Correlation Between Tumour Size (T) and Salivary Lactate Dehydrogenase (sLDH) Levels in Oral Squamous Cell Carcinoma (OSCC)

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Abstract

Objectives: To evaluate the correlation between tumour size (T) and salivary LDH levels in patients with OSCC.

Methods: A prospective cross-sectional pilot study was conducted by reviewing clinical and laboratory records of 30 histopathologically confirmed OSCC patients treated at Dhaka Dental College Hospital, over a period of 6 months, from May 2017 to November 2017. Tumour size was categorised according to the AJCC TNM classification (T1–T4). Unstimulated saliva samples, collected in the morning using the spitting method, were analysed using an enzymatic spectrophotometric assay to determine salivary LDH activity. Comparative analysis of LDH levels across tumour size groups was performed using Student's t-test.

Results: The mean salivary LDH concentration demonstrated a progressive rise with increasing tumour size. Patients with T1 lesions exhibited a mean LDH of 650.33 U/L, while those with T4 tumours had markedly elevated levels averaging 2447 U/L. Intermediate tumour categories showed mean LDH levels of 1223.5 U/L (T2) and 1371.2 U/L (T3). Statistical analysis confirmed a significant difference in mean LDH values among tumour size groups ($p < 0.05$).

Conclusions: Elevated salivary LDH levels correlate with increasing tumour size in OSCC, supporting its role as a promising non-invasive adjunctive biomarker for disease progression.

Keywords: Lactate dehydrogenase (LDH), liquid biopsy, oral potentially malignant disorder (OPMD), oral squamous cell carcinoma (OSCC), salivary biomarker.

Introduction

Oral squamous cell carcinoma (OSCC) represents more than 90% of all oral malignancies and continues to pose a major global health burden.[1] Despite advances in diagnostic and therapeutic modalities, the overall prognosis and survival rates for OSCC remain unsatisfactory, largely because patients often present at advanced stages of the disease.[2] Among the various prognostic determinants, the clinical stage at diagnosis plays a pivotal role, with tumour size (T) being one of the most important parameters influencing both treatment planning and outcomes.[3] In recent years, saliva has gained considerable attention as a diagnostic medium and liquid biopsy, owing to its non-invasive, cost-effective, and easily accessible nature.[4] Being in

close proximity to the primary tumour site, saliva has the potential to reflect local as well as systemic pathophysiological changes. Several salivary biomarkers have been investigated in relation to OSCC, among which lactate dehydrogenase (LDH) has emerged as a promising candidate.[5]

LDH is an intra-cytoplasmic enzyme involved in anaerobic glycolysis, catalysing the conversion of pyruvate to lactate. Its elevation in biological fluids is closely associated with tissue breakdown, hypoxia, and altered tumour metabolism. The phenomenon known as the "Warburg effect", wherein cancer cells preferentially utilise glycolysis even in the presence of oxygen, further contributes to increased LDH release.[6]

Previous studies have consistently demonstrated that salivary LDH concentrations are significantly higher in patients with OSCC compared to healthy individuals and those with oral potentially malignant disorders.[7,8] Furthermore, a positive association has been reported between salivary LDH levels and tumour differentiation, with poorly differentiated carcinomas exhibiting the highest values.[8] However, there is a relative paucity of literature specifically addressing the relationship between tumour size (T1–T4) and salivary LDH levels.

The aim of this study was to investigate the relationship between tumour size and salivary LDH levels in patients with OSCC, with the objective of evaluating the potential of salivary LDH as a non-invasive biomarker for assessing disease progression.

Methods

Study design and setting: This prospective cross-sectional pilot study was conducted by reviewing data extracted from the author's dissertation entitled "Analysis of Salivary LDH (Lactate Dehydrogenase) as a Screening Tool for OSCC". The study was carried out at the Department of Oral and Maxillofacial Surgery, Dhaka Dental College Hospital, during the period 2017–2018. A total of 30 histopathologically confirmed OSCC patients were included.

