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RESEARCH ARTICLE

HPV status and colposcopy: key predictors in cervical cancer and precancerous lesion diagnosis

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ABSTRACT

Objective: This study aims to evaluate the diagnostic value of high-risk human papillomavirus (HR-HPV) positivity—particularly HPV type 16—together with cytological findings and colposcopic assessment in detecting cervical intraepithelial neoplasia (CIN) and cervical cancer.

Materials and Methods: We retrospectively analyzed 781 women who underwent colposcopic examination at a tertiary healthcare center between January 2020 and April 2024. HPV DNA results and cytological evaluations prior to colposcopy were reviewed. Histopathological outcomes from cervical biopsy, endocervical curettage (ECC), and probe curettage (P/C) were examined. Multivariate logistic regression was used to determine the predictors of CIN 2 or more severe lesions.

Results: HPV type 16 was found to be a significant independent predictor of CIN2+ lesions, with an odds ratio of 22.36 (p=0.002) compared to HPV-negative individuals. The model demonstrated statistical significance, and the area under the curve (AUC) was calculated as 0.679, indicating moderate diagnostic performance. Other HPV genotypes and unknown HPV status also showed a significant association with higher-grade lesions.

Conclusion: HR-HPV, and particularly HPV 16, is strongly associated with the presence of advanced cervical lesions. Women testing positive for HPV 16 should undergo close surveillance and timely colposcopic evaluation by specialists to enable early diagnosis and prevent progression to invasive cervical cancer.

Keywords: HPV 16, cervical cancer, colposcopy, CIN2+, precancerous lesion

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INTRODUCTION

Cervical cancer remains one of the most common malignancies affecting women worldwide and ranks fourth among all cancers in terms of incidence (1). What makes this disease unique is that it has a well-defined and preventable cause—persistent infection with high-risk human papillomavirus (HR-HPV) (2). Thanks to advancements in vaccination and screening programs, the burden of cervical cancer has decreased in many countries; however, it continues to be a serious public health issue, especially in regions with limited access to preventive care (3).

The early stages of cervical cancer and precancerous lesions often present no symptoms, complicating timely detection. Symptoms such as abnormal vaginal discharge or postcoital bleeding typically appear in more advanced stages (4,5). Therefore, early detection methods are vital to identify and treat lesions before they progress (6).

Among the established risk factors, persistent HR-HPV infection—especially with types such as HPV 16 and 18—has been recognized as the principal cause of high-grade cervical intraepithelial neoplasia (CIN) and cervical cancer (7-10). Although most HPV infections resolve spontaneously, a small proportion may persist and eventually lead to malignant transformation (11,12). This underlines the importance of HPV-based screening strategies, in addition to traditional cytology (13-15).

Colposcopy serves as a bridge between screening and definitive diagnosis. It allows targeted biopsy of suspicious areas, increasing the diagnostic yield in patients with abnormal cytology or positive HPV tests. However, the accuracy of colposcopic evaluation can vary depending on the examiner's experience and the nature of the lesion, which makes it essential to combine clinical findings with objective markers like HPV status (16-18).

In this study, we aim to explore the diagnostic value of HR-HPV positivity—especially HPV 16—and its correlation with cytological results and colposcopic findings. We also investigate their collective utility in predicting high-grade lesions (CIN2+), which are crucial for timely intervention.

MATERIALS AND METHODS

A total of 781 patients who underwent colposcopy in the gynecological oncology clinic of a tertiary hospital between January 2020 and April 2024 were included in this study. Considering the cytological evaluation and HPV status of these patients prior to the colposcopy procedure, the results of their cervical biopsy, endocervical canal curettage, and probe curettage performed during colposcopy were statistically evaluated. The pathological diagnoses based on cervical biopsy were categorized as CIN I (mild dysplasia; 170 cases), CIN II (moderate dysplasia; 16 cases), CIN III (severe dysplasia and carcinoma in situ; 73 cases), and cervical cancer (6 cases) (19).

