

Research Article

Oral Biological and Immunohistochemical Correlates of p53 and Ki-67 with Histological Grading and Clinical Outcomes in Oral Squamous Cell Carcinoma: A Pakistani Cohort Study

Sarosh Iqbal¹, Varda Jalil², Maryam Nazir Kiani³, Nida Rasheed⁴, Muhammad Waqas Rashid⁵, Roshan Zafar⁶

¹Assistant Professor Department of Oral Biology Dental College UMDC Sargodha Road Faisalabad, Pakistan

²Associate Professor, Department of Oral Pathology, FMH College of Medicine and Dentistry, Lahore, Pakistan

³Assistant Professor, Oral Pathology Department, Islamic International Dental College and Hospital, Riphah International University. Islamabad, Pakistan

⁴Senior Demonstrator, Department of Oral Biology, Azra Naheed Dental College, Lahore, Pakistan

⁵BDS, M.Phil. Associate Professor Oral Biology, Dental College, Niazi Medical & Dental College, Sargodha, Pakistan

⁶Demonstrator Oral Biology, Sharif Medical and Dental College, Lahore, Pakistan

Corresponding Author: Maryam Nazir Kiani, Assistant Professor, Oral Pathology Department, Islamic International Dental College and Hospital, Riphah International University. Islamabad, Pakistan
Email: maryam.nazir@riphah.edu.pk

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a biologically aggressive malignancy where molecular biomarkers such as p53 and Ki-67 may help in assessing tumor behavior and prognosis.

Objective: To assess p53 and Ki-67 expression in OSCC patients and its correlation with histological grade and clinical outcomes.

Methodology: This retrospective observational study was conducted on 180 histologically confirmed OSCC cases from two tertiary care hospitals. Immunohistochemical analysis was performed to assess p53 and Ki-67 expression, and tumors were categorized into well, moderately, and poorly differentiated grades. Statistical analysis was carried out using Chi-square test, Pearson and Spearman correlation, and Cohen's Kappa test, with $p < 0.05$ considered significant.

Results: Out of 180 patients, 64 (35.6%) had well-differentiated, 78 (43.3%) moderately differentiated, and 38 (21.1%) poorly differentiated OSCC. High p53 expression increased significantly with tumor grade, from 6 (9.38%) in well-differentiated to 20 (52.63%) in poorly differentiated tumors ($\chi^2 = 42.18, p < 0.001$). Similarly, high Ki-67 expression rose from 6 (9.38%) in well-differentiated to 16 (42.11%) in poorly differentiated cases ($\chi^2 = 39.52, p < 0.001$). A strong positive correlation was observed between p53 and Ki-67 ($r = 0.62, p < 0.001$), while Ki-67 showed a strong association with recurrence ($r = 0.65, p < 0.001$). p53 also demonstrated a moderate correlation with tumor stage ($r = 0.58, p < 0.001$).

Conclusion: p53 and Ki-67 are significantly associated with higher histological grade and aggressive clinical behavior in OSCC and may serve as useful prognostic biomarkers.

Keywords: Oral squamous cell carcinoma, p53, Ki-67, immunohistochemistry, histological grade, prognosis, tumor proliferation.

INTRODUCTION

One of the most common cancers of the head and neck area is oral squamous cell carcinoma (OSCC), which is distinguished by its aggressive biological behavior, strong tendency for regional metastasis, and high potential for local invasion [1,2]. It arises from the stratified squamous epithelium of the oral cavity and is frequently

diagnosed at advanced stages, particularly in developing regions where risk factors such as tobacco chewing, smokeless tobacco use, areca nut consumption, alcohol intake, and poor oral hygiene are widely prevalent [3]. Despite advancements in diagnostic and therapeutic modalities, OSCC continues to exhibit considerable variability in clinical outcomes,

largely due to its heterogeneous biological nature and underlying molecular diversity that is not fully captured by conventional histopathological assessment [4].

Molecular changes that control cell division, apoptosis, and genomic stability have a significant impact on the biological behavior of OSCC [5]. Among these, the tumor suppressor gene p53, which controls DNA repair and cell cycle arrest in response to cellular damage, is essential for preserving genomic integrity [6]. Malignant transformation and disease progression are frequently linked to p53 mutations or overexpression [7]. Similar to this, Ki-67, a nuclear protein that is produced during the cell cycle's active phases, is a well-known indicator of cellular proliferation and has been extensively researched in a number of cancers, including OSCC [8].

