

**Research Article**
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## Bcl-2 Protein Expression in Oral Squamous Cell Carcinoma and Associated Clinicopathological Features at a Tertiary Teaching Institution in Uganda

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### ABSTRACT

**Background:** Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and a significant public health challenge in sub-Saharan Africa. Conventional histopathology often fails to predict clinical outcomes accurately, leading to a search for molecular biomarkers. The B-cell lymphoma 2 (Bcl-2) protein, an anti-apoptotic factor, is involved in cell survival and treatment resistance. This study determined the prevalence of Bcl-2 expression in OSCC and its association with clinicopathological features in Uganda.

**Methods:** This cross-sectional laboratory study analyzed 104 archived formalin-fixed paraffin-embedded (FFPE) tissue blocks of OSCC cases from Department of Pathology Makerere university (2010–2020). Histological subtyping and grading followed WHO (2017) criteria. Immunohistochemistry (IHC) was performed using the anti-Bcl-2 clone 124. Expression was scored semi-quantitatively (intensity + percentage of positive cells). Data were analyzed using Chi-square tests and multivariate logistic regression.

**Results:** Bcl-2 was expressed in 29.8% (31/104) of OSCC cases, predominantly in a granular cytoplasmic pattern. In well-differentiated tumors, staining was most intense at the invasive periphery. Multivariate analysis identified male sex (aOR = 4.76, p = 0.025) and the basaloid histological subtype (aOR = 38.77, p = 0.003) as independent predictors of Bcl-2 expression. No significant associations were found with age, tumor site, or histological grade.

**Conclusion:** Approximately 30% of OSCC cases in Uganda express Bcl-2, with significant associations noted for male patients and the aggressive basaloid subtype. These findings suggest Bcl-2 as a prognostic indicator and potential therapeutic target.

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common head and neck malignancy, frequently presenting at an advanced stage [6].

### Introduction

Oral squamous cell carcinoma (OSCC) is an invasive epithelial neoplasm, representing over 90% of all oral malignancies [1]. Globally, OSCC is the eighth most common cancer, with approximately 500,000 new cases reported annually [2,3]. Despite its prevalence, OSCC has historically received less attention than other major malignancies, yet it remains a substantial health burden in developing countries, where nearly two-thirds of the global cases occur [4,5]. In Uganda, OSCC is the second most

The prognosis for OSCC patients remains a significant clinical challenge. The global five-year survival rate has stagnated between 45% and 50% for several decades, failing to show meaningful improvement despite advancements in diagnostic and therapeutic modalities [7]. In the Ugandan context, the outcomes are even more distressing. Patients treated at the National Referral Hospital exhibit a five-year survival rate of only 20.7%, with nearly half of all patients dying within two years of diagnosis [8]. This high mortality is primarily attributed to late-stage detection and

the limitations of predicting tumor behavior based solely on conventional histopathological parameters, which often fail to capture the underlying molecular complexity [9].

Recent research has focused on the role of apoptotic regulatory proteins, such as the B-cell lymphoma 2 (Bcl-2) family, in the pathogenesis and progression of OSCC [10,11]. Bcl-2 is a 26-kDa anti-apoptotic protein that functions as a critical regulator of the cell cycle [12]. By preventing programmed cell death, Bcl-2 facilitates the survival of mutated cells, promoting the accumulation of further genetic alterations and mediating resistance to conventional therapies like radiation and chemotherapy [13,14].

While international studies report Bcl-2 expression in OSCC ranging from 8% to 83%, its profile within the Ugandan population remains uncharacterized [15,16]. Given the potential for Bcl-2 inhibitors to serve as effective therapeutic adjuvants, characterizing local expression patterns and their clinicopathological associations is essential [17,18]. This study addresses this knowledge gap by determining the prevalence of Bcl-2 expression in OSCC cases in Uganda, providing vital baseline data for future clinical management and targeted therapy design.

## Methods

### Study Design

A cross-sectional, laboratory-based study was employed to evaluate the expression of Bcl-2 protein in oral squamous cell carcinoma (OSCC).

