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Research Article

Predictors of CIN2+ Lesions in Women Referred for Colposcopy: A Five-Year Retrospective Study of 783 Cases

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Abstract

Objectives: Colposcopy follows abnormal cervical screening, but high-grade disease is confirmed in only a subset of referred women. We aimed to describe the histopathological yield of colposcopy and identify independent predictors of CIN2+ in a real-world referral population.

Methods: We retrospectively reviewed 783 consecutive women who underwent colposcopy over five years and had definitive histopathology from directed biopsy, endocervical sampling, or excision. Cytology, HPV status, and colposcopic impression were evaluated against final histology. CIN2+ included CIN2, CIN3, adenocarcinoma in situ, and invasive carcinoma. Associations were assessed using chi-square/Fisher tests and logistic regression.

Results: CIN2+ was detected in 213 women (27.2%). Detection increased with cytological severity, from 8.8% in NILM to 78.9% in HSIL, and was higher with high-grade than with low-grade/negative cytology (68.0% vs. 14.4%; p<0.001). CIN2+ rates were 8.2% in HPV-negative, 16.7% in other high-risk HPV-positive, and 50.2% in HPV 16/18-positive women (p<0.001). High-grade or cancer-suspicious colposcopic impression showed the strongest association (72.7% vs. 11.1%; p<0.001). In multivariable analysis, high-grade or cancer-suspicious colposcopic impression, high-grade cytology, and HPV 16/18 positivity independently predicted CIN2+.

Conclusion: One in four referred women had CIN2+. Cytology, HPV genotype, and colposcopic impression should be interpreted together for risk stratification.

Keywords: Cervical intraepithelial neoplasia, Colposcopy, Papanicolaou test, Papillomavirus infections, Uterine cervical neoplasms

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Cervical cancer remains the fourth most commonly diagnosed malignancy and the fourth leading cause of cancer death among women, with an estimated 660,000 new cases and 350,000 deaths recorded worldwide in 2022.[1]

Most of this burden falls on low- and middle-income settings, and the disease is now the principal target of a coordinated global effort: the World Health Organization's strategy to eliminate cervical cancer as a public health problem, built around the 90-70-90 vaccination, screening, and treatment targets to be reached by 2030.[2]

Because nearly all cervical cancers arise from persistent infection with oncogenic human papillomavirus (HPV), and because the precancerous phase is long and detectable, the disease is uniquely amenable to organized prevention through vaccination and screening.[3]

In Türkiye, population-based screening is delivered through Cancer Early Diagnosis, Screening and Education Centers and primary care, where women aged 30-65 are tested every five years with HPV-DNA and cytology; those who are HPV 16/18-positive or who have an abnormal cytology result are referred for colposcopic evaluation.[4]

Management itself has shifted from a results-based logic to a risk-based one, in which the decision to perform colposcopy, treat, or simply survey follows the estimated probability of high-grade disease rather than any single test result.[5]

The difficulty is that colposcopy is an inherently subjective examination. Its accuracy for detecting histologic high-grade lesions varies with the colposcopist's experience, the visibility of the transformation zone, and the threshold used to call an impression abnormal, and pooled estimates of sensitivity and specificity leave considerable room for both missed disease and unnecessary biopsy.[6,7]

Several pre-colposcopy variables carry information about that risk. The severity of the cytological abnormality, positivity for HPV genotypes 16 and 18, and a high-grade colposcopic impression have each been linked to a higher probability of CIN2+ in referral cohorts.[8,9] Even features identified on simple clinical inspection of the cervix have been shown to predict premalignant and malignant disease.[10]

What is less well characterized is how these factors behave together and with what relative weight in an unselected real-world colposcopy population.

We therefore reviewed five years of consecutive colposcopy referrals at our center to describe the histopathological yield of the procedure and to identify the factors—cytology, HPV status, and colposcopic impression—that independently predict CIN2+ detection.

Methods

Study Design and Population

This was a single-center, retrospective observational study of women who underwent colposcopy at Ankara Atatürk Sanatorium Training and Research Hospital, Department of Obstetrics and Gynecology, between 01.01.2021 and 31.12.2025. Consecutive women referred for colposcopic evaluation were eligible. Consistent with the national screening algorithm and routine clinical practice, indications for referral included an abnormal cervical cytology result, high-risk HPV positivity, or a clinical or colposcopic finding suspicious for cervical pathology. Women were included only when a definitive histopathological diagnosis was available from colposcopy-directed biopsy, endocervical sampling, or an excisional procedure performed when clinically indicated. Women without histological confirmation, those with a prior diagnosis or treatment of cervical intraepithelial neoplasia or cervical cancer, those who had undergone hysterectomy, and those with incomplete records were excluded. A total of 783 women met these criteria.

