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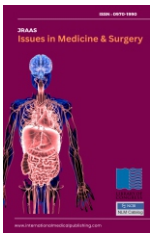

Research Article

Section: Pathology

Role of P63 in Premalignant & Malignant Lesions of Oral Cavity

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HIGHLIGHTS

- p63 overexpression in lesions
- Correlates with dysplasia severity
- Highest in OSCC cases
- Valuable diagnostic biomarker
- Aids early cancer detection

Key Words:
p63
Oral squamous cell carcinoma
Oral potentially malignant disorders
Immunohistochemistry
Dysplasia

ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) is a major public health problem in India, largely due to tobacco, areca nut, and alcohol use. Oral potentially malignant disorders (OPMDs) can progress to OSCC, but predicting this transformation is difficult. Therefore, reliable biomarkers such as p63, which regulates epithelial proliferation and differentiation, are needed to improve diagnosis and risk assessment. **Aim & Objectives:** To evaluate the expression of p63 in normal oral mucosa, OPMDs, and OSCC, and to determine its diagnostic and prognostic significance by correlating its expression with histopathological grading and disease progression. **Materials & Methods:** This immunohistochemical study analyzed tissue samples from normal oral mucosa, OPMDs with varying grades of epithelial dysplasia, and OSCC. p63 expression was assessed based on nuclear staining pattern, labeling index, and distribution within epithelial layers. The findings were correlated with histopathological grades and relevant clinical parameters to evaluate the role of p63 in oral carcinogenesis. **Results:** In normal oral mucosa, p63 expression was restricted to the basal and parabasal cell layers. OPMDs exhibited increased p63 expression with extension into suprabasal layers, which correlated with the severity of epithelial dysplasia. The highest expression was observed in OSCC, showing diffuse and intense nuclear staining. A progressive increase in labeling index was noted from normal mucosa to dysplasia and carcinoma. Furthermore, elevated p63 expression was associated with poorer tumor differentiation and more aggressive biological behavior. **Conclusion:** p63 is a valuable immunohistochemical biomarker for evaluating epithelial dysregulation and malignant transformation in oral lesions. Its progressive overexpression from normal mucosa to OSCC supports its utility in early diagnosis, risk assessment, and prognostic evaluation, although it should be used as an adjunct to conventional histopathology.

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INTRODUCTION

Oral cancer remains a major global health concern, with approximately 389,800 new cases of lip and oral cavity cancer reported worldwide in 2022, of which nearly 30.8% are attributed to smokeless tobacco and areca nut consumption [1]. India bears a disproportionately high burden, reporting around 77,000 new cases and 52,000 deaths annually, with oral cancer ranking among the most common cancers, particularly in men [2]. This high incidence is largely driven by lifestyle-related risk factors such as tobacco use, areca nut chewing, alcohol consumption, and poor oral hygiene, with strong evidence linking areca nut use to increased cancer risk (4). Despite being preventable, oral cancer is often diagnosed at advanced stages due to lack of awareness, inadequate screening, and limited access to healthcare, resulting in poor outcomes and significant socioeconomic impact [3].

Oral Potentially Malignant Disorders (OPMDs), including leukoplakia, erythroplakia, oral submucous fibrosis, and oral lichen planus, represent lesions with an increased risk of malignant transformation. These conditions may progress to oral squamous cell carcinoma (OSCC) through stages of epithelial dysplasia characterized by architectural and cytological abnormalities [4]. However, progression is unpredictable, with only a subset of lesions undergoing malignant change. Transformation rates vary widely, necessitating the identification of reliable biomarkers for early detection and risk stratification [5].

Although several molecular and salivary biomarkers have been studied, none have achieved universal clinical acceptance, leading to a preference for combined biomarker approaches to improve diagnostic accuracy [6].

