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PJMLS OPEN ACCESS
Print ISSN: 2707-4471. Online ISSN: 2707-448X

Research Article	Pak-Euro Journal of Medical and Life Sciences
DOI: 10.31580/2kybra85	Copyright © All rights are reserved by Corresponding Author
Vol. 8-9 No. Special 3, 2025-26: pp. S37-S44	
www.readersinsight.net/pjmls	**Revised:** November 30, 2025 **Accepted:** December 20, 2025
Submission: July 28, 2025	**Published Online:** December 31, 2025

NON-INVASIVE SALIVARY BIOMARKER PANELS FOR EARLY DETECTION OF ORAL EPITHELIAL DYSPLASIA: NOVEL DIAGNOSTIC INSIGHTS

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Abstract

Oral Epithelial Dysplasia (OED) can be a precancerous alteration of the oral epithelium that may be a precursor to oral squamous cell carcinoma (OSCC). This study assessed the diagnostic accuracy of a salivary biomarker panel for early detection and risk stratification of OED. A cross-sectional study (september 2022 to February 2023) included 120 participants using non-probability consecutive sampling method. Unstimulated saliva samples were collected under standard conditions and tested for a set of markers, including, IL-6, IL-8, MMP-9, LDH, and Cyfra 21-1, by enzyme-linked immunosorbent assay (ELISA). The reference standard was histopathological assessment of the lesions for diagnosis of benign, mild dysplasia, moderate/severe dysplasia and oral squamous cell carcinoma. The data was analysed statistically using SPSS version 26.0. A chi-square testing and logistic regression were used, $p \leq 0.05$ was considered statistically significant. Mean age was 47.9 ± 11.4 years and 61.7% of the study population were male. Histopathological evaluation showed that the diagnosis of OED was confirmed in 39.2% while the diagnosis of oral squamous cell carcinoma was confirmed in 18.3% of the cases. Salivary levels of IL-6, IL-8, MMP-9, LDH and Cyfra 21-1 significantly rose with the severity of the histopathology ($p<0.001$). An association between high-risk salivary biomarker profiles and moderate to severe dysplasia and malignant transformation was found ($\chi^2=29.84$, $p<0.001$). The combined panel yielded sensitivity 89.2% (95% CI: 82.4–94.1), specificity 84.6% (95% CI: 76.3–91.0), and AUC 0.91 (95% CI: 0.86–0.95). The combined salivary biomarker panel demonstrated high diagnostic accuracy for identifying OED and distinguishing high-risk lesions from benign oral mucosal conditions.

Keywords: *IL-6, IL-8, Matrix metalloproteinase-9, Oral epithelial dysplasia, Oral cancer screening, Salivary biomarkers*

INTRODUCTION

Oral epithelial dysplasia (OED) is a histopathological diagnosis that is marked by changes in architecture and cytology of the oral epithelium, and is well recognized as a precancerous condition for oral squamous cell carcinoma (OSCC) (1, 2). The severity of epithelial dysplasia is one of the best indicators for the risk of malignant transformation with more severe dysplasia being linked to a higher risk for progression to invasive carcinoma (3). Although there are improvements in the management of oral cancers, delayed diagnosis is a very significant problem and is a major cause of morbidity, mortality, and health care burden globally.

The use of saliva has evolved as a useful diagnostic biofluid to be collected easily, without needles, in a cost-effective manner, and that can reflect local and systemic pathological changes (4). Because saliva is in direct contact with oral lesions, it may offer enriched local biomarker concentrations. Salivary diagnostics have been a major part of the focus in oral medicine since saliva contains a variety of proteins, cytokines, enzymes, metabolites and nucleic acids that are potential biomarkers of disease progression (5).

A few studies have shown changes in inflammatory and tumor-associated markers in the patients with oral potentially malignant disorders (OPMDs) and oral cancer. The salivary markers most thoroughly

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studied include interleukins and matrix metalloproteinases. Pro-inflammatory cytokines such as IL-6 and IL-8 have been associated with chronic inflammation, angiogenesis and tumor progression (6). MMP-9 may be involved in extracellular matrix degradation and tissue invasion; LDH is an indicator of cell metabolism changes and tissue damage (7, 8). A soluble Cyfra 21-1 has been linked to epithelial dysplasia and malignant transformation in several epithelial cancers (9, 10).

