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Original Research Article

To Establish the Role of IL8 and LDH Biomarkers in Saliva for the Diagnosis of Oral Malignancy

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Abstract

Background: Oral squamous cell carcinoma is frequently diagnosed at an advanced stage, creating a need for reliable, non-invasive biomarkers capable of identifying malignant transformation and reflecting disease severity. Salivary interleukin-8 (IL-8) and lactate dehydrogenase (LDH) may indicate tumour-associated inflammation, cellular injury, and metabolic activity.

Objectives: To compare salivary IL-8 and LDH levels among healthy individuals, patients with oral potentially malignant disorders (OPMD), and patients with oral squamous cell carcinoma (OSCC); evaluate their diagnostic accuracy; and assess their correlation with TNM stage.

Materials and Methods: This prospective observational analytical study included 75 participants divided equally into healthy, OPMD, and OSCC groups. Sociodemographic, clinical, habit-related, and histopathological data were recorded. Standardized saliva samples were analysed for IL-8 and LDH using enzyme-linked immunosorbent assay. Statistical analysis included Chi-square test, Welch's one-way ANOVA, receiver operating characteristic curve analysis, and Spearman correlation.

Results: Mean salivary IL-8 levels increased from 15.4 ± 4.38 pg/mL in healthy participants to 52.1 ± 14.86 pg/mL in OPMD and 161.1 ± 42.06 pg/mL in OSCC. Corresponding LDH levels were 200 ± 25.6, 304 ± 56.8, and 519 ± 88.2 U/L, respectively ($p<0.001$). The combination of biomarkers showed 94% sensitivity, 90% specificity and AUC of 0.94. IL-8 and LDH were highly correlated with TNM stage ($\rho=0.72$ and $\rho=0.75$; $p<0.001$).

Conclusion: Salivary IL-8 and LDH are promising non-invasive adjunctive biomarkers for detection of oral malignancy, for differentiating OPMD from OSCC and for monitoring disease progression.

Keywords: Saliva; IL-8; Lactate Dehydrogenase; Oral Potentially Malignant Disorders; Oral Squamous Cell Carcinoma; Biomarkers.

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Introduction

The oral cavity is lined by stratified squamous epithelium and is continually exposed to carcinogens. Saliva contains enzymes, cytokines and metabolites; its contact with mucosal lesions and non-invasive collection make it suitable for biomarker assessment. In a 40-participant study of tobacco users without lesions, leukoplakia, oral submucous fibrosis and oral squamous cell carcinoma (OSCC), salivary IL-8 and LDH increased progressively and were highest in OSCC.

[1] OSCC is the predominant oral malignancy and may arise from oral potentially malignant disorders (OPMDs). Its burden is relevant in India because tobacco and areca-nut exposure remain common. A meta-analysis found significantly higher salivary IL-6, IL-8, TNF-α and LDH in OSCC than in healthy controls. [2] An Indian validation study found elevated salivary IL-8 in OSCC, with stronger discrimination for late-stage disease, although OPMDs were not reliably separated from controls. [3] Histopathology remains definitive but is invasive and unsuitable for repeated screening. LDH, released after cellular disintegration, may reflect tissue injury and tumour metabolism. A meta-analysis of 13 case–control studies involving 755 participants found higher salivary LDH in oral cancer than in controls and oral leukoplakia, but emphasized heterogeneity and the need for standardized cut-offs. [4] A later meta-analysis confirmed higher LDH in oral cancer than in controls and OPMDs, with greater levels in poorly differentiated tumours. [5] Indian research evaluated serum and salivary LDH with uric acid as a combined diagnostic profile in OSCC. [6] Another case–control study reported elevated salivary LDH and MMP-9 in OSCC compared with controls. [7]

A network meta-analysis of 40 studies including 1,280 oral-cancer patients and 1,254 controls found elevated salivary IL-8, IL-6, TNF-α, IL-1β and IL-10; IL-8 showed 80% sensitivity and 80% specificity, whereas TNF-α had the highest diagnostic accuracy. [8] Optical and electrochemical point-of-care platforms may facilitate rapid IL-8 detection, although clinical translation remains challenging. [8] A study assessing 23 salivary biochemical parameters in 68 OSCC patients, 50 patients with non-cancerous oral disease and 114 healthy volunteers found combinations more informative than single parameters; prognostic significance was linked to malondialdehyde and the salivary Na/K ratio. [10] These findings support evaluating combined salivary IL-8 and LDH for non-invasive diagnosis and prognostic assessment in an Indian tertiary-care population.