Histopathological evaluation using hematoxylin and eosin staining remains the gold standard for diagnosing dysplasia, identifying features such as abnormal epithelial stratification, nuclear atypia, and increased mitotic activity [7]. Lesions are graded as mild, moderate, or severe dysplasia based on these features, reflecting their malignant potential. However, this method has limitations, including subjectivity, interobserver variability, and sampling errors, as biopsies may not capture the most representative area of the lesion [8]. Additionally, not all dysplastic lesions progress to cancer, while some non-dysplastic lesions may transform, highlighting the need for adjunctive molecular markers [9].

The p63 protein, encoded by the TP63 gene on chromosome 3q28, is a member of the p53 family and plays a critical role in epithelial development and homeostasis. It exists in two major isoforms, TAp63 and ΔNp63, with distinct functions; the latter is primarily involved in maintaining epithelial stem cells and promoting proliferation. In normal oral mucosa, p63 expression is confined to basal and parabasal layers, reflecting its role in regulating progenitor cell populations and epithelial differentiation [10].

Altered p63 expression has been observed in dysplastic lesions and OSCC, with increased expression extending beyond basal

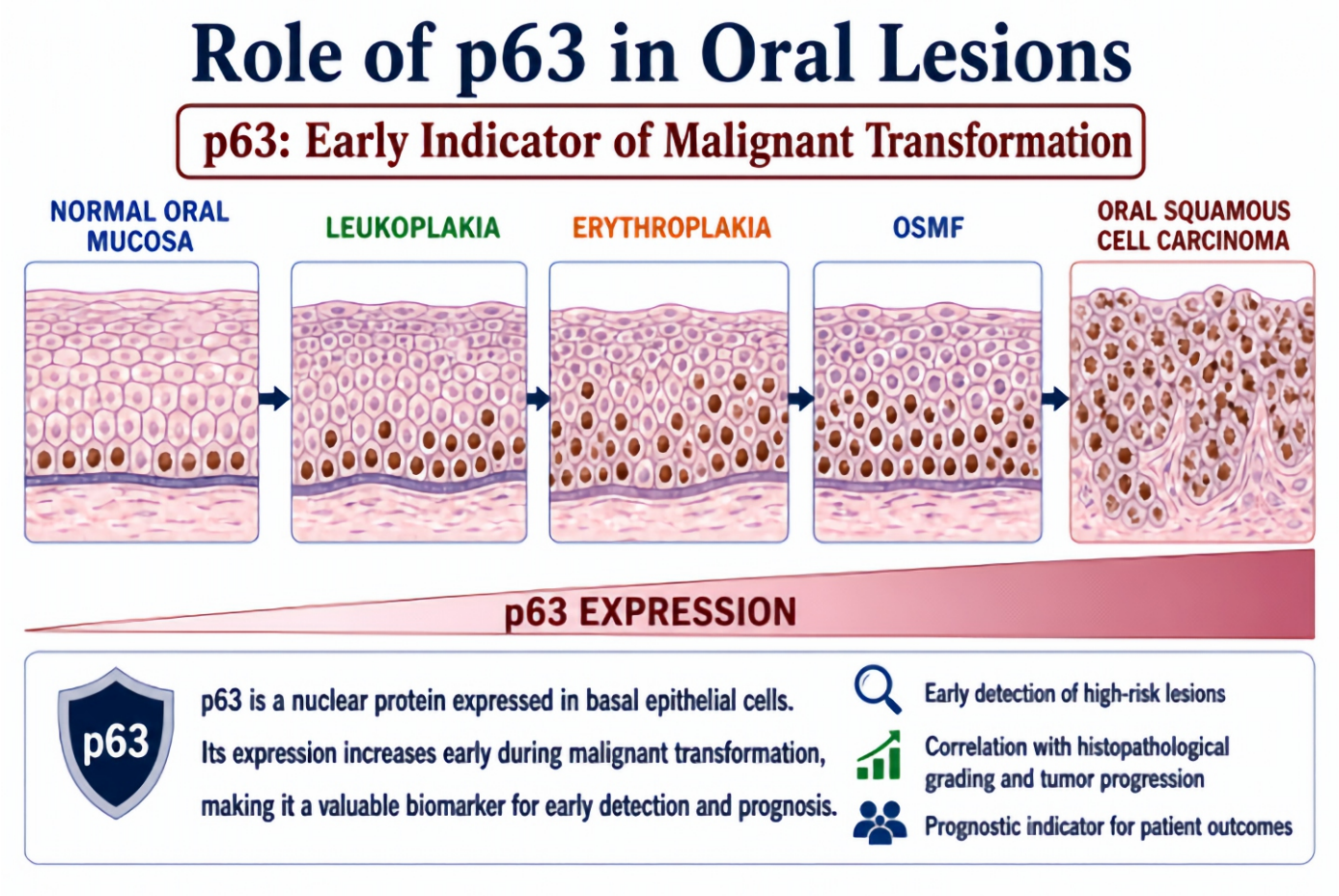

Figure 1. Role of p63 expression in oral potentially malignant disorders and oral squamous cell carcinoma.

layers as disease severity progresses [11]. This progressive upregulation suggests that p63 serves as an early indicator of malignant transformation and can aid in identifying high-risk lesions, particularly in cases with ambiguous histopathological findings. Furthermore, high p63 expression has been associated with aggressive tumor behavior, poor differentiation, and reduced survival in OSCC patients, underscoring its prognostic significance [12]. **Figure 1.** Progressive increase in p63 expression from normal oral mucosa through oral potentially malignant disorders (leukoplakia, erythroplakia, OSMF) to oral squamous cell carcinoma, highlighting its role as an early biomarker of malignant transformation.