Eligibility criteria: Patients with histopathologically confirmed oral squamous cell carcinoma (OSCC) at any site within the oral cavity, who have discontinued contributory oral risk habits—such as betel quid/pan masala chewing, smoking, and alcohol consumption—for at least three con secutive weeks prior to incisional biopsy, were included. Exclusion criteria comprised patients with severe periodontal or oral conditions—including advanced periodontitis, extensive gingivitis, and acute oral mucosal infections—as well as systemic diseases such as coronary artery disease, liver disease, kidney disease, megaloblastic anemia, and immunocompromised states as well as patients unwilling to provide consent. Candidates were screened via clinical history, physical examination, and investigations including orthopantomogram (OPG), complete blood count, liver function tests (ALT, AST, serum bilirubin), and renal function tests (serum creatinine, blood urea nitrogen).

Tumour size (T) was recorded from patient files and categorised according to the American Joint Committee on Cancer (AJCC) TNM classification into T1, T2, T3, and T4 groups.

Saliva Collection, Transport, and Processing Protocol: Unstimulated whole saliva was collected in a disposable sterile plastic container by the spitting method. To minimize diurnal variation in salivary chemistry, whole unstimulated saliva samples were collected between 8:00 AM and 10:00 AM. Prior to collection, all participants were instructed to refrain from eating, drinking, smoking, or performing oral hygiene procedures for at least one hour. Samples were obtained via the passive drool method using sterile, wide-mouth polypropylene containers to prevent mechanical stimulation and preserve baseline enzyme levels. Each container was filled to optimal capacity to minimize tube headspace and immediately sealed with an airtight screw cap to prevent oxidation, evaporation, and airborne exposure.

Collected specimens were placed in sealed secondary biohazard containers and immediately transported to the processing laboratory of same institition—located approximately 15 minutes from the patient ward — within 15 minutes via an insulated cold-chain carrier kept at 4°C. For samples gathered prior to full laboratory operational status, specimens were temporarily stored in a monitored 4°C refrigerator to preserve enzyme

stability. Upon arrival, processing and centrifugation were conducted inside a certified Class II Biosafety Cabinet (BSC) equipped with aerosol-tight sealed rotors to ensure biological containment before salivary lactate dehydrogenase (LDH) estimation.[8]

Laboratory analysis: Salivary lactate dehydrogenase (LDH) activity was estimated using the ARCHITECT Lactate Dehydrogenase (LDH) Reagent Kit (Abbott Diagnostics, Abbott Park, IL, USA) on an automated clinical chemistry analyzer (ARCHITECT Plus c8000; Abbott Diagnostics). expressed in units per litre (U/L).

Ethical considerations: Ethical approval was obtained from the Institutional Review Board of Dhaka Dental College Hospital, and written informed consent was taken from all patients prior to participation.

Data were extracted from the above-mentioned dissertation and tabulated as follows in Table 1.

Table 1: Presenting tumour size of OSCC cases with related sLDH level.

Sl	Tumor Size (T)	Salivary LDH Value (u/L)
1	T_3	1172
2	T_2	782
3	T_3	1508
4	T_1	625
5	T_1	1334
6	T_1	417
7	T_2	3428
8	T_3	1334
9	T_3	1508
10	T_1	408
11	T_3	1172
12	T_2	889
13	T_1	137
14	T_3	1508
15	T_2	1491
16	T_4	3428
17	T_2	1144
18	T_3	1334
19	T_2	786
20	T_2	1163
21	T_2	748
22	T_3	1508
23	T_4	3428
24	T_4	1343
25	T_4	2040
26	T_3	1334
27	T_2	1491
28	T_4	3428

29	T_4	1422
30	T_2	1491

The mean and standard deviation of LDH values were calculated for each T category. Comparative analysis between tumour size groups was carried out using Student's t-test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22.

