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Research Protocol

Pathology Section

Role of Ki-67, Cyclin D1, and p53 in Early Diagnosis and in the Prognosis of Oral Squamous Cell Carcinoma: A Cross-sectional Study Research Protocol

KHUSHI SONI[1], KESHAV HIWALE[2]

ABSTRACT

Introduction: Oral Squamous Cell Carcinoma (OSCC) accounts for more than 90% of all oral cancers. It is among the top three cancers in India, along with cervical and breast cancer. Oral Epithelial Dysplasia (OED) represents a premalignant lesion that can evolve into OSCC. Early detection of OED and prediction of OSCC prognosis remain a major challenge in clinical practice. Molecular markers have emerged as promising adjuncts to histopathology in the assessment of OED and OSCC.

Need of the study: Histopathological grading is the most widely used method for assessing OED and OSCC. Despite updated grading systems, histology often fails to reliably predict malignant progression and clinical outcomes. A delay in diagnosis affects survival rates, underscoring the need for additional laboratory tools for early detection and prognosis. Immunohistochemistry (IHC) biomarkers such as Ki-67, Cyclin D1, and p53 have shown individual promise in several studies. On the other hand, studies on their combined use remain limited. This study aims to investigate the combined potential of these three biomarkers in early diagnosis and prognosis across the full histological spectrum of OED and OSCC.

Aim: To correlate the expression levels of Ki-67, Cyclin D1, and p53 with the histopathological grades of OED and OSCC and to demonstrate their utility in early diagnosis and prognosis.

Materials and Methods: A single-centre prospective cross-sectional study will be conducted between July 2025 and May 2026 at the Department of Pathology, Jawaharlal Nehru Medical College, DMIHER, Sawangi (Meghe), Wardha, Maharashtra, India. The target sample is planned to consist of 61 cases (30 OED, 31 OSCC), with a projected dropout rate of 10% to provide at least 55 analysable cases. According to the "World Health Organisation WHO 5th edition (2022)" criteria, OED will be classified as mild, moderate, or severe, and OSCC as Well Differentiated (WD), Moderately Differentiated (MD), or Poorly Differentiated (PD). IHC will be performed using validated antibody clones. The scoring will assess the labelling index (LI %) for Ki-67 and p53, the Immunoreactivity Score (IRS) for Cyclin D1, and layer-specific expression patterns. Inter-observer agreement will be assessed. Spearman's rho (ρ) correlation coefficient will be employed to determine the association between biomarker expression scores and OED/OSCC histopathological grade progression. A p-value of less than 0.05 will be regarded as statistically significant.

Keywords: Cyclin D1, Immunohistochemistry, Ki-67, Oral epithelial dysplasia, OSCC, p53

INTRODUCTION

Globally, over 90% of all oral cancers are OSCC, which ranks among the top three cancers in India, particularly in males [1]. Major preventable risk factors are tobacco chewing and alcohol consumption, associated with more than 40% of OSCC cases. Delay in diagnosis is linked with poor outcomes, contributing to over 178,000 deaths globally in a year [2]. These data suggest an urgent and significant need for tools capable of early detection. Although histopathological grading of OED is the gold standard for predicting progression to OSCC, this approach is hampered by subjectivity, inter-observer variability, and limited predictive power. Similarly, the histopathological grading of OSCC based on differentiation is ineffective in reflecting the biological heterogeneity and variable clinical outcomes among patients of the same grade [3,4].

This study emphasises the necessity of a new tool that can be a valuable morphologic complement, provide more objective prognostic information, and enable early detection before overt carcinoma develops. Molecular markers may be the new tool that facilitates the detection of changes before morphological alterations become evident [5]. Among the several investigated biomarkers, Ki-67, Cyclin D1, and p53 are particularly well studied due to their involvement in fundamental pathways of proliferation, cell cycle regulation, and tumour suppression, respectively. Individually, the expression of these markers has been shown to correlate well with OED and OSCC histological grade and clinical outcome. Yet few studies have investigated their combined expression in Indian cohorts, despite India's high disease burden and unique risk factor profile [6]. Their combined analysis should provide a more profound understanding of tumour biology. This study aims to investigate the utility of Ki-67, Cyclin D1, and p53 biomarkers in early diagnosis and in the prognosis of OSCC.