Overall, p63 immunohistochemistry provides an objective and reliable adjunct to conventional histopathology by detecting early molecular changes preceding morphological alterations. Its ability to enhance diagnostic accuracy and provide prognostic insight makes it a valuable biomarker for improving risk assessment and guiding clinical management of oral potentially malignant disorders and oral cancer [13].

The study aimed to investigate the role of p63 as an immunohistochemical biomarker to determine its diagnostic and prognostic significance in premalignant and malignant lesions of the oral cavity. It sought to assess p63 expression levels across these lesions, correlate its expression with histo-pathological features and tumor grading, and evaluate its potential as a predictive marker for disease progression and patient outcomes, thereby supporting early diagnosis and risk stratification.

MATERIALS & METHODS

This prospective study was conducted at the Department of pathology, GSVM medical college, Kanpur and LLR and Associated hospitals from August 2022 to January 2024. Ethical approval has been obtained from the Ethical Approval Committee of GSVM medical college, Kanpur and LLR and Associated hospitals.

Study Population

The study population comprised patients with clinically suspected premalignant and malignant oral cavity lesions attending Surgery and Oncology outpatient departments or referred to Pathology for biopsy, with consecutive eligible cases enrolled to reduce selection bias and ensure representativeness, including consenting males and females with histologically confirmed leukoplakia, erythroplakia, dysplasia, OSMF, and squamous cell carcinoma, while excluding non-consenting individuals, autolysed or insufficient biopsy specimens, and those receiving chemotherapy or radiotherapy in treatment.

Data Analysis

Data analysis was performed systematically following structured data collection, including screening, enrollment, clinical evaluation, biopsy handling, histopathology, immunohistochemistry, data compilation, quality checks, risk stratification, and final data locking. Statistical analysis was conducted using SPSS software, with results expressed as number, percentage, and mean ± standard deviation.

Correlations between p63 expression, clinical findings, tumor grade, and stage were assessed using Pearson's correlation or Chi square test, while Kaplan Meier survival analysis evaluated prognostic significance on outcomes.

