RESEARCH PAPER

IMMUNOHISTOCHEMICAL STUDY OF E-CADHERIN EXPRESSION IN VARIOUS GRADES OF EPITHELIAL DYSPLASIA AND SQUAMOUS CELL CARCINOMA OF ORAL CAVITY

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Abstract

Background: Oral epithelial dysplasia (OED) and oral squamous cell carcinoma (OSCC) represent a continum of oral carcinogenesis characterized by progressive disruption of epithelial integrity. E-cadherin, a key cell–cell adhesion molecule, plays a crucial role in maintaining epithelial cohesion, and its altered expression is implicated in tumor progression and invasion. This study was aimed to evaluate E-cadherin expression by immunohistochemistry across various grades of OED and OSCC and to assess its correlation with histopathological severity and clinicopathological parameters.

Materials and Methods: This prospective study included 50 histopathologically confirmed cases of oral biopsy. E-cadherin expression was assessed using immunohistochemistry and evaluated based on staining pattern, intensity, percentage of positive cells, and immunoreactive score (IRS). Expression levels were correlated with dysplasia grades and tumor differentiation.

Results: The mean age noted was 57.4 ± 11.8 years with male predominance (56%). Predominantly membranous staining was observed (96%). In OED, high E-cadherin expression was noted in 100% of mild dysplasia, 66.67% of moderate dysplasia, and absent in severe dysplasia, showing a significant association ($p = 0.0356$). In OSCC, high expression decreased from 85.71% in well-differentiated tumors to 35.29% in moderately differentiated and 25% in poorly differentiated tumors ($p = 0.005$). A shift toward reduced intensity and occasional cytoplasmic localization was observed with increasing severity.

Conclusion: E-cadherin expression shows a significant inverse relationship with histopathological severity in OED and OSCC. Progressive loss of membranous expression and altered localization reflect increasing tumor aggressiveness. E-cadherin may serve as a useful adjunct biomarker for risk stratification and prognostic assessment in oral potentially malignant and malignant lesions.

Keywords: E-cadherin, Oral epithelial dysplasia, Oral squamous cell carcinoma; Immunohistochemistry, Cell adhesion, Tumor progression.

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Introduction

Oral cancer continues to represent one of the most challenging oncological problems worldwide, particularly in regions with high consumption of tobacco, alcohol, and areca nut–based products, and the World Health Organization has consistently ranked it among the major causes of cancer-related deaths in South-Asian populations, reflecting significant global disparities in incidence and survival outcomes and emphasizing the necessity for improved diagnostic and prognostic approaches in early oral carcinogenesis [1].

The sequence of events leading from normal oral mucosa to invasive oral squamous cell carcinoma (OSCC) is complex and multifactorial, involving accumulative genetic mutations, epigenetic modifications, and altered signaling pathways; this multistep model highlights the importance of recognizing oral epithelial dysplasia (OED) as a premalignant stage, although its progression cannot be reliably predicted with routine histopathology alone[2]. While histological assessment remains the standard for grading OED, subjective interpretation and inter observer variability necessitate the integration of objective biomarkers that reflect biological aggressiveness [3].

In this context, E-cadherin, a calcium-dependent transmembrane glycoprotein essential for epithelial cohesion and polarity, plays a pivotal role in tumor progression, as its disruption leads to loss of cellular adhesion and increased invasiveness[4]. The CDH1 gene encoding E-cadherin is frequently downregulated in OSCC and other epithelial malignancies, contributing to epithelial–mesenchymal transition (EMT) and enhanced metastatic potential [5].

OSCC constitutes the majority of oral malignancies and often presents at advanced stages with poor prognosis, highlighting the need for reliable biomarkers. Immunohistochemical (IHC) evaluation of E-cadherin expression provides a practical approach to assess protein alterations within tissue context [6]. Studies have shown progressive reduction of membranous E-cadherin expression from normal mucosa to dysplasia and carcinoma, correlating with increased invasiveness and poor prognosis [7].

