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A STUDY ON THE EXPRESSION OF BCL-2, KI-67, AND E-CADHERIN AND THEIR CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS IN ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a common malignancy across the globe with a considerable amount of morbidity and mortality. Although contemporary therapeutic interventions have advanced, assessment of prognosis is largely dependent on the histopathological evaluations; however, in some cases, the histopathology may fail to reflect the behaviour of the tumor. Therefore, immunohistochemical markers such as BCL-2, Ki-67, and E-cadherin, which show the aspects of apoptosis, proliferation, and cell adhesion, are being considered to determine prognosis. The present study aimed to determine the immunohistochemical expression of BCL-2, Ki-67, and E-cadherin in histopathologically confirmed cases of OSCC.

Materials and Methods: This prospective study was done on 60 confirmed cases of OSCC histopathologically. Immunohistochemical staining of the formalin-fixed and embedded tissue sections was done for BCL-2, Ki-67, and E-cadherin. Semiquantitative analysis of expression patterns was performed through immunoreactive scoring systems. A comparison of clinicopathological variables such as age, gender, tumor stage, histological grade, and lymph node metastasis was done using Chi-square and Spearman correlation tests.

Results: The results of this study showed that BCL-2 positivity (IRS > 3) was observed in 26.7% of cases. A high Ki-67 index (>20%) was found in 68.3% of the cases. Loss or reduced expression of E-cadherin was found in 63.3% of cases of OSCC. The evaluation of high expression of Ki-67 and low E-cadherin was found to have a significant correlation, and the p-values were found to be significant. Poor histopathological differentiation and nodal metastasis were also found to be positively correlated with increased markers. The expression of BCL-2 was increased in higher stages and nodal metastasis of OSCC cases, and the p-values were significant. There was a negative correlation between Ki-67 and E-cadherin expression ($r = -0.41$ and $p = 0.001$).

Conclusion: The change in the expression of immunohistochemical markers such as BCL-2, Ki-67, and E-cadherin is an indication of tumor progression and aggressiveness in OSCC. Higher grade tumors and metastasis are contributed to by high proliferative activity as well as loss of adhesion integrity and increased anti-apoptotic signaling. Therefore, a combined assessment of the immunohistochemical markers with histopathology can be used to assess prognosis as well as guide the management of these cases.

Keywords: BCL-2, Ki-67, E-cadherin, Oral squamous cell carcinoma (OSCC).