### Study Setting and Population

The study was carried out at the Department of Pathology, School of Biomedical Sciences, Makerere University College of Health Sciences in Kampala, Uganda. This department provides comprehensive pathology services, including autopsy and research. The study population consisted of archived formalin-fixed paraffin-embedded (FFPE) tissue blocks of patients diagnosed with OSCC at the department between January 2010 and September 2020.

### Eligibility Criteria

Cases were included if they had a histologically confirmed diagnosis of OSCC, corresponding request forms or histology reports with complete demographic and clinical data (age, sex, site, grade), and accessible tissue blocks in good condition. Exclusion criteria included blocks with extensive tumor necrosis, tissue blocks that were extensively damaged, or untraceable archival materials.

### Sample Size and Sampling

The sample size (n) was calculated using the Kish Leslie formula [19]. Given the unknown prevalence of Bcl-2 in the Ugandan population, an estimate of 50% was utilized to ensure the largest possible sample size. With a margin of error set at 5% and a confidence interval of 95%, the initial calculated sample size was 384. After applying the finite population correction for the approximately 120 available tissue blocks, the minimum required sample size was determined to be 92. Through convenience sampling, a total of 104 eligible cases were retrieved for the study.

### Eligibility Criteria

- Cases were included if they had a histologically confirmed diagnosis of oral squamous cell carcinoma (OSCC), along with complete archival records (including age, sex, and histology reports) and tissue blocks in viable condition.
- Cases were excluded if they exhibited extensive necrosis that

interfered with immunohistochemistry (IHC), if the tissue blocks were damaged, or if the archival materials could not be traced.

### Study Procedure: Tissue Processing and H&E Staining

The Formalin-Fixed, Paraffin-Embedded (FFPE) tissue blocks were retrieved. Serial sections of 4 microns were cut using a microtome. One set of sections was prepared for routine Hematoxylin and Eosin (H&E) staining, while another set was designated for immunohistochemistry (IHC).

H&E staining was performed according to the standard operating procedures (SOP) of the department. The sections were dewaxed in xylene, hydrated through graded alcohol (from 100% to 80%), and rinsed in water. They were then stained with hematoxylin, differentiated in 1% acid alcohol, blued in tap water, counterstained with 1% eosin, dehydrated, cleared in xylene, and mounted with DPX.

Diagnosis, subtyping, and grading were done following the World Health Organization (WHO) guidelines (2017).

### Immunohistochemical (IHC) Staining

Immunohistochemical staining for Bcl-2 was performed using a mouse monoclonal primary antibody (anti-Bcl-2 clone 124, Dako). The staining protocol included several steps: first, sections were dewaxed and hydrated through xylene and graded alcohol solutions. Next, heat-induced epitope retrieval was conducted in a pH 6.0 buffer using a decloaking chamber at 125°C for 35 seconds, followed by 90°C for 20 seconds. Endogenous peroxidase activity was then inhibited with a peroxidase block for 5 minutes. Following this, the sections were incubated with the primary Bcl-2 antibody for 30 minutes. Detection was achieved using the Novolink polymer system, with the post-primary antibody incubated for 30 minutes, followed by the polymer for an additional 30 minutes. Visualization was accomplished with DAB chromogen applied for 30 seconds to produce brown staining. Finally, Mayer's hematoxylin was used for counterstaining, followed by blueing and dehydration. Controls included sections of Diffuse Large B-cell Lymphoma as a positive control and sections without the primary antibody as a negative control, with lymphocytes serving as internal positive controls.

### Evaluation of IHC Scoring

The evaluation of immunohistochemical (IHC) scoring was performed semi-quantitatively, taking into account both the intensity of staining and the percentage of positive cells. Positive staining was characterized by brown granular cytoplasmic staining, with occasional nuclear staining observed. Intensity was scored as follows: 0 for negative, 1 for weak, 2 for moderate, and 3 for strong. The percentage of positive cells was scored as 0 for less than 5%, 1 for 5–25%, 2 for 26–50%, and 3 for more than 50%. The Final Immunoreactive Score (IRS) was calculated by summing the intensity and percentage scores, with a final IRS greater than 1 considered positive. The scores were confirmed through a consensus between the principal investigator and the supervising pathologists.

