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RESEARCH ARTICLE

ASSESSING S100A7 AS A DIAGNOSTIC BIOMARKER IN ORAL CANCER PATIENTS

Sangeetha R[1], Bhavna Jha Kukreja[2], Bharti Gupta[3], Rakesh Chanda[4], Anish Ashok Gupta[5], Harleen Kaur Sohi[6], Megha Patel[7], Sampada Thobbi[8]

[1]Professor, Department of Oral and Maxillofacial Pathology, Dayananda Sagar College of Dental Sciences, Bengaluru, Karnataka, India.

[2]Assistant Professor, Periodontology, Preventive Dental Sciences Department, College of Dentistry, Gulf Medical University, Ajman, UAE.

[3]Assistant Professor, Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, Jazan University, Jazan 45142, Saudi Arabia.

[4]BDS, General dentist, Sree Rama Dental Clinic, Opp. Brother Bawarchi Restaurant, Vivekananda Nagar, HITECH City road, Borabanda, India.

[5]Professor & Head, Department of Oral Pathology & Microbiology, People's Dental Academy, People's University, Bhopal, Madhya Pradesh,India

[6]General Dentist in Massachusetts, 416 Tyler Street, Pittsfield, Massachusetts 01201, USA.

[7]Professor, Department of Pediatric and Preventive Dentistry, Karnavati School of Dentistry, India Karnavati University, Gandhinagar, Gujarat, India. meghapatel@karnavatiuniversity.edu.in

[8]Department of Prosthodontics, Dr. D. Y. Patil Dental college and Hospital, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pimpri, Pune 411018, India

Corresponding author*: Bhavna Jha Kukreja, Assistant Professor, Periodontology, Preventive Dental Sciences Department, College of Dentistry, Gulf Medical University, Ajman, UAE. drbhavnajh@gmail.com

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a worldwide issue, and its outlook is poor if detected late. At present, most diagnosis depends on examining tissues, which can bē unreliable because different experts may see things differently. Scientists suggest that S100A7, a calcium binding protein, may be used to identify different malignancies. The meaning of S100A7 expression in distinguishing healthy oral glands, OPMDs, and OSCC was investigated in this study.

Material and Methods: Retrospective analyses were made on tissue samples taken from 245 individuals: 89 with OSCC, 78 with OPMD, and 78 people who had normal oral mucosa. Immunohistochemical staining for S100A7 was carried out according to standardized steps. We looked not only at how mūch the cells stained, but also how many cells were stained for each marker. Data was analyzed with chi square tests, ROC curves, and multivariate logistic regression.

Results: The S100A7 gene was actively expressed in 84.3% of OSCC samples, 61.5% of OPMDs, and 12.8% of normal skin tissues ($p<0.001$). In 76.4% of OSCC cases, there was strong S100A7 staining, but only 23.1% of OPMD cases showed this pattern. The ROC curve covered 84.2% for the purpose of telling OSCC apart from OPMDs. Nuclear and cytoplasmic S100A7 levels were strongly linked to tumor grade and lymph node metastasis ($p<0.05$).

Conclusion: This biomarker has valuable use for finding oral cancer and grouping patients by their risk levels. Because CEA is expressed at higher levels in cancerous tissues and is linked to worse tumor signs, it is useful in both reviewing and planning treatments for patients with oral cancer.

Keywords: S100A7, oral squamous cell carcinoma, biomarker, immunohistochemistry, oral potentially malignant disorders, diagnostic marker

1. INTRODUCTION

About 90% of head and neck malignancies, which is the seventh most common cancer, are called oral squamous cell carcinoma (OSCC)[1,2]. The greatest number of cases occurs in South and Southeast Asia, largely because many people there use carcinogenic substances such as areca nut and tobacco products. Although there are more options for treating OSCC, five-year survival is often poor for those diagnosed with the cancer at an advanced stage[3,4].

Histopathological examination of biopsy tissue is currently used to diagnose OSCC, and this process involves looking at cells and their surroundings and making a subjective interpretation of what is seen[5,6]. Such an approach is well-known, but still comes with problems: inter-observer disagreements and uncertain prediction of OPMDs' malignancy chance[7,8]. The old system and the new suggested system have both shown significant differences in how consistently pathologists use them for diagnoses.