RESULTS

The study included 217 participants aged between 20 and 84 years, with a mean age of 53.03 ± 18.79 years and a median of 53 years, indicating a predominantly middle-aged to elderly population. The interquartile range of 37 to 71 years reflects substantial age variability, with most individuals falling within clinically relevant age groups for oral lesions. The distribution was broad and without significant outliers, supporting its suitability for analysis. A male predominance was observed, with 64.1% males and 35.9% females, consistent with higher exposure to risk factors like tobacco, while still allowing meaningful sex-based comparisons. The comparison of age distribution between sexes showed that females had a slightly higher mean and median age than males; however, both groups demonstrated overlapping interquartile ranges and similar variability. Statistical analysis using the Mann–Whitney U test revealed no significant difference ($p = 0.1877$), indicating comparable age distribution across sexes **(Table 1)**.A statistically significant association was observed between tobacco use and risk stratification ($\chi^2 = 24.53$, $p = 0.00041$), with high-risk lesions predominantly seen in paan masala users and those with combined bidi and paan masala use. While tobacco exposure strongly influenced disease severity, a notable proportion of high-risk cases among non-users suggests involvement of additional risk factors **(Table 2)**. A highly significant association was observed between p63 intensity and risk category ($\chi^2 = 188.88$, $p < 0.0001$), with moderate and strong expression exclusively seen in high-risk cases, while negative and weak expression predominated in low- and moderate-risk groups **(Figure 2)**. This demonstrates a clear positive correlation between increasing p63 intensity and disease severity, supporting its role as a reliable biomarker for risk stratification. A highly significant association was observed between clinical and histopathological diagnoses ($\chi^2 = 530.88$, $p < 0.0001$), with strong concordance for OSCC and OSMF, while lesions like erythroplakia and suspicious ulcers showed variable outcomes including dysplasia and carcinoma. These findings highlight the limitations of clinical diagnosis alone and confirm histopathology as the gold standard for accurate diagnosis and risk assessment **(Table 3)**. A highly significant association was found between p63 intensity and histopathological diagnosis ($\chi^2 = 322.72$, $p < 0.0001$), with moderate and strong expression predominantly seen in OSCC and severe dysplasia, while negative and weak expression were associated with benign and premalignant lesions. This indicates a clear correlation between increasing p63 intensity and disease severity, supporting its role as a reliable marker of malignant transformation **(Table 4)**. Heatmap of p63 Expression in Histopathological Diagnoses **(Figure 3)**. Symptom Distribution Across Oral Sites **(Table 5).**

Table 1: Comparison of Age Distribution Between Sexes

Sex	Age								Mann-Whiteny	p-value
	Count	Mean	Std.	Min	25%	50%	75%	Max		
Female	78	55.19	18.46	20	40.25	55.5	71.75	83	**4836.0**	**0.1877**
Male	139	51.81	18.93	20	35.50	51.0	70.50	84		

Table 2: Association Between Tobacco Use and Risk Stratification

Tobacco Used	Risk n (%)			
	High	Low	Moderate	Total
Bidi	1 (0.5)	2 (0.9)	3 (1.4)	6 (2.8)
Bidi and Pan Masala	20 (9.2)	0 (0.0)	1 (0.5)	21 (9.7)
Paan Masala	70 (32.3)	12 (5.5)	22 (10.1)	104 (47.9)
No Answer	43 (19.8)	23 (10.6)	20 (9.2)	86 (39.6)
Total	134 (61.8)	37 (17.1)	46 (21.2)	217 (100.0)
Chi-square (χ^2) test: 24.5339, and p -value: 0.00041				

Table 3: Cross-tabulation showing the distribution of histopathological diagnoses across different clinical diagnostic categories, expressed as number of cases and percentage of the total study population (n = 217)

Clinical diagnosis	Histopathological diagnosis							
	Carcinoma in situ	Chronic ulcer	Dysplasia	Leukoplakia	OSCC	OSMF	Severe dysplasia	Total
Erythroplakia	10 (4.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (7.8%)	0 (0.0%)	16 (7.4%)	43 (19.8%)
Leukoplakia	0 (0.0%)	0 (0.0%)	8 (3.7%)	19 (8.8%)	3 (1.4%)	0 (0.0%)	0 (0.0%)	30 (13.8%)
OSCC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	50 (23.0%)	0 (0.0%)	0 (0.0%)	50 (23.0%)
OSMF	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	41 (18.9%)	0 (0.0%)	41 (18.9%)
Suspicious ulcer	0 (0.0%)	10 (4.6%)	16 (7.4%)	0 (0.0%)	27 (12.4%)	0 (0.0%)	0 (0.0%)	53 (24.4%)
Total	10 (4.6%)	10 (4.6%)	24 (11.1%)	19 (8.8%)	97 (44.7%)	41 (18.9%)	16 (7.4%)	217 (100%)
Chi-square (χ^2) test: 530.88, and p -value: <0.0001								