Histological grading remains a cornerstone in evaluating tumor aggressiveness, providing insight into differentiation patterns and potential clinical behavior [9]. However, conventional grading systems alone may not fully capture the biological complexity of OSCC. Integration of immunohistochemical markers such as p53 and Ki-67 with histopathological assessment has therefore gained increasing attention, as it may offer a more comprehensive understanding of tumor dynamics and prognostic behavior [10]. Correlating these molecular markers with clinical outcomes could potentially refine diagnostic accuracy and improve stratification of disease severity and prognostic prediction [11].

In populations with high exposure to oral carcinogens, such as in South Asia, OSCC often demonstrates distinct clinicopathological characteristics that may differ from Western cohorts [12]. Understanding these variations at both histological and molecular levels is essential for developing context-specific diagnostic and prognostic frameworks that are particularly relevant to resource-limited healthcare settings like Pakistan.

Research Objective

To assess p53 and Ki-67 expression in OSCC and examine their relationship to clinical outcomes (such as tumor stage, lymph node status, and recurrence) and histological grading in a Pakistani population.

METHODOLOGY

Study Design

This observational analytical study used a retrospective cohort-based methodology to assess the immunohistochemistry expression of p53 and Ki-67 in OSCC and examine their relationship with histological grading and clinical outcomes.

Study Setting and Duration

The study was carried out at two tertiary care hospitals. These centers serve as major referral facilities with well-established departments of Oral and Maxillofacial Pathology and Histopathology, providing access to a sufficient number of diagnosed OSCC cases and relevant clinical records.

Study Population and Sample Size

The study population comprised patients with histopathologically confirmed Oral Squamous Cell Carcinoma whose biopsy specimens were processed in the pathology departments of the selected institutions. A total of 180 cases were included in the study.

Sampling Technique

Convenience sampling was used. To reduce selection bias within the realistic limitations of retrospective data availability, all eligible cases that satisfied the inclusion criteria throughout the research period were successively enrolled until the necessary sample size was reached.

Data Collection Procedure

Clinical and demographic data were obtained from hospital medical records, biopsy requisition forms, and pathology reports. Archived formalin-fixed paraffin-embedded tissue blocks were retrieved from the pathology departments of both institutions. Tissue sections were prepared and subjected to routine histopathological evaluation and immunohistochemical staining for p53 and Ki-67. Histopathological grading and immunohistochemical assessment were performed according to standardized laboratory protocols.

Histopathological Evaluation

All cases were reviewed and classified histologically into well-differentiated, moderately differentiated, and poorly differentiated OSCC. Tumor grading was performed by experienced histopathologists to ensure diagnostic accuracy and consistency.

Immunohistochemical Analysis

Immunohistochemical staining for p53 and Ki-67 was performed on formalin-fixed paraffin-embedded tissue sections using standardized protocols. Nuclear staining patterns were evaluated under light microscopy, and the proportion of positively stained tumor cells was recorded. p53 expression was assessed based on nuclear positivity and staining intensity, while Ki-67 labeling index was determined by calculating the percentage of positively stained tumor nuclei among the total number of tumor cells in selected high-power fields. Appropriate positive and negative controls were included in each staining batch to ensure reliability and validity of results.

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and inter-observer consistency was ensured through dual histopathologist review.

Clinical Outcome Assessment

Clinical outcome data were obtained from patient records where available. Parameters such as tumor stage, lymph node involvement, recurrence status, and follow-up information were documented and correlated with histopathological and immunohistochemical findings. Follow-up data were extracted from hospital records and patient follow-up visits where available, ensuring consistency in outcome assessment.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26. Descriptive statistics were applied to summarize demographic, clinical, and pathological variables. Associations between p53 and Ki-67 expression and histological grading were assessed using the Chi-square test. Inter-observer agreement for histological grading and immunohistochemical scoring was assessed using Cohen’s Kappa (κ) test, with values interpreted as poor, fair, moderate, strong, or almost perfect agreement. Correlation between variables was analyzed using Pearson or Spearman correlation tests where

appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic, clinical, histopathological, and immunohistochemical characteristics of 180 OSCC patients. The majority of patients were in the 41–60 years age group (n = 92, 51.11%), followed by >60 years (n = 50, 27.78%) and ≤40 years (n = 38, 21.11%). Males predominated (n = 118, 65.56%) compared to females (n = 62, 34.44%). Tobacco use was highly prevalent (n = 132, 73.33%), while only 48 patients (26.67%) reported no tobacco exposure. The most common tumor site was buccal mucosa (n = 78, 43.33%), followed by tongue (n = 56, 31.11%), gingiva (n = 26, 14.44%), and other sites (n = 20, 11.11%). Histologically, moderately differentiated OSCC was most frequent (n = 78, 43.33%), followed by well differentiated (n = 64, 35.56%) and poorly differentiated tumors (n = 38, 21.11%). Regarding immunohistochemistry, moderate p53 expression was most common (n = 74, 41.11%), while high expression was seen in 54 patients (30.00%). For Ki-67, intermediate proliferation index was predominant (n = 82, 45.56%), followed by high (n = 50, 27.78%) and low (n = 48, 26.67%).

Table 1: Clinicopathological Characteristics and Immunohistochemical Profile of OSCC Patients (n = 180)

Variable	Category	Frequency (n)	Percentage (%)
Age Group	≤40 years	38	21.11
	41–60 years	92	51.11
	>60 years	50	27.78
Gender	Male	118	65.56
	Female	62	34.44
Tobacco Use	Yes	132	73.33
	No	48	26.67
Site of Lesion	Buccal mucosa	78	43.33
	Tongue	56	31.11
	Gingiva	26	14.44
	Others	20	11.11
Histological Grade	Well differentiated	64	35.56
	Moderately differentiated	78	43.33
	Poorly differentiated	38	21.11
p53 Expression	Low (<25%)	52	28.89
	Moderate (25–50%)	74	41.11
	High (>50%)	54	30.00
Ki-67 Index	Low (<20%)	48	26.67
	Intermediate (20–40%)	82	45.56
	High (>40%)	50	27.78

The combined analysis of p53 expression and Ki-67 index across histological grades demonstrates a clear trend of increasing biomarker expression with poorer tumor differentiation (figure 1). In well-differentiated OSCC, low p53 expression was

most common (n = 36, 56.25%), followed by moderate (n = 22, 34.38%) and high expression (n = 6, 9.38%), while Ki-67 also showed predominance of low proliferative activity (n = 34, 53.13%). In moderately differentiated tumors,

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both p53 and Ki-67 showed a shift toward moderate expression, with p53 moderate levels in 38 patients (48.72%) and Ki-67 intermediate index in 40 patients (51.28%). In poorly differentiated OSCC, high biomarker expression was most prominent, with high p53 expression observed in

20 cases (52.63%) and high Ki-67 index in 16 cases (42.11%), indicating a strong association of increased p53 and Ki-67 expression with aggressive tumor behavior and poorer histological differentiation.