Primary objective: 1) To correlate the IHC expression levels of Ki-67, Cyclin D1, and p53 with the histopathological grades of OED and OSCC.

Secondary objectives:

1) To compare the expression of each biomarker between OED and OSCC.
2) To assess biomarker expression across OED grades (mild, moderate, and severe),
3) To assess biomarker expression across OSCC grades (WD, MD, and PD).
4) To analyse layer-specific expression patterns and their correlation with both the Labelling Index (LI) and the histopathological grade of OED.
5) To evaluate inter-marker correlations (Ki-67 vs. Cyclin D1, Ki-67 vs. p53, and Cyclin D1 vs. p53)

6) To evaluate the diagnostic performance of each biomarker in distinguishing between low-grade (e.g., mild OED, WD OSCC) and high-grade (e.g., severe OED, PD OSCC) lesions.

7) To determine the inter-observer agreement for histopathological grading and IHC scoring.

LITERATURE REVIEW

The current study aims to determine how each biomarker (Ki-67, Cyclin D1, and p53) has a different contribution to the understanding of oral carcinogenesis and to provide a rationale for their combined use as a diagnostic and prognostic tool.

Ki-67: Ki-67 is a nuclear antigen that is strongly expressed in cells undergoing division (G_1, S, G_2, and M phases of the cell cycle). It is absent in non-dividing cells. Many researchers have shown a stepwise progression of the Ki-67 LI with the severity of epithelial dysplasia and its association with low differentiation, late stage, and shorter survival of patients with OSCC [7].

Doctor P et al., (2023) studied the Ki-67 expression in OED and OSCC of various histological grades. The researchers identified a linear increase in LI% from mild dysplasia to poorly differentiated carcinoma. Thus, the authors considered Ki-67 an important proliferation marker and a potent histopathological grading supplement [8].

Chandrakanta NP et al., (2021) determined the link between OSCC grading and the proliferative marker Ki-67. They found the maximum expression of Ki-67 in the group of poorly differentiated OSCC, indicating the marker's prognostic character. They strongly suggested its inclusion in diagnostic IHC panels [9].

Wang T et al., (2024) developed a nomogram depicting Ki-67 as a biomarker for the prognosis of head and neck squamous cell carcinoma. The study emphasised that Ki-67 is one of the variable risk factors, and so it has a role in prognostic stratification [10].

Takkem A et al., (2018) used a similar approach and studied the expression of Ki-67 in OED and OSCC. According to the results, expression increased along with histological grades. They supported the statement that Ki-67 can be an early marker of OED onset and severity of OSCC [11].

Most of the research evidence suggests Ki-67 as a strong proliferation marker for the early identification of dysplastic changes as well as a prognostic marker in OSCC. It should be noted that Ki-67, together with other markers such as Cyclin D1 and p53, provides more information about tumour biology and patient outcome.

Cyclin D1: The Cyclin D1 gene regulates the critical G1/S phase. Overexpression of Cyclin D1 leads to the disruption of normal cell cycle control, which in turn causes uncontrolled proliferation and genomic instability. The higher level of Cyclin D1 in OSCC has been linked to the late stage of the disease. Research results yielded mixed findings regarding the extent of Cyclin D1 expression and its prognostic significance [12].

Mishra V et al., (2020) found a strong presence of Cyclin D1 expression in OSCC as well as in its histological differentiation. Their research indicated that high expression of Cyclin D1 was more obvious in high-grade OSCC, although the study results varied across different populations [13].

John RR et al., (2018) investigated Cyclin D1 expression in oral carcinogenesis and found that its expression was continually high in poorly differentiated OSCC. They concluded that Cyclin D1 was the main driving force of cancer development, especially in the parts of India from where the data were taken; thus, it may be used as a prognostic marker [14].

