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ORIGINAL RESEARCH

A study of serum beta 2-microglobulin (β2M) and lipid bound sialic acid (LSA) levels in oral carcinoma patients

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ABSTRACT

Background: Oral cancer is a significant global health issue, with India accounting for nearly one-third of global cases. The late-stage diagnosis common in India leads to poor survival outcomes, highlighting the need for early detection and effective biomarkers. **Introduction:** This study explores the potential of serum β2-microglobulin (β2M) and lipid-bound sialic acid (LSA) as diagnostic and prognostic biomarkers in oral carcinoma, with a focus on the Indian population, where the disease burden is exceptionally high. **Methodology:** This case-control study involved 200 subjects (100 oral cancer cases and 100 healthy controls) aged 20-60 years. Serum β2M and LSA levels were measured using ELISA kits. Statistical analysis, including ROC analysis and correlation studies, was performed using SPSS software to assess the diagnostic accuracy and clinical relevance of these biomarkers. **Results:** Serum β2M and LSA levels were significantly higher in oral cancer cases compared to controls, with β2M showing near-perfect diagnostic accuracy (AUC 0.999) and LSA demonstrating excellent accuracy (AUC 0.945). Both biomarkers strongly correlated with advanced AJCC stages, underscoring their potential in assessing disease severity and aiding early detection. **Conclusion:** Serum β2M and LSA levels are promising biomarkers for the diagnosis and assessment of oral carcinoma. Their incorporation into clinical practice could enhance early detection, prognosis, and treatment monitoring, ultimately improving patient outcomes. Further research with larger cohorts is needed to validate these findings and explore their longitudinal applicability.

Keywords: Oral carcinoma, β2-microglobulin (β2M), lipid-bound sialic acid (LSA), biomarkers, early detection, prognosis

INTRODUCTION

Oral cancer, a major global health concern, is defined by malignancies occurring in the oral cavity, including the tongue, gums, lips, and mouth. According to the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), oral cancer encompasses a complex range of tumor pathologies that affect not only the oral cavity but also surrounding areas like the oropharynx and salivary glands**[1]**. It is recognized as the sixth most common cancer worldwide. However, in India, oral cancer represents an even more pressing issue, accounting for nearly one-third of global cases. Each year, India reports approximately 77,000 new cases and 52,000 deaths from this disease, making it a significant public health challenge**[2]**.

The high prevalence of oral cancer in India is linked to various socio-cultural factors, including the widespread use of tobacco in both smoked and smokeless forms, the consumption of areca nut, and alcohol abuse. These risk factors, along with poor oral hygiene and dietary deficiencies, contribute to the alarming incidence rates. Notably, a large percentage of oral cancer cases in India are diagnosed at advanced stages, leading to poor survival outcomes. The American Joint Committee on Cancer (AJCC) notes that around 70% of oral cancer cases in India are detected at stages III or IV, resulting in a five-year survival rate of merely 20%**[2]**. This contrasts sharply with the Western world, where early detection is more common and outcomes are generally better**[3]**.

Given the high burden of disease and poor prognosis associated with late-stage diagnosis, early detection of oral cancer is crucial. Emerging biomarkers, such as Beta-2 Microglobulin (β2M) and Lipid-Bound Sialic Acid (LSA), offer promising non-invasive diagnostic

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tools for early detection and monitoring of oral cancer**[4,5,6]**. These biomarkers, which can be identified in serum or saliva, have shown potential in detecting oral cancer in its initial stages, thereby improving prognosis and reducing mortality**[2]**. Our study aims to explore the significance of β2M and LSA as diagnostic and prognostic markers in oral carcinoma, with a particular focus on the Indian population, where the disease burden is exceptionally high. By advancing our understanding of these biomarkers, we hope to contribute to the development of more effective screening protocols and targeted interventions that can mitigate the impact of oral cancer, especially among vulnerable and marginalized groups.