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most prevalent oral cancer. It is estimated to be 90% of all the cancers detected in the oral cavity. It is one of the major global health concerns, and its prevalence is increasing in developing countries. It is ranked as the 6th most prevalent malignancy in the world. OSCC is known to have a high rate of morbidity and mortality because of delayed presentation and diagnosis, as well as a significantly high potential for local invasion and metastasis.[1] The burden of OSCC is increasing in countries such as India and Southeast Asian countries due to the existence of habits such as tobacco consumption, betel quid, and alcohol use.[2] Although therapeutic advances in the treatment of OSCC have taken place, the 5-year survival of cases with OSCC remains at 50% which indicates that there is a requirement for earlier diagnosis with predictive biomarkers.[3] The biological behaviour of the OSCC appears to be heterogeneous even in cases with similar histological presentation. This heterogeneity is because of differences in genetic, molecular, and cellular alterations, which are responsible for tumor initiation, progression, and metastasis.[4] Thus, the analysis of molecular markers that indicate the proliferative, anti-apoptotic, and adhesive properties of tumor cells can provide information about the aggressiveness of tumors and their prognosis. BCL-2 (B-cell Lymphoma 2), Ki-67, and E-cadherin have become important biomarkers of tumor biology and clinical prognosis in OSCC amongst the other biomarkers examined. [5,6] BCL-2 oncoprotein is anti-apoptotic in function and is responsible for regulation of apoptosis. Increased expression of BCL-2 leads to inhibition of apoptosis which allows genetically mutated cell to survive and proliferate.[7] Studies have shown that BCL-2 increase is correlated with aggressive behaviour of tumors and potential for metastasis.[8] Ki-67 is a nuclear protein existing all the active cell cycle stages however, remains absent in the resting state of the cell cycle. It is a reliable marker of cell proliferation. Ki-67 is used in the assessment of the proliferative potential of the tumor, given by its index. An increased level of Ki-67 index is known to be associated with high tumor grade, aggressive growth, and poor prognosis in oral squamous cell carcinoma. [9,10] E-Cadherin is also another important biomarker which is a calcium dependence cell adhesion glycoprotein. It plays a vital role in epithelial integrity and intercellular adhesion. The loss or downregulation of E-cadherin functionality leads to cell-cell adhesion disruption, which intensifies epithelial-mesenchymal transition (EMT) that increases the capability of the cancer cell to metastasise.[11] Research has revealed that a reduced E-cadherin in OSCC is linked to a higher lymph node metastasis, poorly differentiated malignant cell, and a poor prognosis in OSCC.[12,13] The simultaneous assessment of the BCL-2, Ki-67, and E-cadherin expressions can aid in understanding the molecular dynamics of OSCC progression. These markers with clinicopathological parameters such as tumor grade, stage, and lymph node involvement can help in identifying the high-risk cases and instituting appropriate management strategies.[14] With this background, we in the current study aimed to assess the expression patterns of BCL-2, Ki-67, and E-cadherin in oral squamous cell carcinoma presenting to our tertiary care hospital.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Pathology with specimens received from the Department of Oral Surgery, ENT, and Oncology. Institutional Ethical approval was obtained for the study. The cohort included was based on a convenience sample method determined by case availability and institutional resources.

Inclusion Criteria

1. Patients with samples confirmed as oral squamous cell carcinoma by initial histopathology examination.
2. Availability of the formalin-fixed and paraffin-embedded tumor blocks.
3. Availability of the clinical details, including age, sex, risk habits, tumor site, TNM staging, and nodal status.

Exclusion Criteria

1. Recurrent cases
2. Specimens with insufficient tumor tissue in blocks and poor fixation
3. Non-squamous histology or metastatic lesions of the oral cavity.
4. Non-availability of the clinical details

A total of n=60 consecutive samples were included in the study based on the inclusion and exclusion criteria during the duration of the study. All the cases had adequate formalin-fixed paraffin-embedded (FFPR) tumor tissue sufficient for immunohistochemistry staining and availability of the clinicopathological details. The clinicopathological details included age, sex, tobacco/betel/alcohol habits, tumour site, and clinical TNM stage. The histopathological parameters were recorded from H&E sections, which included tumor grade (well/moderately/poorly differentiated). Depth of invasion and nodal metastasis. The tumor staging was done according to the AJCC/UICC TNM classification.

Tissue processing and immunohistochemistry (IHC) were done using representative FFPE blocks selected. A 4 µm section was cut on a microtome and mounted on poly-L-lysine-coated slides. One slide was stained with H&E for confirmation of tumour region and grade, and adjacent sections were used for IHC.

Antibodies and reagents used for BCL-2: monoclonal antibody (clone 124 or equivalent). Dilution 1:100 (optimize as per manufacturer). Ki-67: MIB-1 monoclonal antibody. Dilution 1:100. E-cadherin: clone NCH-38 or equivalent. Dilution 1:100. The

final clone and dilutions were done as per the manufacturer's recommendations.

Scoring systems

Ki-67 (proliferation index) was determined by identifying "hotspot" areas in low power. The count was done for at least 500–1000 tumour cell nuclei under high power (40×) and the Ki-67 labeling index (LI) = (number of positive nuclei / total nuclei counted) ×100. For analysis, cases were categorized as low vs high proliferation using a predefined cutoff at 20%.