Data Collection and Definitions

Demographic and clinical data, cytology and HPV results, colposcopic findings, and histopathology reports were extracted from medical records. Cervical cytology was reported according to the Bethesda system as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells that cannot exclude HSIL (ASC-H), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), or unsatisfactory. HPV results were grouped as negative, HPV 16/18-positive, other high-risk HPV-positive, or unknown when genotyping was unavailable or undocumented. Colposcopy was performed after application of 3–5% acetic acid and Lugol's iodine, and findings were classified according to the International Federation of Cervical Pathology and Colposcopy nomenclature as normal, low-grade, high-grade, suspicious for invasion, or unsatisfactory.[6] Histopathology served as the reference standard and was categorized as benign (including cervicitis, squamous metaplasia, and other non-neoplastic changes), CIN1, CIN2, CIN3, adenocarcinoma in situ, or invasive carcinoma. The primary outcome was the detection of CIN2+, defined as CIN2, CIN3, adenocarcinoma in situ, or invasive cancer; women with benign histology or CIN1 were classified as CIN2+ negative.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages. The distribution of CIN2+ across cytology,

HPV, and colposcopic impression categories was compared using the chi-square test, with Fisher's exact test used where expected cell counts were small. For modelling, three binary predictors were defined a priori: high-grade cytology (ASC-H, HSIL, or AGC) versus negative or low-grade cytology (NILM, ASC-US, or LSIL); HPV 16/18 positivity versus HPV-negative or other high-risk HPV; and a high-grade or cancer-suspicious colposcopic impression versus a normal or low-grade impression. Univariable logistic regression was used to estimate crude ORs, and these predictors were then entered, together with age, into a multivariable logistic regression model to identify factors independently associated with CIN2+. Records with an unsatisfactory or undocumented result for a given variable were excluded from the corresponding comparison. Results are reported as crude and adjusted ORs with 95% confidence intervals (CIs). A two-sided *p* value below 0.05 was considered statistically significant. Analyses were performed using SPSS ver. 25.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Approval Date: 08.07.2026; Approval No.: 2024-BÇEK/629). Given the retrospective design, the requirement for informed consent was waived.

Results

A total of 783 women who underwent colposcopic evaluation during the five-year study period were included in the final analysis. All patients had a documented histopathological diagnosis obtained after colposcopy-directed biopsy, endocervical sampling, or an excisional procedure when clinically indicated. The cohort represented a routine colposcopy referral population, including women referred because of abnormal cervical cytology, high-risk HPV positivity, or suspicious colposcopic findings.

Histopathological examination revealed benign findings, including cervicitis, squamous metaplasia, or other non-neoplastic changes, in 289 patients (36.9%). CIN1 was identified in 281 patients (35.9%), CIN2 in 95 patients (12.1%), CIN3 in 95 patients (12.1%), adenocarcinoma in situ in 6 patients (0.8%), and invasive cervical cancer in 17 patients (2.2%). Overall, CIN2+ lesions were detected in 213 women (27.2%), whereas 570 women (72.8%) had benign or CIN1 histopathology and were classified as CIN2+ negative (Table 1).

Table 1. Overall histopathological outcomes of the study population

Histopathological diagnosis	n	%
Benign / cervicitis / metaplasia	289	36.9
CIN1	281	35.9
CIN2	95	12.1
CIN3	95	12.1
Adenocarcinoma in situ	6	0.8
Invasive cervical cancer	17	2.2
Total	783	100.0
CIN2+	213	27.2
CIN1 or less	570	72.8

CIN: Cervical intraepithelial neoplasia; CIN2+: Cervical intraepithelial neoplasia grade 2 or worse.

When histopathological outcomes were evaluated according to cytology, CIN2+ detection increased with the severity of cytological abnormality. CIN2+ lesions were detected in 18 of 205 women with NILM cytology (8.8%), 34 of 210 women with ASC-US (16.2%), and 32 of 170 women with LSIL (18.8%). In contrast, CIN2+ lesions were identified in 29 of 55 women with ASC-H (52.7%), 75 of 95 women with HSIL (78.9%), and 17 of 28 women with AGC (60.7%). When cytology was grouped as low-grade/negative cytology versus high-grade cytology, the CIN2+ detection rate was significantly higher in the high-grade cytology group (68.0% vs. 14.4%, p<0.001).