IHC further enables assessment of protein localization patterns, which carry functional significance, and allows standardized comparison across lesion stages [8]. Therefore, evaluation of E-cadherin expression bridges histopathology with molecular insights, aiding in early detection, risk stratification, and therapeutic planning[9]. Hence, studying E-cadherin expression across different grades of OED and OSCC is both scientifically and clinically valuable in improving diagnostic accuracy and understanding oral carcinogenesis [10].

Materials and Methods

The prospective study was carried out in the Department of Pathology at Adichunchanagiri Institute of Medical Sciences over a period of 18 months (April 2024 to October 2025). The sample size consisted of 50 oral biopsy specimens and only those meeting the inclusion criteria were taken for further analysis. Institutional Ethical clearance was obtained before the commencement of the study.

Inclusion Criteria

All histopathological confirmed cases of oral epithelial dysplasia, premalignant condition and oral squamous cell carcinoma were included.

Exclusion Criteria

Individuals diagnosed with oral squamous cell carcinoma who received neoadjuvant chemotherapy or radiotherapy, along with biopsy specimens that were poorly preserved or not adequately processed.

Study Procedure

Oral biopsies sent for histopathological examination had been considered for the study, and only those meeting the criteria were taken forward for evaluation. After fixation in 10% formalin, the specimens had undergone gross examination to identify representative areas for further processing. Representative bits from tumors, margins, and lymph nodes had been routinely processed in accordance with standard laboratory procedures. Paraffin-embedded blocks where prepared from these processed tissues. These paraffin blocks was subsequently cut into sections that were 3–5 µm thick for microscopic and immunohistochemical studies. Confirmed oral epithelial dysplasia, premalignant and squamous cell carcinoma cases had been subjected to immunohistochemistry using monoclonal mouse anti-Human E cadherin antibodies. The sections had undergone the polymer labeling technique to facilitate antigen detection. The tissue sections had also been dewaxed, followed by washing in alcohol to remove residual paraffin. Antigen retrieval had been carried out in a decloaking chamber with Citra solution. Endogenous peroxidase had been blocked before antibody application. The sections had then been incubated with the primary antibody and subsequently with the polymer. Chromogen application using diaminobenzidine had been performed, followed by counterstaining with hematoxylin. Finally, microscopic examination had been carried out to assess immunoreactivity. Normal oral mucosa serve as a positive control.

Data Analysis

Data was collected, entered into Microsoft Excel and analyzed using the SPSS version 26.0. Chi square test was used to compare variables across the study samples. A p-value of less than 0.05 had been considered statistically significant.

Result

Table 1: Demographic and Clinical Profile (n=50)

Variable	Category	Frequency (%)
Age	31–40	3 (6%)
	41–50	11 (22%)
	51–60	17 (34%)
	61–70	9 (18%)

	71–80	10 (20%)
Gender	Male	28 (56%)
	Female	22 (44%)
Site	Left	28 (56%)
	Right	14 (28%)
	Floor of mouth	8 (16%)

Predominance of middle-aged to elderly individuals was noted, with the highest frequency observed in the 51–60 year's age group (34%), followed by 41–50 years (22%).A minor predominance of males was observed, accounting for 56%, resulting in a male-to-female ratio of 1.27:1. Regarding lesion site, the left side was involved (56%), followed by the right side (28%) and floor of mouth (16.00%). These findings indicate that oral lesions in this study were more frequent in older males and showed a predilection for the left side of the oral cavity.

Table 2: Clinical Diagnosis Distribution (n=50)

Diagnosis	**Frequency (%)**
OSCC	42 (84%)
OED	8 (16%)

The majority of cases were diagnosed as oral squamous cell carcinoma (OSCC) (84%), while oral epithelial dysplasia (OED) constituted a smaller proportion (16%). This reflects a higher representation of malignant lesions compared to premalignant conditions in the study sample.