Results

Patient profile: This study included 30 subjects with histopathologically confirmed OSCC, comprising 18 females and 12 males, aged between 35 and 65 years. Figure 1 represents gender distribution of participants.

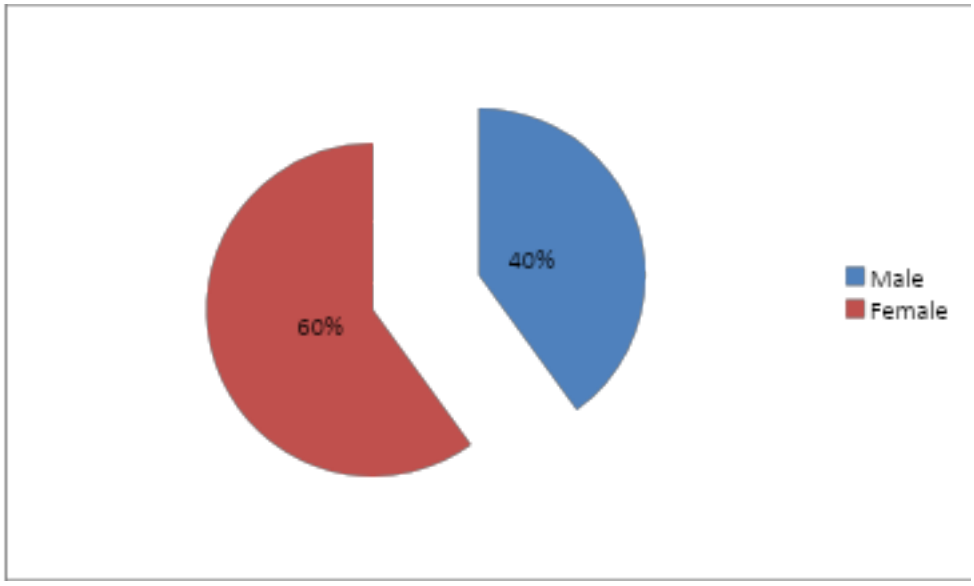


Figure 1: Pie chart shows proportional involvement of male and female subjects where blue section stands for male, brown area for female.

Tumour size of each participant was clinically evaluated and categorised according to TNM class, presented in Table 2.

Table 2: Presents frequency of tumour size of participants (n=30).

Tumour Size	Number of cases (n)
T 1	5
T 2	10
T 3	9
T 4	6

LDH values: The mean salivary LDH concentration increased with tumour size. Patients with T1 lesions had a mean LDH of 650.33 U/L, while those with T4 lesions had a mean LDH of 2447 U/L. Intermediate groups T2 and T3 demonstrated values of 1223.5 U/L and 1371.2 U/L, respectively. Student's t-test revealed a

statistically significant difference in mean LDH levels across the groups ($p < 0.05$). Table 3 describes how tumour size influenced sLDH value.

Table 3: Correlation of Tumor Size (T-stage) with Mean Salivary LDH (sLDH) Values.

Tumour Size	Maximum Clinical Dimention	Mean Salivary LDH level (U/L)
T 1	2 cm or less	650.33
T 2	more than 2 but less than 4 cm	1223.5
T 3	More than 4 cm	1371.2
T 4	Tumor invades adjacent structure	2447

These results demonstrate a clear positive correlation between tumour size and salivary LDH levels, supporting the potential of sLDH as a biomarker of disease progression in OSCC.