Table 4: Association Between p63 Intensity Score and Histopathological Diagnosis

p63 Intensity Score	Histopathological diagnosis							
	Carcinoma in situ	Chronic ulcer	Dysplasia	Leukoplakia	OSCC	OSMF	Severe dysplasia	Total
0 (Negative)	0 (0.0%)	10 (4.6%)	11 (5.1%)	19 (8.8%)	0 (0.0%)	41 (18.9%)	0 (0.0%)	81 (37.3%)
1 (Weak)	0 (0.0%)	0 (0.0%)	13 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (6.0%)
2 (Moderate)	3 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	52 (24.0%)	0 (0.0%)	7 (3.2%)	62 (28.6%)
3 (Strong)	7 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	45 (20.7%)	0 (0.0%)	9 (4.1%)	61 (28.1%)
Total	10 (4.6%)	10 (4.6%)	24 (11.1%)	19 (8.8%)	97 (44.7%)	41 (18.9%)	16 (7.4%)	217 (100%)
Chi-square (χ^2) test: 322.72, and p -value: <0.0001								

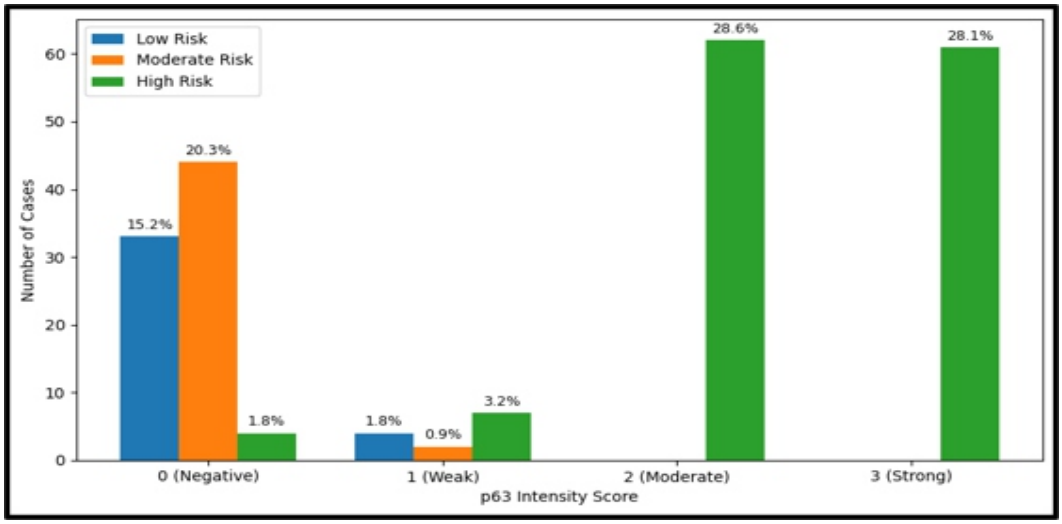

Figure 2: Grouped bar chart showing the distribution of p63 intensity scores across low, moderate-, and high-risk categories. Percentages displayed above bars represent proportions calculated from the total study population