Clinical diagnosis SCC	**Frequency**	**Percentage**
Well differentiated	21	50%
Moderately differentiated	17	40.48%
Poorly differentiated	4	**9.52%**
Total	42	100%

Table 3: Histological Grade Distribution of Squamous Cell Carcinoma Cases (n=42)

Histological Grade Distribution
OSCC (n = 42)

- Well-differentiated – 21 cases (50%)
- Moderately differentiated – 17 cases (40.48%)
- Poorly differentiated – 4 cases (9.52%)

Clinical diagnosis oral epithelial dysplasia	**Frequency**	**Percentage**

Table 4: Histological Grade Distribution of Oral Epithelial Dysplasia Cases (n=8)

Mild	2	25%
Moderate	3	37.50%
Severe	3	37.50%
Total	8	100%

Oral Epithelial Dysplasia (n = 8)

- Mild dysplasia – 2 cases (25%).
- Moderate dysplasia – 3 cases (37.50%).
- Severe dysplasia – 3 cases (37.50%)

Table 5: E-Cadherin Immunohistochemical Parameters (n=50)

Parameter	**Category**	**Frequency (%)**
Pattern	Membranous	48 (96%)
	Cytoplasmic	1 (2%)
	Mixed	1 (2%)
% Cells Score	Score 1	3 (6%)
	Score 2	14 (28%)
	Score 3	28 (56%)
	Score 4	5 (10%)
Intensity	Mild	11 (22%)
	Moderate	29 (58%)
	Strong	9 (18%)
	Negative	1 (2%)
	4	13 (26%)
	5	15 (30%)
	6	14 (28%)
Expression	High	29 (58%)
	Moderate	18 (36%)
	Low	3 (6%)

Membranous positivity was the predominant staining pattern (96%), with minimal cytoplasmic or mixed expression. The majority of cases exhibited score 3 (50–80% positive cells) (56%), indicating substantial cellular positivity. In terms of staining intensity, moderate intensity was most common (58%), followed by mild (22%) and strong (18%) staining, with very few negative cases (2%). Overall, these findings demonstrate preserved but variably expressed E-cadherin in most lesions.

Table 6: E-Cadherin Expression and IRS Scoring (n=50)

Score/Category	Type	Frequency (%)
IRS Score	1	1 (2%)
	2	2 (4%)
	3	5 (10%)

Most cases showed higher immunoreactive scores, with IRS scores of 4–6 accounting for the majority. Accordingly, 58% of patients showed strong E-cadherin expression, followed by moderate expression (36%) and low expression (6%). This indicates that, in a sizable percentage of instances, e-cadherin expression was comparatively well preserved.

Table 7: Association of E-Cadherin Expression with Squamous cell carcinoma Grade(n=42)

E-cadherin expression and SCC grade

were shown to be significantly correlated (p = 0.005). High expression was present in 18/21 well-differentiated cases (85.71%), 6/17 moderately differentiated cases (35.29%), and 1/4 poorly differentiated cases (25%). Low expression was 0/21 (0%), 1/17 (5.88%), and 1/4 (25%), respectively.

Table 8: Association of E-Cadherin Expression with Dysplasia Grade (n=8)

E cadherin expression	Clinical diagnosis oral epithelial dysplasia			P-Value
	Mild	Moderate	Severe	
High	2 (100)	2 (66.67)	0 (0)	**0.0356**
Low	0 (0)	0 (0)	1 (33.33)	
Moderate	0 (0)	1 (33.33)	2 (66.67)	
Total	2 (100)	3(100)	3(100)	

E-cadherin expression and dysplasia grade were shown to be significantly correlated (p = 0.0356). High expression was seen in mild dysplasia 2/2 (100%), moderate dysplasia 2/3 (66.67%), and severe dysplasia 0/3 (0%). Low expression was 0/2 (0%), 0/3 (0%), and 1/3 (33.33%), respectively, while moderate expression was 0/2 (0%), 1/3 (33.33%), and 2/3 (66.67%).

