The association of pathological findings in HPV-31 positive women with high-grade squamous intraepithelial lesions

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Abstract

Objective: To evaluate pathological findings in patients positive for human papillomavirus (HPV)-31.

Material and Methods: This retrospective study included patients evaluated in a tertiary colposcopy clinic. The 3,546 patients tested for high-risk HPV were evaluated from September 2019 to December 2023. The study comprised 130 (3.7%) patients who tested positive for HPV-31. Isolated HPV-31 positivity indicated the presence of HPV-31 alone. Combined positivity indicated coexistence with other high-risk HPV types. If the following lesions were positive, high-grade squamous intraepithelial lesions (HSILs), adenocarcinoma *in situ*, microinvasive cancer, and cervical cancer, we classified the final pathology as ≥HSIL. Statistical analysis was performed using IBM SPSS Statistics version 20.0.

Results: The mean age was 44.4±9.24 years. Isolated HPV-31 positivity was present in 69 (53.1%) patients. The final pathologic result was ≥HSIL in 9 (6.9%) patients, with only 1 (0.8%) patient had squamous cell cervical cancer. No significant association was observed between HPV-31 positivity type (isolated or combined) and ≥HSIL (respectively, 7.2% vs. 6.6%; p=0.578).

Conclusion: Approximately 7% of women positive for HPV-31 have HSIL and higher lesions. The isolated or combined HPV-31 positivity does not affect the existence of HSIL or higher lesions. [J Turk Ger Gynecol Assoc. 2026; 27(2): 120-4]

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Introduction

Worldwide, millions of women aged 15 years and older are at risk of developing cervical cancer (1). GLOBOCAN 2020 data shows that there are approximately 604,000 new cases of cervical cancer and 342,000 deaths each year and ranks as the fourth most common cancer among women worldwide, following breast, colorectal, and lung cancers. In addition, cervical cancer ranks second among cancers in women aged 15-44 years worldwide (1,2). Persistent human papillomavirus (HPV) infection is the main etiological factor in cervical cancer development. Long-term persistence of oncogenic HPV genotypes may result in cervical intraepithelial lesions, which can subsequently progress to invasive cervical cancer (3,4). The use of HPV nucleic acid testing in cervical cancer screening programs has increased detection of high-grade squamous intraepithelial lesions (HSILs) but reduced cervical cancer incidence (5,6).

Over 200 HPV genotypes have been identified, and nearly 40 of these infect the anogenital epithelium. These genotypes are broadly grouped into high-risk and low-risk categories, based on their oncogenic potential (7). Among oncogenic HPV types, HPV-16 and HPV-18 are responsible for nearly 70% of cervical cancer cases. The prevailing high-risk subtypes of HPV,

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following HPV-16/18, include HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 (1).

There is limited knowledge about how HPV-31 is related to cervical intraepithelial lesions, particularly HSIL and cervical cancer, although HPV-31 is the second most prevalent HPV subtype associated with these lesions (8). Previous studies have reported that HPV-31 infection is associated with a cumulative risk of HSIL [cervical intraepithelial neoplasia (CIN) 2-CIN 3] ranging between approximately 9% and 11% (8-10).

This study evaluated final histopathological outcomes in patients positive for HPV-31. A secondary aim was to determine whether the coexistence of other high-risk HPV genotypes together with HPV-31 influenced the final pathological findings.

Material and Methods

Data were collected from a tertiary care colposcopy outpatient clinic and the study was conducted retrospectively. A total of 3,546 patients tested for high-risk HPV between September 2019 and December 2023 were evaluated. The study population consisted of 130 patients (3.7%) who tested positive for HPV-31. The exclusion criteria included pregnant women, patients receiving immunosuppressive therapy, individuals who were not positive for HPV-31, and HPV-positive patients with unknown genotypes. Ethical approval for this study was obtained from the Ankara Bilkent City Hospital Ethics Committee (approval number: TABED 1-24-481, date: 25.09.2024).

Cervical cancer screening in Türkiye is conducted using HPV testing and the pap smear program. Using the HPV polymerase chain reaction (PCR) kit, the obtained DNA was subsequently detected and classified. Cervical samples were collected using a cytobrush, and the samples were subsequently used for genomic DNA extraction. HPV DNA isolation was performed using the QIAsymphony DSP Virus/Pathogen Midi Kit, and detection and genotyping were carried out with the QIAscreen HPV PCR Kit (Qiagen Inc., Germany). Liquid-based cytology preparations were prepared using the NOVAprep® system (Novaprep Inc., Russia). Liquid-based cytology samples were prepared using the Max-prep cytology system (Corebiotech Co. Ltd, Korea).