MATERIALS & METHOD

The study protocol was evaluated and approved by the Institutional Ethical Committee of UPUMS, Saifai, Etawah. Written informed consent was obtained from each participant after a detailed explanation of the study's nature. The research, conducted over one and a half years, was a case-control study based in the Out-Patient Department of Radiotherapy & Biochemistry at U.P. University of Medical Sciences, Saifai, Etawah. The study involved 200 subjects aged 20-60 years, divided into 100 healthy controls and 100 individuals diagnosed with various types of oral cancer.

The sample size estimation was based on a 64.8% prevalence of oral cancer in Central India **[7]**, yielding a minimum required sample size of 92. Considering potential drop-outs, this number was rounded up to 100 for each group. Inclusion criteria for cases included individuals clinically and histopathologically diagnosed with oral squamous cell carcinoma or leukoplakia with exposure to carcinogens but without oral lesions. Exclusion criteria included those with allergic, inflammatory, systemic diseases, or other malignancies. Healthy controls were required to be free of oral lesions, other malignancies, and chronic conditions like diabetes or cardiovascular diseases.

Blood samples (5 ml) were collected under aseptic conditions and stored at -40°C for analysis. Serum β-2 Microglobulin and Lipid Bound Sialic Acid levels were measured using commercially available ELISA kits. The biochemical analysis employed the GENLISA™ ELISA kits from KRISHGEN BioSystems. The sandwich ELISA technique was used, where specific antibodies were pre-coated onto microwells. Samples and standards were added, followed by biotin-labeled antibodies and Streptavidin-HRP to form a complex. After washing to remove non-specific bindings, a substrate solution (TMB) was added, and color development, proportional to the analyte concentration, was measured at 450 nm using a microplate reader. Detailed reagent preparation and assay procedures were followed as per the kit manuals to ensure accuracy and reliability of the results.

STATISTICAL ANALYSIS

SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis with the Windows program (26.0 version).

RESULTS

The study analyzed the distribution of age, gender, chief complaints, habits, examination findings, serum β2M, and LSA levels between cases and controls. Age distribution revealed no significant difference ($p=0.2359$), with 19% of cases and 26% of controls aged 20-39, and 81% of cases and 74% of controls aged 40-60. Gender distribution was also non-significant ($p=0.0914$), with 6% of cases and 13% of controls being female, and 94% of cases and 87% of controls being male**(Table 1)**. Chief complaints, such as difficulty swallowing, neck swelling, and ulcers, were exclusively present in cases, indicating a strong association with the condition**(Figure 1)**.

Habits like alcoholism and smoking were significantly more prevalent in cases (57% and 72%, respectively) than controls (12% and 15%, respectively), with p-values <0.0001 for both, suggesting a strong link between these habits and the condition**(Figure 2)**. Examination findings showed cases had significantly lower Karnofsky Performance Status scores (60.4 ± 10.2) compared to controls (90.5 ± 5.2), and 100% of cases exhibited poor oral hygiene, with a chi-square value of 117.5 and p-value <0.0001. All cases were diagnosed with squamous cell carcinoma, with notable tumor characteristics and staging detailed, including average tumor size (3.5 ± 1.2 cm), irregular margins (73%), and local/regional lymph node involvement (88%)**(Table 2)**.

Serum biomarker analysis demonstrated significantly higher mean levels of LSA (1932.69 ± 2000.86) and β2M (69.21 ± 50.81) in cases compared to controls (1182.73 ± 1112.77 for LSA and 1.46 ± 4.94 for β2M), with p-values of 0.0012 and <0.0001, respectively**(Table 3)**. ROC analysis indicated near-perfect diagnostic accuracy for β2M (AUC 0.999) and excellent accuracy for LSA (AUC 0.945), with β2M showing a sensitivity of 97.87% and specificity of 100.00%, and LSA showing a sensitivity of 80.85% and specificity of 94.34%**(Table 4)**. Correlation analysis demonstrated strong positive correlations of β2M ($r=0.97$, $p=0.006$) and LSA ($r=0.86$, $p=0.008$) with AJCC stages, highlighting their potential as diagnostic markers**(Table 5)**. These findings underscore the importance of β2M and LSA levels in diagnosing the condition and distinguishing between cases and controls.