IMAGES

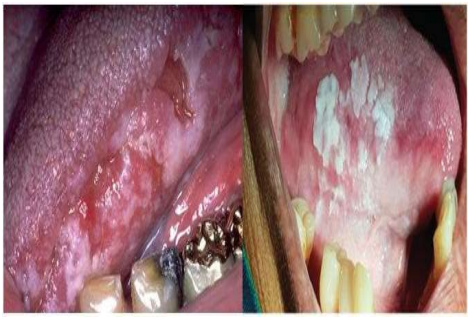


Figure 1 : (A) and (B) Specimen showing ulceroproliferative grey white solid tumour involving lateral border of tongue (Gross photography)

E cadherin expression	Clinical diagnosis SCC			P-Value
	Well	Moderate	Poor	
High	18 (85.71)	6 (35.29)	1 (25)	**0.005**
Low	0 (0)	1 (5.88)	1 (25)	
Moderate	3 (14.29)	10 (58.82)	2 (50)	
Total	21 (100)	17 (100)	4 (100)	

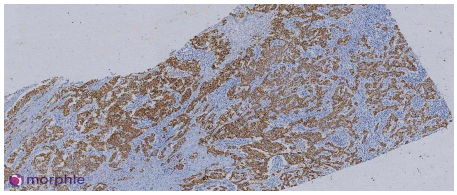


Figure 2: Normal oral mucosa showing strong, continuous membranous E-cadherin expression in basal and suprabasal epithelial layers (Immunohistochemistry, x40).

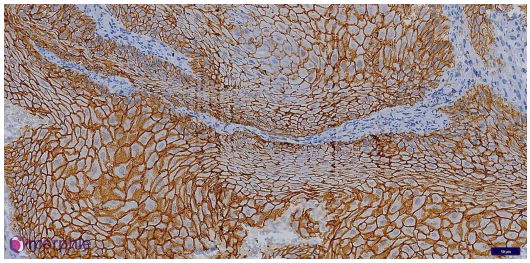


Figure 3: Mild oral epithelial dysplasia showing basal cell hyperplasia and mild nuclear atypia confined to the lower third of epithelium (H&E stain, x40).

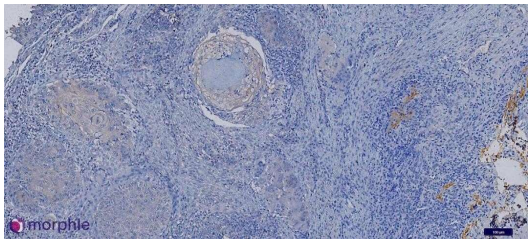


Figure 4: Mild dysplasia showing preserved strong membranous E-cadherin expression (Immunohistochemistry, x40).

Figure 5: Well differentiated squamous cell carcinoma showing High E cadherin expression with Membrane positive (Immunohistochemistry, x40)

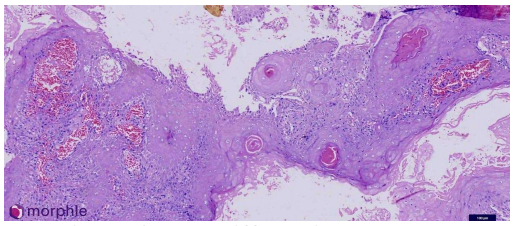


Figure 6: Well-differentiated oral squamous cell carcinoma showing keratin pearl formation and tumor islands (H&E stain, x20).