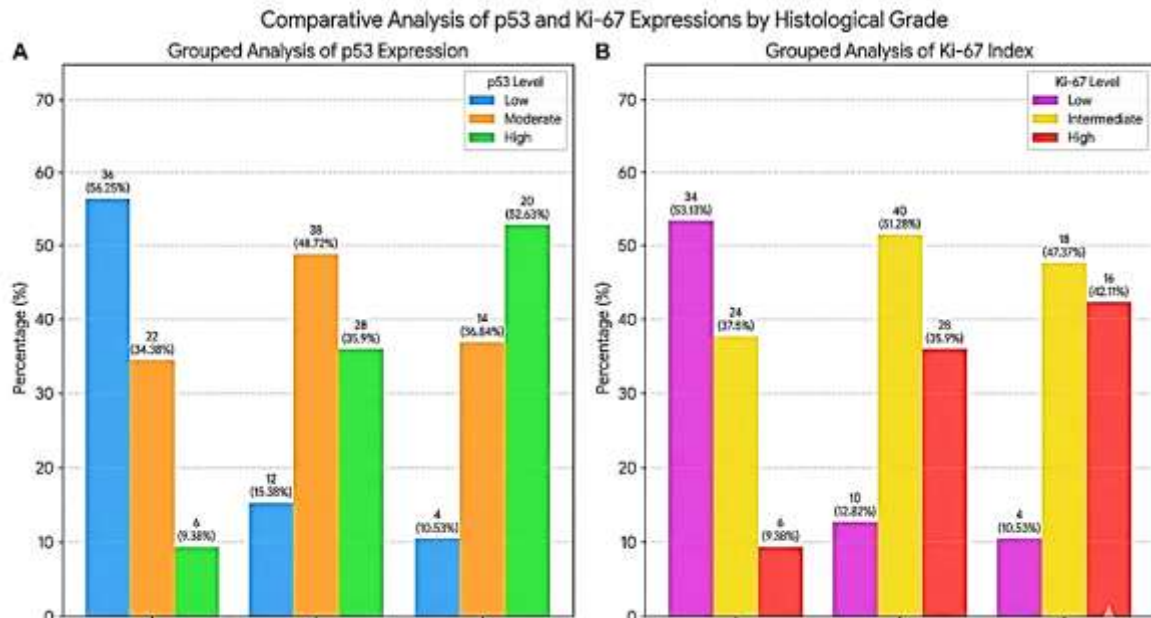


Figure 2 shows that most OSCC patients presented with advanced disease stage (III–IV), accounting for 112 patients (62.22%), while 68 patients (37.78%) presented at early stages (I–II). This

indicates a predominance of late-stage presentation in the studied cohort, reflecting delayed diagnosis and aggressive disease behavior in the population.

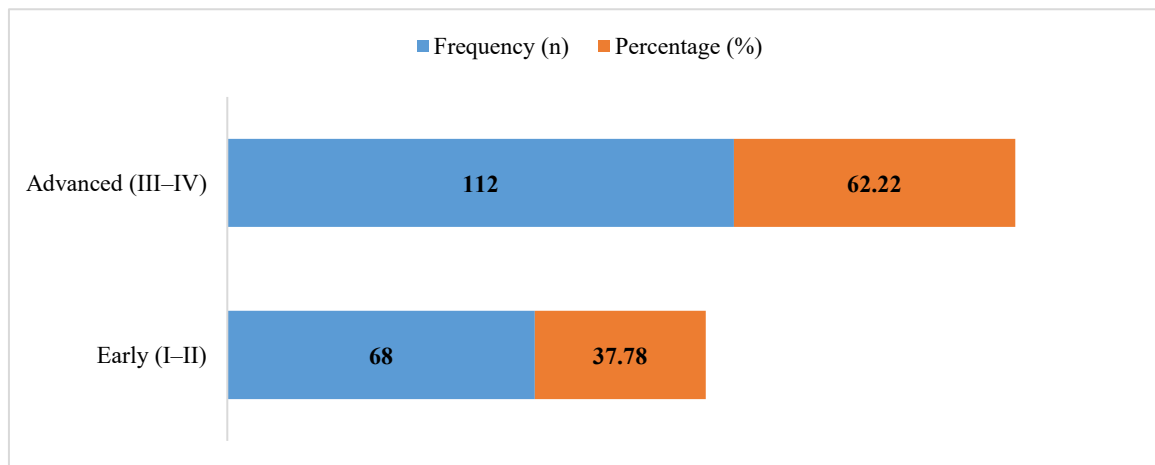


Figure 2: Clinical Stage Distribution in OSCC (n = 180)

Table 2 summarizes clinical outcomes and follow-up patterns in OSCC patients. Lymph node metastasis was present in 104 patients (57.78%), while 76 patients (42.22%) had no nodal involvement. Recurrence was observed in 66 patients (36.67%), whereas 114 patients (63.33%) remained disease-free. Follow-up data were available for 142 patients (78.89%), while 38

patients (21.11%) had no follow-up information. Regarding follow-up duration, most patients were followed for 7–12 months (n = 62, 34.44%), followed by ≤6 months (n = 46, 25.56%) and >12 months (n = 34, 18.89%). Data sources included hospital records only (n = 88, 48.89%), combined records and visits (n = 54, 30.00%), and follow-up visits only (n = 38, 21.11%).