Discussion

The present study demonstrates a progressive increase in salivary lactate dehydrogenase (LDH) levels with advancing tumour size in oral squamous cell carcinoma (OSCC). This finding aligns with the biological understanding that larger tumours exhibit higher cellular turnover and metabolic activity, resulting in elevated release of LDH into the saliva.[9-13]

Similar observations have been reported in recent studies, which indicate a direct association between tumour burden and salivary LDH concentration.[14,15] So, Salivary LDH predominantly reflects local tissue necrosis, cellular turnover, and primary mucosal breakdown in the oral cavity, rather than systemic or distant metastatic spread. Salivary LDH has emerged as a reliable, non-invasive biomarker for OSCC, consistently showing higher levels in patients compared to those with oral potentially malignant disorders such as oral lichen planus, lichenoid reactions, and healthy controls.[14,16,17] Notably, a few studies have suggested that salivary LDH may be more sensitive than serum LDH for early detection of OSCC, reinforcing its diagnostic potential.[18,19] Histopathological evaluation further supports this observation. This is further supported by Imam F. et al. (2026), who highlighted the potential of salivary LDH as a valuable biomarker not only for screening and diagnosis, but also for evaluating prognosis and cervical node outcomes in OSCC patients.[20] Poorly differentiated OSCCs tend to exhibit higher salivary LDH levels compared to well-differentiated tumours, reflecting the link between tumour aggressiveness and metabolic activity.[21,22] Given that tumour size and histological grade often parallel disease progression, salivary LDH may provide an integrated reflection of both tumour burden and malignancy potential. Furthermore, the variability in sLDH levels across different histological grades highlights that sLDH should be interpreted alongside tumor grading rather than as a standalone biomarker. While grade-induced variations remain an inherent limitation, future large-scale studies utilizing multivariable analysis or subgroup stratification can effectively adjust for these confounding differences.

From a mechanistic standpoint, the increase in LDH can be attributed to enhanced anaerobic glycolysis within the hypoxic tumour microenvironment—a phenomenon known as the Warburg effect. Tumour hypoxia and necrosis promote the release of LDH from malignant cells, which explains the observed positive correlation between tumour size and salivary LDH in our cohort. Larger tumours inherently possess more hypoxic regions, thereby contributing to higher enzymatic levels in saliva.

Clinically, these findings highlight the potential of salivary LDH as a simple, cost-effective, and non-invasive adjunct for OSCC assessment. Its incorporation into routine screening or prognostic panels may facilitate early detection, risk stratification, and monitoring of disease progression, particularly in resource-

limited settings though mean sLDH increases progressively with advancing T-stage, overlap exists due to inter-individual metabolic variations and tumor heterogeneity.

Several systemic conditions, including coronary artery disease, liver and kidney disease, megaloblastic anemia, and immunocompromised states, are associated with elevated serum lactate dehydrogenase (LDH). This elevation primarily reflects increased cellular injury, membrane disruption, tissue ischemia or necrosis, and/or accelerated cellular turnover, leading to the release of the predominantly intracellular enzyme into the circulation. Depending on the underlying disease and the mechanisms regulating the transfer of circulating constituents into saliva, elevated serum LDH may also be reflected, to some extent, in increased salivary LDH concentrations, so we excluded these systemic conditions.

Although our cross-sectional study design limits our findings to baseline risk stratification, longitudinal tracking of post-operative sLDH holds significant potential. A post-surgical decline likely reflects the clearance of tumor burden, making serial sLDH monitoring an ideal focus for future prospective validation.

However, this study is limited by its cross-sectional design and modest sample size, consistent with prior pilot studies in the field. To establish robust clinical utility, larger, prospective investigations are warranted to validate these preliminary findings and to standardise salivary LDH thresholds for clinical application. Finally, ROC curve analysis was not performed to determine optimal quantitative cutoffs for differentiating T1, T2, and T3 lesions. Future prospective studies with larger cohort sizes are warranted to establish these diagnostic thresholds.

Conclusions

In our pilot study, salivary LDH levels show a significant positive relation with tumour size in OSCC patients. These findings also highlight the potential of Salivary LDH serves as a convenient, non-invasive adjunctive biomarker that correlates with local primary tumor burden (T-stage) in OSCC, rather than a definitive marker for overall disease progression, although validation in larger prospective studies is required.

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