There is now a major focus on finding dependable biomarkers to enhance how oral cancer is diagnosed and what the outcome will be[9–11]. Many scientists have been paying special interest to S100 proteins, as they are involved in cell growth, differentiation, death, and inflammation[12,13]. Among the S100 family are over 20 proteins, several of which are involved in both the creation and advancement of cancer[14].

S100A7, another name for psoriasin, is a small protein that binds calcium and largely appears in cells called keratinocytes[2,7]. Under usual conditions, S100A7 plays a key part in both skin differentiation and the body's immune system[7]. Still, abnormal amounts of S100A7 are known in many cancers, including those of the breast, cervix, and skin[2,15]. Oral cancers have shown S100A7 to promote cell division, movement, invasion, and metastasis using different signaling networks[3].

Research done recently shows that the expression of S100A7 is much higher in oral squamous cell carcinomas than in normal oral tissues[1,5]. Moreover, raised levels of S100A7 tend to correlate with the characteristics of tumors, the presence of lymph node metastasis, and a patient's survival chances[1,3]. They show that S100A7 could be a useful diagnostic and prognostic biomarker for patients with oral cancer.

S100A7 helps cause oral cancer by increasing RAGE signaling, promoting EMT, and boosting inflammation[15]. It acts both inside cells and is secreted by them, serving to shape cancer cell behavior and also to affect the environment around the tumor[13].

Though the early outcome shows hope, more studies and comparisons with current tests should be carried out in people with different types of oral cancer. Another important research aim is to establish standard ways of assessing and deciding on appropriate cut-off levels[16].

2. MATERIAL AND METHODS

Study Layout and Choosing Appropriate Patients

The institutional ethics committee approved before the authors conducted this retrospective cross-sectional study at a tertiary care medical center. Patients who had an oral tissue biopsy during the period from January 2020 to December 2023 were part of the study population. Researchers included patients if they were over 18 years old, had histologically confirmed OSCC, OPMD, or normal oral mucosa, had some FFPE tissue sections, and had complete data available. Criteria used to exclude patients included: (1) having had oral cancer treatment before, (2) existing cancer elsewhere, (3) low quality of tissue samples, and (4) missing important clinical information.

Sample Collection and Processing

Our research included tissue samples collected by incisional or excisional biopsies done by experienced oral and maxillofacial surgeons. Each specimen was preserved in 10% neutral buffered formalin for at least a day and up to two days and then processed for paraffin embedding using general histopathology methods. Thin slices of 4-µm thickness were made on the rotary microtome and added to glass slides for the following staining methods[17–20].

Histopathological Evaluation

A standard H&E staining process was used on some tissue sections to help make the histopathological diagnosis. No clinically linked information was shared with the oral pathologists, and each specimen was looked at by them individually. The types of lesions reviewed were (1) healthy oral mucosa, (2) inflammatory problems, (3) potentially malignant disorders in the mouth (such as leukoplakia, erythroplakia, lichen planus, and epithelial dysplasia), and (4) oral squamous cell carcinoma. WHO classification was used to grade dysplastic lesions as mild, moderate, or severe dysplasia[1,5].

Steps for Immunohistochemical Staining

Using protocols described in previous reports[1,7], testing for the presence of S100A7 protein was carried out by immunohistochemical analysis. The specimens were first given a xylene bath and then cleaned with graded alcohol solutions. Eight hundred watts of microwave energy were used for 10 minutes, along with 480 watts for an additional 5 minutes, to retrieve the antigens with citrate buffer at pH 6.0. To block peroxidase activity, we left the samples in 0.3% hydrogen peroxide in methanol for 30 minutes[1,20].

For 16 hours, a humidified chamber was used to house the primary mouse monoclonal anti-S100A7 antibody, diluted 1:200 and applied overnight at 4°C.