Material and Methods

Study Design: A prospective observational analytical study was conducted to assess the diagnostic and prognostic utility of salivary IL-8 and LDH in oral malignancy.

Study Setting: The study was undertaken in the Department of Surgery, with participants recruited from outpatient clinics and dental-care centres during the study period.

Study Population and Sample Size: A total of 75 participants were enrolled through convenience sampling and divided equally into three groups:

- **Group A:** 25 healthy individuals without smoking or tobacco-chewing habits
- **Group B:** 25 at-risk individuals with long-term tobacco exposure
- **Group C:** 25 patients with confirmed oral malignancy

Inclusion Criteria: Participants willing to provide informed consent and fulfilling the eligibility criteria of the respective study group were included. Group C comprised patients with histopathologically confirmed carcinoma of the oral cavity.

Exclusion Criteria: Participants with recent oral surgery, systemic inflammatory or infectious diseases, hepatic or haematological disorders, or other conditions likely to influence salivary IL-8 or LDH levels were excluded. Those unable to produce an adequate sample of saliva were also excluded.

Data Collection and Investigations: Sociodemographic details, history of tobacco use, medical history, oral hygiene status and clinical findings were noted in a structured proforma. Oral lesions were measured for size and site. Histopathological confirmation and grading of malignancy was done. Clinical staging was performed based on the TNM classification, and relevant laboratory and radiological investigations.

Saliva collection and laboratory analyses: Unstimulated whole saliva Unstimulated whole saliva was collected in a standardized method and by a standardized collection protocol. Samples were labelled correctly, processed rapidly or stored at low temperatures until analysis. Salivary IL-8 and LDH levels were assessed by enzyme-linked immunosorbent assay with appropriate laboratory quality controls.

Ethical Considerations: The approval of the Institutional ethics committee was obtained. Written informed consent was secured from all participants, and confidentiality of clinical and laboratory data was maintained.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Chi-square test and Welch's one-way ANOVA were applied as appropriate. ROC-curve analysis assessed sensitivity, specificity and area under the curve. Spearman correlation evaluated the relationship of IL-8 and LDH with TNM stage. A p-value <0.05 was considered statistically significant.

Results

Table 1: Comparison of Salivary IL-8 Levels (pg/mL) Across Study Groups (Mean ± SD).

Group	IL-8 Level (pg/mL) (Mean ± SD)	p-value
Group A (Healthy)	15.4 ± 4.38	<0.001
Group B (OPMD)	52.1 ± 14.86	<0.001
Group C (OSCC)	161.1 ± 42.06	<0.001

Statistical test: One-way ANOVA (Welch's test)

A statistically significant, stepwise increase in mean salivary IL-8 levels was observed in the three groups from 15.4 ± 4.38 pg/mL in healthy controls to 52.1 ± 14.86 pg/mL in OPMD and 161.1 ± 42.06 pg/mL in OSCC (Table 1). Welch's ANOVA indicated a significant group difference (p <.001).

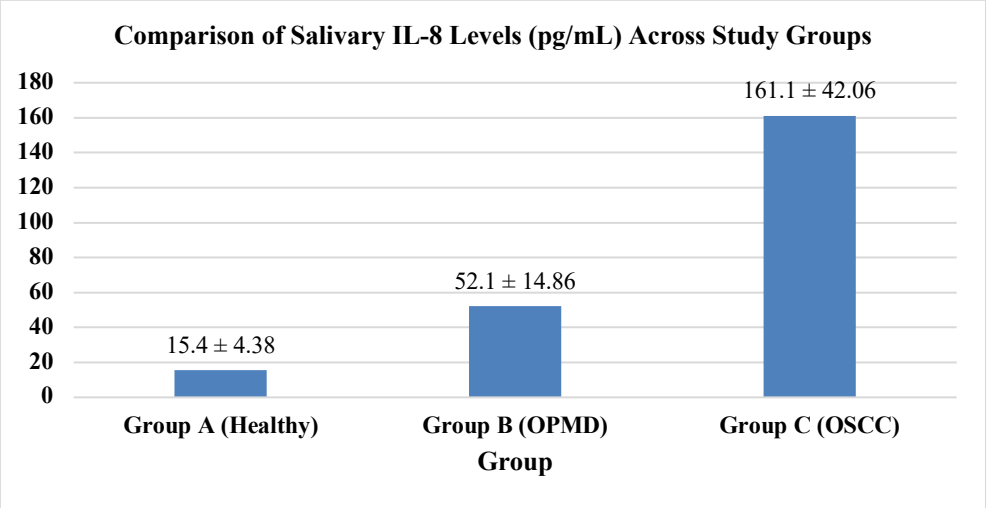

Figure 1: Comparison of Salivary IL-8 Levels (pg/mL) Across Study Groups

Table 2: Comparison of Salivary LDH Levels (U/L) Across Study Groups (Mean ± SD).