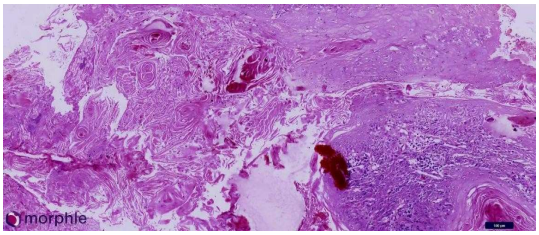


Figure 7: Microscopic characteristics displaying Squamous cell cancer with moderate differentiation (H&E, x20)

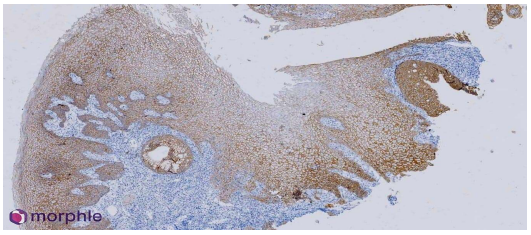


Figure 8: Squamous cell cancer with moderate differentiation, Moderate expression of E-cadherin (Immunohistochemistry, x5)

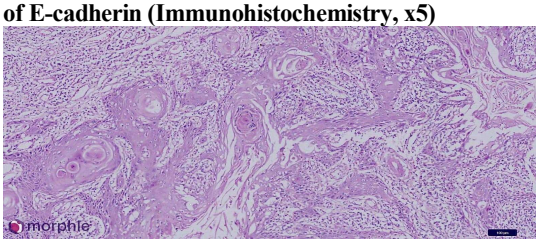
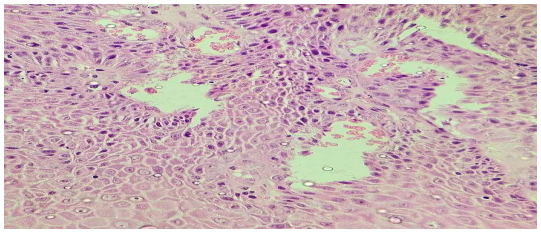


Figure 9: Poorly differentiated squamous cell carcinoma Showing Low E- Cadherin expression with cytoplasmic positivity- (Immunohistochemistry, x40)



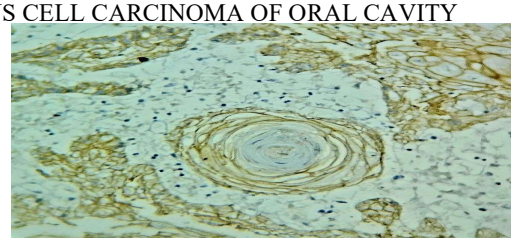


Figure 10: Microscopic Features showing Poorly differentiated Squamous cell carcinoma – (H&E, x20)

Discussion

The present study evaluated E-cadherin expression across oral epithelial dysplasia (OED) and oral squamous cell carcinoma (OSCC), integrating clinicopathological parameters with immunohistochemical findings to understand its role in oral carcinogenesis.

The study population predominantly comprised individuals in the 5th–6th decades, with a mean age of 57.4 ± 11.8 years, and a slight male predominance. This age distribution is consistent with the findings of Puneeta et al.[11] and Akhtar et al.[12], who reported that dysplastic lesions tend to occur earlier, while OSCC presents at relatively older ages. However, existing literature suggests that E-cadherin expression is more strongly influenced by histological severity than by age or sex alone, as emphasized by Yuwanati et al.[13]. Similarly, male predominance observed in this study reflects exposure patterns rather than a direct molecular determinant of E-cadherin expression, in agreement with Gupta et al. [14].

The predominance of OSCC cases over OED indicates a higher burden of malignant lesions in the study cohort. Histological grading revealed that most OSCC cases were well to moderately differentiated, while OED cases were largely moderate to severe, suggesting progression along the dysplasia–carcinoma sequence. This aligns with the multistep model of oral carcinogenesis described in previous studies.

Immunohistochemical analysis demonstrated predominantly membranous E-cadherin expression, with most cases showing moderate staining intensity and 50–80% cellular positivity. These findings indicate that while E-cadherin expression is largely preserved, qualitative and quantitative alterations occur with disease progression. Similar observations were reported by Kalaimani et al. [15], who highlighted that functional integrity depends more on membranous localization than mere positivity.

The overall immunoreactive score distribution showed that the majority of cases exhibited moderate to high expression, but stratification by lesion grade revealed significant differences. A statistically significant correlation between histological grade and E-cadherin expression was observed in both OSCC ($p = 0.005$) and OED ($p = 0.0356$), confirming a graded decline in expression with increasing severity.