While multiplex salivary panels have been explored for OSCC, most studies focus on advanced disease or single markers. Limited data exist on an integrated panel covering the full spectrum from benign lesions through mild/moderate/severe dysplasia to early OSCC, a gap this study addresses. The objective of the present study was to assess the use of a non-invasive salivary biomarker panel (IL-6, IL-8, MMP-9, LDH and Cyfra 21-1) for detecting and risk stratifying OED, with the histopathology results used as the reference standard.

METHODOLOGY

STUDY DESIGN AND SETTING

A cross-sectional analytical study was carried out in the department of Oral Medicine of a tertiary care teaching hospital. Recruitment and data collection were completed over six months at a single tertiary care center; sample processing and analysis continued for an additional four months. The aim of this study was to assess the potential of a non-invasive salivary biomarker panel that includes IL-6, interleukin-8 IL-8, matrix MMP-9, LDH and Cyfra 21-1 for the early detection of OED. The institutional review board approved all ethical aspects prior to the start of the study. One hundred and twenty individuals (with ages 18 years and above) with clinically suspicious oral mucosal lesions were recruited using non-probability consecutive sampling of 120 participants.

INCLUSION AND EXCLUSION CRITERIA

Adults ≥18 years with clinically suspicious oral lesions were included. The following were excluded from the study: patients who had received treatment for oral cancers, patients with ongoing systemic inflammatory diseases, patients with autoimmune diseases, patients with severe systemic illness, and patients who were taking a systemic immunosuppressive medication. After informed consent, demographic and clinical data such as age, gender, history of tobacco use, location of lesions, duration of the lesions and appropriate medical history were obtained on a proforma.

DATA COLLECTION AND CLINICAL EXAMINATION

An intraoral examination was done comprehensively by well-experienced oral medicine specialists in a standardized clinical setting. Incisional or excisional biopsy determined by clinical situation was performed on lesions that were suspicious for dysplasia. The reference standard method was histopathological evaluation, and the lesions were graded as benign lesions, mild dysplasia, moderate dysplasia, severe dysplasia and early OSCC. Histopathologists were blinded to biomarker results and clinical data.

Tissue biopsy specimens were fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin wax. Sections of 4–5 μm thickness were prepared using a rotary microtome and stained with hematoxylin and eosin (H&E) stain (Sigma-Aldrich, St. Louis, MO, USA). Histopathological grading was performed independently by two experienced oral pathologists according to the World Health Organization (WHO) criteria for oral epithelial dysplasia and oral squamous cell carcinoma, and any diagnostic discrepancies were resolved by consensus review.

SAMPLE COLLECTION AND PROCESSING

Whole saliva (unstimulated) was gathered during a 4-hour overnight fast, between 09:00 AM and 11:00 A.M. Also, participants were instructed not to eat, drink (except water) or smoke tobacco products for at least one hour prior to the collection. The saliva samples were centrifuged for 15 minutes at 3000 rpm and then kept in a refrigerator at −80°C until analyzed. Commercial enzyme-linked immunosorbent assay (ELISA)

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kits (Elabscience Biotechnology Inc, Wuhan, China) were used to measure the concentration of IL-6, IL-8, MMP-9, LDH and Cyfra 21-1, according to the manufacturer's instructions.

STATISTICAL ANALYSIS

The data were analyzed with a statistical package for social sciences (SPSS) version 26.0. Continuous variables were summarized as mean ± standard deviation and categorical variables as frequencies and percentages. One way Analysis of Variance (ANOVA) and Chi-square tests were used for appropriate comparisons between groups. To determine independent predictors of moderate to severe dysplasia and early OSCC, multivariate logistic regression analysis was used. The diagnostic value of the combined salivary biomarker panel was evaluated using receiver operating characteristic (ROC) curve analysis. A p-value of ≤0.05 was considered statistically significant.