Group	LDH Level (U/L) (Mean ± SD)	p-value
Group A (Healthy)	200 ± 25.6	<0.001
Group B (OPMD)	304 ± 56.8	<0.001
Group C (OSCC)	519 ± 88.2	<0.001

Statistical test: One-way ANOVA (Welch's test).

As shown in Table 2, an increasing trend of mean salivary LDH levels from healthy controls (200 ± 25.6 U/L) to OPMD (304 ± 56.8 U/L) and OSCC (519 ± 88.2 U/L) was seen. Higher levels of OSCC are associated with increased cellular damage and metabolic activity with disease progression. A Welch ANOVA showed a significant difference between groups (p < 0.001).

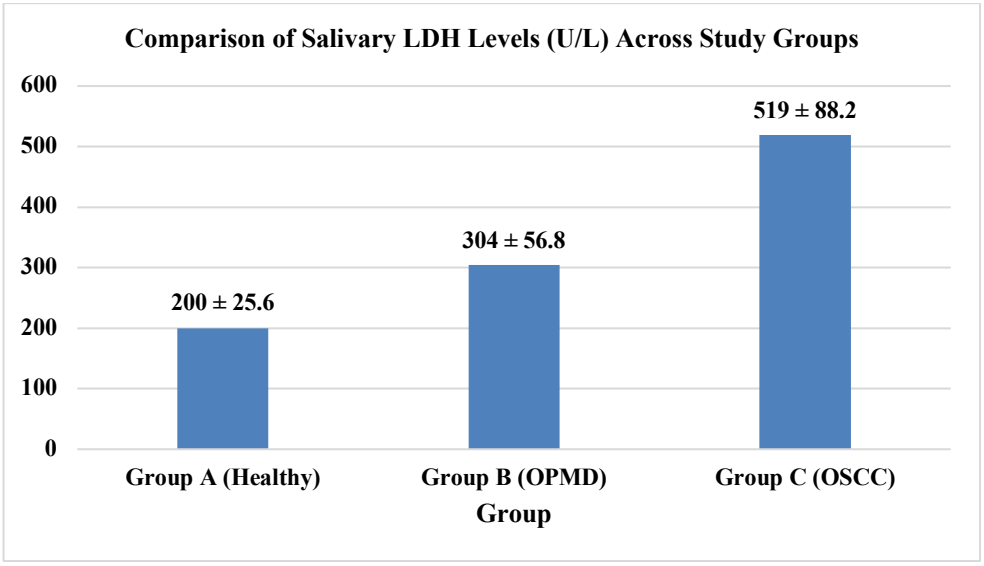

Figure 2: Comparison of Salivary LDH Levels (U/L) Across Study Groups

Table 3: Association of IL-8 Diagnostic Status with Study Groups (n = 75).

IL-8 Diagnostic	Group A (n=25)	Group B (n=25)	Group C (n=25)	Total (n=75)
Negative	25 (100.0%)	13 (52.0%)	0 (0.0%)	38 (50.7%)
Positive	0 (0.0%)	12 (48.0%)	25 (100.0%)	37 (49.3%)
Total	25 (100%)	25 (100%)	25 (100%)	75 (100%)

Statistical test: Chi-square test. P-Value < 0.001.

Table 3. Statistically significant association of IL-8 diagnostic status and study groups ($p < 0.001$). All controls found to be negative for IL-8 and all OSCC cases were found to be positive. 48.0% positive, 52.0% negative (OPMD patients) IL-8 positivity was increased with increasing disease severity.

Table 4: Association of LDH (MNLDH) Diagnostic Result with Study Groups (n = 75).

LDH Diagnostic	Group A (n=25)	Group B (n=25)	Group C (n=25)	Total (n=75)
Negative	25 (100.0%)	13 (52.0%)	0 (0.0%)	38 (50.7%)
Positive	0 (0.0%)	12 (48.0%)	25 (100.0%)	37 (49.3%)
Total	25 (100%)	25 (100%)	25 (100%)	75 (100%)

Statistical test: Chi-square test. P-Value < 0.001.

Table 4 shows statistically significant association between LDH diagnostic status and study groups ($p < 0.001$). All the healthy controls were LDH negative and all the OSCC cases were LDH positive. In OPMD group 48.0% were positive and 52.0% were negative. There was gradual increase in positivity of LDH as the oral disease categories increased.