BCL-2 was estimated by evaluating cytoplasmic (and/or membranous) staining in tumour cells. Record percentage of positive tumour cells and intensity (0 = none, 1 = weak, 2 = moderate, 3 = strong). An immunoreactive score (IRS) may be calculated (percentage score × intensity) and dichotomized (IRS > 3 = positive).

E-cadherin was assessed by a membranous staining pattern. Record intensity (0–3) and percentage of positive cells. Define preserved versus reduced/lost expression using an IRS or cutoff (for example, IRS ≤4 = reduced/lost; IRS >4 = preserved). Loss of normal, strong membranous staining will be considered significant.

Observer variation: Two experienced pathologists were independently scoring all slides. Discrepancies will be resolved by joint review, and interobserver agreement will be quantified using Cohen's kappa.

Statistical Analysis: The data were segregated, refined, and uploaded to an MS Excel spreadsheet and analyzed by SPSS version 26 in Windows format. The continuous variables were represented as mean, standard deviation, frequencies, and percentages. The continuous comparisons were done by the Mann-Whitney U test. The categorical variables were tested using the Chi-square test for differences between two groups. Correlation between markers will be assessed by Spearman's rank correlation coefficient test.

RESULTS

A total of 60 consecutive cases of confirmed oral squamous cell carcinoma were included in the study. The baseline characteristics of the cases are given in Table 1. A critical analysis of the table shows that of the 60 cases, most of the cases (70%) were aged more than 50 years, and the mean age of the cohort was 58.4 ± 10.2 years, implying that this lesion is more predominant after the age of 50 years. The gender analysis showed that male was 68.3% of total cases, with a male-to-female ratio of 2.1:1. Approximately, this could be because risky habits are more common in male counterparts. The analysis of risk habits showed that 80% of the cases had a positive history of betel nut or tobacco consumption, which establishes the role of these agents in oral carcinogenesis. The anatomical location of the tumor showed that the tongue was the common site in 41.7% of cases, followed by buccal mucosa in 33.3% and alveolus in 13.3% of cases. The identification of cases based on the staging showed that 63.3% of cases were in the advanced stage of the disease (Stage III and IV), which could be because of delayed diagnosis or poor awareness. Histopathology examination showed that 46.7% of tumors were moderately differentiated, 41.7% were well differentiated, and the remaining 11.7% had poor differentiation. The lymph node metastasis was found to be present in 53.3% of cases, indicating the high potential for regional spread, which shows the aggressive nature of the tumors.

Expression of BCL-2, Ki-67, and E-Cadherin immunohistochemistry is given in Table 2. A critical analysis of the table showed that BCL-2 positivity with IRS scores of (>3) were found to be present in 26.7% of cases (Figure 1) and remaining 73.3% of cases were negative for BCL-2 positivity. Therefore, BCL-2 expression is not uniform in all cases of OSCC it tends to occur in few varieties of OSCC. The Ki-67 proliferation index of (>20%) was found to be present in 68.3% of cases (Figure 2) the overall mean values of Ki-67 was 32.5 ± 14.2% was recorded in the cases of the study. Cellular adhesion integrity which is recorded by E-cadherin expression was found to be preserved in 36.75% of cases of the study and the remaining 63.3% showed decreased of loss of membranous staining (Figure 3). The overall results found here shows that there is a tendency in considerable number of cases having high proliferative indices with decreased cell adhesion and anti-apoptotic resistance which increases the risk of tumor progression and metastasis.

In Table 3, the expression of the markers was significantly related to significant clinicopathological parameters. The presence of BCL-2 in the advanced tumors (III and IV grades) ($p = 0.03$) was also significantly higher, as well as its presence in tumors that metastasized to the lymph nodes ($p = 0.01$) indicating that it contributed to the survival and metastasis of the tumor. Ki-67 high expression was observed in much more advanced tumor ($p = 0.018$), poorer differentiation ($p < 0.001$) and metastasis ($p < 0.005$) of the lymph nodes. Also, it was found that the reduction/loss of E-cadherin had significant correlations with higher tumor stage ($p = 0.009$), poor differentiation ($p = 0.002$), and nodal metastasis ($p = 0.001$). But all three markers did not significantly correlate with age or gender ($p > 0.05$), so their expression is more related to tumor biology than demography. These findings indicate that the deregulation of the functions of the molecules of apoptosis, proliferation, and adhesion pathways has a complex effect on the aggressiveness and clinical progression of OSCC.