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TABLE 1: Socio-demographic parameters distribution among cases and controls

Socio-demographic parameters		CASE		CONTROL		P-VALUE
		N	%	N	%	
AGE	20-39	19	19.00%	26	26.00%	X=1.405 p=0.2359
	40-60	81	81.00%	74	74.00%	
	Grand Total	**100**	**100.00%**	**100**	**100.00%**	
SEX	FEMALE	6	6.00%	13	13.00%	X=2.850 p=0.0914
	MALE	94	94.00%	87	87.00%	
	Grand Total	**100**	**100.00%**	**100**	**100.00%**	

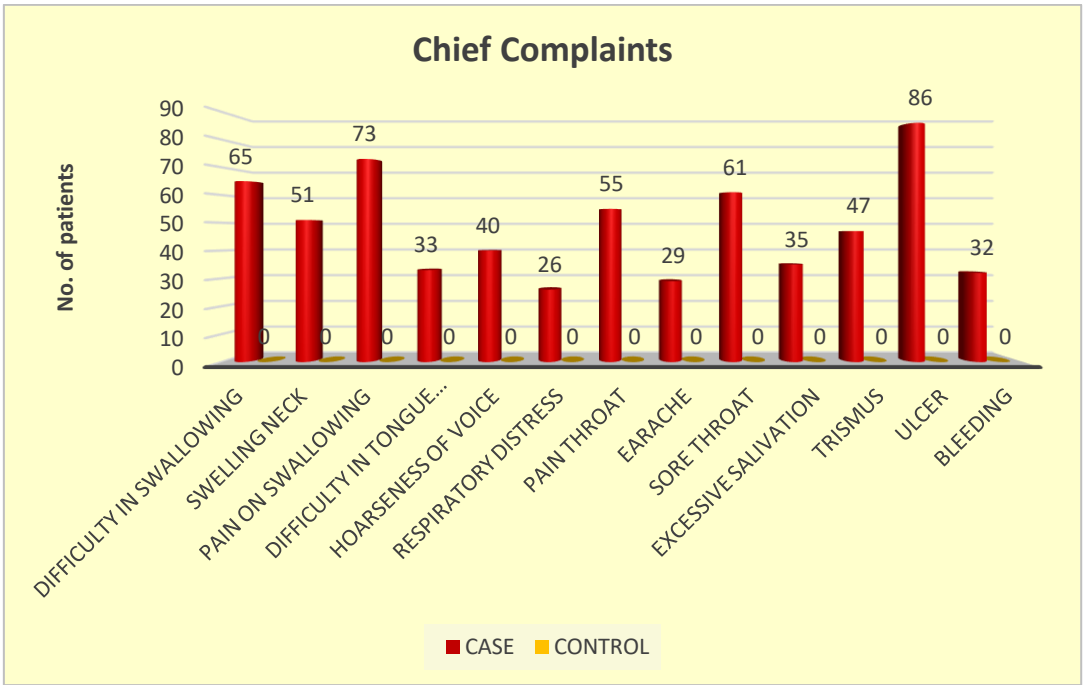

Figure 1: Graphical representations of Chief Complaints Among Cases and Controls.