Table 5: Diagnostic Performance of Salivary Biomarkers (IL-8, LDH, and Combined) for Detection of Oral Disease.

Biomarker	Sensitivity (%)	Specificity (%)	AUC	p-value
IL-8	88.0	84.0	0.89	<0.001
LDH	86.0	82.0	0.87	<0.001
Combined Biomarker	94.0	90.0	0.94	<0.001

Statistical test: ROC curve analysis.

As shown in Table 5 salivary IL-8 and LDH have a good performance for diagnosing oral disease. IL-8 had 88% sensitivity, 84% specificity and AUC of 0.89, while LDH had slightly lower values. The best accuracy was obtained in their combined assessment with 94% sensitivity, 90% specificity and an AUC of 0.94 ($p < 0.001$).

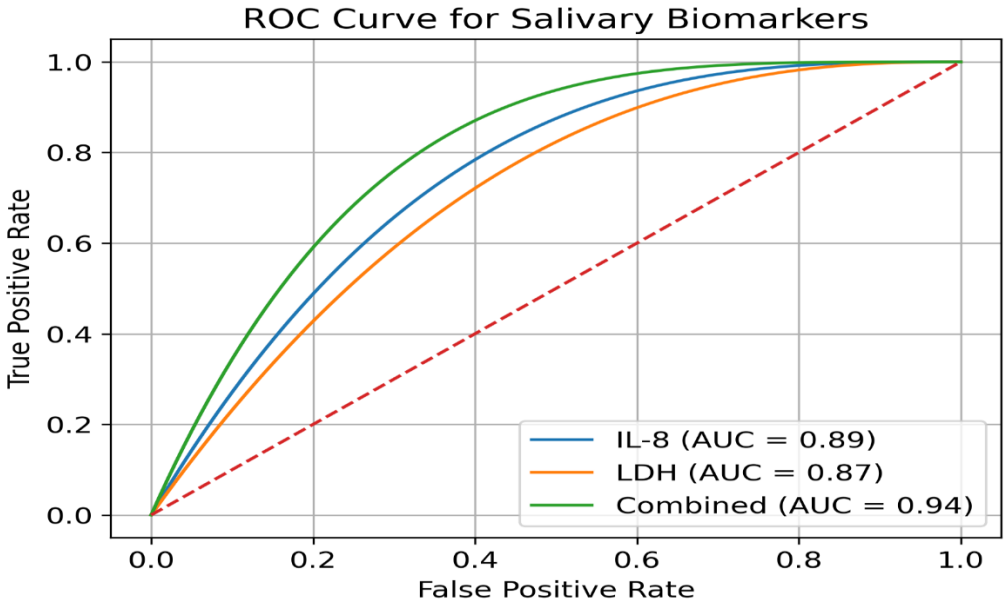

Figure 3: ROC Curve for salivary Biomarkers

Table 6: Spearman Correlation of Biomarkers with TNM Stage (OSCC Group, n = 25)

Variable	Correlation coefficient (ρ)	p-value
IL-8 vs TNM stage	0.72	<0.001
LDH vs TNM stage	0.75	<0.001

Statistical test: Spearman correlation.

Salivary biomarker levels and TNM stage in OSCC patients showed strong statistically significant positive associations (Table 6). IL-8 correlated with $\rho = 0.72$ and LDH correlated slightly higher with $\rho = 0.75$. Both associations were significant ($p < 0.001$) suggesting that the higher the stage of disease, the higher the levels of biomarkers.

Discussion

Intergroup difference was significant. IL-8 levels in saliva of healthy subjects were 15.4±4.38 pg/mL and significantly increased in OPMD (52.1±14.86 pg/mL) and OSCC (161.1±42.06 pg/mL) ($p<0.001$). This is in concordance with the study by Venkatesh et al., (2025) [1] where they reported a linear increase in IL-8 levels with increasing tobacco, OPMD and OSCC exposure and Perry et al., (2023)2 who showed increased levels of IL-8 in OSCC with an effect estimate of 2.20 (95% CI: 0.11-4.30; p=0.04). Oral cancer grew significantly. (Huang et al, 2024) [8]. Singh, et al., (2020) [3] However the reports did not provide directly comparable groupwise mean concentrations.

The salivary LDH of healthy subjects was 200 ± 25.6 U/L, OPMD group was 304 ± 56.8 U/L and OSCC group was 519 ± 88.2 U/L with significant variation amongst the groups ($p<0.001$). Similar progression was reported by Venkatesh et al. [1]. Perry et al. [2] found significantly increased LDH in OSCC with an effect estimate of 8.71 (95% CI: 4.52-12.90; $p<0.0001$), and Iglesias-Velázquez et al. [4] reported an SMD of 9.49 vs controls and 5.62 vs leukoplakia. Owecki et al. (2025) [5] also reported large increases.