A comparative correlation analysis between the BCL-2, Ki-67, and E-Cadherin Expression is given in Table 4. A critical analysis of the table showed that a weak positive correlation was found between BCL-2 and Ki-67, which may indicate that the effect of anti-apoptotic activity is positively correlated with the increased proliferation, although not statistically significant. There was a weak negative correlation

between BCL-2 and E-cadherin (r = -0.22, p = 0.089), indicating that tumors that have greater anti-apoptotic capacity have lower cell adhesion, suggesting a potential mechanism of action of invasiveness. This study found that the statistically significant moderate negative correlation between Ki-67 and E-cadherin (r = -0.41, p = 0.001) was existing and therefore it implied that more the proliferative activity, the less the E-cadherin expression. All these correlations combined promote the notion that deregulation of apoptosis, proliferation, and adhesion is additive to promote OSCC aggressiveness.

Table 1: Baseline Clinicopathological Characteristics of the Study Cohort (n=60)

Characteristic	Category	Number of Patients	Percentage (%)
Age (Years)	≤ 50	18	30
	≥ 50	42	70
Mean ± SD	58.4 ± 10.2		
Gender	Male	41	68.3
	Female	19	31.7
Tobacco/Betel Nut Habit	Present	48	80
	Absent	12	20
Tumour Site	Tongue	25	41.7
	Buccal Mucosa	20	33.3
	Alveolus	8	13.3
	Other	7	11.7
TNM stage (AJCC/UICC)	I & II	22	36.7
	III & IV	38	63.3
Tumour Grade	Well Differentiated	25	41.7
	Moderately Differentiated	28	46.7
	Poorly Differentiated	7	11.7
Lymph Node Metastasis	Present	32	53.3
	Absent	28	46.7

Table 2: Expression Profiles of BCL-2, Ki-67, and E-Cadherin in Oral Squamous Cell Carcinoma

Immunohistochemical Marker	Expression Pattern	Number of Cases	Percentage (%)
BCL-2 Expression	Positive (IRS > 3)	16	26.7
	Negative (IRS ≤ 3)	44	73.3
Ki-67 Labeling Index (Mean ± SD)	32.5% ± 14.2%		
Ki-67 Category	Low (≤ 20%)	19	31.7
	High (> 20%)	41	68.3
E-Cadherin Expression	Preserved (Normal)	22	36.7
	Reduced/Loss	38	63.3

BCL-2 positivity is defined as an immunoreactive score (IRS = percentage score x intensity) > 3. Ki-67 high proliferation is defined as Labeling Index > 20% (based on median split or predefined cutoff). E-Cadherin reduced/Loss is defined as an IRS ≤ 4 or a clear reduction in loss of normal, strong membranous staining.

Table 3: Correlation of Immunohistochemical Markers with Clinicopathological Parameters

Clinicopathological Parameter	BCL-2 Positive (n=16)	BCL-2 Negative (n=44)	p-value	Ki-67 high (n=41)	Ki-67 low (n=19)	p-value	E-Cadherin Reduced/ Loss (n=38)	E-Cadherin preserved (n=12)	p-value
Age									
< 50 years	4	14	0.45	12	6	0.801	10	8	0.223
≥ 50 years	12	30		29	13		28	14	
Gender									
Male	12	29	0.77	29	12	0.394	27	14	0.587
Female	4	15		12	7		11	8	
Tumour Stage									
I & ll	2	20	0.03*	10	12	0.018*	9	13	0.009*
III & IV	14	24		31	7		29	9	
Tumour Grade									
Well Diff.	3	22	0.04*	10	15	<0.001 *	10	15	0.002*
Moderate/Poor Diff.	13	22		31	4		28	7	
Lymph Node Metastasis									
Present	12	20	0.01*	27	5	<0.005 *	27	5	0.001*
Absent	4	24		14	14		11	17	
*Significant									