The patients who met the following criteria were included in this research:

- Detection of HR-HPV DNA and colposcopy;
- Subjective symptoms such as bleeding after sexual intercourse or increased vaginal discharge;
- Comprehensive clinical and imaging data;
- Age of 18 years or older and sexual experience;
- Patient agreement to participate in the current research.

The following criteria were used to exclude patients from the study:

- Administration of radiotherapy and/or chemotherapy;
- Pregnancy or lactation;
- Previous cervical surgery;
- Other gynecological malignancies;
- Infections caused by other viruses;
- Infectious lesions in the vagina;
- Autoimmune disorders;
- History of hysterectomy;
- Less than 24 hours since last sexual intercourse;
- Within 48 hours of using vaginal medication;
- Ongoing menstruation.

In this study, SPSS 26 was used for statistical analysis of the data. For continuous variables, the mean ± standard deviation was used to describe the distribution. Categorical variables were expressed as frequencies and percentages. The performance of age, HPV status, and single or multiple HPV infections in predicting the presence of CIN 2 and higher lesions on cervical biopsy was analyzed using logistic regression. The model's performance in predicting CIN 2 and above lesions was visualized by the area under the ROC curve (AUC). The statistical significance level was set at $p < 0.05$ and two-tailed.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Necmettin Erbakan University Faculty of Medicine (Approval No: 19293, Date: 17.05.2024). Since the study was retrospective in nature, all data were collected anonymously, and informed consent was deemed not required as per the ethics board's decision.

RESULTS

In this study, 781 patients who underwent colposcopy were analyzed. The mean age of the patients was 42.7 ± 9.48 years. The distribution of HPV positivity, additional HPV presence, smear results, cervical biopsy results, Endocervical Canal Curettage (ECC) results and Probe Curettage (P/C) results is presented in Table 1.

In Table 2, the distribution of cervical smear results according to HPV status is presented. The striking situation here is that HPV DNA positivity increases the cytological ASCUS status.

In Table 3, the distribution of cervical biopsy results according to HPV status is presented. It is noteworthy that HPV 16 DNA-positive patients constitute 20.3% of the CIN 2 and above lesions in cervical biopsy results.

In Table 4, the distribution of endocervical curettage (ECC) results according to HPV status is presented. Again, the association of HPV DNA 16 with lesions of CIN 2 and above was observed to increase.

In Table 5, the distribution of probe curettage (PC) results according to HPV status is presented.

Table 1. Clinical features and histopathological findings in a cohort of patients undergoing colposcopy

Variable (n=781)	**Mean ± SD, n (%)**
Age (year)	42.7 ± 9.48
HPV	
HPV 16	277 (35.5%)
HPV18	72 (9.2%)
Unknown	56 (7.2%)
Other	283 (36.2%)
Negative	93 (11.9%)
Presence of additional HPV	
HPV18	18 (2.7%)
Other	78 (11.9%)
None	560 (85.4%)
Smear Results	
AGC	1 (0.1%)
ASC-H	13 (1.7%)
ASCUS	199 (25.5%)
Unknown	81 (10.4%)
Inflammation	20 (2.6%)
HSIL	2 (0.3%)
LSIL	76 (9.7%)
Negative	378 (48.4%)
Insufficient	11 (1.4%)
Cervical Biopsy Results	
Not Taken	115 (14.7%)
Benign	401 (51.3%)
CIN1	170 (21.8%)
CIN2	16 (2.0%)
CIN3	73 (9.3%)
Malignant	6 (0.8%)
ECC	
Not Taken	309 (39.6%)
Benign	435 (55.7%)
CIN1	14 (1.8%)
CIN2	1 (0.1%)
CIN3	20 (2.6%)
Malignant	2 (0.3%)
PC	
Not Taken	700 (89.6%)
Benign	76 (9.7%)
Premalignant	4 (0.5%)
Malignant	1 (0.1%)

AGC: Atypical Glandular Cells; ASC-H: Atypical Squamous Cells-High; ASCUS: Atypical Squamous Cells Undetermined Significance; HSIL: High Grade Squamous Intraepithelial Lesion; LSIL: Low Grade Squamous Intraepithelial Lesion; CIN: Cervical Intraepithelial Neoplasia; ECC: Endocervical Canal Curettage; PC: Probe Curettage.

