ISSN: 2581 – 3633

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: https://www.ijmacr.com

Volume – 9, Issue – 6, November – 2026, Page No.: 228 – 237

Expression of p53, p16 and Ki-67 in Cervical Intraepithelial Lesions and Cervical Carcinoma

[1]Nitesh Rawat, Assistant Professor, Department of Pathology, Ram Krishna Medical College Hospital & Research Centre, Bhopal, Madhya Pradesh, India

[2]Swati Gupta, Assistant Professor, Department of Pathology, Ram Krishna Medical College Hospital & Research Centre, Bhopal, Madhya Pradesh, India

[3]Tonushree Purohit, Assistant Professor, Department of Pathology, People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh, India

Corresponding Author: Swati Gupta, Assistant Professor, Department of Pathology, Ram Krishna Medical College Hospital & Research Centre, Bhopal, Madhya Pradesh, India

How to citation this article: Nitesh Rawat, Swati Gupta, Tonushree Purohit, "Expression of p53, p16 and Ki-67 in Cervical Intraepithelial Lesions and Cervical Carcinoma", IJMACR– November – 2026, Volume – 9, Issue – 6, P. No. 228 – 237.

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Cervical intraepithelial neoplasia (CIN) encompasses a spectrum of human papillomavirus-associated epithelial alterations. Histological distinction between benign mimics, low-grade lesions and high-grade lesions may benefit from selected immunohistochemical markers. This study examined p16, Ki-67 and p53 immunoreactivity across cervical lesions.

Methods: An observational analytical study of 110 cervical tissue specimens was structured at the Department of Pathology, Ram Krishna Medical College Hospital & Research Centre, Bhopal, during August 2024–July 2026. Specimens were classified as benign cervicitis, low-grade squamous intraepithelial lesion (LSIL/CIN 1), high-grade squamous intraepithelial lesion (HSIL/CIN 2 or CIN 3), or invasive squamous cell carcinoma. p16 block positivity, Ki-67 labeling index, and p53 nuclear labeling were evaluated. Associations with histological category and descriptive performance for CIN 2+ were analyzed.

Results: The 110 specimens comprised 15 benign lesions, 25 CIN 1, 20 CIN 2, 20 CIN 3, and 30 squamous carcinomas. p16 block positivity increased from 6.7% in benign lesions and 32.0% in CIN 1 to 75.0% in CIN 2, 95.0% in CIN 3, and 96.7% in carcinoma ($P < 0.001$). A Ki-67 index ≥30% was recorded in 0%, 12.0%, 60.0%, 95.0% and 96.7%, respectively ($P < 0.001$). p53 nuclear labeling ≥10% showed a less consistent association with histology ($P = 0.073$). For CIN 2+ classification, the

sensitivity/specificity were 90.0%/77.5% for p16, 85.7%/92.5% for Ki-67, and 38.6%/85.0% for p53.

Conclusion: Strong p16 block expression and increased Ki-67 labeling were associated with higher-grade cervical lesions. p53 labeling varied across categories and added limited discriminatory value under the evaluated threshold. Histomorphology remains central to classification, with p16 used selectively as an ancillary marker.

Keywords: cervical intraepithelial neoplasia; cervical carcinoma; immunohistochemistry; p16; Ki-67; p53; squamous intraepithelial lesion.

Introduction

Cervical carcinoma is a major cause of preventable cancer morbidity, particularly in health systems with gaps in human papillomavirus (HPV) vaccination, organized screening and timely treatment. Persistent high-risk HPV infection is the dominant etiological driver of most cervical squamous neoplasms. The progression from an HPV-associated low-grade lesion to a high-grade precursor or invasive carcinoma is not inevitable, making accurate classification of biopsy findings important for avoiding both under-treatment and unnecessary intervention [1,2].