Across OED grades, there observed a gradual decline in E-cadherin expression along with moderate dysplasia, showing high expression, while severe dysplasia exhibited absence of high expression and increased moderate to low expression. This pattern is in strong agreement with Yuwanati et al. [13], Gupta et al. [14], Sharma et al. [16], and Kani et al. [17], all of whom reported a profound inverse correlation between E-cadherin expression and dysplasia severity. Molecular evidence from Sathish et al.[18] further supports this observation, demonstrating a stepwise reduction in CDH1 expression with increasing dysplasia grade.

Similarly, in OSCC, well-differentiated tumors exhibited predominantly high expression, whereas moderately and poorly differentiated tumors showed reduced expression, indicating progressive loss of epithelial cohesion with dedifferentiation. These results closely resemble those of Yuwanati et al. (2013) and Gupta et al. (2014), who found that poorly differentiated OSCC had a significant decrease of E-cadherin. Sharma et al. [16] and Kani et al.[17] further demonstrated that poorly differentiated tumors show minimal to absent membranous staining, reinforcing its association with tumor aggressiveness.

The present study has several strengths, including its structured evaluation of E-cadherin immunoexpression across the full histopathological spectrum from oral epithelial dysplasia to oral squamous cell carcinoma, enabling meaningful correlation between molecular alterations and morphological progression. The use of histologically confirmed cases with standardized grading enhances internal validity, while immunohistochemistry allows direct assessment of protein localization, including membranous continuity and cytoplasmic redistribution. Evaluation based on both intensity and distribution patterns improves the ability to detect biologically relevant changes, and correlation with clinicopathological parameters increases translational relevance. Additionally, the use of a structured scoring system and a widely available technique like E-cadherin IHC supports reproducibility and practical applicability in routine pathology settings. However, certain limitations must be considered. The relatively small sample size and subgroup distribution may affect statistical power. Use of archival tissue may introduce variability in staining, and subjective elements in immunohistochemical scoring can lead to inter observer variation. Intratumoral heterogeneity and limited biopsy sampling may not fully represent tumor behavior, particularly at the invasive front. Furthermore, evaluation of E-cadherin alone may not capture the complexity of oral carcinogenesis, and absence of additional molecular markers limits comprehensive pathway analysis. Lastly, findings from a single-center cohort may have limited generalizability.

Conclusion

The present immunohistochemical study demonstrates that E-cadherin expression exhibits a clear and statistically significant inverse relationship with histopathological severity across the spectrum of oral epithelial dysplasia and oral squamous cell carcinoma. A progressive reduction in membranous expression, accompanied by decreased staining intensity and occasional cytoplasmic redistribution, was observed with increasing grades of dysplasia and worsening tumor differentiation. These findings indicate that disruption of epithelial cell–cell adhesion is an early and progressive event in oral carcinogenesis, contributing to epithelial disorganization, invasion, and tumor aggressiveness.

In oral epithelial dysplasia, higher grades showed reduced membranous integrity and lower expression levels, suggesting increased risk of malignant transformation. Similarly, in OSCC, poorly differentiated tumors demonstrated greater loss of E-cadherin expression, reflecting dedifferentiation and enhanced invasive potential. The observed alterations in both quantitative (intensity and proportion) and qualitative (localization pattern) aspects of E-cadherin expression reinforce its biological relevance in tumor progression.

Overall, the study supports the utility of E-cadherin as a valuable adjunct biomarker that complements routine histopathological grading. Its evaluation, particularly with emphasis on membranous continuity and staining intensity, may aid in risk stratification of dysplastic lesions and assessment of tumor aggressiveness in OSCC. Incorporation of E-cadherin immunohistochemistry into routine diagnostic practice may enhance prognostic accuracy and contribute to improved clinical decision-making in oral potentially malignant disorders and oral cancer.

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