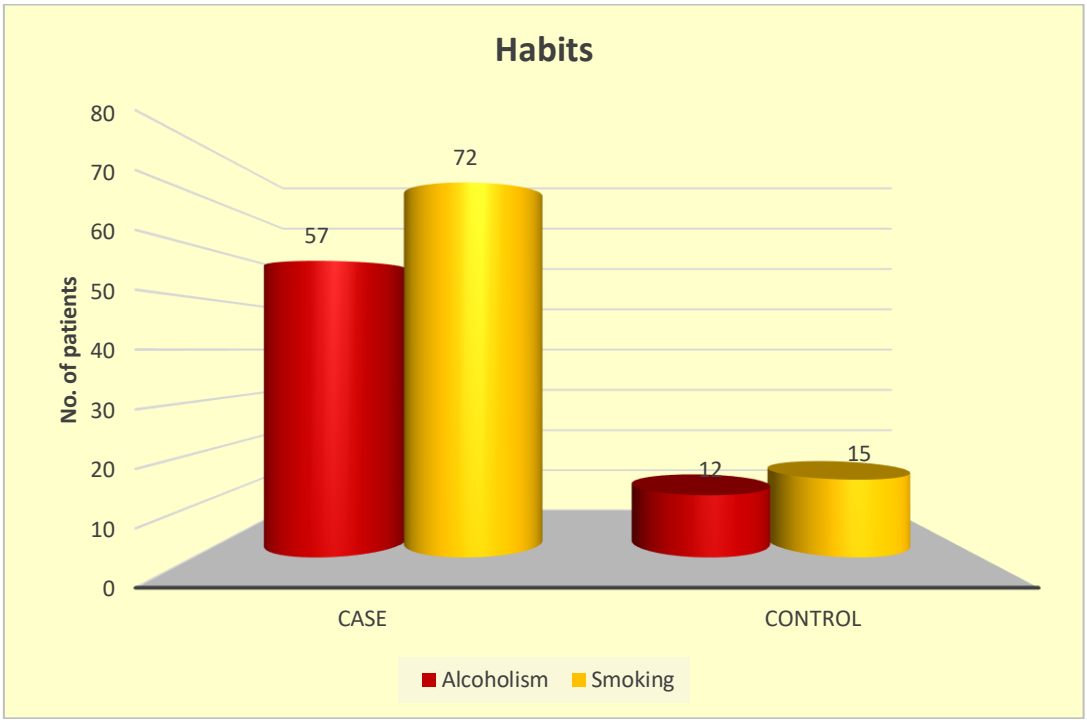

Figure 2: Graphical representations of Habit among case and control

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Table 2: Examination Findings among case and control

Examination	CASE	CONTROL	P-VALUE
Karn of sky Performance Status	60.4 ± 10.2	90.5 ± 5.2	t=26.29 **p<0.0001***
Poor Oral Hygiene	100	26	X=117.5 **p<0.0001***
Tumor Type	Squamous cell carcinoma	-	
Tumor Size (cm)	3.5 ± 1.2	-	
Irregular Tumor Margins	73	-	
Involvement of surrounding areas	41	-	
Local/Regional lymph nodes	88	-	
Number	2.03 ± 1.17	-	
Size (cm)	2.38 ± 0.82	-	
Clinical stage as per AJCC 2018		-	
Stage II	62	-	
Stage III	30	-	
Stage IV	8	-	

Table 3: Serum β2M and LSA Levels

	CASE		CONTROL		P-VALUE
	MEAN	SD	MEAN	SD	
LSA	1932.69	2000.86	1182.73	1112.77	t=3.276 **p=0.0012***
β 2M	69.21	50.81	1.46	4.94	t=13.27 **p<0.0001***

Table 4: ROC Analysis of β2M and LSA levels

	AUC	95% CI	Optimal Cutoff	Sensitivity	Specificity
β2M Levels	0.999	0.994- 1.000	2714.20	97.87%	100.00%
LSA Levels	0.945	0.900- 0.990	2234.84	80.85%	94.34%

Table 5: Pearson correlation coefficients for β2M and LSA levels with AJCC stages

Marker	r Value	95% CI	p Value
β2M Levels	0.97	0.95-0.98	**p= 0.006***
LSA Levels	0.86	0.79-0.90	**p= 0.008***

DISCUSSION

Neoplastic cells exhibit various genetic alterations, including gene rearrangements, amplifications, and mutations, which disrupt critical pathways controlling cell growth, survival, and metastasis. These alterations, when common in specific tumor types, can serve as biomarkers for detection and targeted therapy **[8,9]**. Diagnostic and prognostic biomarkers, such as serum β2-microglobulin (β2-M), play a crucial role in identifying individuals at risk, diagnosing early-stage cancers, guiding treatment decisions, and monitoring responses **[10]**. β2-M, a small protein component of the HLA antigen, is expressed on nearly all nucleated cells and can be detected in bodily fluids. Elevated serum levels of β2-M in cancer may result from increased cellular activity, membrane turnover, or altered HLA expression, potentially helping tumors evade immune detection. These characteristics suggest a correlation between β2-M levels, tumor burden, and cellular turnover, highlighting its potential as a valuable tumor marker in oral carcinoma research **[11-13]**.