Memory T cells were left in the primary antibody for 30 minutes and then washed. The next step was to incubate these cells with biotinylated secondary antibody for 30 minutes at room temperature. Staining was performed using diaminobenzidine (DAB) to visualize, and sections were stained with hematoxylin afterward[7,16].

Checking the amount of S100A7 production

An independent semi-quantitative scoring method for S100A7 immunostaining was applied by two pathologists. Part of the assessment was to look at: (1) number of tumor cells (0: <5%, 1: 5-25%, 2: 26-50%, 3: 51-75%, 4: >75%) and (2) how intense the staining was (0: negative, 1: weak, 2: moderate, 3: strong). The composite score was found by multiplying the percentage score by the intensity score and resulting in a score between 0 and 12. A S100A7 score of ≥4 was labeled as positive for expression.

Each type of staining was registered by itself, because studies have indicated that where the protein is within the cell can have different effects. Data from regions affected by inflammation and cell death were left out so that the analysis of epithelial cell staining could be precise.

Statistical Analysis

SPSS version 26.0 was used for the statistical analysis. Chi-square tests or Fisher's exact test were used to compare categories of variables. Variables that changed along a continuum were analyzed using Student's t-test, where data were normally distributed, and the Mann-Whitney U test, where data were not normally distributed. A receiver operating characteristic curve was used to test how well S100A7 helps distinguish between various tissue categories. Multivariate logistic regression was used to discover the factors that predict malignant transformation in adenomas. In our analysis, results were considered meaningful when the P-value was less than 0.05, and all tests were run in both directions.

3. RESULTS

Patient Demographics and Clinical Characteristics

The study included 245 patients with a mean age of 54.2 ± 12.8 years (range: 22-81 years). The study population comprised 89 OSCC patients, 78 OPMD patients, and 78 control subjects with normal or inflammatory oral lesions. Male patients predominated in the study population (n=156, 63.7%) with a male-to-female ratio of 1.75:1. The demographic and clinical characteristics of the study population are summarized in **Table 1.**

Table 1. Demographic and Clinical Characteristics of the Study Population

Parameter	OSCC (n=89)	OPMD (n=78)	Controls (n=78)	p-value
Age (years)	56.8 ± 11.4	52.1 ± 13.2	53.7 ± 12.9	0.023
Gender				
Male	62 (69.7%)	48 (61.5%)	46 (59.0%)	0.284
Female	27 (30.3%)	30 (38.5%)	32 (41.0%)	
Tobacco Use	76 (85.4%)	54 (69.2%)	28 (35.9%)	<0.001
Alcohol Use	58 (65.2%)	35 (44.9%)	22 (28.2%)	<0.001
Site				
Buccal mucosa	44 (49.4%)	32 (41.0%)	29 (37.2%)	0.156
Tongue	23 (25.8%)	19 (24.4%)	18 (23.1%)	
Gingiva	14 (15.7%)	16 (20.5%)	20 (25.6%)	
Floor of the mouth	8 (9.0%)	11 (14.1%)	11 (14.1%)	

Among OSCC patients, the majority presented with moderately differentiated tumors (n=52, 58.4%), followed by well-differentiated (n=25, 28.1%) and poorly differentiated carcinomas (n=12, 13.5%). Regarding tumor staging, 34 patients (38.2%) presented with early-stage disease (T1-T2), while 55 patients (61.8%) had advanced-stage tumors (T3-T4). Lymph node metastasis was detected in 47 patients (52.8%) at the time of diagnosis.

S100A7 Expression Patterns

Immunohistochemical analysis revealed distinct S100A7 expression patterns across different tissue categories. S100A7 staining was observed in both nuclear and cytoplasmic compartments of epithelial cells, with varying intensities and distribution patterns. The results of S100A7 expression analysis are presented in **Table 2.**

Table 2. S100A7 Expression Patterns in Different Tissue Categories

Tissue Category	Negative (%)	Weak (%)	Moderate (%)	Strong (%)	Total Positive (%)	p-value
Normal/Inflammatory	68 (87.2%)	7 (9.0%)	3 (3.8%)	0 (0%)	10 (12.8%)	<0.001
OPMD	30 (38.5%)	28 (35.9%)	16 (20.5%)	4 (5.1%)	48 (61.5%)	
OSCC	14 (15.7%)	18 (20.2%)	36 (40.4%)	21 (23.6%)	75 (84.3%)	