Bertoli C et al., (2013) demonstrated the deregulation of Cyclin D1 leading to genomic instability in cancer cells, thereby hinting at its utility as a clinical biomarker [15].

These results suggest that Cyclin D1 overexpression is related to the progression of carcinoma and higher histopathological grades in OSCC. Despite different expression between populations, the biological role of Cyclin D1 supports its inclusion among prognostic markers. By using IRS scoring and correlating it to histopathological grade, our study intends to evaluate Cyclin D1's prognostic value.

p53: p53 acts as a tumour suppressor by inducing cell cycle arrest, DNA repair, or apoptosis in response to genotoxic stress. The loss of p53 function, most commonly via TP53 mutations, leads to the absence of proper cell cycle regulation, overgrowth of cells, and genomic instability. TP53 gene mutations cause the accumulation of inactive p53 in the nucleus. This fact makes IHC a very convenient method for the detection of mutant p53 proteins as a proxy for the mutation status of TP53. Its utility as a standalone biomarker is limited due to intratumoural heterogeneity [12,16]. Abnormal p53 expression is found in about 60% of OSCC cases; therefore, the inclusion of p53 in a multimarker panel may be more meaningful. Khandelwal R et al., (2018) suggested a scoring system for p53 overexpression in OSCC as a usable method for clinical implementation. Furthermore, they found correlations between p53 levels and tumour grades occurring consistently, thus implying p53's role as a prognostic factor [17].

Mercadante AA and Kasi A (2025) have thoroughly studied the genes of the cancer cell cycle and indicated the significance of p53 as the mainstay of genomic integrity. They indicated the pathways through which malfunctioning p53 accelerates cancer development, thereby confirming its biological significance in oral cancer [16].

Ravindran S et al., (2025) found multi-marker panels useful in oral cancer diagnostics in poorly resourced scenarios. According to them, in high-risk populations, the combined use of Ki-67, Cyclin D1, and p53 may improve diagnostic capability and also aid in prognostic stratification [6].

Despite heterogeneity, p53 plays an important role in tumour suppression. Its frequent expression in OSCC supports its place in multi-marker studies, particularly when combined with Ki-67 and Cyclin D1 [6,16,17].

The above studies suggest the role of Ki-67, Cyclin D1, and p53 in diagnosis and prognosis in OED and OSCC when used as independent biomarkers. Changes in cell proliferation (Ki- 67), cell cycle regulation (Cyclin D1), and genomic surveillance (p53) have a role in the development of oral cancer. Since all these changes occur at the molecular level, a panel-based approach can better correlate the biochemical changes across the transition spectrum from OED to OSCC than depending on a single marker. This study is designed to correlate histopathology grading with a multi-marker IHC expression, which may enable improved risk stratification and the potential for earlier detection in high-risk groups.

MATERIALS AND METHODS

Study Design

A single-centre prospective cross-sectional study will be conducted between July 2025 and May 2026 at the Department of Pathology, Jawaharlal Nehru Medical College, DMIHER, Sawangi (Meghe), Wardha, Maharashtra, India. The study has been approved by the Institutional Ethics Committee (DMIHER (DU)/IEC/2024/141) and registered with the Clinical Trials Registry of India (CTRI/2025/06/088485). The target recruitment will be 61 cases, with an anticipated 10% dropout, ensuring at least 55 analysable cases.

Inclusion criteria: Confirmed OSCC cases from resection specimens and OED biopsy specimens with adequate tissue for analysis.

Exclusion criteria: All benign inflammatory oral lesions, post-treatment recurring OSCC cases, patients with a previous history of treatment with chemotherapy or radiotherapy, as verified through patient interviews or medical records, inadequate tissue for IHC

processing/antigen retrieval, and patients who decline to provide consent.