Isolated HPV-31 positivity indicated detection of HPV-31 alone, whereas combined HPV-31 positivity indicated detection of HPV-31 together with other high-risk HPV strains. Patients in our clinic are managed based on the American Society for Colposcopy and Cervical Pathology guidelines. Patients diagnosed with HSIL, microinvasive cancer, or adenocarcinoma *in situ*, based on colposcopic biopsy findings, as well as cases with inconsistency between biopsy results and clinical evaluation, underwent conization. The final pathological result was determined based on the highest-grade lesion identified from smear, cervical biopsy, conization, or hysterectomy specimens (Table 1). If the following lesions were positive, HSIL, adenocarcinoma *in situ*, microinvasive cancer, and cervical cancer, we classified the final pathology as ≥HSIL. Gynecologic oncologists performed all colposcopic examinations and conization procedures. Experienced gynecologic pathologists evaluated the surgery specimens.

Statistical analysis

Statistical analyses were conducted with SPSS, version 20.0 (IBM Corp., Chicago, IL, USA). Descriptive data are presented as mean ± standard deviation, median (range), and number (percentage).

Table 1. Final pathology decision

Cervicovaginal smear	ECC pathology	Colposcopic biopsy pathology	Conization pathology	Final pathology
Benign/LSIL/ASCUS	Benign/LSIL	Benign/LSIL	Benign/LSIL	Benign/LSIL
HSIL	Benign/LSIL	Benign/LSIL	Benign/LSIL	HSIL
Any result	HSIL	Benign/LSIL	Benign/LSIL	HSIL
Any result	Benign/LSIL	HSIL	Benign/LSIL	HSIL
Any result	Benign/LSIL	Benign/LSIL	HSIL	HSIL
Any result	Benign/LSIL	HSIL	HSIL	HSIL
Any result	HSIL	Benign/LSIL	HSIL	HSIL
Any result	HSIL	HSIL	Benign/LSIL	HSIL
Any result	HSIL	HSIL	HSIL	HSIL
Any result	If any of the result is squamous cell cancer or adenocancer			Cancer

ECC: Endocervical curettage, ASCUS: Atypical squamous cells undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion

Results

The analysis included 130 patients, and their mean age was 44.4±9.24 years. Isolated HPV-31 positivity was detected in 69 patients (53.1%), whereas combined HPV-31 positivity was present in the remaining 61 (46.9%). Among patients with combined HPV-31 positivity, high-risk HPV strains were distributed as follows: HPV-16 HPV-16 in seven patients (11.4%), HPV-18 in eight (13.1%), HPV-33 in five (8.2%), HPV-35 in nine (14.7%), HPV-39 in seven (11.4%), HPV-45 in five (8.2%), HPV-51 in 12 (19.7%), HPV-52 in eight (13.1%), HPV-56 in 10 (16.4%), HPV-58 in five (8.2%), HPV-59 in three (4.9%), and HPV-68 in four patients (6.5%) (Table 2).

The final pathologic result was ³HSIL in nine (6.9%) patients. The final pathologic results were benign in 68 (52.3%), low-grade squamous intraepithelial lesion in 53 (40.8%), HSIL (CIN 2) in five (3.8%), HSIL (CIN 3) in three (2.3%), and cancer in one (0.8%) patient (Table 2). The patient was diagnosed with squamous cell carcinoma following a colposcopic biopsy, tested positive for isolated HPV-31, presented with atypical squamous cells of undetermined significance from a smear, and had a 3.5 cm mass in the cervix spreading into the endocervical canal. Following this, type III radical hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy was performed. The patient, classified as stage 1b2 according to the 2018 FIGO staging system, did not undergo adjuvant therapy. The association between isolated or combined HPV-31 positivity and ≥HSIL is shown in Table 3. No significant association was found for isolated or combined HPV-31 positivity and the presence of ≥HSIL. ≥HSIL lesions were observed in five isolated HPV-31 positive patients (7.2%) and in four patients with combined HPV-31 positivity (6.6%) (p=0.578).

Discussion

In our tertiary care center HPV-31 positivity was detected in 3.7% of HPV-positive women. Nearly half of the cases (46.9%) demonstrated co-infection with at least one additional high-risk HPV genotype, with HPV-51 being the most frequently accompanying type (19.7%). High-grade cervical pathology (≥HSIL) was identified in 6.9% of women with HPV-31 positivity, and the presence of any additional high-risk HPV types accompanying HPV-31 did not increase the possibility of ≥HSIL. Cervical cancer was detected in only one patient (0.8%) in the final pathological evaluation.