Table 2: Clinical Outcomes and Follow-Up Characteristics in OSCC Patients (n = 180)

Variable	Category	Frequency (n)	Percentage (%)
Lymph Node Metastasis	Present	104	57.78
	Absent	76	42.22
Recurrence	Yes	66	36.67
	No	114	63.33
Follow-up Availability	Yes	142	78.89
	No	38	21.11
Follow-up Duration	≤6 months	46	25.56
	7–12 months	62	34.44
	>12 months	34	18.89
Data Source	Records only	88	48.89
	Records + follow-up visits	54	30.00
	Follow-up visits only	38	21.11

Table 3 shows strong to almost perfect inter-observer agreement for histopathological and immunohistochemical assessments. Agreement for histological grading was strong ($\kappa = 0.84$), as was p53 scoring ($\kappa = 0.81$). Ki-67 scoring

demonstrated almost perfect agreement ($\kappa = 0.88$), while overall diagnostic agreement was strong ($\kappa = 0.85$), indicating high reliability and reproducibility of pathological evaluation.

Table 3: Inter-Observer Agreement Using Cohen’s Kappa (κ) Test

Parameter	Test Used	κ Value
Histological grading	Cohen’s Kappa (κ)	0.84
p53 scoring	Cohen’s Kappa (κ)	0.81
Ki-67 scoring	Cohen’s Kappa (κ)	0.88
Overall diagnostic agreement	Cohen’s Kappa (κ)	0.85

Table 4 demonstrates risk stratification based on combined p53 and Ki-67 expression patterns. Low-risk patients (low p53 and low Ki-67) accounted for 36 cases (20.00%) and were generally associated with early-stage disease and no recurrence. The intermediate-risk group (mixed

expression patterns) was the largest, comprising 78 patients (43.33%) with moderate disease progression. High-risk patients (high p53 and high Ki-67) included 66 cases (36.67%) and were strongly associated with advanced stage disease and recurrence.

Table 4: Risk Stratification Based on Biomarkers

Risk Group	Criteria	Frequency (n)	Percentage (%)	Outcome Trend
Low risk	Low p53 + Low Ki-67	36	20.00	Early stage, no recurrence
Intermediate risk	Mixed expression	78	43.33	Moderate progression
High risk	High p53 + High Ki-67	66	36.67	Advanced stage, recurrence

Table 5 presents statistically significant associations and correlations between biomarkers and clinicopathological features. A strong association was observed between p53 and histological grade ($\chi^2 = 42.18$, $df = 4$, $p < 0.001$), as well as Ki-67 and grade ($\chi^2 = 39.52$, $df = 4$, $p < 0.001$). Correlation analysis revealed a strong

positive correlation between p53 and Ki-67 ($r = 0.62$, $p < 0.001$), a moderate positive correlation between p53 and tumor stage ($r = 0.58$, $p < 0.001$), and a strong positive correlation between Ki-67 and recurrence ($r = 0.65$, $p < 0.001$), indicating that higher biomarker expression is associated with aggressive disease behavior.

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Table 5: Chi-Square Association and Correlation Analysis of p53 and Ki-67 with Histological Grade and Clinical Outcomes in OSCC (n = 180)

Analysis Type	Variables	Test Used	Statistic	df / r value	p-value	Interpretation
Association (Chi-square)	p53 vs Histological Grade	Chi-square (χ^2)	42.18	df = 4	<0.001	Significant
Association (Chi-square)	Ki-67 vs Histological Grade	Chi-square (χ^2)	39.52	df = 4	<0.001	Significant
Correlation	p53 vs Ki-67	Spearman correlation	r = 0.62	—	<0.001	Strong positive correlation
Correlation	p53 vs Tumor Stage	Pearson correlation	r = 0.58	—	<0.001	Moderate positive correlation
Correlation	Ki-67 vs Recurrence	Spearman correlation	r = 0.65	—	<0.001	Strong positive correlation

DISCUSSION

The present study demonstrated a significant association between p53 expression and histological grading of oral squamous cell carcinoma (OSCC), where p53 positivity increased with poorer differentiation. In our cohort, a strong correlation was observed between p53 and tumor grade with a Chi-square value of 42.18 (df = 4, p < 0.001). Similar findings were reported by previous research study who observed that aberrant p53 expression significantly increased in poorly differentiated OSCC, reflecting its role in tumor progression and genomic instability [13]. Likewise, another research study reported a statistically significant association between TP53 alterations and increasing histological aggressiveness in OSCC (p < 0.05), supporting our findings of p53 as a marker of tumor dedifferentiation [14].