Table 4: Inter-correlation Between BCL-2, Ki-67, and E-Cadherin Expression

Marker Correlation	Spearman's Correlation Coefficient (ρ)	p-value
BCL-2 vs. Ki-67	0.18	0.162
BCL-2 vs. E-Cadherin	-0.22	0.089
Ki-67 vs. E-Cadherin	-0.41	0.001*
*Significant		

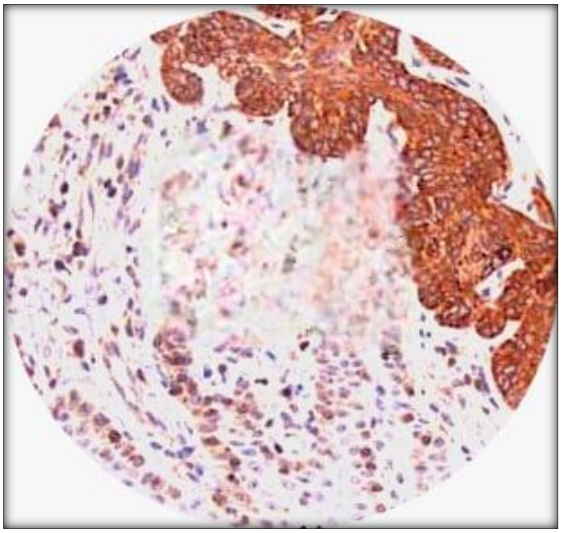

Figure 1: Immunohistochemical expression of BCL-2 in oral squamous cell carcinoma (OSCC) showing strong cytoplasmic positivity in tumor cells at the invasive front (brown staining), indicating anti-apoptotic activity. Adjacent stromal and inflammatory cells show weak or negative staining. (IHC, DAB chromogen, ×400)

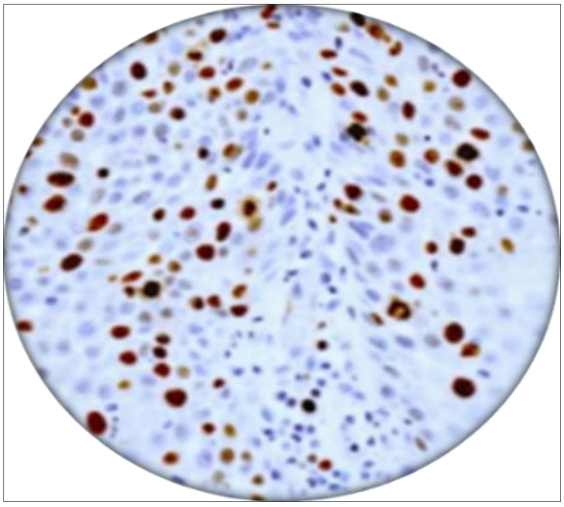

Figure 2: Immunohistochemical expression of Ki-67 in oral squamous cell carcinoma (OSCC) showing strong nuclear positivity (brown staining) in numerous tumor cells, indicating high proliferative activity. The labeling index reflects increased cellular turnover associated with tumor aggressiveness. (IHC, DAB chromogen, ×400)

