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Histopathological Study of Expression of E- Cadherin in Precancerous Lesion and in Squamous Cell Carcinoma of Oral Cavity

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a major global health concern with poor prognosis due to late diagnosis and limited availability of reliable biomarkers. E-cadherin, a key cell adhesion molecule, plays a critical role in maintaining epithelial integrity, and its loss is associated with epithelial–mesenchymal transition (EMT), tumor progression, and metastasis. However, its expression across the spectrum of oral epithelial dysplasia and OSCC remains inconsistently defined. To evaluate and correlate the immunohistochemical expression of E-cadherin in precancerous lesions and oral squamous cell carcinoma of the oral cavity.

Materials and Methods: This prospective observational study included 100 histopathologically confirmed cases comprising 35 cases of oral epithelial dysplasia and 65 cases of OSCC. Immunohistochemical staining for E-cadherin was performed using the streptavidin–biotin technique. Expression was assessed using the immunoreactive score (IRS), based on the percentage of positive cells and staining intensity. Statistical analysis was performed using the Chi-square test and one-way ANOVA, with $p < 0.05$ considered significant.

Results: A statistically significant reduction in E-cadherin expression was observed with increasing severity of dysplasia and tumor grade ($p < 0.001$). In dysplasia, mean IRS decreased from 10.00 in mild dysplasia to 2.80 in severe dysplasia. In OSCC, mean IRS declined from 8.70 in well differentiated tumors to 1.50 in poorly differentiated tumors. All poorly differentiated carcinomas showed absent membranous expression and <10% positive cells (100%), whereas well differentiated tumors predominantly demonstrated higher positivity (60–100% in 55.6% cases). These findings indicate a progressive loss of E-cadherin expression with disease advancement.

Conclusion: E-cadherin expression shows a significant inverse correlation with histopathological grade in both oral epithelial dysplasia and OSCC. Its progressive loss reflects tumor progression and epithelial–mesenchymal transition, suggesting that E-cadherin may serve as a useful adjunct biomarker for early detection, risk stratification, and prognostic evaluation in oral carcinogenesis.

Keywords: *E-cadherin, Oral squamous cell carcinoma, Oral epithelial dysplasia, Immunohistochemistry, EMT, Biomarker.*

INTRODUCTION

Head and neck cancers (HNC) represent a significant global health concern and rank among the most commonly diagnosed malignancies worldwide, with an estimated incidence of nearly 500,000 new cases annually. Despite continuous advancements in diagnostic techniques and therapeutic approaches, the incidence of these cancers continues to increase, particularly in developing regions. Oral squamous cell carcinoma (OSCC), which constitutes the majority of oral

malignancies, remains one of the most prevalent cancers affecting the oral cavity. A notable rise in OSCC incidence has been reported in populations with high prevalence of betel quid chewing, underscoring the strong influence of lifestyle-related risk factors in oral carcinogenesis. Furthermore, delayed clinical presentation and inadequate early detection contribute to poor prognosis, with OSCC exhibiting relatively low five-year survival rates compared to other malignancies [1].

The pathogenesis of OSCC is a complex and multistep process characterized by the gradual accumulation of genetic and molecular alterations. This transformation is driven by a combination of environmental exposures and host-related factors, including tobacco use, alcohol consumption, chronic inflammation, viral infections, and inherited susceptibility. These risk factors collectively promote genomic instability and disrupt key cellular regulatory pathways, ultimately leading to malignant transformation of the oral epithelium [2].

A critical mechanism underlying tumor progression is the epithelial–mesenchymal transition (EMT), a dynamic biological process in which epithelial cells lose their polarity and intercellular adhesion while acquiring mesenchymal properties. This transition enhances cellular motility, invasiveness, resistance to apoptosis, and extracellular matrix remodeling. Under normal physiological conditions, epithelial cells maintain strong adhesion to each other and to the basement membrane, preserving tissue integrity. However, during EMT, these interactions are disrupted, enabling tumor cells to detach, migrate, and invade surrounding tissues, thereby facilitating metastasis [3].

Cell–cell adhesion plays a fundamental role in maintaining epithelial structure and function. Epithelial cells are interconnected through a complex system of junctions, including tight junctions, adherens junctions, and desmosomes. Among these, adherens junctions are particularly important in preserving tissue architecture, primarily through the action of cadherins. These calcium-dependent transmembrane proteins mediate intercellular adhesion and are essential for maintaining epithelial cohesion. Disruption of cadherin-mediated adhesion contributes to loss of tissue organization and promotes tumor progression [4].