Our study reveals no statistically significant association between age groups (20-39 and 40-60 years) and the likelihood of being a case or control in oral carcinoma. While 19% of individuals aged 20-39 are cases compared to 26% controls, the prevalence shifts notably in the 40-60 age group, with 81% cases and 74% controls. The chi-square test with X=1.405 and p-value of 0.2359 underscores this lack of significance, indicating that older individuals are disproportionately more likely to be cases compared to younger individuals. The **Sequeira et al' s[10]** study involved 25 patients with OSCC were in the range of 30–71 years with maximum incidence in the age group of 41–60 years and more commonly occurring in male which is in accordance to various epidemiological studies of oral cancer done in India**[14-17]**.

The study highlights a notable contrast in the prevalence of alcoholism and smoking between cases and controls. Specifically, 57% of cases report alcoholism compared to only 12% of controls, while 72% of cases are smokers versus 15% of controls. These substantial differences (alcoholism: p<0.0001;

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smoking: p<0.0001) underscore a robust association between these behaviors and the studied condition. The findings suggest that individuals with alcoholism and smoking habits are significantly more likely to develop oral carcinoma compared to those without these risk factors. Our study aligns with findings from **Kulkarni et al., [18]** which also observed a significant prevalence of alcoholism and smoking among oral carcinoma cases compared to controls. **Kulkarni et al.** found that the primary harmful behaviour observed in both groups was tobacco chewing, with prevalence rates of 83.33% in Group A and 73.33% in Group B**[18]**. Additionally, **Kulkarni et al.** noted tobacco chewing as a predominant habit among their subjects, reinforcing its role as a major risk factor for oral cancer, especially in male patients**[18]**.