Sample Size Determination: Fisher's z-transformation for correlation studies was applied for the calculation of the minimum sample size [18,19], assuming a moderate effect size (r=0.4) based on Cohen's conventions [20]. With α=0.05 and power=80%, the required sample size was calculated as 46 cases. To ensure adequate power for subgroup analyses across multiple histological grades and to align with comparable studies [8,13,17], the target was set to 55 analysable cases. Accounting for an anticipated 10% dropout rate, the final recruitment target is 61 cases. (30 OED: 10 mild, 10 moderate, 10 severe; 31 OSCC: 10 WD, 11 MD, 10 PD). This sample size will allow at least 55 analysable cases (27 OED, 28 OSCC) for the primary correlation analysis. The exact numbers of cases in each subgroup will be shown in the final analysis.

Methodology

Sample definition and distribution: Formalin-Fixed, Paraffin-Embedded (FFPE) tissue blocks with newly diagnosed cases confirmed by histopathology will be used.

The target recruitment will be 61 cases, ensuring at least 55 analysable cases after an anticipated 10% dropout. Stratified sampling will be used to ensure balanced representation across grades.

Group-A (OED): 30 cases (10 mild, 10 moderate, 10 severe).

Group-B (OSCC): 31 cases (10 WD, 11 MD, 10 PD).

Histopathology: Routine Haematoxylin and Eosin (H&E) staining will be done for all biopsy samples according to institutional Standard Operating Procedures (SOPs). According to the WHO (5th edition, 2022) criteria, OED will be classified as mild, moderate, or severe, and OSCC as WD, MD, or PD [21].

Immunohistochemistry (IHC) Protocol: The antibody clone selection will be based on its use in at least five published OSCC studies. Ready-to-use pre-optimised primary antibodies will be used for IHC [Table/Fig-1]. FFPE sections (4 µm) will be deparaffinised, rehydrated, and subjected to heat-induced epitope retrieval (pH 9 .0 for 30 min). Immunostaining will use Poly Excel HRP detection with positive (e.g., tonsil tissue or as per supplier guidelines) and negative (no primary antibody) controls. Staining will be done in batches to reduce variability {Coefficient of Variation (CV) <10% between batches}.

Marker	Clone	Supplier	Dilution/Use
Ki-67	MIB-1	Dako	Ready-to-use
Cyclin D1	SP4	Dako	Ready-to-use
p53	DO-7	Dako	Ready-to-use

[Table/Fig-1]: Primary antibodies for IHC.

To assess inter-observer reliability: for 1) histopathological grading; and 2) IHC scores, two pathologists will independently review all slides. Evaluation of inter-observer agreement will be done by using Cohen's Kappa (κ) for histopathological grading and the Intraclass Correlation Coefficient (ICC) for IHC scoring. Any discrepancy will be resolved by joint review using a multi-headed microscope until consensus is reached.

IHC scoring and layer-specific expression pattern analysis: IHC expression patterns will be assessed visually using a standard light binocular microscope. An initial low-power (100x) scan will be performed to select densely stained hotspot regions. Each section will be examined for 4-5 such representative hotspots under high-power fields (400x); necrotic areas and artifacts will be avoided. Only brownish nuclear staining will be considered positive. In each section, a minimum of 1000 cells will be counted from all selected hotspots to calculate the LI% [22].

For Ki-67 and p53, LI alone will be used; for Cyclin D1, the Intensity score (1: weak, 2: intermediate, 3: strong) will be multiplied by the LI score to calculate the IRS [13].

Scoring criteria: Different validated scoring systems will be adopted for each biomarker (LI for Ki-67 and p53, IRS for Cyclin D1) as per prior studies to maintain comparability with published literature.

1) The scoring for Ki-67 as per Doctor P et al., [8] is based on the LI%.

   Score 1 (+): 1-25%, score 2 (++): 26-50%, score 3 (+++): 51-75%, score 4 (++++): 76-100%.