HPV status was also significantly associated with CIN2+ detection. CIN2+ lesions were detected in 9 of 110 HPV-negative women (8.2%), 128 of 255 women with HPV 16/18 positivity (50.2%), and 56 of 335 women with other high-risk HPV positivity (16.7%). HPV status was unavailable in 83 patients, of whom 20 (24.1%) had CIN2+ lesions. The CIN2+ detection rate differed significantly across HPV groups (p<0.001), with the highest rate observed among women with HPV 16/18 positivity.

Colposcopic impression showed the strongest association with final histopathological outcome. CIN2+ lesions were detected in 10 of 160 women with normal colposcopic findings (6.3%) and 52 of 400 women with low-grade colposcopic impression (13.0%). In contrast, CIN2+ lesions were found in 134 of 190 women with high-grade colposcopic impression (70.5%) and in 15 of 15 women with colposcopic findings suspicious for invasive disease (100.0%). The CIN2+ detection rate was significantly higher in women with high-grade or cancer-suspicious colposcopic impression than in those with normal or low-grade colposcopic findings (72.7% vs. 11.1%, p<0.001) (Table 2).

In univariate analysis, high-grade cytology, HPV 16/18 positivity, and high-grade or cancer-suspicious colposcopic impression were significantly associated with CIN2+ de-

Table 2. Histopathological outcomes according to cytology

Cytology	Total n	Benign	CIN1	CIN2	CIN3	AIS / Cancer	CIN2+ n	CIN2+ %
NILM	205	105	82	10	7	1	18	8.8
ASC-US	210	94	82	20	13	1	34	16.2
LSIL	170	55	83	18	13	1	32	18.8
ASC-H	55	10	16	13	15	1	29	52.7
HSIL	95	8	12	28	42	5	75	78.9
AGC	28	7	4	4	4	9	17	60.7
Unsatisfactory / unknown	20	10	2	2	1	5	8	40.0
Total	783	289	281	95	95	23	213	27.2

Chi-square test for CIN2+ detection across cytology groups: p<0.001
NILM: Negative for intraepithelial lesion or malignancy; ASC-US: Atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H: Atypical squamous cells, cannot exclude HSIL; HSIL: High-grade squamous intraepithelial lesion; AGC: Atypical glandular cells; AIS: Adenocarcinoma in situ; CIN: Cervical intraepithelial neoplasia; CIN2: Cervical intraepithelial neoplasia grade 2 or worse.

tection. High-grade cytology was associated with markedly increased odds of CIN2+ lesions compared with NILM/ASC-US/LSIL cytology (crude OR: 12.66, 95% CI: 8.49–18.89, p<0.001). HPV 16/18 positivity was also associated with higher CIN2+ detection compared with HPV-negative or other high-risk HPV results (crude OR: 5.41, 95% CI: 3.78–7.75, p<0.001). High-grade or cancer-suspicious colposcopic impression showed the strongest univariate association with CIN2+ detection (crude OR: 21.36, 95% CI: 14.08–32.42, p<0.001) (Table 3).

In multivariable logistic regression analysis, high-grade cytology, HPV 16/18 positivity, and high-grade or cancer-suspicious colposcopic impression remained independently associated with CIN2+ detection. After adjustment for age, cytology group, HPV status, and colposcopic impression, high-grade cytology was associated with an approximately six-fold increase in the odds of CIN2+ lesions (adjusted OR: 5.86, 95% CI: 3.61–9.51, p<0.001). HPV 16/18 positivity was independently associated with CIN2+ detection (adjusted OR: 3.24, 95% CI: 2.02–5.19, p<0.001). High-grade or cancer-suspicious colposcopic impression remained the strongest independent factor associated with CIN2+ lesions (adjusted OR: 9.78, 95% CI: 5.98–15.99, p<0.001). Age was not independently associated with CIN2+ detection in the adjusted model (adjusted OR per year: 1.01, 95% CI: 0.99–1.03, p=0.286) (Table 4).