Routine hematoxylin-and-eosin (H&E) sections remain the basis of cervical histopathological diagnosis. Histological LSIL corresponds broadly to CIN 1, whereas HSIL encompasses CIN 2 and CIN 3, consistent with the Lower Anogenital Squamous Terminology (LAST) framework. Architectural distortion, nuclear atypia and abnormal maturation may overlap with immature squamous metaplasia, reactive epithelial changes and tangentially sectioned epithelium. Lesions at the CIN 2 boundary can be particularly difficult to classify reproducibly [3–5].

p16INK4a is an indirect indicator of deregulated HPV-associated cell-cycle signaling. Strong continuous nuclear or nuclear-cytoplasmic block-type staining supports a transforming HPV-associated lesion when the H&E morphology is concordant. p16 positivity alone does not establish histological grade, and routine application to every unambiguous CIN 1 or CIN 3 biopsy is not recommended. Its principal value lies in the selective adjudication of morphologically equivocal lesions and high-grade mimics [3,5,6].

Ki-67 is a nuclear proliferation marker and reflects the proportion and distribution of actively cycling cells. In normal squamous epithelium, proliferative activity is largely confined to the basal/parabasal region. Increasing suprabasal proliferation accompanies higher-grade dysplastic change, and high labeling indices may be observed in invasive carcinoma. Although quantitative Ki-67 evaluation can support a description of proliferative activity, the cutoff used for research categorization is not a universally endorsed stand-alone clinical diagnostic threshold [7–10].

p53 has a more complex relationship with cervical tumor biology because high-risk HPV E6 can promote p53 degradation; immunohistochemical p53 expression is not equivalent to TP53 mutation and may not rise uniformly with lesion grade. Previous studies and a systematic review have shown less consistent p53 relationships than those reported for p16 or Ki-67 [7,11,12].

This study assessed the expression patterns of p53, p16 and Ki-67 across benign cervical lesions, CIN 1, CIN 2, CIN 3 and invasive squamous carcinoma. The primary objective was to compare marker expression according to histopathological category. Secondary objectives were to examine the Ki-67 labeling index, associations among

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markers, and their descriptive diagnostic performance for identifying CIN 2 or more severe histology (CIN 2+).

Materials And Methods

Study design and setting

A hospital-based observational analytical study was conducted in the Department of Pathology, Ram Krishna Medical College Hospital & Research Centre, Bhopal, Madhya Pradesh, over two years from August 2024 to July 2026. Cervical biopsy and excision tissue specimens evaluated during the study period were categorized on the basis of histomorphological assessment. A sample of 110 cases was included for comparison of marker expression across disease categories.

Eligibility criteria and specimen selection

Eligible specimens comprised cervical tissue with preserved epithelial architecture and adequate formalin-fixed, paraffin-embedded material for H&E review and all three immunohistochemical stains. Both non-neoplastic and squamous neoplastic lesions were included to provide a morphological spectrum, with invasive squamous carcinoma forming the malignant comparison group. Cases with extensively necrotic tissue, inadequate viable epithelium, exhausted paraffin blocks, severe processing artifacts or uninterpretable immunostaining were excluded. Only one representative specimen per patient was included in the analytical dataset.

Histomorphological classification

H&E-stained slides were independently assessed for epithelial maturation, cytological atypia, nuclear-to-cytoplasmic ratio, atypical mitotic activity, architectural disturbance and stromal invasion. Cases were categorized as benign/reactive cervicitis, LSIL (CIN 1), HSIL (CIN 2), HSIL (CIN 3) or invasive squamous cell carcinoma. For consistency of analysis, CIN 2 and CIN 3 were retained as separate morphological categories while both were included under HSIL. The high-grade binary outcome, CIN 2+, comprised CIN 2, CIN 3 and squamous carcinoma. The H&E-based category was established before examination of the research marker scores to reduce incorporation bias in the diagnostic-performance analysis.

Immunohistochemical procedure

Representative sections measuring approximately 3–4 µm were cut from formalin-fixed, paraffin-embedded blocks and mounted on adhesive-coated slides. After deparaffinization, rehydration and antigen retrieval, sections were subjected to an immunoperoxidase-based staining procedure for p16INK4a, Ki-67 and p53, using appropriate positive and negative controls. Sections were counterstained with hematoxylin. Staining intensity, localization and percentage of labeled cells were assessed in morphologically representative regions, excluding necrotic or poorly preserved areas. Two pathology observers independently reviewed the stained sections; discrepant categorizations were resolved through joint microscopic review.