The distribution of chief complaints in our study highlights significant disparities between cases and controls. Among cases, various symptoms are prominently observed: 65% experience difficulty in swallowing, 51% have neck swelling, 73% report pain on swallowing, 33% encounter difficulty in tongue protrusion, 40% suffer from hoarseness of voice, 26% face respiratory distress, 55% complain of throat pain, 29% report earache, 61% have a sore throat, 35% experience excessive salivation, 47% exhibit trismus, 86% present with ulcers, and 32% report bleeding. In contrast, none of these symptoms are reported in controls. This stark contrast underscores a strong association between these symptoms and oral carcinoma, indicating their utility as critical indicators in clinical diagnosis and management. Furthermore, our study comprehensively compares examination findings between cases and controls, revealing substantial differences. Cases exhibit a significantly lower Karnofsky Performance Status score (60.4 ± 10.2) compared to controls (90.5 ± 5.2), with a t-value of 26.29 and a p-value less than 0.0001, indicating a pronounced decline in functional status among cases. Poor oral hygiene is uniformly prevalent in cases (100%) versus controls (26%), with a chi-square statistic of 117.5 and a p-value less than 0.0001, emphasizing a robust association with oral hygiene status. All cases are diagnosed with squamous cell carcinoma tumors, characterized by an average size of 3.5 ± 1.2 cm and irregular margins in 73% of cases. Additionally, 41% of cases show involvement of surrounding areas, and 88% have local/regional lymph node engagement, with an average of 2.03 ± 1.17 lymph nodes affected and an average size of 2.38 ± 0.82 cm. According to AJCC 2018 staging, 62% of cases are classified as Stage II, 30% as Stage III, and 8% as Stage IV, indicating an advanced disease presentation compared to controls. These findings collectively underscore the severe clinical profile and advanced stage of oral carcinoma among cases in our study compared to controls. **Rajapakshe et al. [19] and Geum et al., [20]**underscored the pivotal role of TNM stage in influencing the prognosis of OSCC patients. According to **Suresh et al., [21]**there was a notable decrease in overall survival (OS) rates with advancing stage (P < 0.001). **Rogers et al. [22]**reported a stark contrast in 5-year OS rates between OSCC cases without cervical lymph node metastasis (87%) and those with metastasis (54%). Furthermore, the OS rates varied significantly across lymph node stages: 87% for N0, 68% for N1, and 40% for N2-3, as observed in **Suresh et al.'s** study**[21]**. These results reaffirm the significant prognostic impact of cervical lymph node staging in OSCC (P < 0.001, log-rank test). Our study contrasts significantly with Pires et al.'s findings across several key parameters. **Pires et al. [23]**presented findings on various types of carcinoma: microinvasive carcinoma affected males and females equally, with a mean age of 67.2 years (SD±13.05). The mean complaint duration was 18.4 months (SD±22.7), with leukoerythroplakic areas seen in 73.1% and ulcerated areas in 50% of cases. Tumors predominantly affected the border of the tongue (56%) and lower lip (16%), with a mean size of 1.9 cm (SD±1.6). Most patients reported no tobacco (52.6%) or alcohol use (53.3%). Verrucous carcinoma predominantly affected elderly females (mean age 73.2 years, SD±14.3), presenting with leukoerythroplakic (78%) and ulcerated (56%) areas. The tumors were mainly located on the alveolar mucosa/gingiva (44.4%) and buccal mucosa/buccal sulcus (33.3%), with a mean size of 3.8 cm (SD±1.3). Tobacco use was reported in 60%, but alcohol use was minimal (33.3%). Spindle cell carcinoma primarily affected male adults (mean age 57 years, SD±10.4), presenting with ulcerated areas (80%) and affecting various sites including the border of the tongue (40%) and alveolar mucosa/gingiva (20%). The mean tumor size was 4.3 cm (SD±1.5), and all patients reported both tobacco and alcohol use. Basaloid OSCC cases included a male with a 10 cm lesion on the buccal mucosa and a female with a 2.5 cm lesion on the border of the tongue, both presenting as ulcerated and leukoerythroplakic. One patient reported tobacco use. Papillary OSCC was observed in a 64-year-old male on the buccal mucosa, presenting as a 5 cm ulcerated lesion in a non-tobacco and non-alcohol user.These comprehensive findings underscore the severe clinical presentation and advanced stage of oral carcinoma among cases in our study, reflecting a more challenging disease profile compared to the cases reported by **Pires et al. [23]Sequeira et al. [10]**observed a significant association between serum β2-M levels and nodal status in their study, suggesting its potential as a predictive marker for nodal involvement, crucial for prognosis and postsurgical outcomes in carcinoma. Our study similarly found a progressive increase in serum β2-M levels across clinical stages of OSCC, with a notable elevation observed in Stage IV cases (44%). This pattern aligns with findings by **Kadam et al. [24] and Wilma et al., [25]**indicating higher β2-M levels in OSCC with combined endophytic and exophytic growth patterns

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compared to pure endophytic or exophytic growth. Elevated β2-M levels have been linked to various lymphoid malignancies such as multiple myeloma and B-cell non-Hodgkin's lymphoma**[26-29]**.Additionally, studies like those by **Hagberg et al., [30]Chronowski et al., [31]**and **Constantinides et al. [32]**have associated elevated β2-M levels with disease stage and prognosis in Hodgkin's disease, highlighting its prognostic relevance across different cancers.