RESULTS

In total, 120 patients whose oral mucosal lesions had shown a clinical suspicion were included in the study. Histopathological findings revealed benign lesions, different grades of OED and early OSCC. Salivary biomarker analysis showed progressive increase in the concentration of biomarkers with increasing histopathology. The salivary biomarker risk profiles showed significant associations with the dysplastic progression, suggesting that they could be useful for early diagnosis and risk assessment. Tobacco exposure exposure was reported by 65.8% of participants as mentioned in Table I and the majority of the participants were in the age group (41-60 years). Histopathological evaluation showed that 59.2% of the lesions had various types of OED and 13.3% were diagnosed as early OSCC.

Table I. Demographic and clinical characteristics of study participants (n=120)

Variable s	Category	Frequency (n)	Percentage (%)
Age group (Years)	20-40	35	29.2
	41-60	57	47.5
	> 60	28	23.3
Gender	Male	74	61.7
	Female	46	38.3
Tobacco use	Yes	79	65.8
	No	41	34.2
Histopathological Diagnosis	Benign lesions	33	27.5
	Mild dysplasia	24	20.0
	Moderate dysplasia	23	19.2
	Severe dysplasia	24	20.0
	Early OSCC	16	113.3

All evaluated salivary biomarkers demonstrated a statistically significant increase with worsening histopathological severity ($p<0.001$). The highest concentrations of IL-6, IL-8, MMP-9, LDH, and Cyfra 21-1 were observed in patients with early OSCC, indicating progressive molecular alterations during oral carcinogenesis (Table II).

Table II. Salivary biomarker levels according to histopathological severity

Biomarker	Benign lesions Mean ±SD	Mild dysplasia Mean ±SD	Moderate/Sever e dysplasia Mean ±SD	Early OSCC Mean ±SD	P-value
IL-6 (pg/mL)	3.2±1.1	5.4±1.5	8.1±2.0	11.5±2.6	<0.001
IL-8 (pg/mL)	22.8±5.6	35.7±7.1	54.6±10.3	76.4±12.8	<0.001
MMP-9 (ng/mL)	118±25	186±34	259±45	348±58	<0.001
LDH (U/L)	182±39	255±48	341±56	442±71	<0.001
Cyfra 21-1 (ng/mL)	1.2±0.4	2.0±0.6	3.4±0.8	5.1±1.2	<0.001

A highly significant association was observed between salivary biomarker risk categories and histopathological severity ($\chi^2=34.82$, $p<0.001$). High-risk biomarker profiles were predominantly associated with moderate-to-severe dysplasia and early OSCC, supporting the prognostic relevance of salivary biomarker stratification, as described in Table III.

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Table III. Association between salivary biomarker risk categories and histopathological severity (n=120)

Biomarker risk category	Benign/Mild dysplasia (n)	Moderate/ Severe dysplasia (n)	Early OSCC (n)	χ^2 (df)	p-value
Low Risk	36	6	1	34.82(4)	<0.001
Intermediate Risk	18	24	5		
High Risk	3	17	10		

The combined salivary biomarker panel demonstrated excellent diagnostic performance for identifying OED as represented in Table IV. Sensitivity and specificity were 89.2% and 84.6%, respectively, while ROC analysis produced an AUC of 0.91, indicating outstanding discriminatory ability for distinguishing dysplastic lesions from benign oral conditions.

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Table IV. Diagnostic performance of combined salivary biomarker panel for detection of oral epithelial dysplasia

Diagnostic parameters	Value (%)	95% Confidence interval
Sensitivity	82.2	82.4-94.1
Specificity	84.6	76.3-91.0
Positive Predictive value (PPV)	86.9	79.7-92.5
Negative Predictive value (NPV)	87.5	80.2-93.1
Area Under Curve (AUC)	0.91	0.86-0.95

Fig. 1 presents representative hematoxylin and eosin (H&E)-stained histopathological images (100X) demonstrating progressive epithelial alterations from benign oral mucosa to early oral squamous cell carcinoma (OSCC). Panel A shows normal epithelial maturation without atypia. Panel B demonstrates mild dysplasia characterized by minimal architectural disturbance and basal cell atypia. Panel C depicts moderate-to-severe dysplasia with loss of epithelial polarity and increased nuclear pleomorphism. Panel D illustrates early OSCC showing invasive epithelial nests, keratin pearl formation, and stromal invasion.