Interpretation of immunostaining

p16 was classified as block positive when strong, continuous nuclear or combined nuclear-cytoplasmic staining extended from the basal layers into at least the lower one-third of the affected squamous epithelium, or exhibited corresponding diffuse staining in invasive squamous carcinoma. Focal, discontinuous or weak staining was classified as non-block positive. Ki-67 labeling index was calculated as the percentage of tumor or lesional epithelial nuclei with unequivocal nuclear staining among approximately 500 counted nuclei in representative proliferative regions. The continuous

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percentage was retained for analysis; a labeling index of at least 30% was additionally designated as a high-proliferation category for descriptive comparisons. p53 nuclear staining was reported as the percentage of lesional cells stained, with labeling in at least 10% of cells classified as increased nuclear immunoreactivity. This p53 threshold was used descriptively and was not interpreted as proof of a TP53 pathogenic variant [3,6–9].

Variables and outcomes

Extracted analytical variables included age, histological category, p16 block status, Ki-67 labeling index and high-index status, and p53 nuclear-labeling status. The primary outcomes were the proportion of marker-positive cases across diagnostic groups. Secondary outcomes included the distribution of Ki-67 labeling, correlations with histological severity, and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of the three predefined marker categories for detecting CIN 2+ histology.

Statistical analysis

Continuous variables were summarized using mean ± standard deviation (SD) and median with interquartile range (IQR). Categorical data were expressed as frequencies and percentages. Between-group marker-expression patterns were compared with Pearson's chi-square test. The Kruskal–Wallis test was used for Ki-67 index comparisons across histological categories. Spearman's rank correlation assessed the relation between ordered histological severity and Ki-67 labeling and between p16 status and Ki-67 labeling. For the CIN 2+ diagnostic comparison, 2×2 tables were used to calculate sensitivity, specificity, PPV, NPV and accuracy, with Wilson 95% confidence intervals for key proportions. All tests were two-sided, with $P < 0.05$ considered statistically significant. The unit of analysis was the individual patient/specimen; repeated specimens from the same patient were not included [13].

Results

Histopathological distribution and age

The series included 110 cervical specimens. Benign cervicitis or reactive lesions accounted for 15 (13.6%), CIN 1 for 25 (22.7%), CIN 2 for 20 (18.2%), CIN 3 for 20 (18.2%), and squamous carcinoma for 30 (27.3%) cases. Mean age was 44.9 ± 11.1 years, and the age distribution differed across histological categories (Kruskal–Wallis $P < 0.001$). The highest mean age was observed in the carcinoma group (53.9 ± 9.6 years) (Table 1).

Table 1: Histological distribution and patient age (n = 110).

Histopathology	n	%	Age (years), mean ± SD	Age, median (IQR)
Chronic cervicitis / benign	15	13.6	34.9 ± 7.9	34 (30–39)
LSIL (CIN 1)	25	22.7	40.1 ± 8.5	39 (34–47)
HSIL (CIN 2)	20	18.2	41.9 ± 9.9	40 (37–48)
HSIL (CIN 3)	20	18.2	47.9 ± 8.6	50 (44–52)
Squamous cell carcinoma	30	27.3	53.9 ± 9.6	54 (49–60)
Total	110	100.0	44.9 ± 11.1	—

CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

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Expression patterns of p16, Ki-67 and p53

p16 block positivity was detected in 72 (65.5%) specimens overall, increasing from 1/15 (6.7%) in benign lesions to 29/30 (96.7%) in carcinoma ($P < 0.001$). A Ki-67 labeling index ≥30% was identified in 63 (57.3%) specimens, with highest frequencies in CIN 3 and carcinoma (both ≥95%; $P < 0.001$). Increased p53 nuclear labeling occurred in 33 (30.0%) specimens; its distribution varied less strongly across histology ($P = 0.073$) (Table 2; Figure 1).

