storage, and low-cost point-of-care assays.

CONCLUSION

The study concluded that this comparative study in a Mardan population showed that OSCC patients had significantly higher salivary levels of CYFRA 21-1, MMP-9, and IL-6 than healthy controls. The stage and grade of the tumor were associated with CYFRA and IL-6 levels. Each biomarker demonstrated strong diagnostic accuracy when used alone, and a panel of biomarkers improved discriminative performance even more. These findings imply that screening for salivary biomarkers may be a useful noninvasive supplement to early OSCC detection in high-risk populations. Before clinical application, however, more extensive, prospective, multicenter validation is needed.

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