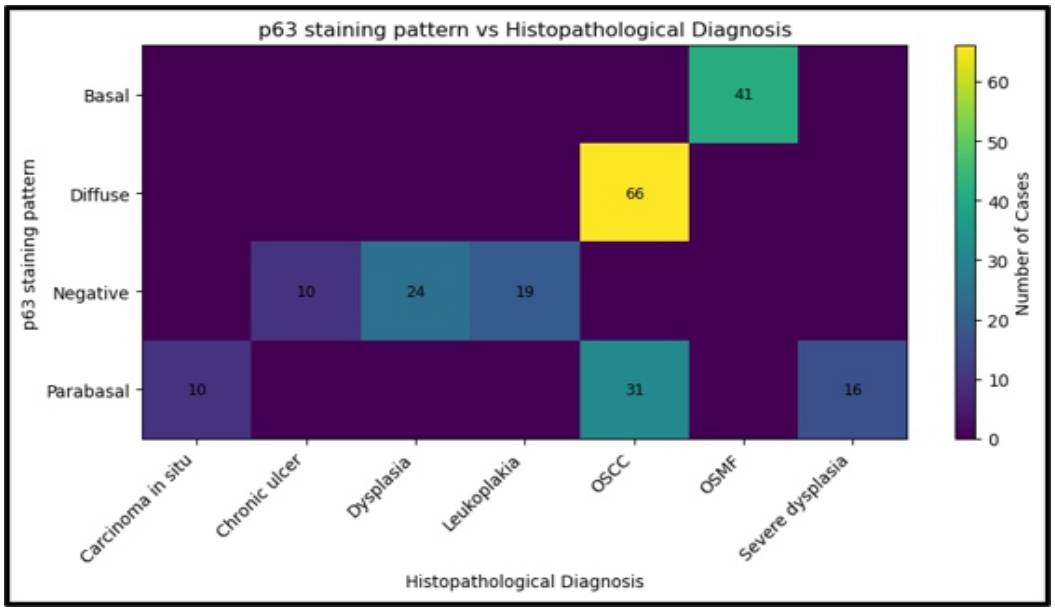

Figure 3: Heatmap showing the distribution of p63 staining patterns across different histopathological diagnostic categories based on the number of cases

Table 5: Distribution of Presenting Symptoms Across Anatomical Sites of the Oral Cavity

Symptom	Site					
	Buccal mucosa	Floor of mouth	Gingiva	Lip	Palate	Tongue
Burning sensation	6 (2.8%)	7 (3.2%)	2 (0.9%)	4 (1.8%)	4 (1.8%)	3 (1.4%)
Non-healing ulcer	10 (4.6%)	10 (4.6%)	4 (1.8%)	6 (2.8%)	10 (4.6%)	5 (2.3%)
Pain	8 (3.7%)	11 (5.1%)	14 (6.5%)	6 (2.8%)	1 (0.5%)	5 (2.3%)
Red patch	5 (2.3%)	5 (2.3%)	9 (4.1%)	8 (3.7%)	5 (2.3%)	6 (2.8%)
Swelling	7 (3.2%)	9 (4.1%)	6 (2.8%)	2 (0.9%)	7 (3.2%)	10 (4.6%)
White patch	4 (1.8%)	4 (1.8%)	4 (1.8%)	4 (1.8%)	6 (2.8%)	0 (0.0%)

DISCUSSION

The p63 protein, encoded by the TP63 gene, is a transcription factor belonging to the p53 family and plays a crucial role in the regulation of growth, differentiation, and survival of stratified squamous epithelium. Unlike classical tumor suppressors, p63 exhibits functional diversity due to its multiple isoforms, contributing variably to epithelial homeostasis. In normal oral mucosa, p63 expression is restricted to basal and parabasal layers, supported epithelial stem cell maintenance and controlled proliferation, thereby preserving tissue integrity and regeneration [14].

During the transition from normal mucosa to premalignant lesions, alterations in p63 expression become evident. Oral epithelial dysplasia and other potentially malignant disorders demonstrated increased p63 expression with extension beyond basal layers into suprabasal regions, indicating expansion of proliferative cell populations [15]. This aberrant distribution reflects reactivation of progenitor-like cellular programs and loss of normal differentiation control, suggesting early neoplastic transformation. Increased p63 labeling index and suprabasal staining are therefore considered indicators of heightened malignant potential. Similarly, conditions such as oral submucous fibrosis and leukoplakia show elevated p63 immunoreactivity, even when histopathological grading may vary, indicating that molecular alterations often precede visible morphological changes [16].