Table 2: Immunohistochemical marker positivity across cervical lesion categories.

Histology	n	p16 block positive	Ki-67 ≥30%	p53 ≥10%
Chronic cervicitis / benign	15	1 (6.7%)	0 (0.0%)	1 (6.7%)
LSIL (CIN 1)	25	8 (32.0%)	3 (12.0%)	5 (20.0%)
HSIL (CIN 2)	20	15 (75.0%)	12 (60.0%)	6 (30.0%)
HSIL (CIN 3)	20	19 (95.0%)	19 (95.0%)	8 (40.0%)
Squamous cell carcinoma	30	29 (96.7%)	29 (96.7%)	13 (43.3%)
Total	110	72 (65.5%)	63 (57.3%)	33 (30.0%)

Overall Pearson chi-square P values: p16 <0.001; Ki-67 <0.001; p53 0.073. The p53 criterion denotes nuclear labeling and not aberrant/mutation-type staining.

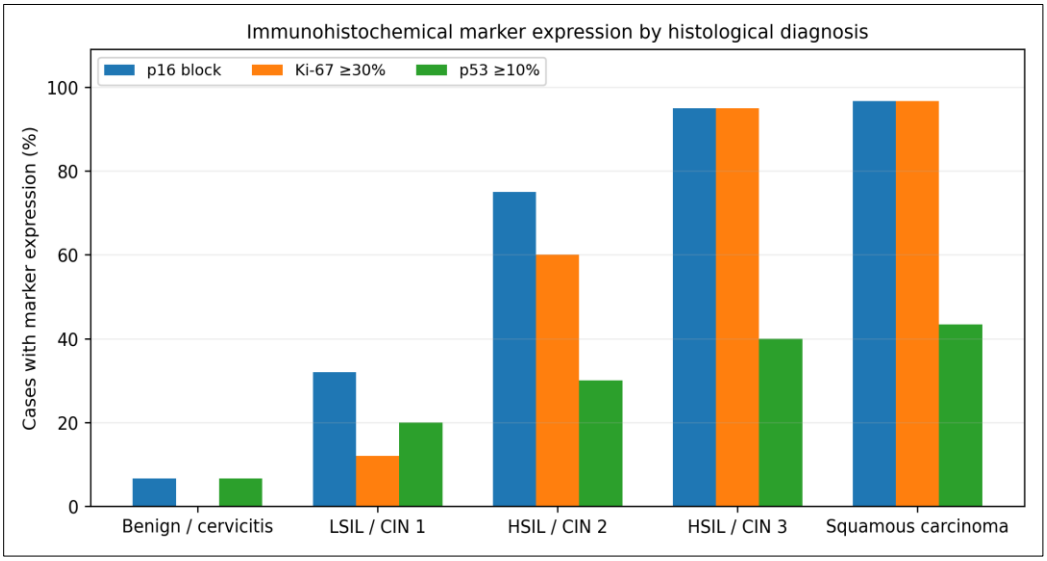


Figure 1: Proportion of cases demonstrating p16 block positivity, high Ki-67 labeling (≥30%), and p53 nuclear labeling (≥10%) by histopathological category.

Quantitative Ki-67 labeling

The Ki-67 labeling index increased progressively across the diagnostic spectrum. Group means rose from 6.5 ± 2.0% in benign lesions and 20.7 ± 7.4% in CIN 1 to 34.0 ± 7.9% in CIN 2, 53.1 ± 7.7% in CIN 3 and 68.7 ± 11.7% in squamous carcinoma. Differences among diagnostic groups were significant (Kruskal–Wallis $H = 96.87$; $P < 0.001$), and the relationship between ordered histological severity and Ki-67 labeling was strong (Spearman $\rho = 0.942$; $P < 0.001$) (Table 3; Figure 2).

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Table 3: Quantitative Ki-67 labeling index by histological diagnosis.