In contrast, Bel'skaya et al. (2020) [10] found that no single biochemical marker was independently sufficient for diagnosis.

There was significant association ($p<0.001$) between positivity for IL-8 diagnosis in healthy controls was 0%, OPMD was 48.0% and OSCC was 100.0% while negativity in healthy controls was 100.0%, OPMD was 52.0% and OSCC was 0%. The graded pattern is also consistent with the findings of Venkatesh et al (2025)1 and Singh et al (2020)[3] who noted increased expression of IL-8 in malignant and late stage disease . (As described in Perry et al 2023 [2]. Huang et al. (2024) [8] also showed discrimination of OSCC with 80% sensitivity and specificity for IL-8. The exact categorical distribution observed here was unique. In contrast, Bel'skaya et al. (2020) [10] cautioned that individual salivary markers may be insufficient when used alone. Diagnostic positivity of LDH increased progressively from 0% in healthy controls to 48.0% in OPMD and 100.0% in OSCC and respective negativity decreased from 100.0% in healthy controls to 52.0% in OPMD and 0% in OSCC showing a significant association with disease category ($p<0.001$). Similarly Venkatesh et al (2025) [1] have reported elevation of salivary LDH in tobacco exposed individuals, potentially malignant disorders and OSCC. Oral cancer had higher LDH levels than controls (SMD=9.49; 95% CI: 6.97-12.00; p=0.00001) and leukoplakia (SMD=5.62; 95% CI: 2.14-9.11; p=0.002) [4]. Also large increases in levels were reported by Owecki et al. (2025) 5 and Qasim et al. (2025) [6,7]. However, Bel'skaya et al. (2020) [10] found that no individual biochemical marker was independently adequate for diagnosis.

Salivary IL-8 had a sensitivity of 88.0%, specificity of 84.0% and an area under the curve (AUC) of 0.89 while LDH had a sensitivity of 86.0%, specificity of 82.0% and an AUC of 0.87, all $p<0.001$. The best accuracy was given by the assessment of the two with 94.0% sensitivity, 90.0% specificity and an AUC of 0.94. Huang et al. (2024)8 also had lower values with 80% sensitivity and specificity, for IL-8. The AUC of IL-8 was reported as 0.7619 (Singh et al., 2020) [3] and combined biomarker profile showed diagnostic power of 77% (Anitha et al., 2022) [6]. Bel'skaya et al. (2020) [10] likewise supported biomarker combinations over single-marker assessment.

Salivary IL-8 and LDH showed positive correlation with TNM stage in OSCC patients with strong correlation coefficient ($\rho=0.72$ and $\rho=0.75$ respectively) which are statistically significant ($p<0.001$). Venkatesh et al. (2025) [1] also suggested that the two biomarkers could be markers of progression and prognosis of disease.

IL-8 was better able to distinguish OSCC from controls in late stage disease supporting its association with tumour progression (Singh et al., 2020) [3]. Also Owecki et al (2025) [5] reported higher salivary LDH levels in poorly differentiated tumors compared to well differentiated tumors suggesting association with aggressive disease. Bel'skaya et al. (2020) [10] demonstrated prognostic value for combined salivary biochemical profiles, although no individual parameter was independently sufficient. The exact Spearman coefficients observed here were not reported in these comparator studies.

Conclusion

The results show a gradual increase in salivary IL-8 and LDH levels from healthy individuals to patients with oral potentially malignant disorders and oral squamous cell carcinoma indicating their close association with malignant transformation and tumor burden. IL-8 increased from 15.4 to 52.1 and 161.1 pg/mL. LDH increased from 200 to 304

and 519 U/L respectively. Significant differences were found between the groups ($p<0.001$).

Both biomarkers showed good diagnostic utility but the best result was obtained when evaluated together showing sensitivity of 94%, specificity of 90% and AUC of 0.94. Furthermore, IL-8 ($\rho=0.72$) and LDH ($\rho=0.75$) were significantly and positively correlated with TNM stage, supporting their prognostic significance in OSCC. Our findings support the utility of salivary IL-8 and LDH as a practical, non-invasive adjunct for early detection, risk stratification and monitoring of disease, especially in tobacco-exposed individuals on follow-up for oral lesions. Histopathological confirmation should continue to be the gold standard for definitive diagnosis and treatment planning.

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