### Statistical Analysis

Data analysis was conducted using Stata version 14.0. Descriptive statistics, including means, frequencies, and proportions, were employed to summarize the clinicopathological features of the study population. Bivariate analysis utilizing Chi-square tests was performed to examine the associations between Bcl-2 expression

and various independent variables. Additionally, multivariate logistic regression was used to identify independent predictors of Bcl-2 positivity. A significance level of  $p \leq 0.05$  was established for all statistical tests.

## Results

### Clinicopathological characteristics

The study included 104 cases of oral squamous cell carcinoma (OSCC). The age range of participants was 9 to 91 years, with a mean age of 56.0 years (SD  $\pm 14.2$ ). The youngest patient (9-year-old) had xeroderma pigmentosa and later also developed tongue lesion. Males constituted the majority, accounting for 72.1% of the cases. The tongue was the most common site of occurrence (42.3%), followed by the palate (23.1%), buccal mucosa (7.7%), and lip (6.7%) shown in Table 1. Most tumors were classified as the conventional histological subtype (88.5%) (Table 2), and 58.7% of the tumors were well-differentiated (Grade I) (Figure 1). Moderately differentiated (Grade II) (Figure 2) and poorly differentiated (Grade III) (figure 3) tumors represented 28.9% and 12.5%, respectively.

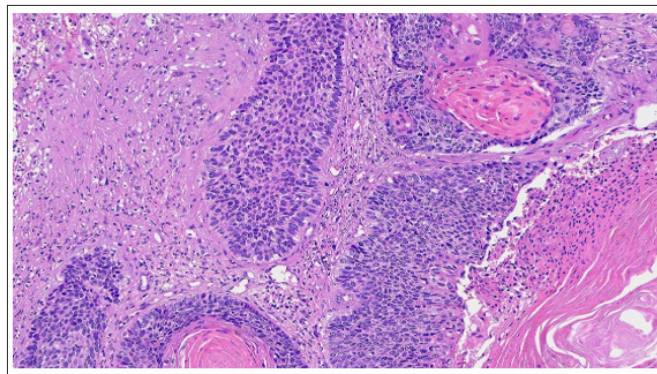
**Table 1: Showing Clinical Characteristics of Oral Squamous Cell Carcinoma**

Characteristic	Frequency	Proportion (%)
<b>Age</b>		
≤ 55years	49	47.2
> 55years	55	52.8
<b>Sex</b>		
Male	75	72.1
Female	29	27.9
<b>Topographical Sites</b>		
Tongue	44	42.3
Palate	24	23.1
Buccal Mucosa	8	7.7
Floor of Mouth	1	1
Lip	7	6.7
Others*	20	19.2

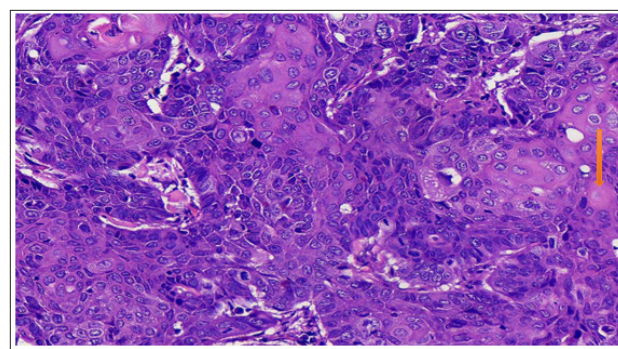
\*Includes Gingiva, Alveolar Ridge, Tonsil and those from Unspecified Sites.