Histopathology	n	Mean ± SD (%)	Median (IQR), %	Range, %
Chronic cervicitis / benign	15	6.5 ± 2.0	6.6 (5.4–7.8)	2.5–10.3
LSIL (CIN 1)	25	20.7 ± 7.4	21.6 (15.2–24.5)	9.6–35.9
HSIL (CIN 2)	20	34.0 ± 7.9	36.8 (26.7–40.0)	22.2–47.6
HSIL (CIN 3)	20	53.1 ± 7.7	53.5 (49.4–57.8)	28.7–66.7
Squamous cell carcinoma	30	68.7 ± 11.7	70.2 (62.5–76.3)	26.3–83.7

The Ki-67 labeling index was compared across categories by the Kruskal–Wallis test ($P < 0.001$).

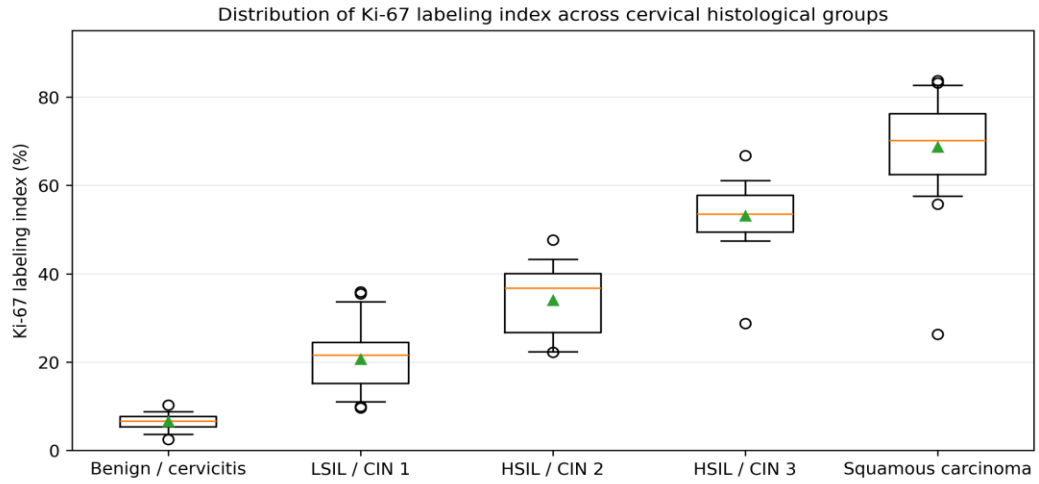


Figure 2: Ki-67 labeling-index distribution across histological categories. Central lines indicate medians; boxes show the interquartile range; whiskers extend to the 5th–95th percentiles; mean values are indicated by triangles.

Proliferation strata and marker association

The fraction of cases with a Ki-67 index ≥30% increased with histological severity. Nearly all benign specimens showed labeling ≤10%, whereas 29 of 30 carcinomas had a Ki-67 index ≥30%. p16 block positivity correlated with the continuous Ki-67 index (Spearman $\rho = 0.759$; $P < 0.001$). High Ki-67 labeling was confined to p16 block-positive cases within this analytical series (Table 4).

Table 4: Distribution of the Ki-67 labeling index by histology.

Histology	n	≤10%	>10% to <30%	≥30%
Chronic cervicitis / benign	15	14 (93.3%)	1 (6.7%)	0 (0.0%)
LSIL (CIN 1)	25	2 (8.0%)	20 (80.0%)	3 (12.0%)
HSIL (CIN 2)	20	0 (0.0%)	8 (40.0%)	12 (60.0%)
HSIL (CIN 3)	20	0 (0.0%)	1 (5.0%)	19 (95.0%)
Squamous cell carcinoma	30	0 (0.0%)	1 (3.3%)	29 (96.7%)

Cell entries are frequencies and row percentages. The 30% cutoff is a research classification threshold.