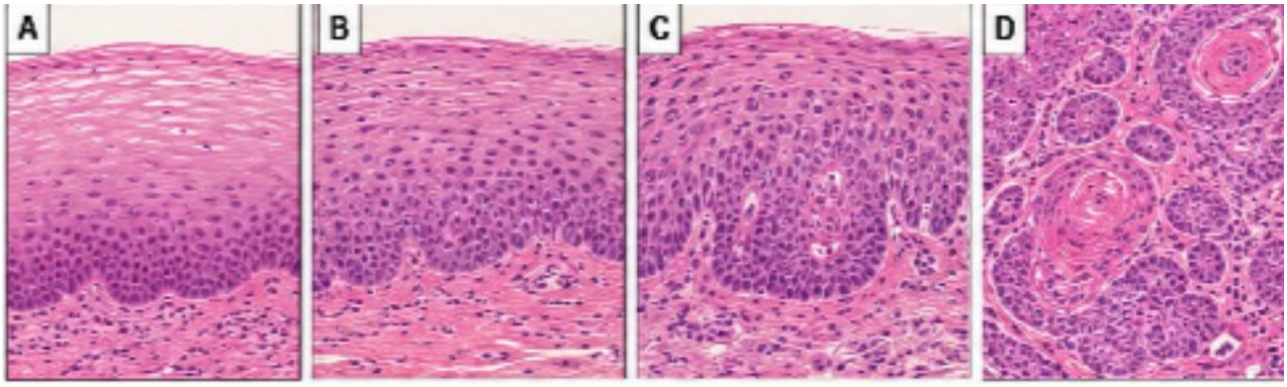

Fig. 1. Histopathological evaluation of oral epithelial dysplasia

Multivariate analysis identified elevated Cyfra 21-1, MMP-9, and IL-6 levels as independent predictors of advanced dysplasia and early OSCC, as presented in Table V. Tobacco use also demonstrated a significant association with disease progression. Cyfra 21-1 exhibited the strongest predictive value (OR=4.18, p<0.001), suggesting its potential role as a key biomarker in non-invasive oral cancer risk assessment.

Table V. Multivariate logistic regression analysis for predictors of moderate-to-severe dysplasia and early OSCC

Variable	Adjusted OR	95% CI	p-value
Elevated IL-6	3.21	1.58–6.51	0.001
Elevated IL-8	2.84	1.41–5.73	0.003
Elevated MMP-9	3.75	1.86–7.54	<0.001
Elevated LDH	2.46	1.19–5.10	0.015
Elevated Cyfra 21-1	4.18	2.02–8.66	<0.001
Tobacco Use	2.69	1.28–5.64	0.008

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DISCUSSION

The current study aimed to assess the diagnostic value of a non-invasive salivary marker panel (IL-6, IL-8, MMP-9, LDH and Cyfra 21-1) for early detection and risk stratification of OED. All five biomarkers increased in a step-wise manner from benign lesions to early OSCC, which is evidence of the biological continuum of oral carcinogenesis ($p<0.001$ for all). The risk category analysis showed significant correlation between moderate/severe dysplasia and early OSCC with close association of high-risk biomarker profiles ($\chi^2 = 34.82$, $p < 0.001$), supporting the possibility of using this panel for risk triage. Cyfra 21-1 (OR = 4.18), MMP-9 (OR = 3.75) and IL-6 (OR = 3.21) were the best independent markers of advanced dysplasia and early malignancy, with Cyfra 21-1 being the best.