E-cadherin, a key component of adherens junctions, functions as a tumor suppressor by maintaining epithelial integrity and inhibiting cellular motility. Its downregulation or functional loss is widely recognized as a hallmark of malignant transformation and progression. In OSCC, reduced E-cadherin expression has been associated with loss of differentiation, increased invasiveness, and unfavorable clinical outcomes. Clinically, OSCC most commonly involves sites such as the tongue, lips, and floor of the mouth, which are frequently exposed to carcinogenic agents [5,6].

Tumor invasion represents an early and essential step in cancer dissemination. Increasing evidence highlights the role of EMT and epithelial plasticity as central drivers of this process. Through EMT-related molecular alterations, tumor cells acquire the ability to breach the basement membrane and infiltrate adjacent tissues, thereby promoting disease progression and metastasis [7].

Despite significant advances in understanding the molecular mechanisms underlying oral carcinogenesis, early diagnosis and accurate prognostic stratification of oral squamous cell carcinoma (OSCC) remain major clinical challenges. Although epithelial–mesenchymal transition (EMT) and loss of E-cadherin expression are well-established contributors to tumor progression, existing evidence regarding their histopathological and immunohistochemical correlation across the spectrum of oral epithelial dysplasia and OSCC remains inconsistent. Variations in study design, sample size, and evaluation criteria have limited the translation of these findings into routine diagnostic practice. Furthermore, the role of E-cadherin as a reliable biomarker for early detection, assessment of disease progression, and prognostication has not been conclusively established.

In this context, the present study is undertaken to systematically evaluate the immunohistochemical expression of E-cadherin in precancerous lesions and oral squamous cell carcinoma, and to correlate its expression with the degree of epithelial dysplasia and tumor differentiation. By providing a comprehensive analysis across different stages of oral carcinogenesis, this study aims to bridge existing gaps in knowledge and to explore the potential utility of E-cadherin as a clinically relevant biomarker for early diagnosis and prognostic assessment.

MATERIAL AND METHODS

Study Design and Setting

The present study was designed as a prospective, observational, non-randomized study aimed at evaluating and correlating the immunohistochemical expression of E-cadherin in precancerous lesions and oral squamous cell carcinoma (OSCC) of the oral cavity. This design was chosen to facilitate direct observation and analysis of histopathological and immunohistochemical changes without therapeutic intervention. The study was conducted over a period of 18 months, from June 2024 to December 2025, in the Department of Pathology at GSVM Medical College, Kanpur, in collaboration with the Departments of Oral and Maxillofacial Surgery and ENT, from which biopsy and surgical specimens were obtained.

Study Population and Sample Size
The study population comprised patients presenting with clinically suspected lesions of the oral cavity, subsequently confirmed histopathologically as oral epithelial dysplasia or OSCC. Only lesions arising from the oral cavity and oropharynx were included. The sample size was calculated using the standard formula $n = Z^2pq/d^2$, assuming a prevalence of 50% for altered E-cadherin expression, with a 95% confidence level and 10% allowable error, yielding an estimated sample size of 96 cases. For improved statistical representation and feasibility, the sample size was rounded to 100 cases. Accordingly, a total of 100 histopathologically confirmed cases of oral epithelial dysplasia and OSCC were included in the study using a consecutive sampling technique.

Inclusion and Exclusion Criteria
Patients aged above 18 years with histologically confirmed oral epithelial dysplasia and oral squamous cell carcinoma were included in the study. Patients who had received prior chemotherapy or radiotherapy, those with recurrent disease, and cases with inadequate biopsy material were excluded to avoid confounding factors affecting immunohistochemical interpretation.

Ethical Considerations and Data Collection
The study was conducted following approval from the Institutional Ethics Committee of GSVM Medical College, Kanpur, and adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion. Confidentiality of patient information was strictly maintained. Detailed clinical data, including demographic characteristics, presenting complaints, lesion site and duration, personal habits (such as tobacco use, smoking, alcohol consumption, and betel quid chewing), family history, radiological findings, and treatment history, were recorded using a pre-designed proforma.