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Diagnostic performance for CIN 2+ histology

For the dichotomous CIN 2+ endpoint, 70 specimens met the higher-grade definition and 40 were classified as benign lesions or CIN 1. The 2×2 marker results are provided in Table 5. p16 had sensitivity 90.0% and specificity 77.5%, while the Ki-67 index ≥30% had sensitivity 85.7% and specificity 92.5%. p53 ≥10% provided sensitivity 38.6% with specificity 85.0%. Ki-67 yielded the highest positive predictive value (95.2%) and overall accuracy (88.2%) under the predefined categories (Table 6; Figure 3).

Table 5: Marker classification against the H&E-based CIN 2+ endpoint (70 positive, 40 negative).

Marker	True positive	False negative	False positive	True negative
p16 block positive	63	7	9	31
Ki-67 ≥30%	60	10	3	37
p53 ≥10%	27	43	6	34

CIN 2+ comprises CIN 2, CIN 3 and invasive squamous carcinoma; non-CIN 2+ comprises benign lesions and CIN 1. Histology was the reference classification.

Table 6: Descriptive diagnostic performance of p16, Ki-67 and p53 for CIN 2+.

Marker	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Accuracy
p16 block positive	90.0% (80.8–95.1)	77.5% (62.5–87.7)	87.5%	81.6%	85.5%
Ki-67 ≥30%	85.7% (75.7–92.1)	92.5% (80.1–97.4)	95.2%	78.7%	88.2%
p53 ≥10%	38.6% (28.0–50.3)	85.0% (70.9–92.9)	81.8%	44.2%	55.5%

Sensitivity and specificity confidence intervals were calculated using the Wilson method. These are within-sample estimates and do not imply screening-test performance in an unselected population.

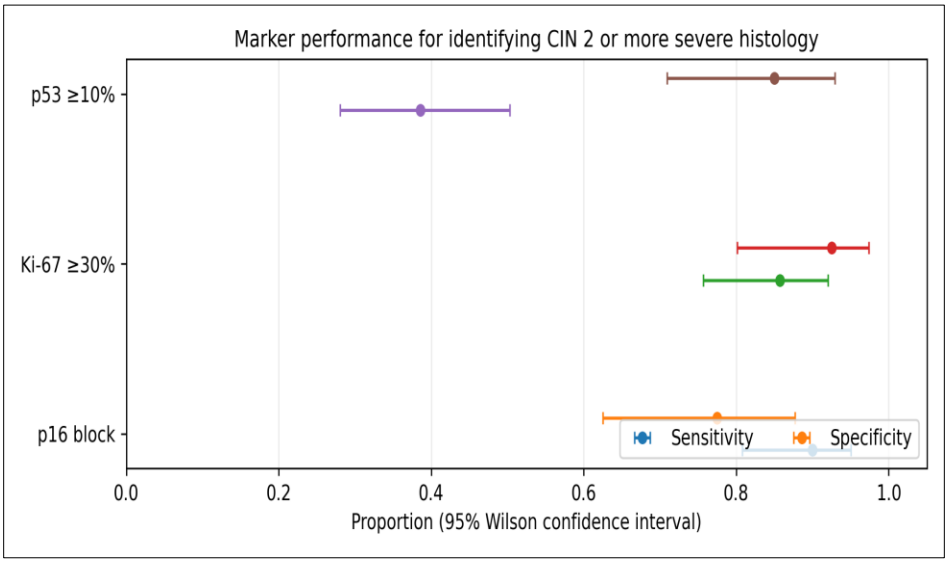


Figure 3: Within-sample sensitivity and specificity for detecting CIN 2+ histology with 95% Wilson confidence intervals.

Discussion

In the present lesion spectrum, p16 block positivity and Ki-67 proliferation indices differed markedly by histological category, whereas increased p53 nuclear labeling showed a weaker association. The pattern of p16 expression was concentrated in CIN 2, CIN 3 and

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invasive squamous carcinoma, supporting its biological association with transforming HPV-related cellular change. The marked rise in Ki-67 labeling across graded lesions provided a complementary indication of increasing epithelial proliferative activity.