The comparison of biomarker levels between cases and controls reveals substantial differences. Specifically, LSA levels are significantly elevated in cases (mean: 1932.69, SD: 2000.86) compared to controls (mean: 1182.73, SD: 1112.77), with a t-value of 3.276 and a p-value of 0.0012, indicating statistical significance. Similarly, β2M levels are markedly higher in cases (mean: 69.21, SD: 50.81) than in controls (mean: 1.46, SD: 4.94), with a higher t-value of 13.27 and a p-value less than 0.0001, highlighting a stronger association. Our study, in comparison to Agrawal et al., highlights significant differences in biomarker levels between cases and controls. **Agrawal et al. [33]**found that serum β2-microglobulin levels differed significantly across groups: 1.88 ± 0.82 µg/ml in controls, 2.23 ± 0.84 µg/ml in oral leukoplakia, and 3.23 ± 0.96 µg/ml in oral squamous cell carcinoma (OSCC). The increase in β2-microglobulin levels from controls to OSCC was highly statistically significant ($p < 0.001$), and OSCC showed a significant increase compared to oral leukoplakia ($p < 0.05$). Although β2-microglobulin levels were higher in oral leukoplakia compared to controls, this difference was not statistically significant ($p > 0.05$). Additionally, β2-microglobulin levels were found to rise significantly with age in the control group. These results suggest that both LSA and β2M are robust biomarkers for distinguishing between individuals with and without oral carcinoma, underscoring their potential diagnostic utility.

The current study reveals robust diagnostic performance metrics for β2M and LSA levels in oral carcinoma. β2M exhibits exceptional diagnostic accuracy, with an AUC of 0.999 (95% CI: 0.994-1.000), an optimal cutoff of 2714.20, sensitivity of 97.87%, and specificity of 100.00%. This indicates near-perfect ability to differentiate cases from controls with minimal misclassification. LSA also shows excellent diagnostic performance, with an AUC of 0.945 (95% CI: 0.900-0.990), an optimal cutoff of 2234.84, sensitivity of 80.85%, and specificity of 94.34%, slightly less accurate than β2M but still highly effective. Moreover, correlation analysis reveals a very strong positive correlation for β2M ($r = 0.97$, 95% CI: 0.95-0.98, $p = 0.006$) and a strong positive correlation for LSA ($r = 0.86$, 95% CI: 0.79-0.90, $p = 0.008$) with the condition studied. These findings underscore the reliability of β2M and LSA levels as diagnostic markers, with β2M demonstrating particularly robust correlation and diagnostic accuracy in oral carcinoma. Similarly, **Viashali and Tupkariet al.,** similarly demonstrated a notable association between serum β2M levels and the histological grading of SCC, proposing this biomarker as a sensitive tool for diagnosis, analysis, and prognosis**[34]**.

This study highlights the potential of serum β2M and LSA as diagnostic biomarkers for oral carcinoma. The marked elevation of these biomarkers in cases, along with their strong correlations with advanced AJCC stages, underscores their clinical relevance in assessing disease severity. The high diagnostic accuracy of β2M and LSA, demonstrated by their AUC values and optimal cutoffs, suggests their effectiveness in distinguishing cases from controls with high sensitivity and specificity. Incorporating these biomarkers into clinical practice could improve early detection, prognosis, and treatment monitoring in oral carcinoma, ultimately enhancing patient outcomes. Further research should validate these findings in larger cohorts and explore their longitudinal applicability to confirm their clinical utility.

CONCLUSION

This study demonstrates the significant utility of serum β2-microglobulin (β2M) and lipid-bound sialic acid (LSA) levels as biomarkers in diagnosing and assessing the severity of oral carcinoma. Elevated levels of β2M and LSA were strongly associated with the presence and progression of the disease, with β2M showing particularly high diagnostic accuracy. Additionally, the analysis highlighted important demographic and clinical characteristics, such as the higher prevalence of cases in older age groups and the significant association of habits like alcoholism and smoking with oral carcinoma. The study also emphasized the clinical impact, with cases exhibiting lower Karnofsky Performance Status and poor oral hygiene. These findings underscore the importance of early detection and intervention, suggesting that β2M and LSA levels could play a crucial role in improving patient management and outcomes. Further research with larger cohorts is needed to validate these biomarkers' effectiveness and explore their potential in long-term disease monitoring.

CONFLICT OF INTEREST: The authors declare that there are no conflicts of interest.

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CONSENT: Written informed consent has been obtained from all participants in accordance with international or university standards and is maintained by the authors.

ETHICAL APPROVAL: Ethical approval was granted in compliance with international or university standards, and the written approval is preserved by the authors.

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