Specimen Handling and Histopathological Examination
Biopsy and surgically excised specimens were received in 10% buffered formalin and subjected to thorough gross examination, including assessment of lesion site, size, shape, external and cut surface features, depth of invasion, and lymph node involvement where applicable. Representative tissue sections were processed routinely, embedded in paraffin, and sectioned at 4–5 µm thickness. Hematoxylin and Eosin (H&E) staining was performed for histopathological evaluation. Grading of OSCC was carried out according to the World Health Organization (WHO) criteria, based on the degree of keratinization, cellular and nuclear pleomorphism, and presence of intercellular bridges, categorizing tumors into well differentiated (Grade I), moderately differentiated (Grade II), and poorly differentiated (Grade III).

Immunohistochemical Analysis
Immunohistochemical staining for E-cadherin was performed on representative paraffin-embedded tissue sections using the streptavidin–biotin immunoperoxidase technique. Sections were mounted on poly-L-lysine-coated slides, followed by deparaffinization, rehydration, and antigen retrieval using appropriate buffer solutions. Endogenous peroxidase activity was blocked prior to incubation with the primary antibody against E-cadherin. Subsequently, sections were treated with secondary antibody and streptavidin–peroxidase complex. Visualization was achieved using diaminobenzidine (DAB) chromogen, producing a brown-colored reaction product, and counterstaining was performed with hematoxylin. Appropriate positive and negative controls were included in each run to ensure validity of staining.

Evaluation of Immunohistochemical Expression
E-cadherin expression was assessed semi-quantitatively based on membranous staining of epithelial cells. Immunoreactivity was evaluated using the immunoreactive score (IRS), calculated as the product of the percentage of positive cells (Score A) and staining intensity (Score B). The percentage of positive cells was scored from 0 to 4, while staining intensity was graded from 0 to 3. The final IRS score ranged from 0 to 12 and was interpreted as negative (0–1), mild (2–3), moderate (4–8), or strong (9–12) expression.

Statistical Analysis
Data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) version 20. Descriptive statistics were used to summarize demographic and clinicopathological variables. The Chi-square test was applied to evaluate the association between E-cadherin expression and histopathological grading. A p-value of less than 0.05 was considered statistically significant, while a p-value of less than 0.01 was considered highly significant.

RESULTS

Table 1: Association of Tumor Differentiation with Membranous Pattern of E-Cadherin Expression (n = 65)

Tumor Differentiation	Reduced Membranous	Discontinuous	Markedly Reduced	Absent	Total (n)
Well Differentiated (n = 27)	15 (55.6%)	12 (44.4%)	0 (0%)	0 (0%)	27
Moderately Differentiated (n = 26)	0 (0%)	15 (57.7%)	11 (42.3%)	0 (0%)	26

Poorly Differentiated (n = 12)	0 (0%)	0 (0%)	0 (0%)	12 (100%)	12
Total (n = 65)	**15**	**27**	**11**	**12**	**65**

The table demonstrates a clear association between tumor differentiation and the membranous pattern of E-cadherin expression. Well differentiated tumors predominantly showed reduced membranous expression (55.6%) and discontinuous expression (44.4%), with no cases exhibiting markedly reduced or absent expression. In moderately differentiated tumors, discontinuous expression was the most common pattern (57.7%), followed by markedly reduced expression (42.3%). In contrast, all poorly differentiated tumors (100%) demonstrated absent E-cadherin expression. These findings suggest that loss of membranous E-cadherin expression increases with decreasing tumor differentiation, indicating that reduced or absent E-cadherin expression is associated with poorer tumor differentiation and greater tumor aggressiveness.

Table 2: Distribution of E-Cadherin Expression in Oral Epithelial Dysplasia (n = 35)

E-Cadherin Expression	Number of Cases (n)	Percentage (%)
Preserved	11	31.4
Reduced	16	45.7
Marked loss	8	22.9
Total	**35**	**100**

The table shows that reduced E-cadherin expression was the most common finding in oral epithelial dysplasia, observed in 16 cases (45.7%). Preserved expression was noted in 11 cases (31.4%), while marked loss of expression was seen in 8 cases (22.9%). These findings indicate that alteration and reduction in E-cadherin expression are common in oral epithelial dysplasia and may increase with disease progression.