Table 3. CIN2+ detection according to HPV status and colposcopic impression

Variable	Total n	CIN2+ n	CIN2+ %	p
HPV status				<0.001
HPV negative	110	9	8.2	
HPV 16/18 positive	255	128	50.2	
Other high-risk HPV positive	335	56	16.7	
HPV unknown	83	20	24.1	
Colposcopic impression				<0.001
Normal	160	10	6.3	
Low-grade impression	400	52	13.0	
High-grade impression	190	134	70.5	
Suspicious for invasive disease	15	15	100.0	
Unsatisfactory / unknown	18	2	11.1	

HPV: Human papillomavirus; CIN2+: Cervical intraepithelial neoplasia grade 2 or worse.

Overall, these findings indicate that approximately one in four women referred for colposcopy had CIN2+ histopathology. The likelihood of CIN2+ detection was lowest among women with NILM cytology, HPV-negative status, and normal colposcopic findings and highest among women with high-grade cytology, HPV 16/18 positivity, and high-grade or cancer-suspicious colposcopic impression.

Discussion

In this five-year series of 783 colposcopy referrals, roughly one woman in four had CIN2+ on final histology, and the probability of high-grade disease tracked closely with three pre-colposcopy variables: the severity of the cytological abnormality, the HPV genotype, and the colposcopist's impression. All three remained associated with CIN2+ after adjustment, with the high-grade or cancer-suspicious colposcopic impression carrying the strongest independent signal. The pattern is coherent and clinically intuitive, and it broadly matches what has been reported from comparable referral populations.

The overall CIN2+ yield of 27.2% is higher than the 14.6% reported in a large Chinese referral cohort that used the

Table 4. Multivariable logistic regression analysis for factors associated with CIN2+ detection

Variable	Crude OR	95% CI	p	Adjusted OR	95% CI	p
Age, per year	1.01	0.99–1.02	0.318	1.01	0.99–1.03	0.286
High-grade cytology	12.66	8.49–18.89	<0.001	5.86	3.61–9.51	<0.001
HPV 16/18 positivity	5.41	3.78–7.75	<0.001	3.24	2.02–5.19	<0.001
High-grade or cancer-suspicious colposcopic impression	21.36	14.08–32.42	<0.001	9.78	5.98–15.99	<0.001

OR: Odds ratio; CI: Confidence interval; HPV: Human papillomavirus; CIN2+: Cervical intraepithelial neoplasia grade 2 or worse.

same outcome definition.[8] The difference most likely reflects referral composition rather than a true difference in disease. Our population was enriched for high-grade cytology and HPV 16/18 positivity, both of which raise the pretest probability of high-grade histology. Where the cytology was NILM, CIN2+ was found in fewer than one in ten women, whereas HSIL cytology was associated with high-grade disease in nearly four of five—a gradient consistent with the long-standing observation that cytological severity scales with underlying histology. The non-trivial CIN2+ rate among women with ASC-H and AGC is a reminder that these indeterminate categories are not low-risk; AGC, in particular, yielded a high-grade or malignant result in three of five women and accounted for a disproportionate share of the glandular and invasive lesions, in keeping with the recognized difficulty of glandular cytology and the more aggressive behavior of cervical adenocarcinoma.[11]

HPV genotyping added a second, partly independent layer of stratification. Women positive for HPV 16/18 had a CIN2+ rate of 50.2%, three times that of women with other high-risk types and far above the 8.2% seen in HPV-negative referrals. This fits the established status of HPV 16/18 as the genotypes most strongly tied to high-grade disease and supports the national algorithm's decision to triage HPV 16/18-positive women directly to colposcopy.[4] At the same time, the 16.7% CIN2+ rate among women with non-16/18 high-risk types is not negligible; a comparable immediate risk has been described in cytology-negative HR-HPV-positive referrals, where direct colposcopy rather than deferred follow-up has been advocated in resource-constrained settings.[9] The small group with undocumented HPV status had an intermediate yield and is hard to interpret, so we treated it descriptively and did not include it in the genotype comparison.