Table 2. Distribution of cervical smear results according to HPV status

Smear	HPV Status				
	HPV Negative	HPV 16	HPV 18	HPV Other	HPV Unknown
Inadequate	2 (2.2%)	7 (2.5%)	1 (1.4%)	1 (0.4%)	0 (0.0%)
Negative	54 (58.1%)	149 (53.8%)	44 (61.1%)	123 (43.5%)	8 (14.3%)
Inflammation	1 (1.1%)	10 (3.6%)	2 (2.8%)	7 (2.5%)	0 (0.0%)
AGC	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASCUS	15 (16.1%)	55 (19.9%)	18 (25.0%)	107 (37.8%)	4 (7.1%)
LSIL	17 (18.3%)	23 (8.3%)	2 (2.8%)	32 (11.3%)	2 (3.6%)
ASC-H	3 (3.2%)	6 (2.2%)	0 (0.0%)	4 (1.4%)	0 (0.0%)
HSIL	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Unknown	1 (1.1%)	25 (9.0%)	5 (6.9%)	8 (2.8%)	42 (75.0%)

AGC: Atypical Glandular Cells, ASC-H: Atypical Squamous Cells-High, ASCUS: Atypical Squamous Cells Undetermined Significance, HSIL: High Grade Squamous Intraepithelial Lesion, LSIL: Low Grade Squamous Intraepithelial Lesion.

Table 3. Distribution of cervical biopsy results according to HPV status

Cervical Bx	HPV Status				
	HPV Negative	HPV 16	HPV 18	HPV Other	HPV Unknown
Not received	13 (14.0%)	32 (11.6%)	12 (16.7%)	56 (19.8%)	2 (3.6%)
Benign	59 (63.4%)	123 (44.4%)	38 (52.8%)	143 (50.5%)	38 (67.9%)
CIN 1	20 (21.5%)	66 (23.8%)	16 (22.2%)	58 (20.5%)	10 (17.9%)
CIN 2	0 (0.0%)	6 (2.2%)	2 (2.8%)	7 (2.5%)	1 (1.8%)
CIN 3	1 (1.1%)	47 (17.0%)	3 (4.2%)	18 (6.4%)	4 (7.1%)
Malignant	0 (0.0%)	3 (1.1%)	1 (1.4%)	1 (0.4%)	1 (1.8%)

Bx: Biopsy, CIN: Cervical intraepithelial neoplasia.

Table 4. Distribution of endocervical curettage results according to HPV status

ECC	HPV Status				
	HPV Negative	HPV 16	HPV 18	HPV Other	HPV Unknown
Not received	38 (40.9%)	117 (42.2%)	11 (15.3%)	120 (42.4%)	23 (41.1%)
Benign	54 (58.1%)	140 (50.5%)	59 (81.9%)	151 (53.4%)	31 (55.4%)
CIN 1	0 (0.0%)	4 (1.4%)	1 (1.4%)	8 (2.8%)	1 (1.8%)
CIN 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
CIN 3	1 (1.1%)	16 (5.8%)	0 (0.0%)	3 (1.1%)	0 (0.0%)
Malignant	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.8%)

ECC: Endocervical curettage, CIN: Cervical intraepithelial neoplasia.

Table 5. Distribution of probe curettage results according to HPV status

Probe curettage	HPV Status				
	HPV Negative	HPV 16	HPV 18	HPV Other	HPV Unknown
Not Taken	76 (81,7%)	254 (91,7%)	68 (94,4%)	253 (89,4%)	49 (87,5%)
Benign	16 (17,2%)	22 (7,9%)	3 (4,2%)	29 (10,2%)	6 (10,7%)
Premalignant	1 (1,1%)	1 (0,4%)	0 (0,0%)	1 (0,4%)	1 (1,8%)
Malignant	0 (0,0%)	0 (0,0%)	1 (1,4%)	0 (0,0%)	0 (0,0%)

Table 6. Logistic multivariate regression analysis to predict CIN2 and above lesions