Table 3: Distribution of % Positive Cells According to Histopathological Grade (n = 65)

Grade	<10% n (%)	10–29% n (%)	30–59% n (%)	60–100% n (%)	Total
Well differentiated (n=27)	0 (0%)	0 (0%)	12 (44.4%)	15 (55.6%)	27
Moderately differentiated (n=26)	0 (0%)	11 (42.3%)	15 (57.7%)	0 (0%)	26
Poorly differentiated (n=12)	12 (100%)	0 (0%)	0 (0%)	0 (0%)	12
Total (n=65)	**12**	**11**	**27**	**15**	**65**

The table demonstrates that well differentiated tumors predominantly showed a higher percentage of positive cells, with 55.6% cases exhibiting 60–100% positivity. Moderately differentiated tumors mainly showed 30–59% positivity (57.7%) and 10–29% positivity (42.3%). In contrast, all poorly differentiated tumors (100%) exhibited less than 10% positive cells. These findings suggest that the percentage of E-cadherin positive cells decreases with decreasing histopathological differentiation, indicating loss of E-cadherin expression in poorly differentiated tumors.

Table 4: Distribution of % Positive Cells According to Histopathological Grade of Oral Epithelial Dysplasia (n = 35)

Grade of Dysplasia	<10% n (%)	10–29% n (%)	30–59% n (%)	60–100% n (%)	Total
Mild dysplasia (n=12)	0 (0%)	0 (0%)	4 (33.3%)	8 (66.7%)	12
Moderate dysplasia (n=13)	0 (0%)	0 (0%)	10 (76.9%)	3 (23.1%)	13
Severe dysplasia (n=10)	0 (0%)	8 (80.0%)	2 (20.0%)	0 (0%)	10

The table demonstrates that most mild dysplasia cases (66.7%) showed 60–100% positive cells, indicating preserved E-cadherin expression. Moderate dysplasia predominantly exhibited 30–59% positivity (76.9%), whereas severe dysplasia mainly showed 10–29% positivity (80.0%). None of the severe dysplasia cases demonstrated high positivity. These findings indicate a progressive reduction in E-cadherin positive cells with increasing severity of dysplasia, suggesting loss of epithelial cell cohesion during disease progression.

Table 5: Comparison of Mean A Score, B Score, and IRS Score According to Histopathological Grade (n = 65)

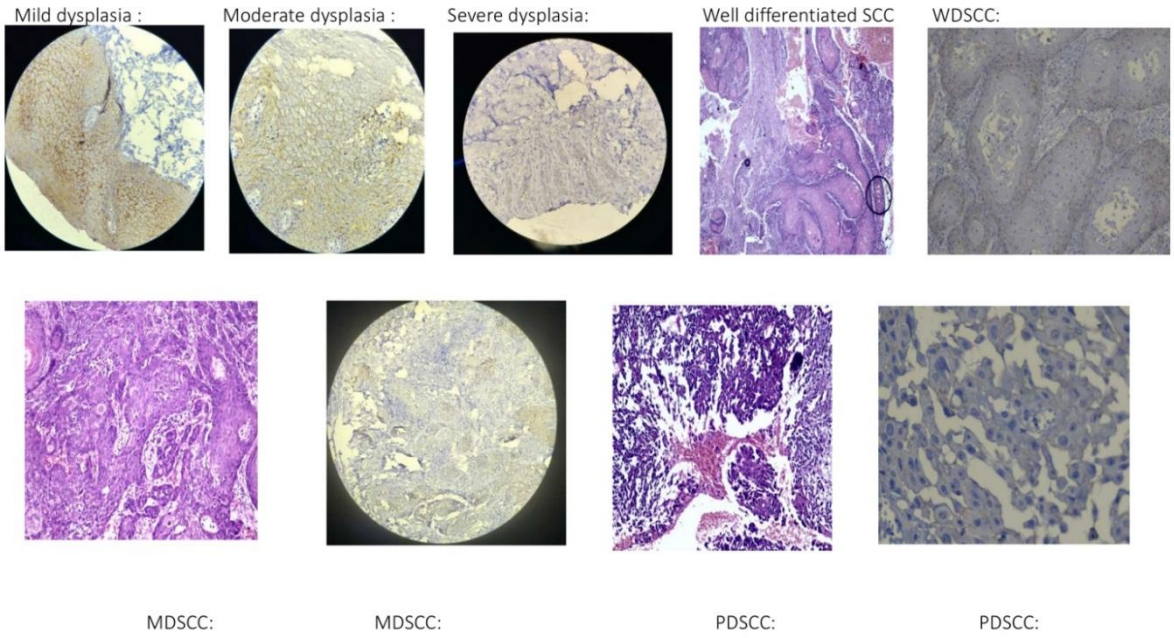
Grade	Mean A Score	Mean B Score	Mean IRS Score
Well differentiated (n=27)	3.56	2.44	8.70
Moderately differentiated (n=26)	2.58	1.50	3.77
Poorly differentiated (n=12)	1.00	1.50	1.50