2) The scoring for Cyclin D1, as per Mishra V et al., [13] is based on the LI% and intensity score. LI is graded as follows: score 1 for 1-25% positive cells, score 2 for 26-50%, score 3 for 51-75%, and score 4 for 76-100% positive cells. Staining intensity is categorised as score 1 for weak staining, score 2 for intermediate staining, and score 3 for strong staining. The IRS is calculated by multiplying the LI score by the staining intensity score (IRS = LI × intensity). The final IRS ranges from 1 to 12 and is interpreted as follows: scores 1-4 are considered weak expression, scores 5-8 are moderate expression, and scores 9-12 are strong expression.

3) The scoring for p53, as per Khandelwal R et al., [17] is based on the LI%. Negative (<5%), score 1 (+): 5-25%, score 2 (++): 26-50%, score 3 (+++): >50%.

Layer-specific expression pattern analysis will be adapted and modified from Raju B et al., [22]. In OED cases, the layer-specific expression pattern will be scored as follows, with upward displacement considered indicative of increasing dysplasia severity. Score 1: Basal layer (confined to the lower third of the epithelium).

Score 2: Parabasal layer (extending to the middle third).

Score 3: Suprabasal layer (extending to the upper third or demonstrating pan-epithelial expression).

Primary outcome: The correlation between the expression scores of Ki-67, Cyclin D1, and p53 and the histopathological grade progression in OED and OSCC as measured by Spearman's ρ (rho) correlation coefficient and associated p-value. A higher ρ (rho) value will indicate a stronger monotonic association.

Secondary outcomes: Evaluation of differences in expression between groups, layer- specific patterns, and inter-marker correlations.

1) The difference in the median expression scores of each biomarker is compared between the OED group (all grades combined) and the OSCC group (all grades combined).
2) The difference in the median expression scores (LI %) of each biomarker (Ki-67, Cyclin D1, p53) across OED grades (mild vs. moderate vs. severe)
3) The difference in the median expression scores (LI %) of each biomarker (Ki-67, Cyclin D1, p53) across OSCC grades (WD vs. MD vs. PD).
4) The correlation between the layer-specific expression patterns (basal, parabasal, and suprabasal) of each biomarker across the different grades of OED.
5) The strength of correlation measured by Spearman's rank correlation coefficient between the expression levels of the different biomarker pairs (e.g., Ki-67 vs. Cyclin D1, Ki-67 vs. p53, Cyclin D1 vs. p53) across all samples.
6) The diagnostic performance, as measured by Receiver Operating Characteristic (ROC) analysis, of each biomarker for distinguishing between low-grade (e.g., mild OED, WD OSCC) and high-grade (e.g., severe OED, PD OSCC) lesions.

7) The degree of inter-observer agreement between two pathologists for histopathological grading as well as IHC scoring.

Subgroup analyses are to be considered exploratory and preliminary in nature.

STATISTICAL ANALYSIS

Statistical analysis will utilise IBM SPSS v27.0, with data normality assessed via the Shapiro-Wilk test, anticipating non-normal distribution and thus employing non-parametric tests. Categorical variables will be reported as frequencies (n) and percentages, and continuous variables as median and Interquartile Range (IQR), with mean ± SD as supplemental data. The primary analysis will use Spearman's ρ to correlate biomarker expression (Ki-67, Cyclin D1, p53) with histopathological grades of OED and OSCC. Secondary analyses include Mann-Whitney U test for OED vs. OSCC biomarker expression, Kruskal-Wallis H test with Dunn's post-hoc for comparisons across OED (mild, moderate, severe) and OSCC (WD, MD, PD) grades, and Spearman's ρ for layer pattern correlations and inter-marker correlations. ROC curve analysis will evaluate biomarkers' diagnostic performance for low-grade vs. high-grade lesions, and Cohen's kappa (κ) /ICC will assess inter-observer agreement for grading and IHC scoring. A p-value <0.05, adjusted with Bonferroni correction for post-hoc tests, will indicate statistical significance.

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PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor, Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Khushi Soni,
Senior Resident, Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
E-mail: khushisoni9723@gmail.com

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