Predictors	Estimate	SE	Z	p	Odds Ratio	95% CI Lower	95% CI Upper
Intercept	-3.83	1.11	-3.42	0.001	0.02	0.002	0.194
Age	-0.01	0.01	-1.37	0.169	0.98	0.960	1.007
HPV status							
HPV 16- Negative	3.10	1.02	3.04	**0.002**	22.36	3.024	165.361
HPV18- Negative	2.08	1.09	1.90	0.057	8.07	0.940	69.346
Unknown- Negative	2.41	1.09	2.20	**0.027**	11.21	1.311	95.820
Other HPV- Negative	2.24	1.02	2.18	**0.029**	9.45	1.265	70.721
Multiple HPV inf. status							
Multi HPV inf. - Single HPV inf.	0.17	0.30	0.55	0.580	1.18	0.647	2.178

Logistic multivariate regression analysis to predict CIN2 and above lesions revealed several important predictors. Several model fit measures were used to assess the overall fit of the model. The deviation value was 541, the AIC (Akaike Information Criterion) value was 555 and the BIC (Bayesian Information Criterion) value was 587. Cox & Snell R^2 value was 0.0648 and Nagelkerke R^2 value was 0.0896. The chi-square (χ^2) value testing the overall goodness of fit of the model was 37.5 with 6 degrees of freedom and a p-value less than 0.001. These results show that the model is statistically significant and explains the data well (N=781). Age was not a significant predictor, with an odds ratio of 0.98 (95% CI: 0.960 to 1.007, p=0.169). Regarding HPV status, HPV 16 was a significant predictor with an odds ratio of 22.36 (95% CI: 3.024 to 165.361, p=0.002) compared to HPV Negative. Compared to HPV Negative, HPV 18 approached significance with an odds ratio of 8.07 (95% CI: 0.940 to 69.346, p=0.057). Compared to HPV Negative, unknown HPV was significant with an odds ratio of 11.21 (95% CI: 1.311 to 95.820, p=0.027). Other HPV types were also significant, with an odds ratio of 9.45 (95% CI: 1.265 to 70.721, p=0.029) compared to HPV Negative. Multiple HPV infections, compared to single HPV infection, were not significant with an odds ratio of 1.18 (95% CI: 0.647 to 2.178, p = 0.580) (Table 6). The model's performance in detecting CIN2 and above lesions is illustrated in Figure 1, with an AUC (Area Under the Curve) of 0.679, indicating a moderate level of diagnostic accuracy. The results of the logistic

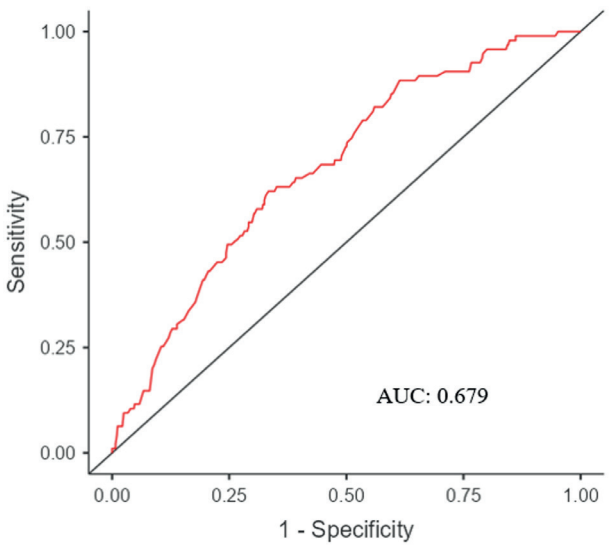

Figure 1. Performance of the logistic regression analysis model in predicting CIN2 and above lesions by ROC Curve

regression analysis show that the model is statistically significant ($p<0.05$) and the AUC value for detecting CIN2 and above lesions is 0.679. This value indicates a moderate level of diagnostic accuracy.