The table reveals that well differentiated tumors had the highest mean A score (3.56), mean B score (2.44), and mean IRS score (8.70). Moderately differentiated tumors showed intermediate values, whereas poorly differentiated tumors demonstrated the lowest scores, with a mean IRS score of 1.50. These findings indicate that E-cadherin expression progressively decreases with worsening histopathological grade, reflecting increased tumor dedifferentiation and aggressiveness.

Table 6: Comparison of Mean A Score, B Score, and IRS Score According to Histopathological Grade of Oral Epithelial Dysplasia (n = 35)

Grade of Dysplasia	Mean A Score	Mean B Score	Mean IRS Score
Mild dysplasia (n=12)	3.67	2.67	10.00
Moderate dysplasia (n=13)	3.23	1.69	5.54
Severe dysplasia (n=10)	2.20	1.20	2.80

The table shows that mild dysplasia exhibited the highest mean A score (3.67), mean B score (2.67), and mean IRS score (10.00). The scores progressively decreased in moderate and severe dysplasia, with severe dysplasia showing the lowest IRS score (2.80). These findings suggest that E-cadherin expression decreases with increasing severity of epithelial dysplasia, indicating progressive loss of cell adhesion during dysplastic transformation.



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DISCUSSION

In the present study, oral squamous cell carcinoma (OSCC) constituted 65% of cases, while oral epithelial dysplasia accounted for 35%, indicating a predominance of malignant lesions among the study population. Similar observations were reported by Yamakanamardi et al. (2023)[8] and Puneeta et al. (2022)[9], who also documented a higher frequency of malignant lesions compared to premalignant lesions. Studies by Zareen et al. (2025)[10], Kalaimani et al. (2023)[11], and Dar et al. (2023)[12] similarly demonstrated a predominance of OSCC cases. The higher proportion of OSCC observed in the present study may be attributed to delayed clinical presentation, poor awareness regarding early oral lesions, and referral bias associated with tertiary care institutions where advanced cases are more frequently encountered.

Histopathological grading of OSCC in the present study showed that 41.5% of tumors were well differentiated, 40.0% were moderately differentiated, and 18.5% were poorly differentiated. These findings are broadly comparable with those reported by Puneeta et al. (2022)[9] and Yamakanamardi et al. (2023)[8]. Studies by Zareen et al. (2025)[10] and Singh et al. (2016)[13] similarly reported predominance of well differentiated tumors, although the proportion of poorly differentiated carcinomas was relatively lower than that observed in the present study. The comparatively higher percentage of poorly differentiated tumors in the present series may indicate aggressive disease presentation and delayed patient reporting.

Evaluation of E-cadherin expression in oral epithelial dysplasia demonstrated that reduced expression was the most common pattern, observed in 45.7% of cases, while marked loss was seen in 22.9% and preserved expression in 31.4% of cases. Thus, a total of 68.6% of dysplastic lesions exhibited altered or reduced E-cadherin expression. These findings are in agreement with studies by Sridevi et al. (2015)[15], Sharma et al. (2022)[16], Singh et al. (2019)[18], and Kalmegh et al. (2023)[17], all of whom reported altered E-cadherin expression in a majority of dysplastic lesions. The present findings support the concept that loss of E-cadherin-mediated cell adhesion begins early during oral carcinogenesis and progressively increases with dysplastic severity.