The results obtained in this study are in close agreement with the earlier studies. Increased salivary IL-6 and IL-8 has been consistently reported in OED and OSCC (11). Measurement of salivary IL-6 and IL-8 was found to be a good indicator of the grade of oral dysplasia in a study, suggesting that these cytokines are pro-inflammatory molecules that might help the progression of the tumour (12, 13). In another study, extracellular matrix remodelling was found to be essential for invasion and MMP-9 was shown to be significantly upregulated in OPSMDs and OSCC (14-16).

Regarding LDH, our observation of stepwise increases with histopathological severity echoes previous work reporting that salivary LDH is a sensitive indicator of cellular damage and metabolic shift in oral precancer and cancer (17,18,19). According to this study, Cyfra 21-1 is the strongest predictor of advanced dysplasia (OR = 4.18), it is consistent with the recent meta-analysis that synthesized evidence that Cyfra 21-1 and other cytokeratins are reliable markers of malignant transformation in oral leukoplakia (20, 21). In addition, a systematic review was conducted on liquid biopsy in cancer monitoring and revealed that multi-analyte panels, including Cyfra 21-1, are better in detecting oral cancer than single markers (22, 23).

The high combined sensitivity (89.2%) and specificity (84.6%) of our panel compare favorably with those reported in a study evaluating salivary α-amylase and associated enzymes, which emphasized the need for multiplex panels to improve diagnostic accuracy (24,25). The AUC (0.91) reflects excellent discriminatory power, similar to findings from a recent systematic review on molecular inflammatory and angiogenic pathways, which also highlighted the value of multiple biomarkers (26, 27). Finally, the independent association of tobacco use with disease progression (OR = 2.69, $p = 0.008$) corroborates large-scale evidence linking chronic tobacco exposure to oral carcinogenesis, as discussed in the context of the tumor microenvironment (28-30). It should be noted that not all previous studies used identical cutoffs or saliva collection methods, which may limit direct comparisons.

This study has several notable strengths. First, the use of histopathology as the reference standard provides a robust gold-standard comparison. Second, the inclusion of a well-characterized cohort across the entire spectrum from benign lesions to early OSCC allows assessment of biomarkers in a clinically relevant continuum. Third, by co-assessing five molecules with different mechanisms of action (cytokines, protease, metabolic enzyme and cytokeratin fragment) offers a comprehensive molecular profile. Fourth, pre-analytical variability is minimized as unstimulated whole saliva was collected under standardized conditions.

Several limitations must be acknowledged. As this is a cross-sectional study it cannot determine causality and/or the temporal course of the change in biomarkers. Although the sample size (n = 120) was sufficient for initial analysis, may limit generalizability; external validation in larger, multi-center cohorts is needed. Moreover, there was no analysis of the biomarker level in healthy controls free of oral lesions to help further delineate the normal range. The study took place in a single tertiary level health training institution, which may have restricted usability to primary care or community care. Furthermore, we did not include healthy controls without any oral lesions, so the reference range in completely asymptomatic individuals remains unknown. Test-retest reliability was not assessed. Lastly, this study does not include a cost-effectiveness analysis, which would be required before population screening.

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CONCLUSION

This study demonstrates that a combined salivary biomarker panel of IL-6, IL-8, MMP-9, LDH, and Cyfra 21-1 offers high diagnostic accuracy (AUC = 0.91, sensitivity 89.2%, specificity 84.6%) for early detection and risk stratification of OED. Cyfra 21-1 and MMP-9 emerged as the strongest independent predictors of advanced dysplasia and early OSCC. This combined salivary biomarker panel demonstrates promising diagnostic accuracy for detecting OED and stratifying high-risk lesions. Cyfra 21-1 and MMP-9 are independent predictors of advanced dysplasia. However, this panel is an adjunctive tool and cannot replace histopathology. Prospective multi-center validation and cost-effectiveness studies are required before clinical implementation.

Funding:

All expenses related to this research were personally borne by the student. No external funding or financial support was received for this study.

Conflict of interest:

Authors declared no conflict of interest.

Author s' contributions:

WAR Conducted the experiments, data collection and write up; MA Conceptualized and supervised the study; ME Result analysis.

Declaration of generative AI-Assisted Tools:

Authors declared that no AI-assisted tools were used.

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