In relation to Ki-67 expression, our study showed a highly significant association with histological grade ($\chi^2 = 39.52$, df = 4, p < 0.001). Ki-67 positivity increased progressively from well-differentiated to poorly differentiated tumors. This pattern is consistent with the previous research study where high Ki-67 labeling index was observed in 75% of poorly differentiated OSCC cases, indicating increased proliferative activity in aggressive tumors [15]. Similarly, Muzafar *et al.*, (2025) reported significant elevation of Ki-67 expression in higher-grade OSCC with p < 0.001, reinforcing its prognostic relevance in tumor grading and biological behavior [16].

When evaluating correlations between biomarkers and clinical stage, our study demonstrated a moderate positive correlation between p53 and stage (r = 0.58, p < 0.001). This aligns with findings by Singh *et al.*, (2024) who reported that p53 overexpression is associated with advanced tumor stage and increased invasiveness in OSCC. The biological explanation may relate to loss of

tumor suppressor function leading to unchecked tumor progression and local invasion. Comparable results were also observed in other head and neck squamous cell carcinoma studies, where TP53 mutations were strongly linked with tumor advancement and poor differentiation patterns [17].

In terms of Ki-67 and tumor recurrence, our study revealed a strong positive correlation (r = 0.65, p < 0.001), indicating that higher proliferative index is associated with increased recurrence risk. This finding is consistent with Wankhade *et al.*, (2025) who reported that high Ki-67 expression correlates with aggressive tumor behavior and poor disease control. Similar outcomes have been documented in broader oncological studies where Ki-67 serves as a predictive marker for tumor recurrence and reduced disease-free survival, particularly in epithelial malignancies [15].

The association between Ki-67 and p53 in our study was also statistically significant, with a Spearman correlation coefficient of 0.62 (p < 0.001), indicating a strong positive relationship between proliferative activity and tumor suppressor gene dysfunction. Comparable results were reported by previous study who observed that combined expression of p53 and Ki-67 significantly enhances prognostic stratification in OSCC compared to single-marker analysis alone [18]. This suggests synergistic biological behavior where loss of cell cycle regulation is coupled with increased cellular proliferation.

Overall, histological grading in our study showed strong interdependence with both biomarkers, supported by p53 ($\chi^2 = 42.18$, p < 0.001) and Ki-67 ($\chi^2 = 39.52$, p < 0.001). Similar trends have been consistently reported across recent studies indicating that higher-grade OSCC exhibits increased genetic instability and proliferative indices [19]. These findings reinforce the importance of integrating immunohistochemical

biomarkers with routine histopathology for more precise tumor characterization in OSCC.

Study Strengths and Limitations

This study demonstrates several methodological strengths that enhance the reliability and clinical relevance of its findings. A relatively robust sample size of 180 histologically confirmed OSCC cases was analyzed across two tertiary care centers, improving generalizability within the local population. The use of standardized immunohistochemical evaluation for both p53 and Ki-67, combined with clearly defined scoring criteria and dual pathologist assessment, strengthened diagnostic consistency and reduced observer bias. Appropriate statistical analyses, including Chi-square tests, Pearson and Spearman correlation, and Cohen's Kappa, allowed for comprehensive evaluation of associations and inter-marker relationships. Furthermore, the integration of biomarker expression with histological grading and clinical outcomes such as stage and recurrence provides strong translational relevance for prognostic stratification. However, certain limitations should be acknowledged. The retrospective observational design limits causal inference, and reliance on convenience sampling may introduce selection bias. Although immunohistochemical scoring was standardized, variability in tissue fixation and staining intensity across centers may have influenced marker expression. Additionally, the study lacks long-term survival data, which restricts evaluation of prognostic impact over time. Molecular confirmation (e.g., TP53 gene mutation analysis) was also not performed, which could have strengthened biological validation of p53 expression patterns.

CONCLUSION

This study demonstrates that both p53 and Ki-67 are significantly associated with increasing histological grade and adverse clinical outcomes in oral squamous cell carcinoma, including advanced tumor stage, lymph node metastasis, and recurrence. The progressive rise in their expression from well to poorly differentiated tumors highlights their role in reflecting tumor aggressiveness and proliferative activity. The strong correlation between p53 and Ki-67 further supports their combined utility in enhancing prognostic stratification beyond conventional histopathological grading alone. These findings suggest that integration of p53 and Ki-67 immunohistochemical profiling with routine histopathological assessment can provide a more comprehensive and reliable approach for predicting tumor behavior and guiding clinical management in OSCC, particularly in resource-limited settings like Pakistan.

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