A clear association between tumor differentiation and the membranous pattern of E-cadherin expression was observed in the present study. Among well differentiated tumors, 55.6% cases showed reduced membranous expression and 44.4% demonstrated discontinuous expression, whereas none exhibited markedly reduced or absent staining. In moderately differentiated tumors, discontinuous expression was the most common pattern (57.7%), followed by markedly reduced expression (42.3%). In contrast, all poorly differentiated tumors (100%) showed complete absence of membranous E-cadherin expression. These findings indicate progressive loss of membranous E-cadherin expression with worsening tumor differentiation. Similar observations were reported by Yuwanati et al. (2011)[19], Yamakanamardi et al. (2023)[8], Puneeta et al. (2022)[9], and Kaur et al. (2009)[20], who also documented reduced or absent membranous staining in poorly differentiated tumors. Diniz-Freitas et al. (2006)[21] further correlated loss of E-cadherin expression with increased invasiveness and poor prognosis.

Analysis of the percentage of E-cadherin-positive cells according to histopathological grade revealed that well differentiated tumors predominantly demonstrated high positivity, with 55.6% of cases showing 60–100% positive cells and 44.4% showing 30–59% positivity. Moderately differentiated tumors mainly showed intermediate positivity, with 57.7% cases exhibiting 30–59% positivity and 42.3% cases showing 10–29% positivity. In contrast, all poorly differentiated tumors (100%) exhibited less than 10% positive cells. These findings demonstrate a progressive decline in E-cadherin-positive cells with decreasing tumor differentiation. Similar findings have been reported by Talukdar and Goswami (2019)[22], Gupta et al. (2018)[23], and Nijkamp et al. (2011)[24], who observed markedly reduced E-cadherin expression in poorly differentiated tumors and metastatic lesions. Similar progressive reduction has also been documented by Balasundaram et al. (2014)[5] and Yuwanati et al. (2011)[19].

Quantitative assessment further demonstrated a progressive reduction in mean A score, mean B score, and mean IRS score with worsening tumor differentiation. Well differentiated tumors showed the highest mean A score (3.56), mean B score (2.44), and mean IRS score (8.70), whereas moderately differentiated tumors demonstrated intermediate values, with a mean IRS score of 3.77. Poorly differentiated tumors exhibited the lowest scores, with a mean IRS score of 1.50. These findings indicate progressive reduction in E-cadherin expression with worsening histopathological grade and increasing tumor dedifferentiation. Comparable findings were reported by Gupta et al. (2018)[23], Talukdar and Goswami (2019)[22], and Balasundaram et al. (2014)[5], who also demonstrated significantly higher immunoreactivity in well differentiated tumors compared to poorly differentiated lesions.

Similarly, in oral epithelial dysplasia, quantitative evaluation revealed progressive decline in E-cadherin expression with increasing dysplasia severity. Mild dysplasia showed the highest mean A score (3.67), mean B score (2.67), and mean IRS score (10.00), whereas moderate dysplasia demonstrated intermediate values with a mean IRS score of 5.54. Severe dysplasia exhibited the lowest expression, with a mean IRS score of 2.80. These findings indicate gradual loss of epithelial cell adhesion during progression from mild to severe dysplasia. Similar observations were reported by Sridevi et al. (2015)[15], Sharma et al. (2022)[16], Singh et al. (2019)[18], and Kalmegh et al. (2023)[17], all of whom documented progressive reduction in E-cadherin expression with increasing dysplastic severity.

The distribution of percentage positivity in dysplastic lesions further emphasized this progressive loss of expression. Most mild dysplasia cases (66.7%) exhibited 60–100% positive cells, indicating preserved E-cadherin expression. Moderate dysplasia predominantly showed 30–59% positivity (76.9%), whereas severe dysplasia mainly demonstrated 10–29% positivity (80.0%). None of the severe dysplasia cases demonstrated high positivity. These findings indicate a progressive reduction in E-cadherin-positive cells with increasing severity of dysplasia, suggesting loss of epithelial cell cohesion during disease progression. Similar patterns have been described by Sridevi et al. (2015)[15], Sharma et al. (2022)[16], Singh et al. (2019)[18], and Kalmegh et al. (2023)[17].

Overall, the present study demonstrates an inverse relationship between E-cadherin expression and both the severity of oral epithelial dysplasia and histopathological grade of OSCC. Progressive reduction and eventual loss of E-cadherin expression from dysplasia to poorly differentiated carcinoma strongly support its role in epithelial–mesenchymal transition (EMT), tumor progression, invasion, and metastasis. The findings of the present study are consistent with previously published literature and suggest that E-cadherin may serve as a valuable adjunct biomarker for early detection, risk assessment, and prognostic evaluation in oral carcinogenesis.