**Table 2: Showing Histological Subtypes of Oral Squamous Cell Carcinoma**

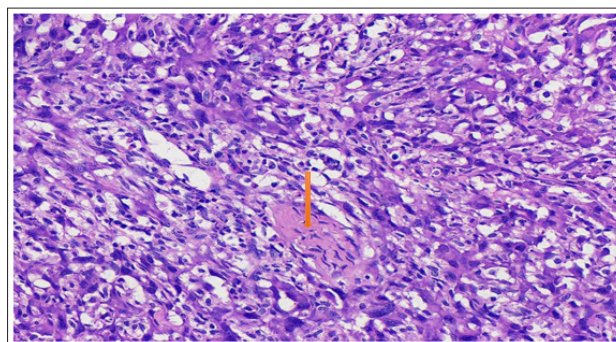
Histological Subtype	Frequency (n = 104)	Proportion (%)
<b>Conventional</b>	92	88.5
Basaloid	8	7.7
Verrucous	0	0
<b>Sarcomatoid</b>	2	1.9
Adenosquamous	0	0
Acantholytic	0	0
<b>Cuniculatum</b>	0	0
Papillary	2	1.9
Palate	24	23.1
Buccal Mucosa	8	7.7



**Figure 1:** Photomicrograph Showing Well Differentiated Squamous Cell Carcinoma, Basaloid Histological Subtype. There are a few Keratin Pearls, the Tumor Cells are Hyperchromatic and show a Periphery Palisading Pattern in the Tumor Islands (H&E stain, X200)



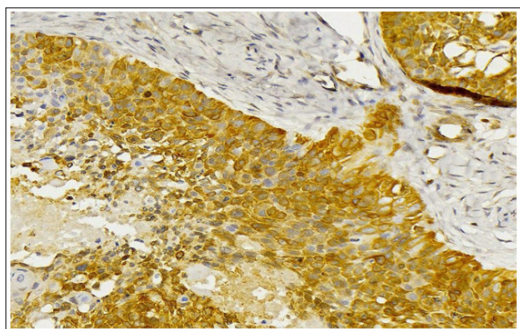
**Figure 2:** Photomicrograph Showing Moderately Differentiated Squamous Cell Carcinoma. The Squamoid Cells Show Moderate Nuclear Pleomorphism and Individual Cell Keratinization (Orange Arrow) (H&E stain, X200)



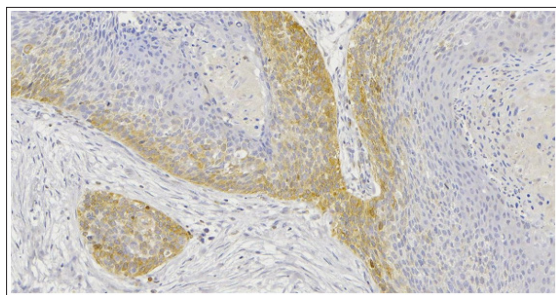
**Figure 3:** Photomicrograph Showing Poorly Differentiated Sarcomatoid Squamous Cell Carcinoma with Spindle Cells having Marked Nuclear Pleomorphism, Prominent Nucleoli and Perineural Invasion (Orange Arrow) (H&E stain, X400)

### Bcl-2 Expression prevalence and pattern

Bcl-2 Expression prevalence and pattern Bcl-2 protein expression was detected in 29.8% (31 out of 104) of the cases. The staining pattern was predominantly granular and cytoplasmic (figure 4). In well-differentiated tumors, a distinct peripheral staining pattern was observed, where the periphery of the tumor nests displayed more intense staining than the center (figure 5). Regarding staining intensity, 21 cases (67.7% of positives) exhibited weak intensity, 8 cases (25.8%) showed moderate intensity, and 2 cases (6.5%) were classified as strong. In terms of cellular distribution, 10 cases demonstrated greater than 50% staining, 4 cases showed 26–50% staining, 9 cases exhibited 5–25% staining and 8 cases less than 5% staining.