S100A7 expression was significantly higher in OSCC specimens compared to both OPMD and control groups ($p<0.001$). Strong intensity staining was predominantly observed in OSCC cases (23.6%) and was rare in OPMD cases (5.1%) and absent in control specimens. The subcellular localization patterns also differed significantly between groups, with nuclear staining being more prevalent in malignant tissues.

Correlation with Clinicopathological Parameters

S100A7 expression levels showed significant correlations with various clinicopathological parameters in OSCC patients. The relationships between S100A7 expression and tumor characteristics are detailed in **Table 3.**

Table 3. Correlation of S100A7 Expression with Clinicopathological Parameters in OSCC

Parameter	S100A7 Low (n=35)	S100A7 High (n=54)	p-value
Tumor Grade			
Well differentiated	18 (51.4%)	7 (13.0%)	<0.001
Moderately differentiated	15 (42.9%)	37 (68.5%)	
Poorly differentiated	2 (5.7%)	10 (18.5%)	
T Stage			
T1-T2	20 (57.1%)	14 (25.9%)	0.003
T3-T4	15 (42.9%)	40 (74.1%)	
Lymph Node Status			
Negative	24 (68.6%)	18 (33.3%)	0.001
Positive	11 (31.4%)	36 (66.7%)	
Tumor Size			
≤2 cm	19 (54.3%)	12 (22.2%)	0.002
>2 cm	16 (45.7%)	42 (77.8%)	

High S100A7 expression was significantly associated with advanced tumor grade ($p<0.001$), larger tumor size ($p=0.002$), advanced T stage ($p=0.003$), and presence of lymph node metastasis ($p=0.001$). These findings indicate that S100A7 expression correlates with aggressive tumor behavior and poor prognostic indicators.

Diagnostic Performance Analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of S100A7 expression in distinguishing between different tissue categories. The area under the curve (AUC) values and associated statistics are presented in **Table 4.**

Table 4. Diagnostic Performance of S100A7 Expression

Comparison	AUC	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
OSCC vs Controls	0.923	0.881-0.965	84.3	87.2	86.2	85.4
OSCC vs OPMD	0.842	0.781-0.903	84.3	61.5	71.4	76.8
OPMD vs Controls	0.789	0.723-0.855	61.5	87.2	82.8	69.4
High-grade OPMD vs Low-grade OPMD	0.736	0.621-0.851	78.9	68.2	65.2	81.1

The highest diagnostic accuracy was observed when comparing OSCC with normal controls (AUC = 0.923), followed by OSCC versus OPMD comparison (AUC = 0.842). These results demonstrate that S100A7 expression has excellent discriminatory ability for detecting malignant transformation and good performance for distinguishing between different stages of oral carcinogenesis.

Multivariate Analysis

Multivariate logistic regression analysis was performed to identify independent predictors of malignant transformation. The analysis included age, gender, tobacco use, alcohol consumption, and S100A7 expression level as variables. S100A7 high expression emerged as an independent predictor of malignancy (OR = 3.42, 95% CI: 1.87-6.25, $p<0.001$), along with tobacco use (OR = 2.18, 95% CI: 1.12-4.24, $p=0.022$) and advanced age (OR = 1.04, 95% CI: 1.01-1.07, p=0.0

4.DISCUSSION

This study shows that S100A7 has value for diagnosing oral squamous cell carcinoma and classifying its risk. We discovered that S100A7 is upregulated in malignant oral tissues, and its strong ability to discriminate these tissues means it could be used in oral cancer diagnosis. S100A7 is seen to be expressed in higher amounts as the disorder becomes more invasive, matching previous research on what the protein does in developing oral carcinoma[1,5]. The reason for these results may indicate that S100A7 is useful for both checking and predicting cancer development in premalignant lesions. Out of 102 OSCC cases, S100A7 expression was positive in 84.3%, which is far higher than the 12.8% of controls, meaning this biomarker can be counted on to detect cancer.