Table 2. Age, HPV-31 type and final pathologic result

Features		**Mean ± SD**	**Median (range)**
Age		44.4±9.24	42 (28-66)
		n	%
HPV-31	**Isolated HPV-31**	69	53.1
	Combined HPV-31	61	46.9
HPV-31 and other HPV type	**HPV-16**	7	11.4
	HPV-18	8	13.1
	HPV-33	5	8.2
	HPV-35	9	14.7
	HPV-39	7	11.4
	HPV-45	5	8.2
	HPV-51	12	19.7
	HPV-52	8	13.1
	HPV-56	10	16.4
	HPV-58	5	8.2
	HPV-59	3	4.9
	HPV-68	4	6.5
Final pathologic results	**Benign**	68	52.3
	LSIL	53	40.8
	HSIL (CIN 2)	5	3.8
	HSIL (CIN 3)	3	2.3
	Cancer	1	0.8

HPV: Human papillomavirus, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia, SD: Standard deviation

Table 3. The relationship between HPV-31 type and ≥HSIL lesion in final pathologic results

HPV-31 type	Benign or LSIL	≥HSIL[1]	p-value
	n (%)	n (%)	
Isolated HPV-31	64 (92.8)	5 (7.2)	0.578
Combined HPV-31	57 (93.4)	4 (6.6)	

[1]: CIN 2 or CIN 3 or cancer
HPV: Human papillomavirus, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia

The distribution of high-risk HPV genotypes varies considerably across different geographical regions. Even within the same country, regional variations in HPV prevalence have been reported (11,12). The worldwide prevalence of HPV-31 is 0.8%, while in Europe it is 2.3% (11). A study reported that the prevalence of HPV-31 was 17.3%, making it the second most prevalent type after HPV-16 (8). In Türkiye, 4 million women were screened as part of a nationwide HPV-based screening program. One of the largest published screening series reported an HPV-31 prevalence of 8.6%, ranking third after HPV-16 (21.9%) and HPV-51 (10.3%) (13). Another study conducted between 2006 and 2010, including 6,388 patients, reported an HPV-31 prevalence of 6%, identifying it as the third most prevalent high-risk HPV type (14). In the present study, which evaluated data from one of the largest tertiary hospitals in Türkiye, the prevalence of HPV-31 was 3.7%.

Current evidence regarding the relationship between HPV-31 infection and cervical cancer remains limited. In our study population, cervical cancer was diagnosed in only 0.8% of women positive for HPV-31. A meta-analysis published in 2007 reported that the prevalence of HPV-31 was 3.8% in squamous cell cervical cancer and 8.6% in HSIL (15). A worldwide meta-analysis published in 2011 evaluated 30,848 cervical cancer patients and reported an HPV-31 prevalence of 3.8% (12). Another study reported a detection rate of HPV-31 in HSIL samples of 23.5%, whereas HPV-31 was not detected in all cases of cervical cancer (8).

The impact of isolated versus multiple high-risk HPV infections on the development of HSIL or more advanced lesions remains unclear. One study compared the effect of HPV-16–HPV 18 co-infection on ≥HSIL lesions with women positive only for HPV-16 and reported no significant difference (16). Another study demonstrated no significant difference in cervical pathology between isolated HPV-31 infection and combined HPV-31 infection (17). No significant association was found between isolated or combined HPV-31 infection and ≥HSIL in the present study but the sample was only 130 women positive for HPV-31. However, another study reported that the HSIL rate increased from 5.8% with isolated infection to 13.1% with combined infection (p=0.089) (18).

Study limitations

This study has certain limitations, including the very small study population, its retrospective design, limited information on previous HPV positivity, and insufficient data on vaccination status. In addition, the study was restricted to a specific region which limits the generalizability of the results. Despite these limitations, our study represents one of the relatively larger series evaluating HPV-31 positivity although much larger populations are required for reliable epidemiological findings. A strength of the present study is that all patients were evaluated in a tertiary care center by experienced gynecologic oncologists and gynecologic pathologists.

Conclusion

Approximately 7% of HPV-31–positive women have HSIL or higher-grade cervical lesions. However, in this HPV-31- positive population, cervical cancer incidence was below 1%. Isolated HPV-31 positivity when compared to combined HPV-31 plus other high-risk HPV types did not appear to increase the risk of HSIL or more severe cervical lesions.

Ethics

Ethics Committee Approval: *Ethical approval for this study was obtained from the Ankara Bilkent City Hospital Ethics Committee (approval number: TABED 1-24-481, date: 25.09.2024).*

Informed Consent: *Informed consent was waived due to the retrospective design of the study.*

Footnotes

Author Contributions: *Surgical and Medical Practices: A.B., H.A., Y.Ö.U., A.A.T., G.T.G., O.A., F.K., T.T., Concept: A.B., H.A., T.T., Design: A.B., H.A., Data Collection or Processing: A.B., Y.Ö.U., A.A.T., G.T.G., O.A., F.K., Analysis or Interpretation: A.B., O.A., F.K., Literature Search: A.B., Y.Ö.U., Writing: A.B., T.T.*

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