The p16 distribution is consistent with the framework developed by the LAST working groups, in which diffuse block-type staining supports high-grade histology when the morphological differential includes CIN 2 or an important benign mimic [3,4]. However, 32.0% of the CIN 1 specimens in this series were also p16 block positive. This underscores the central caution in current guidance: p16 positivity alone should not trigger upgrading morphologically established CIN 1 to HSIL. Site-specific histological context, epithelial maturation and atypia must remain the foundation of the diagnosis [5,6].

The progressive increase in Ki-67 labeling is biologically consistent with the extension of proliferative activity beyond the basal/parabasal compartment in high-grade cervical lesions. The high Ki-67 indices in CIN 3 and invasive carcinoma resemble earlier reports demonstrating an association between increasing proliferation and lesion severity [7–10]. Nevertheless, laboratory thresholds may be affected by field selection, counting method, fixation conditions and observer variability. Accordingly, the 30% cut point in the present analysis should be understood as an operational threshold rather than a validated replacement for morphological grading.

p53 showed a different pattern. Although the frequency of nuclear labeling ≥10% rose numerically from benign lesions to carcinoma, the overall between-category association was not significant at the prespecified threshold. The presence or absence of p53 immunoreactivity cannot be used as a direct proxy for TP53 mutation in HPV-associated cervical tumors. HPV E6-mediated protein turnover and other biological and technical influences complicate interpretation. Silva and colleagues found that p53 expression showed a consistent association with lesion severity in fewer studies than p16 or Ki-67 in their systematic review, supporting a cautious interpretation of isolated p53 staining [11,12].

The binary comparison with CIN 2+ histology suggested that p16 had higher sensitivity, whereas Ki-67 ≥30% offered higher specificity in this selected series. Because disease categories were deliberately represented across the histological spectrum and each specimen was evaluated in a pathology-based rather than screening population, the predictive values should not be generalized to routine community screening. Moreover, incorporation of biomarker findings into the original final diagnostic label could cause reference-standard bias; retaining an independent H&E-based reference category was intended to reduce this problem. No formal evidence of superiority between markers is inferred from the descriptive estimates.

Recent evidence on cervical lesion grading reinforces the value of selective ancillary testing while warning against indiscriminate marker panels. The United Kingdom cervical-screening histopathology guidance and ASCCP recommendations prioritize morphology and targeted p16 IHC, while regarding additional Ki-67 staining as nonessential for routine classification of otherwise clear specimens [5,6]. The findings in this study therefore support a practical distinction between research profiling, in which all three markers may be examined, and clinical diagnosis, where tests should be selected for specific differential diagnostic problems.

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The study has several methodological limitations. It represents a single-center, tissue-selected population with a modest sample and relatively few cases within individual grades. Histological CIN 2 contains a biologically and morphologically heterogeneous group. HPV genotyping, vaccination status, treatment history and longitudinal progression outcomes were not included in the analytical model. Ki-67 and p53 thresholds were selected for descriptive research purposes, and the resulting accuracy measures require external validation. The sample also focused on squamous histology, limiting applicability to glandular cervical tumors.

The principal clinical implication is that p16 block positivity and extent of Ki-67 labeling should be interpreted as adjunctive features of the lesion spectrum rather than stand-alone measures of biological progression or patient outcome. p53 labeling warrants particular caution. Future multicenter, prospectively assembled studies incorporating HPV genotype, standardized scoring, blinded pathological consensus and longitudinal follow-up would help establish whether quantitative marker patterns improve clinically meaningful risk stratification beyond morphology and guideline-based p16 use.

Conclusion

p16 block positivity and Ki-67 labeling showed marked variation across benign cervical lesions, CIN 1, CIN 2, CIN 3 and invasive squamous carcinoma. Strong p16 expression and greater proliferative activity were more frequent in high-grade lesions and carcinoma. p53 nuclear staining displayed a weaker and less consistent relationship with histological severity. Histopathological assessment remains the basis of diagnosis, with p16 IHC applied selectively to appropriate morphological problems and Ki-67 providing supportive proliferative information.

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