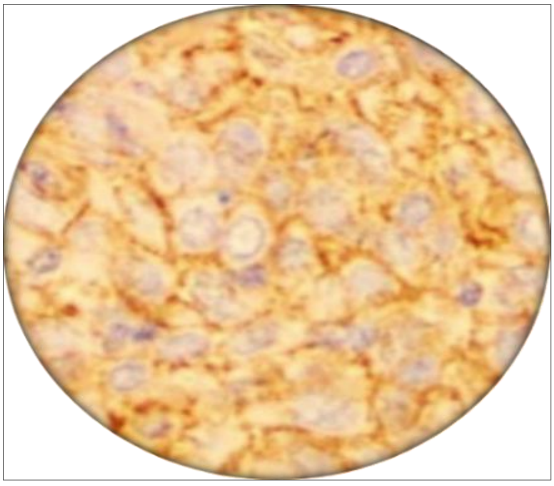

Figure 3: Immunohistochemical staining for E-cadherin in oral squamous cell carcinoma (OSCC) showing loss or marked reduction of membranous staining in tumor cells, indicating disrupted cell–cell adhesion and epithelial integrity. The weak or absent membranous expression corresponds to increased invasiveness and metastatic potential. (IHC, DAB chromogen, ×400)

DISCUSSION

This study was done to evaluate the immunohistochemical expression of three markers, BCL-2, Ki-67, and E-cadherin, in cases of oral squamous cell carcinoma (OSCC). As established, BCL-2, Ki-67, and E-cadherin are involved in apoptosis inhibition, cellular proliferation, and loss of adhesion, respectively, and are involved in tumor aggressiveness. Their expression was correlated with various clinicopathological parameters. The clinicopathological parameters of this study showed (Table 1) that OSCC predominantly occurred in individuals aged more than 50 years and commonly involved males because of the existence of one of the risk habits that included tobacco and betelnut use, which was more common in male counterparts. The anatomical location showed that the tongue and buccal mucosa are the common sites for OSCC, which occurs because chronic mucosal irritation is very common in these areas of the oral cavity, due to the habit of placing tobacco in the buccal mucosa or chewing betelnut, leading these areas to increased carcinogen exposure and increasing vulnerability. The high incidence of the advanced stage (63.3%) of cases and lymph node metastasis (53.3%) of cases underlines the late presentation of OSCC cases and the importance of early molecular screening of the disease to improve the prognosis. The increased expression of BCL-2 was found in 26.7% of the cases, and it was mainly seen in the tumors that were

of advanced stage and those that had lymph node metastasis. The finding indicates that the involvement of anti-apoptotic factors plays a major role in tumor survival and dissemination. BCL-2 inhibits programmed cell death by inhibiting the release of mitochondrial cytochrome c, thus increasing the lifespan of genetically unstable cells. To the extent that the high-stage tumor in our study is accompanied by the BCL-2 positivity, the hypothesis that cell survival prolongs the malignant potential holds. Nevertheless, the overall expression rate is rather low, which suggests that the upregulation of BCL-2 is not likely to be universal among all OSCCs and might be determined by the level of differentiation and molecular subtype. The linking of BCL-2 positivity with advanced-stage tumors shows that prolonged cell survival is the key factor in increasing their malignant potential. Although the overall values of BCL-2 in this study were relatively low, this shows that BCL-2 upregulation may not be uniform in all cases of OSCCs and may involve the degree of differentiation and molecular subtype.[15] The assessment of the Ki-67 index in our study showed that high proliferation (>20%) was found in 68.3% of cases, which indicates increased mitotic activity of the OSCC cells. Ki-67 high level of expression was significantly associated with poor histological differentiation, higher stages and the metastasis of the lymph nodes, and this confirms that it is a marker of tumor aggression. These results indicate the levels are increased in cases of poor differentiation and invasiveness that accompanies higher levels of proliferation. It has been demonstrated that Ki-67 is an effective prognostic biomarker in head and neck cancer because the high level of Ki-67 expression is associated with poorer survival, as well as reduced responsiveness to the treatment with chemoradiation.[16,17] A moderate positive correlation between BCL-2 and Ki-67 expression in this study indicates that there is a link between the anti-apoptotic signaling and accelerated proliferation, and both mechanisms work synergistically to promote tumor progression. OSCCs lost or downregulated e-cadherin expression, which is essential to preserve the epithelial structure. The results of our study showed that loss/decreased E-cadherin which predominantly indicates the epithelial-to-mesenchymal transition (EMT) was correlated with increased tumor stage, poor differentiation and metastasis.