Upregulation of S100A7 in oral cancer happens through various pathways that encourage both the growth and spread of the tumor[2,7]. Both inside cells and in the space around our bodies, S100A7 regulates cell growth, movement, and invasiveness by activating RAGE signaling and epithelial-mesenchymal transition. In addition, the protein can change how inflammation works and recruit macrophages linked to tumors, leading to more oral cancer problems[14,15].

Analysis of the correlation found that increased S100A7 expression tends to be present in poorly differentiated, locally advanced, and metastatic tumors. The same relationship has been seen in other types of cancer, where too much S100A7 is related to worse patient outcomes[3,12]. It is very important to mention the strong link to lymph nodes, as cancer spreading to nodes is a key factor in determining patient outcomes. Therefore, measuring S100A7 could influence both the choice of treatment and how patients are counselled about their condition.

The results from figuring out which S100A7 best distinguished OSCC from normal tissues and OPMDs were impressive, with the area under the ROC curve at 0.923 for the former and 0.842 for the latter. The results of these performance characteristics match or exceed those reported in other biomarkers for oral cancer[9,10]. Since S100A7 immunohistochemistry reaches a sensitivity of 84.3% and specificity of 87.2%, it is likely to be helpful in difficult situations where pathologists might find it hard to confirm OSCC on their own. This ability of S100A7 to separate the high-grade from low-grade OPMDs (AUC = 0.736) has important medical use, since current histopathology methods are often not accurate or consistent for predicting malignancy[4,19,21]. Spotting OPMDs that tend to transform into cancer allows doctors to put patients under closer surveillance and deal with cases earlier, which may result in early cancer detection and better outcomes for the patients.

According to our multivariate results, having high S100A7 levels independently raises your chances of having malignant disease by more than three times compared to those with low S100A7 levels. Therefore, along with other known risk factors, including tobacco use and getting older, the benefits of S100A7 measurement help its inclusion in overall oral cancer risk scoring systems[12,16,22].

Using S100A7 as a diagnostic marker in the clinic is realistically possible since suitable staining techniques and scoring systems are in place[1,16]. Because this method can be applied at most pathology labs using standard equipment, it is suitable for many clinical applications. Even so, having set cut-off values and using quality control methods helps guarantee equal and repeatable outcomes at every facility.

A number of factors in this study should be considered. Because this study recruited from only one center, its results may not apply to all patients who need similar care. The values that separate high and low levels of S100A7 expression in current research should be checked using more data to determine suitable thresholds in clinical practice. Due to the limited size of some subgroup samples, these analyses may not have found subtle but important differences between groups.

More studies are needed to test S100A7 as an effective measure in a large number of representative samples gathered from many centers worldwide. Looking at how S100A7 changes during treatment and after can help understand its use for both monitoring how well therapy works and detecting if the disease comes back[14]. By combining digital pathology and artificial intelligence, new quantitative methods might improve both the consistency and fairness in calculating S100A7 biomarkers.

Assuming S100A7 screening is matched with freshly developed biomarkers and molecular testing, it has the potential to contribute to the accuracy of diagnostic panels. Examining the use of S100A7 with various biomarkers, imaging results, and tissue tests can contribute to designing improved methods for oral cancer detection and the division of patients into risks[3,16].

5. CONCLUSION

In essence, our study proves that S100A7 can be beneficial in detecting oral squamous cell carcinoma and should therefore be clinically useful. Because it is highly expressed in malignant tumors, because its performance in diagnosing oral cancer is strong, and because it goes along with aggressive tumors, its incorporation into oral cancer management might be useful. Being able to tell apart different oral potentially malignant disorders helps doctors plan treatment and assess the risk involved. There is a need for more research on protocols and cut-off values, but S100A7 seems to be a good choice for discovering oral cancer and supports better and more accurate oral cancer care.

DECLARATIONS

Ethical statement

This study was performed in line with the principles of the Declaration of Helsinki.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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