**Figure 4:** Photomicrograph Showing Bcl-2 Protein Expression with Brown Granular Cytoplasmic Staining (IHC stain, X200)



**Figure 5:** Photomicrograph of a Well-Differentiated Squamous Cell Carcinoma with Moderate Bcl-2 Protein Staining Intensity Decreasing towards the Centre of the Tumor Nests and Island (IHC stain, X100)

**Association with Demographic and Clinical Features**

Bcl-2 expression was found to be higher in males (34.7%) compared to females (17.2%). Although this difference was not statistically significant at the bivariate level ( $p = 0.08$ ), it reached significance in the multivariate model. Age ( $p = 0.26$ ) and tumor site ( $p = 0.59$ ) showed no significant associations with Bcl-2 status shown in Table 3.

**Table 3: Showing the Association of Bcl-2 Protein Expression with Patient’s Age and Sex**

Parameter	Bcl-2 expression		p value
	Negative Bcl-2 n (%)	Positive Bcl-2 n (%)	
Age (years)			
≤ 55	37 (75.5)	12 (24.5)	p = 0.26
> 55	36 (63.2)	19 (33.3)	
Sex			
Male	49 (65.3)	26 (34.7)	p = 0.08
Female	24 (82.8)	5 (17.2)	
Topographical sites			
Tongue	33 (75.0)	11 (25.0)	p = 0.59
Palate	15 (62.5)	9 (37.5)	
Buccal mucosa	7 (87.5)	1 (12.5)	
Floor of mouth	1 (100)	0 (0)	
Lip	5 (71.4)	2 (28.6)	
Other sites	12 (60.0)	8 (40.0)	

Other sites include; gingiva, alveolar ridge, tonsil and those from unspecified sites.

**Association with Histological Features**

A significant association was observed between Bcl-2 expression and histological subtypes ( $p = 0.021$ ), with the basaloid subtype exhibiting the highest expression rate at 75%. No significant association was found between Bcl-2 expression and histological grade ( $p = 0.32$ ), although moderately differentiated tumors displayed a higher percentage of positivity (40%) compared to well-differentiated (24.6%) and poorly differentiated (30.8%) tumors. Findings were summarized in Table 4.

**Table 4: Showing the Association between Bcl-2 Protein Expression with Histological Subtypes and Histological Grades of Oral Squamous Cell Carcinoma**

Parameter	Bcl-2 protein expression		p value
	Negative Bcl-2 (n = 73)	Positive Bcl-2 (n = 31)	
Histological Subtypes			
Conventional	69 (75.0)	23 (25.0)	p = 0.021
Basaloid	2 (25.0)	6 (75.0)	
Verrucous	0 (0.0)	0 (0.0)	
Sarcomatoid	1 (50.0)	1 (50.0)	
Adenosquamous	0 (0.0)	0 (0.0)	
Acantholytic	0 (0.0)	0 (0.0)	
Cuniculatum	0 (0.0)	0 (0.0)	
Papillary	1 (50.0)	1 (50.0)	
Histological Grade			
Well Differentiated	46 (75.4)	15 (24.6)	p = 0.32
Moderately Differentiated	18 (60)	12 (40)	
Poorly Differentiated	9 (69.2)	4 (30.8)	

**Multivariate Predictors**

Multivariate analysis identified male sex and the basaloid subtype as independent predictors of Bcl-2 expression. Males were significantly more likely to express Bcl-2 than females (adjusted odds ratio [aOR] = 4.76, 95% confidence interval [CI]: 1.22–18.60,  $p = 0.025$ ). Additionally, the basaloid subtype was highly associated with Bcl-2 expression, being nearly 39 times more likely to be positive than the conventional subtype (aOR = 38.77, 95% CI: 3.53–425.85,  $p = 0.003$ ).

**Discussion**

The prevalence of Bcl-2 expression in our Ugandan cohort was 29.8%, a figure that is consistent with findings from other regions, including Poland, where a rate of 27% was reported by [20], and India, with a reported rate of 30% by [16]. However, studies regarding Bcl-2 prevalence in oral squamous cell carcinoma (OSCC) are highly controversial, with reported rates varying significantly from as high as 63% [15] to as low as 8.6% [22]. These discrepancies may stem from differences in genetic backgrounds, local etiological factors (such as specific forms of tobacco use, including chewing versus smoking), and variations in methodologies related to immunohistochemical (IHC) scoring and antibody selection [20,23].