The loss of E-cadherin makes the intercellular adhesion weak; thus, tumor cells are detached, invading, and metastasizing. These results support the roles of E-cadherin as an invasion-suppressor protein. High Ki-67 and low E-cadherin tumors showed especially aggressive clinicopathological characteristics, indicating that concomitant proliferative activation and loss of adhesion are the key factors to OSCC aggressiveness. Estimation of E-cadherin expression in this study showed that 63.3% of the cases had reduced or lost expression in OSCCs. The further analysis showed that the level of E-cadherin loss was correlated with higher grade tumor stage, poor differentiation, as well as nodal metastasis, indicating its role in epithelial to mesenchymal transition (EMT). The loss of E-cadherin makes the intercellular adhesion weak; thus, tumor cells get detached easily, invading and metastasizing. These results support the roles of E-cadherin as an invasion-suppressor protein. High Ki-67 and low E-cadherin tumors showed especially aggressive clinicopathological characteristics, indicating that concomitant proliferative activation and loss of adhesion are the key factors to OSCC aggressiveness.[18] The correlation analysis between the three makers showed that a significant inverse relationship between Ki-67 and E-cadherin ($r = -0.41$, $p = 0.001$) implies that the higher the cellular proliferation, the lower the adhesion integrity, which allows invasion of local and metastatic processes. The weak positive correlation between BCL-2 and E-cadherin is indicative of the resistance to apoptosis potentially being matched by the adhesion loss, which is typical of invasive tumors. The interactions were similar to the molecular cascade of OSCC development, with dysregulation of apoptotic regulation, an increase in proliferation, and interruption of cell adhesion all contributing to malignant transformation.[19] Therefore, a combination of these markers provides useful diagnostic and prognostic information. BCl-2, Ki-67 and E-cadherin are the immunohistochemical markers which indicates overall aggressiveness of tumor and invasiveness. Therefore, analysis of all these markers is essential to categorize patients based on the risks and they can help in guiding in treatment planning. As an example, BCL-2 inhibitors or proliferation-targeted therapies can be used to add to the conventional management of tumors with high BCL-2 and Ki-67.

As with any other study, this study had its own limitations, which were due to its sample size, giving limited statistical power in finding associations. Long-term survival analysis of the cohort was not assessed. However, this study as with any other research has its own limitations which must be kept in mind before generalizing the results. The first limitation was because of its sample size which was on lower side which may limit the statistical power in finding subtle association. A long term follow up for 5 years was required to determine the survival analysis which was not done due to duration constraints of the study. This study was done on a cohort from one hospital. However, larger multicentric cohorts with additional molecular analysis which may include Bax, p53, and β-catenin will give better understanding of the tumor biology. Moreover, the study did not assess survival outcomes, which could provide stronger prognostic correlations. Future research incorporating larger, multicentric cohorts and molecular analyses, including other apoptosis and adhesion-related markers such as Bax, p53, and β-catenin, may yield a

more comprehensive understanding of OSCC biology.

CONCLUSION

The study, within its limitations, found that changes in the expression of BCL-2, Ki-67, and E-cadherin had a close relationship with the biological behavior of oral squamous cell carcinoma. Increased BCL-2 and Ki-67 are associated with higher tumor stage, low differentiation, and lymph node metastasis, which represent aggressive behaviours and potential for metastasis. On the other hand, decreased E-cadherin is an indicator of a lack of cell adhesion and increased invasiveness. Ki-67 and E-cadherin are complementary since their relationship is inversely associated. Therefore, the joint assessment of these biomarkers will be useful prognostic data and can be used as a supplementary tool in risk classification and therapeutic decision-making for OSCC patients.

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