DISCUSSION

Previous studies have consistently demonstrated that high-risk HPV infections are closely linked to the development of cervical precancerous changes and invasive cervical cancer. Moreover, nearly all cervical cancer specimens have been found to contain high-risk HPV DNA, reinforcing its pivotal role in the carcinogenic process (20). Therefore, the present study focused on evaluating the prevalence of HR-HPV positivity across different categories of cervical lesions. Our findings revealed that HR-HPV positivity was significantly more frequent in CIN2+ lesions compared to CIN1 and benign biopsy outcomes. This observation aligns with findings reported in a previous study, which demonstrated a similar distribution of HR-HPV among high-grade lesions (21).

Notably, patients who tested positive for HPV 16 DNA had a 22.36-fold increased risk of developing CIN2 or more severe lesions compared to those without HPV infection.

Interestingly, individuals with unknown HPV DNA status were also found to have an 11.21 times greater likelihood of harboring CIN2+ lesions compared to HPV-negative counterparts. Salvadó et al. reported that HPV 16 infection, along with a history of HSIL cytology, were significant predictors for the persistence or advancement of CIN2 lesions (22). This finding is in agreement with the results of our study.

In another study by Tian et al., HPV status, somatic mutations, and copy number variations were used as important biomarkers for risk classification of CIN2+ lesions. Machine learning algorithms successfully classified the risk of lesions using these biomarkers (23). These findings support the approach of our study, which also utilized predictive modeling to estimate the risk of CIN2+ lesions prior to diagnostic procedures. The AUC value (0.679) calculated from our logistic regression model indicates a moderate diagnostic capability for identifying CIN2 and more advanced lesions. This result underscores the clinical relevance of HPV genotyping, especially in the context of triaging patients for further evaluation. It also highlights the need for close monitoring of patients with HPV 16 positivity, given the elevated risk levels associated with this genotype.

In a study by Quint et al., it was observed that most CIN lesions were linked to a single HPV genotype, even in the presence of multiple infections. This suggests that individual lesions may be driven predominantly by one high-risk type, which is consistent with our findings (24). The strong association between HPV 16 and CIN2+ lesions observed in our cohort further reinforces this conclusion.

This relationship holds particular significance for family physicians managing primary care and gynecologists working in secondary care settings. Identifying HPV 16-positive patients should prompt referral for colposcopic evaluation by experienced gynecologic oncology specialists. Our findings confirm that HPV 16 is strongly correlated with higher-grade cervical lesions (OR: 22.36, $p=0.002$). This highlights its importance as a clinical marker and underscores the necessity for vigilant follow-up strategies in this population.

Since cervical precancerous lesions are often asymptomatic and lack distinct visual features, early detection is particularly challenging. Colposcopy remains a valuable, non-invasive diagnostic tool that enhances biopsy precision and reduces the likelihood of diagnostic errors (25). When performed by trained specialists, colposcopy allows magnified visualization of cervical surface changes, facilitating targeted biopsies based on vascular and epithelial morphology. Previous research has shown that, despite its utility, colposcopy may sometimes yield inaccurate results due to variability in operator experience and interpretation (26-28). The subjective nature of the procedure can influence diagnostic accuracy, emphasizing the importance of integrating objective markers such as HPV typing into clinical workflows (29-31).

HR-HPV testing has become increasingly vital in cervical cancer screening due to its improved sensitivity compared to cytology. It also allows for risk

stratification in patients with ambiguous cytological findings, reduces the testing burden in HPV-negative individuals, and contributes to a more efficient screening process overall (32-34).

CONCLUSION

The combination of HR-HPV testing and colposcopy contributes significantly to the early detection of cervical cancer and its precancerous stages. Moreover, a higher HR-HPV positivity rate appears to correlate with increased lesion severity. A limitation of this study is its retrospective design and the variability in colposcopic assessment due to different gynecologic oncologists performing the procedures.

Ethical approval

This study has been approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (approval date 17.05.2024, number 19293).

Author contribution

Surgical and Medical Practices: SÖ, RŞ; Concept: SÖ; Design: AA; Data Collection or Processing: ECS; Analysis or Interpretation: FA; Literature Search: SÖ; Writing: SÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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