The strongest predictor in our data was the colposcopic impression itself. CIN2+ was uncommon when colposcopy was read as normal (6.3%) or low-grade (13.0%) but was present in 70.5% of high-grade impressions and in every woman whose examination was judged suspicious for invasion. That a high-grade or cancer-suspicious colposcopic impression was the strongest independent predictor (adjusted OR 9.78, 95% CI 5.98–15.99) echoes a referral cohort in which the colposcopic impression carried by far the largest odds ratio for CIN2+.[8] The crude association in our data was stronger still (OR 21.36) and roughly halved after adjustment for cytology and HPV status—an expected pattern, since a striking colposcopic picture is usually accompanied by high-grade cytology or HPV 16/18 positivity, so part of its apparent predictive power is shared rather than unique to the examination. It should not, however, be read as evidence that colposcopy can stand alone. The examination is observer-dependent: pooled analyses applying the 2011 IFCPC terminology show only moderate sensitivity at the CIN2+ threshold.[6] Single-center data report meaningfully higher accuracy among experienced colposcopists than among trainees.[7] Accuracy falls further when the transformation zone is not fully visible or in older women, in whom biopsy alone underestimates high-grade disease.[12] The 100% CIN2+ rate in the "suspicious for invasion" group is reassuring at face value but rests on only fifteen women and should be read with that fragility in mind. Observations of this kind also explain why clinical inspection of the cervix retains value as an indication for colposcopy independent of cytology and HPV, as has been shown for the clinically suspicious cervix.[10]

In the adjusted model, high-grade cytology (adjusted OR 5.86, 95% CI 3.61–9.51) and HPV 16/18 positivity (adjusted OR 3.24, 95% CI 2.02–5.19) remained independent contributors alongside the colposcopic impression. The rank order of the three factors, and the magnitude of the cytology and HPV 16/18 estimates, were close to those reported from the same Chinese cohort, lending external consistency to the model, although the impression effect was somewhat smaller in our adjusted analysis.[8] Age did not independently predict CIN2+ once these factors were accounted for (adjusted OR 1.01 per year, p=0.286), indicating that the risk signal in this cohort was carried by the tests and the examination rather than by age itself. Taken together, these results support the principle now embedded in risk-based management: no single test should govern the decision, and the combination of cytology, HPV genotype, and colposcopic impression discriminates risk better than any

one of them alone.[5] For a woman with HSIL cytology, HPV 16/18 positivity, and a high-grade impression, the probability of CIN2+ is high enough to justify decisive action, whereas concordantly reassuring results across all three identify a group at genuinely low risk. The corollary is the potential value of adjuncts that might sharpen an uncertain impression; biomarker-based triage with p16/Ki67 dual staining and HPV mRNA testing, and electrical impedance spectroscopy used alongside colposcopy, have all been explored as ways to improve CIN2+ detection while limiting unnecessary biopsy and deserve evaluation in populations such as ours.[13] None of this displaces primary prevention, and wider HPV vaccination remains the upstream measure most likely to reduce the future burden of the high-grade lesions described here.[3]

Several limitations temper these findings. The study was retrospective and single-center, so referral patterns and local colposcopic practice may limit generalizability. Colposcopic impression was recorded in routine practice without central review or formal inter-observer assessment, and we did not stratify by colposcopist experience or transformation-zone type, both of which are known to influence accuracy. HPV genotype was missing for a subset of women. We did not formally assess the model's discrimination or calibration, and it was not validated in an external population, so the estimates should be read as associations within this cohort rather than as a ready-to-use prediction rule. Finally, as a cross-sectional analysis of a single colposcopy episode, the study cannot address longitudinal outcomes such as lesion persistence, regression, or progression.

Within these constraints, the data carry a clear and clinically useful message. In an everyday colposcopy population, the likelihood of CIN2+ ranged from very low in women with NILM cytology, HPV-negative status, or a normal colposcopic impression to very high in those with HSIL/ASC-H/AGC cytology, HPV 16/18 positivity, or a high-grade or cancer-suspicious colposcopic impression. Reading these three pieces of information together, rather than in isolation, allows the women most likely to harbor high-grade disease to be identified at the time of colposcopy.

Conclusion

In this five-year retrospective cohort, CIN2+ was detected in about one quarter of women referred for colposcopy. High-grade cytology, HPV 16/18 positivity, and a high-grade or cancer-suspicious colposcopic impression were each independently associated with CIN2+, with the colposcopic impression showing the strongest association. The findings reinforce a combined, risk-based use of cytology, HPV genotyping, and colposcopy to triage referred women while recognizing the observer-dependent limits of colposcopy and the continued importance of HPV vaccination and organized screening in reducing high-grade cervical disease.

Disclosure

Ethics Committee Approval: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Approval Date: 08.07.2026/Approval No: 2024-BÇEK/629)

Informed Consent: Given the retrospective design, the requirement for informed consent was waived.

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