In our study, we noted that Bcl-2 expression in well-differentiated tumors was most intense at the periphery of the tumor nests, particularly at the invasive front. This pattern has been corroborated

by several authors [22,24,25]. The concentration of anti-apoptotic proteins at the tumor periphery suggests that Bcl-2 provides a survival advantage to the proliferative cellular compartment, facilitating local invasion into surrounding tissues. This peripheral staining supports the hypothesis that Bcl-2 contributes to the biological aggressiveness of OSCC, even in cases classified as low-grade histopathologically.

Our multivariate analysis revealed that male patients are nearly five times more likely to express Bcl-2 compared to females. This finding is consistent with the results reported by [21] but contrasts with some studies in head and neck cancers [26]. The association with male sex may reflect cumulative exposure to risk factors more prevalent among Ugandan men, such as heavy tobacco and alcohol use, which could trigger specific molecular alterations favoring evasion of apoptosis. Notably, age showed no significant association with Bcl-2 expression, indicating that Bcl-2-mediated cell survival occurs independently of the age at diagnosis.

One of the most significant findings of this study was the strong association between the basaloid histological subtype and Bcl-2 positivity (aOR 38.77). Basaloid squamous cell carcinoma (SCC) is recognized as an aggressive variant with a poor prognosis, characterized by high recurrence rates and early metastasis [27]. Our results suggest that Bcl-2 overexpression is a primary driver of the basaloid phenotype, enabling these tumors to evade programmed cell death and survive under adverse conditions. This makes the basaloid subtype a prime candidate for Bcl-2-targeted therapies currently under investigation.

Consistent with findings by [24] and [28], we found no significant association between Bcl-2 expression and histological grade. This implies that while Bcl-2 promotes cell survival, it is not the dominant factor determining cellular differentiation in OSCC. Similarly, the topographical site of the tumor (e.g., tongue versus palate) did not influence Bcl-2 status, suggesting that the apoptotic mechanisms remain consistent across various locations within the oral cavity

### Conclusion

This study demonstrates that approximately 30% of (OSCC) cases in Uganda exhibit Bcl-2 protein expression. A significant association was observed between Bcl-2 protein expression and basaloid subtype of oral squamous cell carcinoma. Males were also significantly more likely to express Bcl-2 than females. These findings highlight Bcl-2 not only as a valuable prognostic biomarker but also a promising therapeutic target, warranting further investigation. No significant association between Bcl-2 protein expression and histological grade was noted. The observed immunohistochemically staining pattern specifically the concentrated expression at the peripheral margins of tumor nests underscores the likely role of Bcl-2 in facilitating tumor invasiveness and survival at the advancing neoplastic front.

### Ethical Considerations

This study was conducted in strict accordance with ethical guidelines, receiving formal approval from the Makerere University School of Biomedical Sciences Research and Ethics Committee (SBSREC) and the Uganda National Council for Science and Technology. Given the retrospective nature of the study and the use of deidentified archival materials, the SBSREC granted a waiver of informed consent (Reference Number: SBS-858). To protect participant privacy, all original patient identifiers,

including names and hospital biopsy numbers, were replaced with unique study specific identification codes.

### Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

### Conflicts of Interest

The authors declare that there are no financial, personal, or professional conflicts of interest that could influence the results or interpretation of this research.

### Funding Statement

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### Authors' Contributions

W.A. was responsible for the study's conceptualization, design, data management, and statistical analysis, and led the initial manuscript development. T.O., M.A., N.V., K.F., and B.K.A provided critical intellectual input and revisions to the manuscript. B.M. contributed to the final drafting and comprehensive proofreading. The project was supervised by A.L.O., H.N., and K.S. All authors have reviewed and provided their final approval for this version of the manuscript.

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