In oral squamous cell carcinoma, p63 expression becomes more intense and diffusely distributed, reflecting deregulated cell cycle control and impaired differentiation. **Momin Z, et. al; 2023,** demonstrated associations between high p63 expression and tumor grade, aggressiveness, and clinical outcomes, highlighting its diagnostic and prognostic value. The progressive increase in p63 expression from normal epithelium to dysplasia and carcinoma underscores its role as a biomarker of epithelial transformation and disease progression [17]. The study was designed to evaluate p63 expression across premalignant and malignant oral lesions and to determine its diagnostic and prognostic relevance. The cohort demonstrated a mean age of 53.03 ± 18.79 years, with most cases clustering in the fifth and sixth decades, consistent with established epidemiological trends. **Venkatesh A, et. al; 2018,** reported in previous studies, confirming that oral epithelial dysplasia and carcinoma predominantly affect middle-aged and older individuals. This age distribution supported the biological plausibility of studying p63 expression in populations with higher exposure to carcinogenic risk factors and increased epithelial turnover [15,18].

A male predominance was observed, with 64.1% males and 35.9% females, aligning with existing literature that attributes higher oral cancer incidence in males to greater exposure to tobacco and related carcinogens [19]. **Rahmani S, et. al; 2024,** compared age distribution between sexes, with no statistically significant difference, minimizes confounding and strengthens the validity of sex-based comparisons in p63 expression [20].

A strong association between tobacco exposure and lesion severity was observed, with high-risk lesions predominantly occurring among users of smokeless and smoked tobacco products [21]. **Sundberg J, et. al; 2021,** supported the role of chronic carcinogenic exposure in inducing epithelial dysregulation and molecular alterations, including p63 upregulation. Statistically significant associations were also found between p63 expression and lesion risk categories, with moderate to strong expression concentrated in high-risk lesions, demonstrating a clear gradient of increasing expression with disease severity [16]. **Maheshwari AM & Kharkar VD. 2020,** revealed strong correlations between clinical and histopathological diagnoses, although variability was noted in ambiguous lesions such as suspicious ulcers, emphasizing the importance of biopsy confirmation. Additionally, p63 expression showed significant association with histopathological grading, with higher intensity and diffuse patterns observed in severe dysplasia and carcinoma, while weaker or basal patterns were seen in benign or mild lesions. This progressive shift from basal to suprabasal and diffuse staining reflects expansion of the proliferative compartment and loss of epithelial maturation control [22].

Clinical presentation varied across anatomical sites, with differences in symptoms such as ulcers, pain, and red or white lesions, consistent with **Warnakulasuriya S. 2018,** demonstrated site-specific variability in oral lesions. **Taruna T, et. al; 2023,** integrated with p63 expression patterns, provide a comprehensive understanding of oral epithelial transformation. Overall, p63 emerges as a reliable biomarker for assessing proliferation, differentiation, and malignant potential, supporting its integration into routine diagnostic and prognostic evaluation of oral lesions [23,24].

CONCLUSION

Based on analysis of 217 cases, p63 is identified as a sensitive and specific biomarker for oral malignancy, showing strong expression in OSCC and severe dysplasia but not in benign lesions, aiding differentiation, especially in small biopsies. Its expression correlates with histopathological severity and tumor progression, enhancing diagnostic accuracy beyond clinical assessment. p63 also demonstrates prognostic value, with higher expression linked to aggressive disease and risk of progression, and shows association with tobacco related etiology, suggesting a role in carcinogenesis and supporting its routine diagnostic and risk assessment use.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical healthcare applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient care, diagnosis, and treatment outcomes. By highlighting real-world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

OSCC: Oral Squamous Cell Carcinoma
OPMD: Oral Potentially Malignant Disorder
IHC: Immunohistochemistry
LI: Labeling Index
NOM: Normal Oral Mucosa
ED: Epithelial Dysplasia
WDSCC: Well-Differentiated Squamous Cell Carcinoma
PDSCC: Poorly Differentiated Squamous Cell Carcinoma
p63: Tumor Protein 63
p53: Tumor Protein 53

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a re-asonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research diretions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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